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Vaccine Safety Pharmacovigilance: Individual Causality Assessment of AEFIs

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Abstract

Vaccines are considered public health tools of proven effectiveness and safety. However, their post-marketing use can be related to the occurrence of adverse events (Adverse Events Following Immunization: AEFI). Proper assessment of causality is vital for decision-making, in that it allows a balancing of known benefits with possible but unverified risks. An increasing number of recent cases contributed to highlight the problem of the AEFIs evaluation process and identify possible reasons why the causal link ends up by being almost always excluded. The reasoning behind such process is standardized and systematized by the application of the 2019 WHO algorithm: a method for individual causality assessment for AEFIs, widely used worldwide by regulatory authorities and pharmacovigilance departments. Increasing cases of serious and sometimes lethal AEFIs systematically valued as non-correlated to vaccines, have led to questioning its validity. The algorithm presents some criticalities, leading to the non-recognition of the vaccine's responsibility in having caused the AEFI, thus to an increase in false negatives. The aim of the research is to investigate these criticalities. The analysis is conducted by following both the pharmacological and epistemological channels. The latter is fundamental in the foundational evaluation of the causal link(s) and for an overall evaluation of the algorithm, as it is conceived and methodologically structured. The foci of the research are: *multifactoriality* (ontology), *evidential pluralism* (epistemology) and *voucher approach* (methodology). Based on these criteria, I will suggest a possible revision of the algorithm by advancing a new theoretical framework. I will then present a case study to show how my proposal could increase the accuracy of the causality assessment procedure, thus reducing the likelihood of false negatives.

Keywords: causality assessment; false negatives; multifactoriality; pluralism.

Introduction

The global impact of the COVID-19 pandemic has led to an unprecedented interest in vaccines (their development, regulatory review, and safety monitoring) by the general public, decision makers, scientific communities and regulatory agencies (WHO, 2021).
In the field of prevention of infectious diseases, vaccines are considered public health tools of proven effectiveness and safety. However, this interest is also due to the fact that vaccines are not risk-free since their use can be related to the occurrence of adverse events (Adverse Events Following Immunization, AEFIs).
When a vaccine-AEFI debate spills over into the public and political arena, proper assessment of causality is vital for decision-making, in that it allows a balancing of known benefits with possible but unverified risks (WHO, 2001; WHO-HIS-EMP, 2013). An increasing number of recent cases of AEFIs contributed to increasing the attention to the problem of their evaluation and of the reasons why the causal link ends up by being almost always excluded.
The reasoning behind such process is standardized and systematized by the application of the 2019 version of the WHO AEFIs algorithm (developed in 2013). It consists in a method for individual causality assessment of AEFIs developed for the staff of national immunization programs, regulatory authorities and pharmacovigilance departments. The tool considers a number of factors in the causal analysis of a possible association between AEFI and vaccine, namely: the presence of possible alternative explanations, prior evidence in the literature, biological plausibility, plausible temporal relationship, frequency of the event reported in the general population, evidence against the vaccine-AEFI association.
Despite its generalized use worldwide, increasing cases of serious and sometimes lethal AEFIs systematically valued as non-correlated to vaccines, have led to questioning its validity. The main opposing voices (Bellavite et al., 2020; H. Lee et al., 2020; Osimani B. & Ilardo, 2022; Puliyel et al., 2018) state that the algorithm presents some criticalities leading to the non-recognition of the vaccine's responsibility in having caused the AEFI.
The aim of this research is to highlight and investigate the WHO algorithm's criticalities underlining the flaws that characterize it both from a methodological and a conceptual point of view.
In Chapter I will introduce vaccination as a fundamental tool for public health protection at global level in the fight against infectious diseases and the main stakeholders involved in the management of these issues and in vaccines' safety monitoring. I'll present the special role of the World Health Organization (WHO) in coordinating global public health surveillance to tackle epidemics and pandemics, in the development and distribution of vaccines worldwide, and in monitoring safety concerns and potential AEFIs. Then, by focusing on the European context, I'll present the regulatory authority responsible in monitoring Adverse Events Following Immunization (AEFIs): the European Medicine Agency (EMA). At the national level I will refer to the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA). I will discuss the key role of Pharmacovigilance systems in the early detection of (new) AEFIs, and then I will underline the differences between pharmacovigilance for drugs and for vaccines.

This will cast light on the paramount importance of ensuring an effective system for detecting (new) signals in case of vaccines. Since vaccines are administered to healthy individuals this implies that safety criteria should be more stringent than those associated with treatments administered to subjects whose health is already more or less severely compromised by a pathology.

Chapter II will focus on causality assessment. Since, in AEFI spontaneous signaling systems, causal inferences operate on two levels, I will first distinguish between population-based and individual causality assessment by then focusing on the latter. I will present the current methods used for individual causal assessment and the criteria for both the quality of causality assessment and the causal diagnosis of adverse events (AEs). Then, I will describe the method used to assess individual causality for the medicinal products and the old system used to assess AEFI causality to highlight the differences between these systems and the current WHO algorithm. Finally, I will go on to present the WHO 2019 algorithm, by underlining that, as it is conceived and structured, it seems to underestimate the complexity of the analysis context in which it operates, leading to increased false negatives.

In Chapter III I will address the biocomplexity in the occurrence of AEFIs by using the related available medical-pharmacological literature. Most of vaccines' severe AEFIs are linked to the interaction of the vaccine with the innate immune response. They occur as excessive or distorted inflammatory or immune responses that can degenerate into possibly irreversible pathologies and/or lethal outcomes. Understanding how the immune system works in helping to protect the body from infection clarifies how and why reactions to the vaccine occur (WHO, 2013). Therefore, I will first provide a definition and categorization(s) of AEFIs, and then, I will divide the discussion into three different sections: immunological, immunopathological and pharmacological.

In Chapter IV I will address the ontological and epistemological underpinnings of causal assessment. On the one hand, I will analyze the notion of causality on the basis of the philosophical literature on the topic. On the other I will present the epistemological dimensions of causal inference, that is the evidence required to justify it.

In the first section I will describe causation accounts and I will underline the need for and importance of adopting a pluralistic approach to the notion of causation. If a *flexible* and *wide* notion of *cause* is embraced in causal assessment procedures, this helps in minimizing the possibility of false negatives. I will then make a distinction between monocausality and multicausality. I will talk about the concepts of context sensitivity, individual uniqueness and individual variability, that make individual causality assessment highly complex and characterized by strong uncertainty. Finally, I will describe the different types of causes and causal relationships that could obtain.

In the second section I will distinguish between token-level (singular) and type-level (general) causality, and then discuss the relation between the two.

Regarding the evidential criteria required for causal assessment, I will distinguish between clinchers vs voucher methods by stressing the capacity of the latter in supporting a decrease in false negatives especially in a context of risk detection. This advantage is also given by a method that is based on evidential pluralism rather on the hierarchy of evidence.

Finally, I will introduce the concept of logical probability by referring to how individual causality assessment is performed in the medico-legal context.
Chapter V consists in an epistemological analysis of the WHO algorithm. The aim is to highlight and analyze the criticalities that characterize it and lead to an increase in the likelihood of false negatives. The current algorithm establishes the causal link in a rigidly deterministic way by excluding *a priori* the possible co-causal role played by the vaccine (contributing cause, i.e., neither necessary nor sufficient) in the occurrence of the AEFI. In fact, this approach, by imposing an epistemological procedure similar to a sort of differential (causal) diagnosis, tends to lead towards the identification of a single *direct* cause (*the* cause) (the disease is thus defined as monocausal), underestimating the role of interacting, mediating and moderating causes. The vaccine is almost never a *direct* and *necessary* cause of the event.
The foci of my research are:

i. *multifactoriality* (ontological aspect). This is a necessary element in the causal diagnosis of AEFIs since most AEFIs are pathological manifestations with multifactorial etiology. They are due to the presence and interaction of multiple co-causes, jointly contributing to the occurrence of the event.
ii. *evidential pluralism* (epistemological aspect). The use of only one type of evidence to support a causal relationship increases the likelihood of false negatives (failure in detecting possible causes of the observed event) (Landes et al., 2018). This justifies the need to gather and consider more and different types of evidence (all heterogeneous evidence) to reduce the likelihood of false negatives thereby increasing the accuracy of the algorithm.
iii. *voucher approach* (methodological aspect). Non-conclusive evidence is admitted (Osimani, 2020; Osimani & Mignini, 2015), and no scientific proof/certainty is required for taking action (decision-making under uncertainty).

The analysis proposed will be conducted by following two main methodological channels, pharmacological and epistemological, expanding from the main scientific literature on the subject.
From a pharmacological point of view, the complexity underlying vaccines' mechanism of action in relation to the AEFIs' manifestation (vaccine's characteristics, complexity of biological systems, functioning of the immune system, microbiota involvement, genetic susceptibility, etc.), is dissected in order to highlight the need for a multi-factorial approach (Chapter III).
From an epistemological point of view, the tools provided by the philosophical literature on causality and the adoption of a multi-causal and evidential pluralistic approach, lead to the necessity to support the pharmacological evaluations mentioned above (Chapter IV). In addition, and above all, the epistemological tools will prove to be fundamental in the qualitative evaluation of the causal link(s) underlying the algorithm's functioning and their adequate categorization, as well as for an overall evaluation of the algorithm as it is conceived and methodologically structured.

The contribution of my research aims to add useful elements to highlight the algorithm's criticalities and then suggest its possible revision.
The proposed alternative(s) would aim at a system that:

i. is more '*flexible*' and '*inclusive*', in which the use of a single evidence does not preclude the admissibility of the next one: in the algorithm the order of the questions and the obligation to respect this order for categorization limits and invalidates causal assessment;
ii. embraces a '*dynamic'* theory of causality (Bertolaso, 2016) applicable at the individual level, e.g., the *dispositionalist view* (Anjium and Mumford, 2018), based on the idea that a cause increases the probability of the effect at the individual level.
iii. allows to take better account of the multifactorial nature of AEFIs where multiple causal factors are involved and all the factors involved are to be considered as contributing causes of the event, so *the* cause can only be established not in absolute terms but by reasoning in probabilistic terms. For example, "the co-cause X contributed with a *higher probability* than another co-cause Y to the occurrence of the AEFI".
iv. considers probabilistic counterfactual dependence – e.g., how likely would it be that this person would have died if he had not taken the vaccine? This way to reason is necessary considering the underlying uncertainty that characterizes science, specifically the individual causality assessment of AEFIs.

Uncertainty should not constitute a reason to absolve possibly related causes under consideration, even if no scientific proof is yet available (precautionary principle).
In the WHO algorithm the judgment is dichotomic and the responsibility of the AEFI must be attributed to a *unique* cause. Regulators therefore tend to look for *the* cause. However, in the presence of a multifactorial disease, there is *no* unique cause by definition. It is therefore essential to reconsider the causal assessment procedure.
The requirement of a *unique* cause necessarily leads to the exclusion of any contributory cause as a possible factor in the occurrence of the AEFI. This naturally leads to a considerable amount of cases in which *no causes* are held responsible for the AEFI, since none of them has been the only cause producing it.
The present research aims to correct such distortions, by drawing on a multilevel analysis (i.e., ontological, epistemological and methodological levels). This analysis produced both theoretical and practical deliverables. On the theoretical side, I developed a new framework characterized by: (i) new ontological and epistemological criteria, (ii) a new methodological structure, and (iii) a new categorization. On the practical side, I developed a new algorithm, correcting the above mentioned distortions. Such tool offers a consistent and systematic procedure for causal assessment of individual AEFIs, thus increasing its reliability and accuracy.

CHAPTER I

1. Global public health and vaccines in the fight against infectious diseases

"*Immunization is a key component of primary health care.*"
(WHO, 2022c)

Health and the fight against infectious diseases are among the main current global challenges (food and nutrition security, water quality, scarcity, water/climate-change nexus) (HRC, 2023). Immunization is a pivotal tool for the prevention and control of serious and life-threatening diseases, especially for the most fragile patients (AIFA, 2014), underpinning global health security (Blough, 2021).

Health is a public good that needs to be achieved and maintained at a global level (A. Müller et al., 2020). In the Oslo Declaration of 2006, it is emphasized as *"one of the most important, still broadly neglected, long-term foreign policy issues of our time"* (Ministers Of Foreign Affairs Of Brazil France Indonesia Norway Senegal South Africa And Thailand, 2007).

In 2012 the World Health Organization (WHO) published a list of 10 Essential Public Health Operations (EPHOs) as part of their action plan to strengthen public health capacities and services worldwide (WHO Regional Committee for Europe, 2012), which was updated in 2015 (WHO Regional Office for Europe, 2015).[1] The main objectives are disease prevention and health promotion globally.

Global health may be described as "*a synthesis of population-based prevention with individual-level clinical care*" (Koplan et al., 2009), and like medicine and other branches of sciences, has the following fundamental tasks:

(1) *to control* spatiotemporal patterns of a medical/health issue worldwide to advance a better understanding of it and assess its global impact;
(2) *to study* the determining and influencing factors associated with a medical/health issue that has global impact;
(3) *to generate* new knowledge and theories on a global health issue, influencing factors, and advance global solutions;
(4) *to set up* evidence-based global solutions, including strategies, frameworks, governances, policies, regulations, and laws;

[1] It includes: (i) surveillance of population health and well-being; (ii) monitoring and response to health hazards and emergencies; (iii) health protection, including environmental, occupational, food safety and others; (iv) health promotion, including action to address social determinants and health inequity; (v) disease prevention, including early detection of illness; (vi) assuring governance for health; (vii) assuring a competent public health workforce; (viii) assuring organizational structures and financing; (ix) information, communication, and social mobilization for health; (ix) advancing public health research to inform policy and practice (WHO Regional Office for Europe, 2015).

(5) *to disseminate* and share knowledge through education, training, publications, etc.;
(6) *to apply* global health knowledge, theories, and intervention strategies in practice to solve a global health issue.

As we have seen with the Corona Virus Disease (COVID-19), the outbreak of epidemics and pandemics is an issue of public health concerns that frequently goes beyond national borders (Šlosarčík et al., 2020).
Throughout history, vaccination has been an important public health intervention contributing to the fight against life-threatening infectious diseases (leading to their eradication and/or reduction of their spread) such as meningitis, tetanus, measles, smallpox, wild poliovirus, and so on around the world (WHO-HIS-EMP, 2013).
Vaccines are considered effective for collective prevention in combating a disease if a high percentage of the population is vaccinated, in which case the protective effect is multiplied thanks to what is called herd immunity. Mass vaccinations, by reducing the number of people who can become infected, make it more difficult for the microbes to spread and reproduce.
In addition, since the decisions that people make about their health are mainly based on individual rather than collective motivations, vaccination is a protection tool that is both individual and collective (ISS, 2011).

1.1. Brief historical overview of vaccines in the fight against infectious diseases

The holder of the title of 'father of vaccines' is the famous English physician Edward Jenner (1746 - 1823) who in 1796 discovered the first vaccine to prevent smallpox. From the observation of people infected with cowpox he noticed that those who had contracted the virus and recovered from it did not get sick with the most serious human variant (smallpox). He thus took the purulent material from a sick person with cowpox and injected it into another person, to whom after a few months he injected the human smallpox pus, which, as hypothesized, did not take root. This was the proof that the inoculated person had become immune to smallpox.
Jenner's discovery was so relevant that in 1799 Luigi Sacco (1769 – 1836) spread Jenner's vaccination in Italy. Others did the same throughout Europe. This helped in reducing the smallpox mortality within a few years to the point that childhood vaccination was made mandatory in Bavaria (1807), Prussia (1835), Denmark (1810), Sweden (1814) and Italy (1861). However, although mortality was drastically reduced in the early 1900s, epidemics continued to occur to the point that in the 20th century the smallpox was still a widespread infectious disease that killed so many people. Thanks to the intervention of international cooperation, which involved the United States, the USSR and India, with more widespread vaccination campaigns, it came to the point that in 1979 the WHO declared smallpox as eradicated (Hotez, 2021).
During the 19th and 20th centuries, other vaccines have been developed to protect people against once-commonly fatal infectious diseases (for further information see **Tab. A** in Appendix). The

20th century has seen the achievement of numerous results in the field of public health thanks to the development of vaccines and international cooperation between countries, UN agencies and scientists, that have brought polio, and measles nearly to global eradication (Hotez, 2021). The 21st century has been characterized by more and more new challenges in the fight against newly emerging and re-emerging infectious diseases, more specifically: outbreaks of new epidemics (SARS, Ebola, avian influenza, swine flu, Zika), the persistence of old epidemic diseases (malaria, AIDS), the return of almost eradicated infectious diseases in developed countries (measles, tuberculosis), as well as the consequences on public health of new migration patterns, the erosion of governance structures in many low-income countries, the raising of antibiotic resistance and "the shift in the vaccination paradigm in many developed countries" (Melchor et al., 2020; Šlosarčík et al., 2020) – see **Tab.1**.

Time Frame	***Infectious disease***
11/2002-05/2004	SARS (Severe Acute Respiratory Syndrome) – the first epidemic disease (caused by an unknown coronavirus in humans) –: broke out in China and then spread to Hong Kong, Singapore, Vietnam, Canada and beyond (26 nations around the world) threatening the global population (NHS, 2019). In 2003, 8,098 reported illnesses cases and 774 deaths worldwide with a mortality rate of about 10% were reported. Several vaccines are being tested in animals and are in an early phase of human research should SARS re-emerge (The College of Physicians of Philadelphia, 2022).
02/2003-11/2006	The reemerge of avian influenza A(H5N1) in China (the first case of human infection was identified in 1997 in Hong Kong). This epidemic mainly infected poultry and did not evolve to spread among humans (ISS, 2006). A H5N1 vaccine was stockpiled by the U.S. government (The College of Physicians of Philadelphia, 2022).
04/2009-04/2010	H1N1 flu (or swine influenza) – the first pandemic of the 21st century –: broke out in Mexico and then reached other parts of the world causing thousands of deaths and infections, mostly in the American continent. The WHO's handling of the pandemic sparked criticism at the time (Abeysinghe, 2017). The WHO was accused of having changed the definition of pandemic (Flynn, 2010) as it was influenced by pharmaceutical industries, which were interested in increasing profits on their patented drugs and flu vaccines (Godlee, 2010), with the serious consequence of "having exposed millions of people to the risk of unknown side effects for insufficiently tested vaccines" (Grippe, 2021; Watson, 2010).
09/2012-today	MERS (Middle East Respiratory Syndrome) epidemic (caused by coronavirus similar to SARS virus): primarily affected the Middle East (Saudi Arabia), but also spread in several other countries (United States, Philippines and Netherlands in 2014, South Korea and United Kingdom in 2015, and Kenya in 2016) and continues today (Harrison, 2006; Melchor et al., 2020; Šlosarčík et al., 2020).
2013-2016	Ebola hemorrhagic fever epidemic in the west Africa.
2015-2016	Zika fever epidemic: triggered an intensive response that followed institutional and legal frameworks already established during previous global epidemics, and that was characterized by an interplay between political, medical, and scientific communities performed within national, European, and global frameworks (Harrison, 2006; Melchor et al., 2020; Šlosarčík et al., 2020).

Table 1: *Overview of major epidemics/pandemics in the 21th century.*

In 2020 the global impact of the COVID-19 pandemic on people's health has led to an unprecedented interest in vaccines' development, regulatory review, and safety monitoring, by the public, policy makers, scientists, scientific institutions, and regulatory agencies (WHO, 2021).

2. The network of actors in managing public health and vaccines' safety issues

Science and public health policy are in a complex ever closer relationship. In 2020 the SARS-COV-2 has emerged as *"the most multilateral virus ever*" (J. M. Müller, 2021) and the COVID-19 outbreak as the most challenging global health crisis of our time.
In such an unprecedented critical situation, political and scientific institutions worldwide were urgently called to act (Berkman, 2020; ET, 2020). Never before science has been so much requested and so crucial in informing policymakers, and in turn never before political decisions have been so systematically dependent on scientific advice and technical expertise (A. Müller et al., 2020). The pandemic has indeed emphasized more than ever before the complex interplay among diverse institutional actors in the management of health emergencies: policymakers, regulatory agencies, scientific international institutions, academia and research centers, the media, healthcare professionals, and the public. The distinct roles and expertise of such agents implies a strong reliance on trust and epistemic delegation – see UNESCO dialogue, 30 March 2020 (UNESCO, 2020).
Therefore, when a pandemic (e.g., SARS-CoV-2) or an epidemic (e.g., Zika) outbreak, a network of actors is involved in its management with the aim to improve health, along with the rules and norms governing their interactions (Frenk & Moon, 2013) – see also (Szlezák et al., 2010). With a focus to the European context, these include:

(i) *Global actors*:
- the World Health Organization (WHO);
- other United Nations and multilateral agencies with health components (e.g., the United Nations International Children's Emergency Fund (UNICEF), the World Bank, the regional development banks, etc.);
- civil society organizations, multinational corporations, foundations, academic, clinical care and PH institutions (non-governmental organizations);
- innovative and influential hybrid organizations, such as the Global Alliance for Vaccines and Immunization (GAVI Alliance), UNITAID and the Global Fund to Fight AIDS, Tuberculosis, and Malaria, which are governed by representatives both from within and from outside national governments (Frenk & Moon, 2013).

(ii) *European actors*:
- the European Council: composed by the European Union (EU) Heads of State it defines the general political direction and priorities of the EU;
- the European Commission (EC): the executive body – it proposes new EU legislation and watches over its implementation;
- the European Parliament: endowed with legislative powers, together with the Council, and with budgetary powers;
- Community Agencies (e.g., Centre for Disease Prevention and Control (ECDC), European Food Safety Authority (EFSA), European Medicine Agency (EMA), etc.);
- Executive Agencies (e.g., European Agency for Health and Consumers (EAHC), etc.).

(iii) *National actors*: public institutions in charge of foreign affairs, public health and global health, research, and science advice (e.g., National Public Health Institutes (NPHIs), National Regulatory Agencies (NRAs), etc.).

In the following sections I will present some of the institutional actors mentioned above, focusing on those who have the most important roles in the issue of global public health and vaccines' safety.

2.1. Global actors: The WHO

Historically speaking, in the wake of multiple epidemics and pandemics, international institutions to facilitate cooperation emerged (Melchor et al., 2020). In the global health system, the role played by the WHO is central. The WHO is the only actor built on the universal membership of all recognized sovereign nation states (Frenk & Moon, 2013). It is an international[2] Intergovernmental Organization (IGO)[3] which exerts international functions with the aim of improving global health and helps generate more efficient information and surveillance systems by strengthening its global monitoring and alert systems (Brown et al., 2006).

The idea of a permanent institution for international health can be traced to the foundation of the International Sanitary Office of the American Republics, then the Pan American Sanitary Bureau and finally the Pan American Health Organization back in 1902 (Brown et al., 2006).

[2] Some other examples of international organizations are the United Nations Children's Fund (UNESCO) as one of the United Nations (UN) 17 specialized agencies, the International Monetary Fund (IMF), the Organization for Economic Cooperation and Development (OECD), the World Trade Organization (WTO), etc.

[3] The term 'intergovernmental' refers to the relations between the governments of sovereign nations, with regard to public health policies and practices (Brown et al., 2006). An IGO is *"an organization established by a treaty, agreement or any other instrument under international law, and often possessing international legal status"* and it is mostly composed *"of sovereign nation states, but other international actors may be also involved"* (Elorza et al., 2021).

In 1945 an international conference ratified the creation of the United Nations and voted for the creation of a new specialized health agency. In June 1948 the first World Health Assembly in Geneva (Switzerland) formally created the WHO (Brown et al., 2006).
Since 1995, the WHO Secretariat has played a decisive role in responding to threats posed by new, emerging, or re-emerging communicable diseases that have taken on an increasingly global dimension. The key to the global strategy to tackle epidemics across borders is the concept of global public health surveillance (PHS), which has been expanded and formalized by WHO and its technical partners (Calain, 2007) – for further information see **Tab. B** in Appendix). It is applied to the detection and monitoring of diseases' outbreaks.
The WHO was also involved in the development and distribution of vaccines worldwide, and in 1949 together with the United Nations Educational, Scientific and Cultural Organization (UNESCO) established the Council for International Organizations of Medical Sciences (CIOMS) (an international, non-governmental and non-profit organization). Vaccines have been recognized as a special group of medicines with specific issues for monitoring and safety assessment, and this has led over time to the creation of various WHO sub-working groups and the implementation of initiatives aimed at vaccine safety – see **Tab.2**.

Date	***WHO sub-working groups & initiatives***	***Tasks & goals***
1999	Establishment of the Global Advisory Committee on Vaccine Safety (GACVS).	Advise WHO on vaccine-related safety issues and enable it to respond promptly and efficiently to vaccine safety issues with potential global importance (GACVS & WHO, 2009).
2000	Launch of the Brighton Collaboration (international voluntary collaboration).	Provide globally accepted standard case definitions for assessing AEFIs, so that safety data across trials and surveillance systems can be compared. Facilitate the development, evaluation, and dissemination of high-quality information about the safety of human vaccines.
	Creation of the Global Alliance for Vaccines and Immunization (GAVI).	Bring together the public and private sectors with the shared goal of creating equitable access to new and underutilized vaccines for children living in the world's poorest countries.
2005	Establishment of the pharmacovigilance technical working group on vaccines by CIOMS.	Develop standardized definitions (or other guidance documents relevant to vaccine safety) to contribute to the harmonization of vaccine pharmacovigilance among the different groups and bodies concerned (e.g., vaccine industry, regulatory agencies, national and international public health agencies, academia, etc.), and the provision of expert advises to other vaccine pharmacovigilance initiatives.
2012	Launch of the WHO-led Global Vaccine Safety Blueprint project[4] by CIOMS.	Ensure a minimum capacity in vaccine safety for low- and middle-income countries, promote enhanced pharmacovigilance activities in countries with specific needs, and establish a comprehensive technical support structure (to be achieved in 2012-2020).

[4]https://www.who.int/groups/global-advisory-committee-on-vaccine-safety/topics/global-vaccine-safety-blueprint#:~:text=In%202011%2C%20WHO%20and%20a,pharmacovigilance%20systems%20in%20all%20countries.

	WHO Collaborating Centre for International Drug Monitoring (i.e., the Uppsala Monitoring Centre, UMC) creates a vaccine dictionary (IVB-WHO, 2012).	Oversee the WHO programme operations, including (i) collecting, evaluating, and reporting information from member countries on the benefits, harm, efficacy and risks of medicines; (ii) cooperation with member countries in the development and practice of pharmacovigilance; (iii) alerting member countries' NRAs to potential medicines safety issues through the WHO reporting process (WHO, 2013)
	Approval of the Global Vaccine Action Plan (GVAP) by the 194 member states of the World Health Assembly.	Enable more equitable access to existing vaccines for people in all communities to prevent millions of deaths by 2020.
2017	Approval of the new resolution on strengthening immunization by the health ministries of 194 countries.	Improve monitoring and surveillance systems, expand immunization services beyond childhood and strengthen international cooperation to achieve GVAP goals (in 2018 approximately 86% of children worldwide (116.3 million) received three doses of diphtheria-tetanus-pertussis (DTP3) vaccine) (WHO, 2013).
2020	Creation of the 2030 Immunization Agenda (IA2030)[5] by the WHO.	Extend the use of vaccines and address vaccine-related challenges over the next decade.
	Set-up of a global strategy for vaccine safety, i.e., the Global Vaccine Safety Blueprint 2.0 (GVSB2.0)[6].	Define priorities in vaccine safety for 2021-2023 and beyond. Support the establishment of effective pharmacovigilance systems on vaccine safety in all countries (WHO, 2013).

Table 2: *The most important WHO working sub-groups & initiatives for managing vaccine safety.*

The WHO plays a central role in the global health system, in the fight against infectious diseases, in the development and distribution of vaccines worldwide. Together with scientific health agencies and regulatory agencies that operate at national and European level, it provides advice to policymakers called upon to make important decisions on public health. Moreover, it closely collaborates with vaccines manufacturers, health officials, researchers, and others to monitor safety concerns and potential Adverse Events Following Immunization (henceforth, AEFIs).

2.2. European and National Actors

In the development of policy proposals and the legislative process, the EU institutions and agencies draw on evidence and advice. This is a complex and diverse picture and there are a number of ways that they do this, including through expert advisory groups and various

[5] https://www.who.int/teams/immunization-vaccines-and-biologicals/strategies/ia2030
[6] https://www.who.int/publications/i/item/9789240036963

consultative processes. As EU competences in social matters continue to develop, EU policymakers are increasingly turning to executive or regulatory agencies outside the Commission's structure, even more so in health-related areas (Perman & Vos, 2010).
Among the public health agencies that advise the EC there is ECDC (EU decentralized agency based in Solna, Sweden), whose mission is to work *"to strengthen Europe's defenses against infectious diseases by identifying, assessing and communicating current and emerging threats to human health posed by infectious diseases"* (ECDC, 2022a). Another example is EMA (EU decentralized agency based in Amsterdam, Netherlands), whose task is to evaluate and supervise the use of medicines across Europe to protect and promote public and animal health and provides a scientific assessment of applications for the marketing of medicines. Member States and/or the EC can request scientific advice on medicines from EMA, which is an example of *"softer, more responsive and reflexive modes of governance"* (Perman & Vos, 2010).
The distribution of competences and tasks among public health agencies is intimately linked to the governance structure of the health system, where aspects such as the degree of centralization or the weight of the public sector vis-à-vis the private sector come into play (Rechel et al., 2018), which sees the organization of the provision of public health services vary in different countries (M. Reiss & Czypionka, 2022). Public health functions are fragmented across institutions, organizations, and levels of governance in many countries.
National governments, with their ministries, departments, or specialized health agencies, coordinate their responses to common health challenges through a variety of mechanisms (Frenk & Moon, 2013). They are responsible for the implementation of the national immunization programme and also draw on their domestic arrangements for seeking scientific advice (The Royal Society, 2022).
National Public Health Institutes (NPHIs), like the Italian National Institute of Health (i.e., Istituto Superiore di Sanità, ISS), are *"science-based governmental organizations that serve as a focal point for a country's public health efforts, as well as a critical component of global disease prevention and response systems"*(Schutte et al., 2021) – see also (D. L. Heymann, 2008). In the situation of the Sars-CoV-2 virus, they monitored the spread of the pandemic and provided scientific evidence, when available, for decision-making in relation to non-pharmaceutical and other measures (e.g., testing and diagnostics, guidelines for healthcare professionals and general practitioners, etc.) (Schutte et al., 2021).
Advice on pharmaceuticals and biological products at national level is given by National Regulatory Agencies (NRAs), which are responsible for ensuring that these products are properly evaluated and meet international standards of quality, safety, and efficacy. Each EU Member State has its own national competent authorities (e.g., Austrian Agency for Health and Food Safety (AGES), the French National Agency for the Safety of Medicine and Health Products (ANSM), Italian Medicine Agency (AIFA), etc.). Among their functions there are: marketing authorization of medicines that do not pass through the centralized procedure (that is managed by EMA), post-marketing surveillance and monitoring of AEFIs.

EMA cooperates closely with NRAs in EU Member States, Medicines Regulatory Authorities in the European Economic Area (EEA) countries[7] and the EC in the so-called European medicines regulatory network[8], a partnership that encouraged the exchange of knowledge and best practices in order to ensure the highest standards in medicines regulation (EMA, 2022b).

2.2.1. The European Medicine Agency (EMA)

Any medical product is subject to rather complex regulations that rule its development phases, its approval for use, circulation, and possible suspension or withdrawal from the market (Osimani, 2007).

Founded in 1995 with the purpose to harmonize the work of existing national medicine regulatory bodies, EMA is a scientific decentralized networking agency of the EU[9] responsible for *"ensuring efficacy and safety of human and veterinary medicines across Europe and promoting research and innovation in the development of medicines"* (EMA, 2022b).

The Agency fulfills its tasks by enabling medicines' development and access, assessing applications for marketing authorizations, monitoring medicines' safety throughout their lifecycle, and providing information to healthcare professionals and patients (EMA, 2020b). It guarantees the scientific evaluation, supervision, and safety monitoring of medicines in the EU involving thousands of experts who carry out the work of its seven scientific committees, that assess medicines along their lifecycle from early stages of development, through marketing authorization to post-marketing safety monitoring (EMA, 2020b, 2022d).

As regards the procedure for the authorization of medicines in the European market, there are two main pathways: a centralized route and a national route. The centralized procedure consists of pharmaceutical companies submitting single marketing authorization applications to EMA's dedicated Committees[10], whose evaluation (in terms of quality, safety, and efficacy of the medicinal product) forms the basis for the authorization of medicines across the EU and the EEA (EMA, 2022a). Many new innovative medicines are evaluated by EMA and the EC legally authorize the marketing of all centrally authorized products in all EU Member States (as well as in the EEA), taking a legally binding decision based on EMA's recommendation (EMA, 2022a).

EMA and the EU Member States constantly monitor and supervise the safety of medicines authorized (i.e., post-marketing surveillance or pharmacovigilance) to ensure that their benefits outweigh their risks. The aim is to protect patients and take prompt action (e.g., changing the information available to patients and healthcare professionals, restricting use or discontinuing

[7] EEA includes Iceland, Liechtenstein and Norway that are not member of the EU.

[8] https://www.ema.europa.eu/en/about-us/how-we-work/european-medicines-regulatory-network

[9] The U.S. Food and Drug Administration (FDA) has much more centralized functions.

[10] The applications for human medicines are sent to the Committee for Medicinal Products for Human Use (CHMP), while the applications for veterinary medicines are sent to the Committee for Medicinal Products for Veterinary Use (CVMP).

a medicine) if new information indicates that the medicine is no longer safe and effective (EMA, 2020b, 2022a).
The Agency tasks are listed in **Fig.1** (EMA, 2022d); while the activities performed by EMA in the safety monitoring of medicines are listed in **Fig.2** (EMA, 2022a).

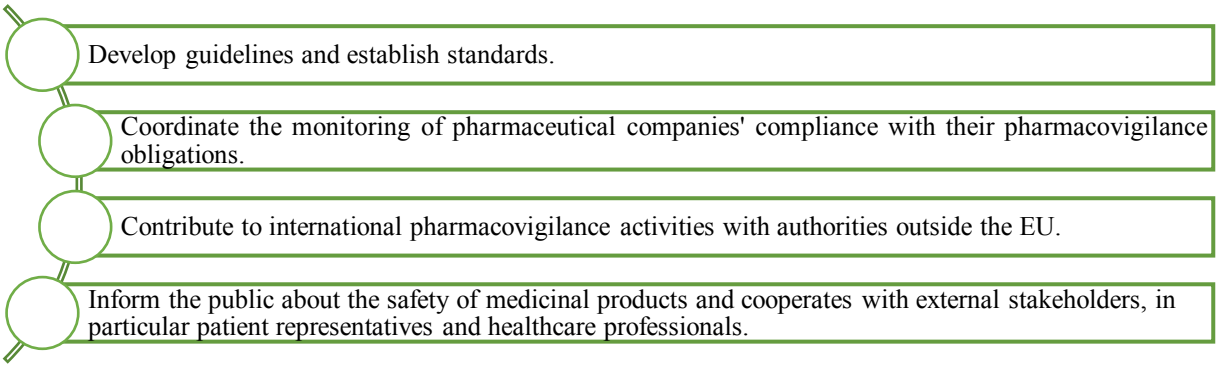

Figure 1: *EMA's tasks.*

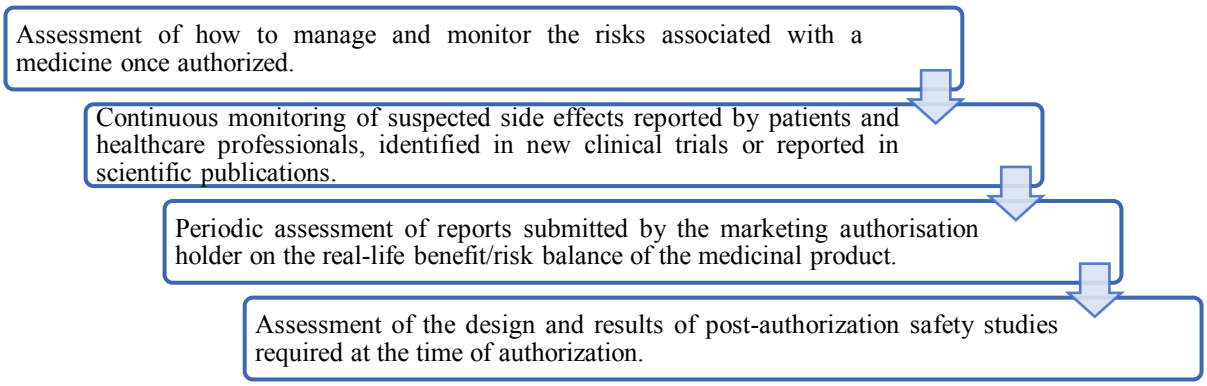

Figure 2: *EMA's activities in the safety monitoring of medicines.*

EMA played an even more important role in monitoring drugs' safety across Europe with the creation of the Pharmacovigilance and Risk Assessment Committee (PRAC) in 2012 (EMA, 2022b).
EMA with the collaboration of ECDC makes use of the EudraVigilance reporting system whose reports are then transmitted to the WHO's global database (Vigibase) to make them available to all relevant international regulatory authorities in the field of pharmacovigilance[11].
EudraVigilance stands for European Drug Agency Vigilance and is the central EMA database, established in December 2001. It contains reports of suspected individual adverse reactions (i.e., Individual Case Safety Reports, ICSRs) of authorized and investigational medicinal products in the EU, coming from regulatory authorities of all EU Member States and pharmaceutical companies. It is considered one of the pillars of the European Risk Management

[11] In the USA the FDA in collaboration with the CDC (Center for Disease Control and Prevention) makes use of the VAERS (Vaccine Adverse Event Reporting System) reporting system as part of the national vaccine safety surveillance program.

Strategy[12], allowing: (i) a rapid exchange of safety information between competent authorities, (ii) the simultaneous sharing of safety information, and (iii) the early identification of warning signals (Unisi, 2015).
However, not all aspects of medicines regulation in Europe fall within the competence of EMA, rather under the remit of NRAs (for further information see **Tab. C** in Appendix). Among them there are the authorization of most medicines in Europe and the important task of ensuring the safety, efficacy, and quality of (bio)pharmaceuticals.

2.2.2. The National Regulatory Agencies (NRAs)

Many of the old medicines available today have been authorized at national level in the EU, as they were marketed before the creation of EMA, and nowadays many of the generic medicines and medicines available without a prescription are also evaluated and authorized at national level. The authorization procedures can happen thought (EMA, 2022a):

(i) mutual-recognition procedure, whereby a marketing authorization requested by a company and granted in one Member State can be recognized in other EU countries;
or
(ii) decentralized procedure, whereby a medicine that has not yet been authorized in the EU can be simultaneously authorized in several EU Member States.

Unlike EMA, NRAs of individual Member States are centralized structures with the task of ensuring that products released for public distribution (pharmaceutical and biological products like vaccines and medical devices) are correctly evaluated and comply with international standards of quality, safety, and efficacy (WHO, 2022b). The NRA is usually the only agency with the mandate to ensure the safety, efficacy, and quality of vaccines (WHO, 2013). All its functions are described in **Fig.3** (WHO, 2013).

[12] A joint project of EMA and NRAs to strengthen pharmacovigilance at European level.

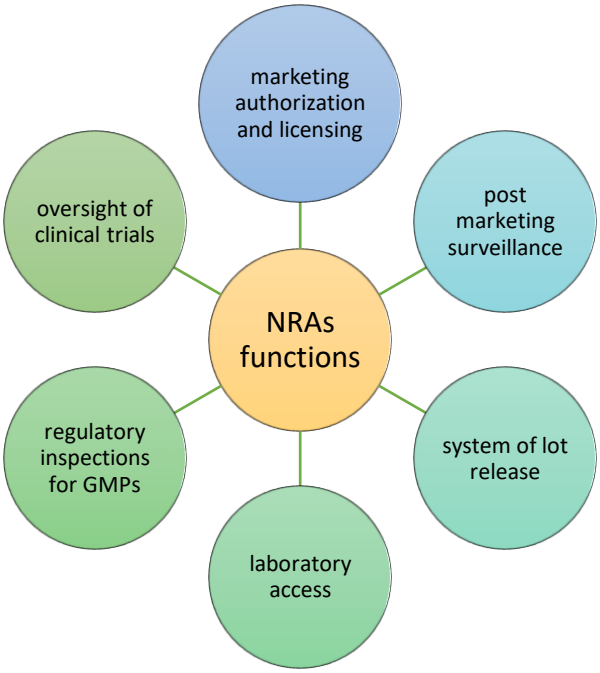

Figure 3: *NRAs functions*.

Post marketing surveillance, or pharmacovigilance, implies the collaboration with the National Immunization Programme with the following objectives:

(i) identify urgent problems for investigation and action;
(ii) detect signals for potential follow-up and research;
(iii) estimate rates for serious AEFIs (for comparison between products, to determine risks and benefits of immunization and to validate pre-licensure data);
(iv) identify programmatic errors and batch problems;
(v) create awareness of risks among health professionals.

As an example, in Italy the AIFA is the national public body that regulates medicines for human use (AIFA, 2022a). Among its strategic priorities in the Activity Plan for the year 2019 is the contribution *"to the promotion and protection of health through the regulation of the placing on the market, use and supervision of pharmaceutical products for human use"* (AIFA, 2019).
The supervision of pharmaceutical products is assigned to the Post-Marketing Surveillance Area (one of the organizational areas of AIFA[13]), that is divided into four offices (see **Tab.3**). It has the functions of coordinating the pharmacovigilance group and activities and of participating in the working groups of the EC and the Council of the European Union on pharmacovigilance and in the transposition processes of Community legislation and in national

[13] AIFA has also other Areas (e.g., the Pre-authorization area, the Medicines Authorization Area, etc.); for further details see (AIFA, 2022b).

standardization processes, in collaboration with the Offices concerned and the Ministry of Health (AIFA, 2022b).

Post-Marketing Surveillance Area Offices	*Functions*
Pharmacovigilance Office	· participation in the work of PRAC; · assessment reports for national and European PSUR procedures and, on behalf of PRAC, Post-Authorization Safety Studies (PASS), Referrals, Drug Utilization Studies (DUS) procedures; · management of Non-Urgent Information (NUI) system and Rapid Alert System (RAS); · providing citizens, patients and healthcare professionals with important information on the safety of medicines; · preparation of measures to revoke the MA for security reasons.
Signal Management Office	· collection and evaluation of reports of suspected adverse reactions; · management of the national pharmacovigilance network, relations with EudraVigilance and relations with the WHO database; · signal analysis activities; · adoption of measures for the implementation of regulatory actions deriving from safety signals.
Risk Management Measures Office	- adoption of risk minimization measures; - preparation of Risk Management Plan (RMP) assessment reports of medicines registered nationally or mutually recognized or centralized.
Scientific Information Office	· training and information activities on medicines for health professionals; · guidelines for the authorization and control of scientific information; · coordination of the Independent Drug Information Centre.

Table 3: *AIFA's Post-Marketing Surveillance Area Offices.*

Regulators, therefore, to have a control over the safety of post-marketing (bio)pharmaceuticals rely on pharmacovigilance systems, which monitor every potential new signal and proceed through the collection and analysis of spontaneous AEFI reports made by health workers, doctors, and vaccinated people.

Adverse events surveillance at national level involves also National Pharmacovigilance Centres (NPCs), National Immunisation Programmes (NIPs), AEFI Review Committee and other support groups. NPCs are part of the so-called WHO Programme for International Monitoring of Drugs (PIDM) – established in 1968 –and are responsible for case reports sent to the WHO Individual Case Safety Report (ICRS) database that is managed by UMC (WHO, 2013).

3. Vaccine safety pharmacovigilance

In clinical practice, in the context of adverse events (AEs) that can occur in persons following a pharmaceutical product administration, it is essential to identify if the medical product is responsible for its occurrence.
The methodological procedure, and its epistemological underpinning are of great importance in a system where more and more pharmaceuticals are flooding the market (Pande, 2018).
This consideration becomes even more relevant when it comes to vaccines and their safety, since, unlike drugs which are administered to treat diseases, vaccines are generally administered to healthy subjects (mainly infants, children, adolescents and even adults) for prophylactic purposes.
The risk-benefit balance of vaccines implies more stringent constraints. There is a lower tolerance for risks from vaccines and the potential problems that could occur following the administration of a vaccine are less acceptable to society, especially if we refer to mandatory vaccinations[14] (WHO-HIS-EMP, 2013). According to Autret-Leca et al. (2006) *"safety of vaccines must be excellent to make vaccine's strategy acceptable, since it usually has a deferred individual benefit but immediate adverse drug reactions (ADRs)"* (Autret-Leca et al., 2006).
From the public health perspective, vaccination brings with itself important benefits, namely the prevention of epidemics and epidemics, and the reduction of morbidity and mortality due to the infectious disease in the target population (Tavares Da Silva et al., 2015). However, although vaccines are considered among the safest tools of medicine that help protect against diseases, they are not risk-free and their use is related to the occurrence of AEFIs, that may involve serious health problems often resulting in hospitalization and/or permanent damage or death of the patient.
However, at the time of regulatory evaluation and registration of vaccines information on the risk of rare serious vaccine reactions is limited and NRAs sometimes find themselves in front of decisions based on limited vaccine safety data (PAHO, 2021). After post-licensure vaccine administration, serious unknown and rare AEs can occur. All this translates into a great need to detect and investigate any AEFI in order to anticipate and minimize risk.
Pharmacovigilance is the institution established internationally with the aim to assess the risk associated with medical treatments and monitor the incidence of AEs potentially associated with them. The aim is to promote safer use of (bio)pharmaceutical products and prevent their possible harmful effects in the population (Budhiraja & Akinapelli, 2010) by monitoring the way the medicines work, and their risk-benefit balance (Herdeiro et al., 2021; Pani, 2015).
Therefore, once a vaccine is authorized, immediate, effective and constant monitoring is essential to identify the emergence of (new) potential AEFIs and to promptly assess possible safety issues associated with its use (PAHO, 2021). The declared aim is to protect public health and strengthen public confidence in vaccines and decision-makers (WHO-HIS-EMP, 2013).

[14] There is a current increasing trend whereby more and more vaccines are made mandatory in several countries. This implies that every individual must get vaccinated (except for a few specific identified groups) not only to protect themselves but also those around them, especially the most vulnerable to the diseases, thus reducing the risk of diseases spreading among other people in the community.

3.1. Pharmacovigilance

Pharmacovigilance is considered one of the most important scientific disciplines within public health (Beninger, 2018). Its golden objective is *"to enhance patient' safety and quality of life, and strictly preserve public health by identifying, preventing, or decreasing the harmful effects and risks related to the use of health products in humans"* (Herdeiro et al., 2021).
The objectives of pharmacovigilance are summarized in **Fig.4**.

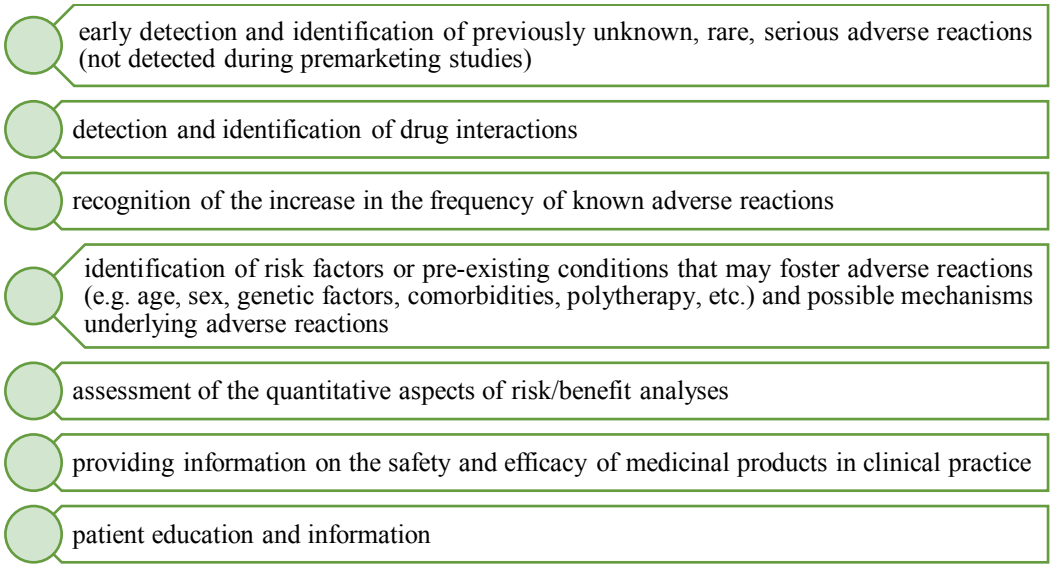

Figure 4: *Pharmacovigilance objectives.*

The birth of pharmacovigilance can be traced back to the thalidomide case, which represents the largest pharmacological disaster in history, having caused serious congenital malformations, especially in the limbs, in about 10,000 newborns. In 1961 the Australian doctor McBride sent a letter to the Lancet journal in which he suggested a connection between congenital malformations observed in many newborns and the hypnotic and antiemetic drug thalidomide, at the time widely used in the treatment of nausea and vomiting typical of the early stages of pregnancy.
The cardinal principles of pharmacovigilance are present, namely:

(i) observation of an unexpected and serious AE in a patient population treated with the medicine;
(ii) communication to the scientific community based on the mere suspicion that there may be a causal relationship with the medicine; and
(iii) need to share information.

Pharmacovigilance is based on active and passive surveillance systems on the one hand and on periodic safety reports [i.e., Periodic benefit risk evaluation report (Pbrer), Risk Management Plan (RMP), Post-authorization safety study (Pass)], that manufacturing companies must send

during the "life" of the product, according to the provisions of Good Pharmacovigilance Practices (GVP), on the other.
After the thalidomide tragedy, spontaneous reporting (i.e., passive surveillance) shifted from non-systematic (unorganized, unsolicited, unregulated) to systematic (organized, solicited, regulated). Spontaneous ADRs/AEs reporting systems (anecdotal and voluntary/organized), represent the main sources of information on (bio)pharmaceutical safety in post-marketing surveillance together with epidemiological studies (case-control, cohort studies), prescription data, and other methodologies, such as PEM (*Prescription Event Monitoring*) and *record-linkage*. These methods can be used either to formulate hypotheses (*Hypothesis-Generating Methods*), i.e., identifying unknown ADRs/AEs, or to verify hypotheses (*Hypothesis-Testing Methods*), ascertaining their validity.
The main purpose of reporting an AE is to "learn from the experience" and share that experience so that others "can prevent" the same unwanted event from happening (Leape, 2002).

3.1.1. The European legislation for Pharmacovigilance

In 2008 the worrying data on adverse drug reactions (ADRs) and often fatal consequences reported by the impact assessment report published by the EC (EC, 2008)[15] underlined the need to strengthen pharmaceutical regulations in force up to that time[16]. The aim was the promotion and protection of public health by reducing the number and severity of ADRs and improving the use of medicines through different types of intervention (Pani, 2015).
The changes aimed at increasing the effectiveness, speed and transparency of pharmacovigilance interventions have been introduced in 2010 through two new pharmacovigilance regulations [see AIFA website: Pharmacovigilance Regulations[17]], namely (AIFA, 2012):

[15] It was estimated that: 5% of all hospital admissions are due to an adverse drug reaction (ADR); 5% of all patients already admitted to hospital have an ADR; ADRs are in fifth place among the causes of death in hospital; in the EU, approximately 197,000 deaths per year from ADR have been estimated; the social cost of ADR in the EU is around €79 billion per year (AIFA, 2012; Pani, 2015; Unisi, 2015).
[16] The changes needed included: (i) clearly defined roles and responsibilities for all parties; (ii) ensuring a robust and rapid European system in taking the necessary pharmacovigilance decisions; (iii) increasing the participation of patients and healthcare professionals; (iv) improving the reporting systems of decisions taken and giving adequate justification for them; (v) increased transparency; (vi) better information on medicinal products; (vi) increasing the efficiency of pharmacovigilance systems; (vii) strengthening of the European pharmacovigilance Network; (viii) strengthening of company pharmacovigilance systems; (ix) increased proactivity/planning of activities to be conducted; (x) rationalization of activities between Member States, e.g., through a sharing of the same activities with sharing of the work carried out, avoiding, or reducing duplication of activities.
[17] https://www.aifa.gov.it/normativa-di-riferimento-farmacovigilanza#:~:text=La%20normativa%20europea%20in%20materia,attualmente%20in%20fase%20di%20recepimento

(1) Directive 2010/84/EU entered into force on 21 July 2012, which applies to medicinal products authorized through a national or mutual recognition or decentralized procedure; and
(2) Regulation 1235/2010/EU entered into force on 02 July 2012, which applies to centrally authorized medicinal products.

With the adoption in 2010 of EU Regulation 1235/2010 and Directive 2010/84 / EU, European legislation on pharmacovigilance has been standardized among the various member countries (Osimani B. & Ilardo, 2022).
The reference text for pharmacovigilance in Italy is represented by Legislative Decree no. 219 of 24 April 2006, in particular by Title IX, which transposes Directive 2001/83/EC in Italy, and which does not apply to ADR reports found during clinical trials, rather to ADR reports in observational studies. All Title IX (Articles 129, 130, 131, 132, 133, 134)[18] of Legislative Decree 219/2006 has been replaced by the new legislation (AIFA, 2012; Unisi, 2015). To summarize the main changes made by the new legislation (AIFA, 2012; Unisi, 2015):

(i) the modification of ADR's definition: the old definition (i.e. *"Harmful and unintentional reaction to a medicinal product used at doses normally administered to humans for prophylactic, diagnostic or therapeutic purposes or to restore, correct or modify its physiological functions"*) is replaced by the new one (i.e. "*Harmful and unintended effect resulting from the use of a medicinal product"),* with which adverse reactions resulting from therapeutic error, abuse, misuse, off-label use, overdose and occupational exposure are also reported;
(ii) greater involvement of patients and citizens in pharmacovigilance: they can report suspected adverse reactions directly via web in all EU countries (in Italy this was already possible before by a paper form);
(iii) strengthening of EudraVigilance database;
(iv) increased transparency and timeliness of crucial info on pharmacovigilance issues;
(v) carrying out additional monitoring on medicines in the appropriate list provided by EMA, including medicinal products containing new active substances (not present in medicines authorized in Europe on 1 January 2011), biologics and biosimilars, products whose authorization is subject to special conditions or authorized in exceptional

[18] Art. 129 defines the role and tasks of AIFA, to which the national pharmacovigilance system belongs; Art. 130 defines the provisions concerning the AIC's holder (obligation to register and notify ADR, identification of a person in charge of the pharmacovigilance service, submission of periodic safety update reports, etc.); Art. 131 defines the tasks of the Head of the pharmacovigilance service of the company holding the AIC; Art. 132 defines the obligations of the structures and Healthcare Professionals and subsequent AIFA obligations (appointment of the Head of pharmacovigilance of the structure, reporting obligations and methods for health professionals, inclusion of the report in the database (National Pharmacovigilance Network), conservation of cards, updating methods, role of AIFA in ensuring the immediate availability of information to the AIC's holder and the inclusion of serious ADRs in the EudraVigilance network); Art. 133 defines the suspension, revocation or amendment of a marketing authorization for pharmacovigilance reasons; Art. 134 defines checks on compliance with pharmacovigilance rules.

circumstances, products subject to safety studies after the granting of the marketing authorization (AIC);

(vi) possibility of requiring AIC holders, at the time of granting or subsequently, to conduct further studies on the safety and/or efficacy of the medicinal product;

(vii) establishment within EMA of PRAC, in which all Member States are represented, with the task of: 1) covering all aspects of risk management arising from the use of medicinal products for human use, including identification, assessment, reduction and communication of adverse reactions' risk; and 2) providing recommendations to the CHMP and the CMD (Coordination Group for Mutual recognition and Decentralized procedures) on any emerging situation in pharmacovigilance and in relation to risk management systems and monitoring their effectiveness.

Under the new legislation, all reports of adverse reactions (including reports from pharmaceutical companies) flow into the European database with a different timeline depending on the severity of the reaction (within 15 days for serious reports and within 90 days for non-serious ones) and the data are made accessible to the public. While the monitoring of the data collected in EudraVigilance is carried out by EMA in cooperation with Member States (the data flowing into national pharmacovigilance networks are transmitted to EudraVigilance), the monitoring of data originating at national level is carried out by the Member State involved (AIFA, 2012).

As an example, I focus on AIFA in Italy. The report form compiled by doctors, pharmacists, nurses, other health professionals, patients, citizens, and so on, must be sent to the Head of Pharmacovigilance of the Health Facility to which they belong or of the competent Health Authority for the territory, who, according to Legislative Decree 219/2006 Title IX art. 132, after verifying the completeness and adequacy of the data, provides:

(i) the insertion of the report no later than seven days from the date of its receipt in the database of the national pharmacovigilance network (RNF, Rete Nazionale di Farmacovigilanza). For the purposes of transmission of data, in addition to cases falling within the definition of a serious reaction, must also be considered cases where the reaction is fatal, caused or prolonged hospitalization, caused severe or permanent disability, endangered the life of the patient, caused congenital anomalies and birth defects;

(ii) verification of the actual forwarding of the message, relating to the insertion, to the region and to the pharmaceutical company concerned;

(iii) the communication to the reporter of the inclusion in the RNF and of the numerical code issued by the system to refer to for sending subsequent updates (in case of adverse reactions with a fatal outcome, the Head of pharmacovigilance is required to acquire from the reporter a detailed clinical report to be sent to AIFA within 15 days).

From RNF serious and non-serious reports are transmitted not only to EudraVigilance but also to the WHO-UMC and in this case all reports are indistinctly sent every week (Pani, 2015).

As reported in the AIFA website, data monitoring activities are aimed at identifying changes in risks or new risks through signal analysis, i.e.: *"information coming from one or more sources, including observations and experiments, which suggests the existence of a new potentially causal association, or a new aspect of a known association, between an intervention and an event or series of related, adverse or beneficial events, considered sufficiently likely to warrant verification"* (AIFA, 2012).
The methodology for signal identification and signal management process has been defined in the Implementing Regulation (EU) 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for by Regulation (EC) No. 726/2004 and Directive 2001/83/EC of the European Parliament and of the Council (AIFA, 2012).

3.1.2. Passive and active surveillance

For both drugs and vaccines, signal acquisition is divided into *active* and *passive* pharmacovigilance (EMA, 2020a). A signal is defined as an *"information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action"* (CIOMS, 2010).
Generally, *active* pharmacovigilance is practiced in the phase of placing new products on the market for a more or less long period (e.g., clinical trials and other sources); *passive* pharmacovigilance in the later stages [it proceeds through spontaneous reporting systems (R. Chen et al., 2005; R. T. Chen et al., 1994)].
Regulatory authorities have the important task of proactively monitoring medicines' safety and do so mostly through the collection and analysis of spontaneous reports made by healthcare professionals, doctors, and vaccinated people. The analysis of spontaneous reports establishes a relationship between the medicine taken by the patient and the AE occurrence (*imputability*) (Autret-Leca et al., 2006). The strength of spontaneous reporting lies in the fact that it investigates the (bio)pharmaceutical product for the entire duration of its life in the market, extending the study to the entire population of patients to whom it is administered, without being limited to a single hypothesis *a priori* (as in the case of pre-marketing studies). This method is indicated to detect rare adverse reactions or events (i.e., not identifiable before a large number of patients are exposed to the (bio)pharmaceutical product) or medicines interactions or cases in which there is a long latency between the administration of the (bio)pharmaceutical product and the development of the adverse reaction or event (Osimani B. & Ilardo, 2022).
The fundamental methodological distinction between *active* and *passive* pharmacovigilance is due to the signal generation mechanism (Biagi et al., 2013; Golder et al., 2016):

(i) in *active* pharmacovigilance, there is a pre-established post-vaccination follow-up period, thanks to which *all* AEs recorded by vaccinated subjects are reported;

(ii) in *passive* pharmacovigilance, reporting is delegated to the free initiative of the vaccinated (and/or vaccinating or treating doctors), and for this reason it is systematically affected by under-reporting.

Spontaneous reporting is indeed fundamental to detect subject safety issues, and consequently to improve people health protection by generating alerts, but it presents the disadvantage of under-reporting. It is difficult to underestimate the real frequencies of ADRs – 1 to 10% of severe ADRs are reported [an important help may come from pharmacoepidemiology studies that confirm the alerts identified by spontaneous reporting (Autret-Leca et al., 2006) – they aim at denying or confirming and quantifying the signals in terms of risk].
The reasons for the persistence of under-reporting of AEs in pharmacovigilance are historically recognized; first, the cumbersome nature of the bureaucratic procedure and the daily lack of time on the part of the sanitary workers (Osimani B. & Ilardo, 2022).[19]
Osimani and Ilardo (2022) report that a study in the *British Journal of Clinical Pharmacology* (Inácio et al., 2017) estimates that only 6% of ADRs are reported in case of spontaneous reporting. In reality, the degree of under-reporting greatly varies greatly depending on the severity of AEs and the treatment administered. They range from 68% of events reported for polio cases following polio vaccinations (severe and easily identifiable) to 1% for cases of skin rash following MMR vaccines (Osimani B. & Ilardo, 2022; Rosenthal & Chen, 1995).
In a *review* of 37 studies dedicated to under-reporting, Hazell and Shakir (2006) calculated an overall median of 94% under-reporting (IQR: 82-98%), with very high proportions also for severe effects (Osimani B. & Ilardo, 2022).[20]
The proportion of under-reporting varies not only according to the mildness or otherwise of the adverse effect but also to its similarity with phenomena that can also be associated with other factors, including the symptomatology that the treatment intends to cure; see also the Brighton Collaboration initiative. Although the mildness of the AEs seems to justify its non-reporting, it should however be noted that many effects that appear harmless *prima facie* (as temporary) may indicate the onset of diseases, for example autoimmune, whose clinical manifestation will emerge at the clinical level after some time. If duly reported, these cases, once aggregated, can help to anticipate the identification of the causal link between AE and pharmacological

[19] In addition to work overload in outpatient practices and hospitals (resulting in marginalization of AE reporting work), the following should be mentioned (Osimani B. & Ilardo, 2022): 1) uncertainty regarding the causal relationship; 2) the fear for some doctors of having made prescription errors and therefore of being investigated; 3) the excessive bureaucratization of the process, lack of available forms and ignorance of reporting pathways and rights by patients; 4) some doctors even believe that serious reactions to the drug have already been documented once placed on the market, and therefore their reporting has no scientific or statistical value.

[20] The under-reporting rate is typically calculated by comparing the number of reports recorded in a given spontaneous reporting system, over a given period of time, with the number of AEs identified by (Osimani B. & Ilardo, 2022): (i) active pharmacovigilance, (ii) "intensive monitoring" in hospital settings; (iii) cross-checking procedure of different sources such as death certificates, health benefits registered in insurance databases, hospital discharge notes and health records; (iv) comparison with controlled clinical or epidemiological studies (clinical trials, post-marketing studies, etc.) that detect the manifestation of AEs in the treated and control groups.

treatment, considerably reducing potential irreversible damage (Kohl et al., 2005; Osimani B. & Ilardo, 2022; Rosenthal & Chen, 1995; Verstraeten et al., 2001).
Recently, many have expressed the importance and need to strengthen pharmacovigilance, including the medicines commission of the ABDA ('Bundesvereinigung Deutscher Apothekerverbände e. V.', i.e., Federal Union of German Associations of Pharmacists)[21], and the Uppsala Monitoring Centre in Sweden. The choice to practice mere passive surveillance, i.e., based exclusively on spontaneous reporting, was considered inadequate (Osimani B. & Ilardo, 2022).

3.1.3. Risk management & risk assessment

The risk analysis paradigm includes three interrelated elements which are risk assessment, risk management and risk communication – see **Fig.5**. These are key tasks carried out by scientific organizations to provide the best possible information for public decision-making, especially in emergencies.

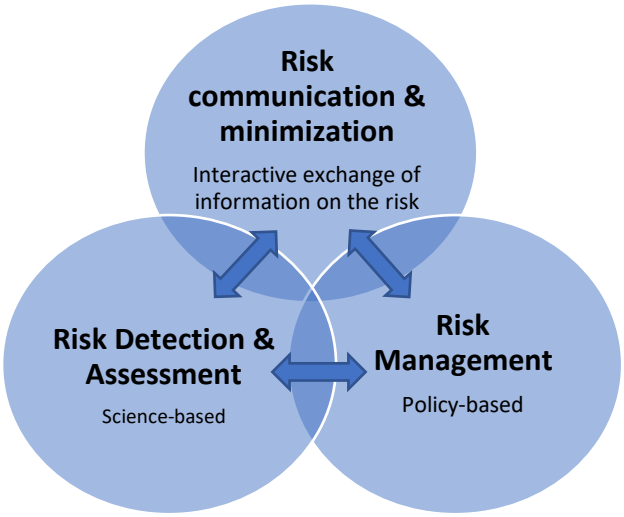

Figure 5*: The risk analysis paradigm: risk assessment, risk management and risk communication (Calvo & Zuñiga, 2011).*

From the perspective of the management of a single risk we can say that it consists of *risk detection and assessment* (identification, understanding and monitoring of the risk – it serves to provide support for decisions on managing risks), and *risk minimization and communication* (communication of the risk and action to reduce it) (Calvo & Zuñiga, 2011). The comprehensive risk management system is the so-called Risk Management Plan (EU-RMP), consisting of two parts: pharmacovigilance and risk minimization (Calvo & Zuñiga, 2011; EMA, 2022c; PAHO, 2021).

[21] The U.S. Food and Drug Administration (FDA) has much more centralized functions.

The aim of risk management is to address uncertainties in the safety profile of the (bio)pharmaceutical at different points in its lifecycle, and to plan accordingly (EMA, 2022c). More specifically it aims to ensure that the benefits of a particular medicinal product (e.g., reducing death, reducing hospitalization, protecting people from serious illnesses, etc.) exceed the risks (e.g., AEs, side effects) *"by the greatest achievable margin for the individual patient and for the target population as a whole"* and *"this can be done either by increasing the benefits or by reducing the risks"* (Sottosanti, 2015).

A fundamental step is risk detection and assessment. A distinction must be made between *identified risk* and *potential risk*. The former is defined as an untoward event for which there is sufficient evidence of a link with the given (bio)pharmaceutical, while the latter is an untoward event for which there is reason to suspect a link with the given (bio)pharmaceutical, but in which this association has not been confirmed (EMA & HMA, 2017). Examples of potential risks are: (i) signal arising from a spontaneous adverse reaction reporting system; (ii) AEs observed in clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparison group (placebo/active substance/unexposed group), on a parameter of interest raises a suspicion, but is not large enough to suggest a causal link; (iii) an event known to be associated with other active substances belonging to the same class or which can be expected to occur based on the properties of the (bio)pharmaceutical; and so on (Cobert, 2013b; Sottosanti, 2015).

An *identified risk* or a *potential risk* is considered important if it has an impact on the risk-benefit balance of the (bio)pharmaceutical and/or have important implications for public health. This depends on risks' severity and on its impact on the individual and on public health. Thus, once the risk has been identified, it should be monitored. The pharmacovigilance plan should propose actions to address identified safety issues (i.e., relevant identified risks, potential risks, and missing information) (Calvo & Zuñiga, 2011).

However, the fact that a (bio)pharmaceutical has a potential risk does not mean that a causal relationship between the medicinal product and the identified risk has been recognized. When a potential signal of a serious risk is identified, it will be important to assess it effectively. In the evaluation process of an AEFI, an essential part is the search for the existence or not of a causal link between the vaccine administered and the subsequent pathological phenomenon (Bellavite, 2020). If the regulatory authority determines that the (bio)pharmaceutical is associated with the risk, it can take a range of actions, including requiring changes to the labeling of the medicinal product, or requiring the development of a Risk Assessment and Mitigation Strategy (REMS), or collecting additional data to better characterize the risk, or withdrawing the medical product from the market, etc. (Cobert, 2013b).

However, faced with a potentially high risk, to which, due to the few confusing and/or uncertain data available, it is difficult to give more precise contours, the most reasonable course of action should be to take precautionary measures in order to minimize the risk and protect the health of individuals. This is the application of the precautionary principle.

3.1.4. The precautionary principle

Normally, the drug is withdrawn from circulation as soon as its risk-benefit profile becomes unfavorable, regardless of the type of evidence that attests to it. For example, if the suspicion of carcinogenicity for an analgesic emerges, experimental evidence should not be awaited before taking countermeasures, as the risk of carcinogenicity is not adequately balanced by the benign action of the drug, especially because there are many analgesics on the market that could possibly replace it. It will therefore be sufficient that the available evidence supports the causal association between drug and potential harm with sufficient probability, where this threshold of sufficiency is determined by the differential between benefit and risk (Osimani, 2013; Osimani B. & Ilardo, 2022). Such an adaptive response to risk monitoring as a function of expected benefit is nothing more than an application of the precautionary principle (Osimani B. & Ilardo, 2022).
The precautionary principle is a norm of expected loss minimization, and it is invoked in case of decisions under uncertainty (Osimani, 2013).
The most common definition of the precautionary principle is that of the 1998 Wingspread conference, known as the "Wingspread Statement", namely:

> "When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause-and-effect relationships are not fully established scientifically"(Wingspread Conference on the Precautionary Principle, 1998).

The precautionary principle is detailed in Article 191 of the Treaty on the Functioning of the European Union (TFEC Art. 191, 2007) and in 2000 the EC wrote:

> "The precautionary principle applies where scientific evidence is insufficient, inconclusive or uncertain and preliminary scientific evaluation indicates that there are reasonable grounds for concern that the potentially dangerous effects on the environment, human, animal or plant health may be inconsistent with the high level of protection chosen by the EU" (EUR-Lex, 2000).

The precautionary principle allows uncertain evidence to underpin risk management and prevention measures. With this rule, the requirement of causal link between the source of danger (e.g., vaccine) and potential damage (e.g., AEFI) is weakened, namely: the causal link does not have to be certain, but it may be probable (well-founded suspicion), and the probability of causal link can be as low as the expected damage is high with respect to the estimated benefit.
The precautionary principle allows risk whose causal link with the pharmaceutical product is uncertain to be included in the risk/benefit assessment[22] (Osimani, 2013).

[22] Risk-benefit assessment is based on a comparative weighing of therapeutic importance and efficacy on the one hand, and of the severity and frequency of risk on the other (Osimani, 2010).

3.2. Vaccines vs Drugs

The CDC defines a vaccine as a preparation that is administered (as by injection) to stimulate the body's immune response against a specific infectious agent or disease (CDC, 2021). Vaccination makes our body able to recognize, through the development of immunological memory, the foreign agent (the pathogen) against which the vaccine is directed and to trigger an immune response.

In the federal FD&C Act (Federal Food Drug and Cosmetic Act, 2011; U.S. Federal Statute, 1944) vaccines are defined as "*a unique class of pharmaceutical products that meet the statutory definition of both a drug and biological product*", but which differ from other drugs and biologicals "*in how they are administered to a large population, in particular, young healthy people to prevent rather than treat disease, their mechanism of action, and their risk/benefit profile"* (Gruber & Marshall, 2018).

Unlike drugs, which are administered to sick subjects in order to treat them, vaccines are (bio)-pharmacologic preparations (biopharmaceuticals), administered to healthy subjects (mainly infants, children, teens, but also adults) to protect them from harmful diseases before they come into contact with them (prophylaxis) (IOM & Vaccine Safety Committee, 1994; WHO 2001; WHO-HIS-EMP 2013), and the perceived need depends on disease burden.

Drugs, unlike vaccines, may be subject to challenge/dechallenge/rechallenge, while vaccines, unlike drugs, have the following elements: (i) herd immunity, (ii) disease eradication, (iii) data on vaccine distribution (batch), (iv) each product is different because of brand product specific manufacturing techniques, and (v) lot-by-lot surveillance is needed (Chatterjee, 2011).

The basic differences between vaccines and drugs are described in **Fig.6** (Chatterjee, 2011; WHO, 2004):

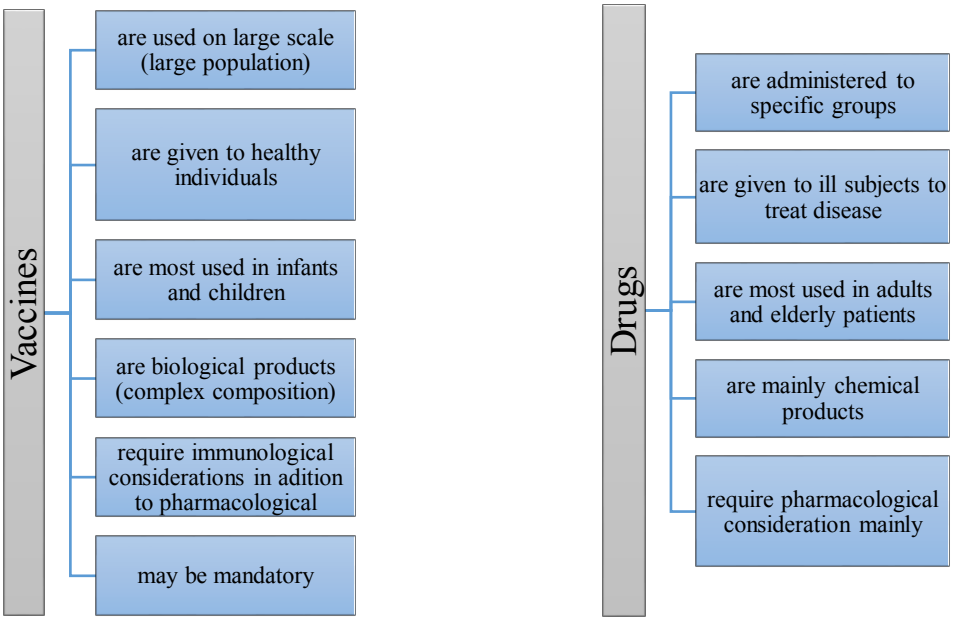

Figure 6: *Main differences between vaccines and drugs*.

Shared features between vaccines and drugs include: (i) the potential for adverse effects and for interaction with diseases and other medicinal products, (ii) the composition made from several ingredients and (iii) the need to comply with safety, efficacy, and quality standards.
Vaccines, as well as all medicines, are not without risks and although the majority of the most well-known adverse effects are usually mild, self-limited, and reversible, some vaccines have been associated with adverse effects that, although often rare, may be very serious or even lethal.
Vaccines may cause adverse reactions because they are "defective" or "contaminated", or because of administration errors, or because the recipient responds in an inappropriate way to the "pathogenic" stimulus. Since they are administered to a vulnerable (children) and healthy population, strict vaccine safety oversight is crucial. The WHO underlines that "*a higher standard of safety is expected of immunizations compared with medications that are used to treat people who are sick (e.g., antibiotics, insulin)"* (WHO, 2022a).

3.3. Vaccine pharmacovigilance

Pharmaceutical regulatory approval is structured into three phases (clinical trials of subsequently larger dimensions and with inclusion/exclusion criteria oriented from time to time to establish the correct dosage, toxicity and efficacy of the medicine), followed by post-marketing monitoring, more intense in the first years following approval and then gradually more and more spaced over time.
Because of its greater vaccination coverage, thus greater diffusion of its administration, it is more likely that vaccine is associated with safety problems (WHO, 2013).
Vaccine pharmacovigilance is defined by the CIOMS & WHO as *"the science and activities relating to the detection, assessment, understanding, prevention, and communication of adverse events following immunization, or of any other vaccine - or immunization-related issues"*(CIOMS & WHO, 2012). It is also essential for: (i) the acquisition of important information for the improvement of vaccines; (ii) the formulation of new generation vaccines; and (iii) the reduction of health expenses in therapeutically addressing the adverse effects (which can sometimes also be important) and not leaving alone the people who could be affected by these effects (WHO, 2013).
As we mentioned earlier, NRAs are responsible for post-marketing pharmacovigilance and thus for carrying out these tasks, by playing a critical role in an immunization safety system.
Post-marketing AEFI surveillance components are enumerated in **Fig.7**. (WHO, 2013).

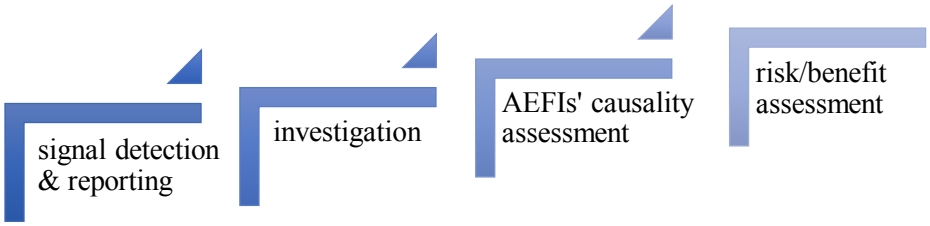

Figure 7: *Components of post-marketing AEFI surveillance*.

Pharmacovigilance aims at the early detection of AEFIs to promptly enable accurate risk assessment and appropriate response (risk-management) to new identified risks associated with the vaccine in order to minimize both the negative effects to the individuals' health and the potential negative impact on the immunization of population (Al-Worafi, 2020; Budhiraja & Akinapelli, 2010; CIOMS & WHO, 2012; WHO Vaccine Safety Basics, 2022). The process of evaluating AEFI relationships in early warning systems involves the search for the existence or not of a causal link between the given vaccine and the subsequent pathological phenomenon (Bellavite, 2020): i.e., causality assessment.
The implementation of efficient pharmacovigilance activities is essential to globally promote and protect public health, particularly by reducing the significant burden of morbidity, mortality and associated increased healthcare costs, triggered by the occurrence of adverse reactions to (bio)pharmaceuticals (A. Santoro et al., 2017).

3.3.1. The role of AEs post-marketing monitoring

Vaccines used in vaccination campaigns are expected to be effective and safe.
Information on the risk of rare serious vaccine reactions is limited to the time of regulatory evaluation and registration of vaccines (authorization procedure) (PAHO, 2021). Pre-marketing experimentation is inherently insufficient to detect all safety concerns (WHO, 2001), for diverse reasons (Osimani, 2014c; Osimani B. & Ilardo, 2022):

i. They are mainly structured to assess the efficacy of the medical product experimentally, while AEs are detected only in a descriptive and observational manner.
ii. Vaccines' safety experiments are often conducted by comparisons with adjuvant and not a true placebo (e.g., the safety of HPV vaccine Gardasil was tested in 6 clinical trials, in 5 of which the control group received Aluminum Hydroxy phosphate Sulfate, while in only one of which physiological solution was used as placebo – see Bellavite, 2020).
iii. The population sample studied can never be large enough to identify rare or delayed adverse effects (Autret-Leca et al., 2006), that indeed require very large samples, whose recruitment, however, would make the approval process of a drug too cost-disadvantageous.
iv. The follow-up period of vaccinated persons (which must be at least one year) is not always sufficient to detect possible medium or long-term effects of the vaccination.

These are, as such, knowable only in the medium to long-term. However, given that waiting several years before making the medicine available to those who could benefit from it could be just as disadvantageous as rushing to place on the market a product that is not adequately screened in terms of risk-benefit, the medicine receive market approval as soon as it is considered that the available evidence on the risks and benefits is sufficient in relation to the severity of the disease that the medicinal product promises to cure or treat – except for the possibility of suspending or withdrawing the medicine, or limiting its use to certain groups of patients, as soon as signs emerge that could reverse the benefit-risk profile in a negative way.

v. Since these AEs are unknown (*latent risk*), studies, even observational, cannot be designed to identify the connection of these effects with the investigated medicine in a statistically significant way.
vi. When an AEFI is attributable to a vaccine, it is important to determine whether there is, for that particular AEFI, a predisposed set of subjects (by age, population, genetic, immunological, environmental, ethnic, sociological or underlying disease conditions) (WHO, 2001), however, pre-registration experimentation has limits with regard to the selection of subjects: inclusion and exclusion criteria do not allow many risk factors to be identified (e.g., age, specific pathologies, interactions with other drugs), and the participation of comorbidities or elderly individuals and pregnant women is generally limited. Thus, such predisposition information is more likely to be identified through "real-world evidence".

Hence the need to continue monitoring pharmaceuticals after they have been placed on the market and gather as much information as possible about how they work in a real-life context.

3.3.2. Why vaccines pharmacovigilance differs from drug pharmacovigilance?

AEFI monitoring versus ADR monitoring is an even more sensitive issue because (Osimani B. & Ilardo, 2022):

a) A vaccine is generally administered prophylactically to healthy people (mainly children) and in this case the attention to possible risk factors is proportional to the differential between the subject's health status at the time of vaccination and the risk that s/he runs by not vaccinating. Thus, a prophylaxis tool administered to healthy people who have a low probability of contracting the virus in a severe or disabling form will have to exceed a very strict tolerability threshold.
b) Vaccines today are also realized through the use of new technologies, such as the mRNA technique, that is new both from the "galenic" point of view and from the pharmacokinetic-pharmacodynamic one, therefore burdened by a radical uncertainty regarding the (patho)physiological mechanisms that the administration of gene material can generate in the short/medium/long term, and the resulting clinical outcomes. In these

circumstances it is essential to identify any signal that may be indicative of latent pathophysiological phenomena.

Other reasons lie in three main points (Budhiraja & Akinapelli, 2010), which I report in **Tab.4** below.

The information to be acquired is complex and different from other medicines
• Vaccines are complex biological products, which can include multiple antigens, live organisms, adjuvants and preservatives. AEs may be due to administration of live wild viruses (e.g. lymphocytic meningitis after mumps vaccine) or may be nonspecific, related to a component other than antigen (aluminium hydroxide involved in "macrophage myofasciitis", allergic reactions to neomycin, latex, egg or gelatin). Each component has unique safety implications, requiring different information to capture than other drugs.
Different ways of assessing causation
• There are some problems, which make the evaluation of vaccines different from other drugs. Local or immediate adverse reactions, which occur due to administrative errors and attenuated viruses, can be attributed with some degree of confidence, but delayed events are difficult to correlate. They have immunological considerations in addition to pharmacological action and require a long time to respond. Commonly used criteria to determine causality such as resolution of the event after discontinuation of treatment and the outcome of the re-challenge cannot be used to assess the causality of an event occurring after vaccination (WHO, 2002).
Reporters and reporting chain
• Vaccines are part of the national health plan, and doctors involved in primary health care conduct mass immunization. So, reporters and reporting chain are different, especially in developing countries where doctors involved in primary health care are not exposed to technology (internet, etc.) and pharmacovigilance awareness.

Table 4. *Reasons why pharmacovigilance for vaccines is different from pharmacovigilance for medicines – see (Budhiraja & Akinapelli, 2010).*

Vaccine pharmacovigilance and the causality assessment procedure of AEFIs are more challenging and complex than those for medicines. The tool used for causality assessment of AEFIs must be appropriate and accurate to avoid the potential of errors that would put the safety of individuals at risk.
Hence, special attention should be paid to how causality assessment is performed to adequately help healthcare professionals and regulatory authorities identify problems with immunization in order to protect people's health from AEs during immunization.

CHAPTER II

1. Causality assessment

Causality assessment is a key element in identifying new signals (new emerging AEs) (Naidu, 2013), and this is where its understanding represents a greater challenge. It is a crucial element in AEFI risk assessment, by playing a key role in informing decisions around vaccine recommendations and regulatory action (Shimabukuro et al., 2015; WHO-HIS-EMP, 2013).
Causality assessment provides the basis for the evaluation of the benefit-risk profiles of a (bio)pharmaceutical product and is crucial for both public health policies and any possibly injured individuals. In fact, regulators use such info for the implementation of public health policies (such as withdrawal of the vaccine from the market, suspension or block of vaccine's administration to the general population (vaccination campaign), limitation to certain subgroups of the population, or the initiation of further investigations to more-in-depth study the observed event, etc.) and for attributing responsibility.
Regulatory authorities[23] legally mandate causality assessment because it is needed to:

(i) establish if the AE should be considered in the signaling review and in the determination of the benefit-risk balance (Cobert, 2013a);
(ii) distinguish the events that are causally related to the medicine from coincidental events – in the former case the events are iatrogenic and avoidable (Pulyel, 2018);
(iii) warn patients, investigators, healthcare professionals (HCPs) (Cobert, 2013a; Cobert et al., 2019) following the identification of potential risk factors with possible contraindications related to vaccination; and
(iv) demonstrate that risk has been effectively managed (Hussain et al., 2019).

Usually, adverse reactions following the administration of (bio)medical products occur in a few patients, while others are unharmed. For such occasional events, attribution of causality is particularly complex (Pulyel, 2018).
Inferring causality is a judgmental process that establishes whether a cause-effect relationship exists. In AEFIs spontaneous reporting systems causal inferences operate on two levels, namely:

1. *Population (general) level*: causality assessment of AEFI consists in the analysis of groups of reports that communicate the same event. This leads to vaccination strategies/recommendations, where the quantitative aspect (incidence) is important to assess the benefit/risk ratio (different in subgroups of the population). The questions

[23] In the United States the FDA, in Europe the EMA, at the national level e.g., the Italian Medicines Agency (AIFA), and other Health Agencies.

asked may be (IOM & Vaccine Safety Committee, 1994; Kramer & Lane, 1992; WHO, 2019):

- '*Can It?'*, i.e., 'Can the vaccine cause the observed AE, at least in certain people under certain circumstances?'. The focus is on *potential* causal propositions for populations.
- '*Will It?',* i.e., 'How frequently will vaccine recipients experience the AE as a result of the vaccine?*'*. The focus is on *predictive* causal propositions for populations.

2. *Individual (singular) level*: causality assessment of AEFI consists in the analysis of a single report. The questions asked may be (IOM & Vaccine Safety Committee, 1994; Kramer & Lane, 1992; WHO, 2019):

   - *'Did It?', i.e.,* 'Given an individual who has received the vaccine and developed the AE, was the event caused by the vaccine?'. The focus is in on the individual in whom a health outcome has already occurred: *retrodictive* causality *(ex post* reconstruction).
   - *'Will It?', i.e., '*Will the next person who receives the vaccine experience the AE because of the vaccine?'. The focus is on *predictive* causal propositions for individuals.

At the population level the hypothesis of a causal association between the administration of a vaccine and the occurrence of an AEFI is tested; while at the individual level prior evidence is used and examined, and logical reasoning (inductive and abductive) is applied to determine a causal association between the use of a vaccine and an AEFI in a particular individual.
In the analysis of individual reports of AEFI the evaluation of the causal link presents difficulties (e.g., complexity of the nature of the AE, individual variability, polytherapy, comorbidity, characteristics and mechanism of action of the vaccine, immune system' response, scarcity of info on genetic characteristics, vulnerability, exposure to risk factors of the vaccinated, lack or incompleteness of data on the vaccine, poor quality data etc.), which make the causal assessment process very challenging.
In the next sections I will describe both the general and individual level of causal analysis, and I will then focus on the latter.

1.1. Causality assessment at the general-population level

In pharmacovigilance, the assessment of the general causal link moves along four fundamental steps (Chandler, 2019; Osimani B. & Ilardo, 2022):

1) *Signal detection:* identification of possible causal relationships (*hypothesis generation*) based on databases (e.g., EudraVigilance), through the use of various data analysis techniques (S. J. W. Evans et al., 2001; Szarfman et al., 2002);
2) *Signal validation:* evaluation phase of the signal's importance (in terms of severity and frequency) in order to determine the costs-benefits of further investigations (post-marketing studies);
3) *Signal assessment:* causality assessment;
4) *Signal evaluation:* confirmation or refutation of the causal hypothesis on the basis of the evidence acquired (A. M. Loughlin et al., 2012).

At the population level, causal knowledge may derive from experiments (e.g., causality is demonstrated by RCTs) or from observational studies, i.e., associations. The association is defined as statistical dependence between variables of a population or a sample in which the degree of disease in those with specific exposure is higher or lower than the rate of disease among those without exposure.
An analysis of groups of reports that communicate the same event is performed, which essentially depends on the aggregation of data relating to individual manifestations of AE (Osimani B. & Ilardo, 2022). Any AE that has been observed after vaccination should be reported promptly, regardless of the individual causal link's assessment. The reports contribute to the aggregate estimation of the possible association between the AE and the (bio)pharmaceutical product. In turn, these support the implementation of public health evidence-based policies (Osimani B. & Ilardo, 2022).

Can it?

The causality assessment procedure determines the likelihood of a causal association between the event and the vaccine received, and it helps determine if an AEFI is attributable to the vaccine or the vaccination programme, and what steps (if any) need to be taken to address the event (WHO, 2022a).
The etiological link between those exposed to the vaccine and an AE is examined (Mota & Kuchenbecker, 2017): it will be tested if a given exposure (e.g., the use of a vaccine) determines an increase in the incidence of the pathology (e.g., the observed AEFI) among the exposed population (ECDC, 2018).
The causality assessment at the population level is intended to answer the question '*Can it?' ('Can* the given vaccine cause a particular event in the population?') (WHO, 2019), that is typically addressed through controlled epidemiological studies. The Hill criteria (A. B. Hill, 1965) have been established and applied with the purpose to answer to this question.

The question *'Can it?'* is usually answered in the affirmative if the relative risk (RR)[24] is greater than 1, provided that it can be shown that systematic error (bias) and random error (sampling variation) are unlikely explanations for the results (IOM & Vaccine Safety Committee, 1994; WHO, 2019). On the other hand, based on the combined evidence of one or more controlled epidemiological studies of high methodological quality and sufficient statistical power (sample size), if no association is detected between a vaccine and a particular AE, this can be judged favorable to the rejection of a causal relationship (IOM & Vaccine Safety Committee, 1994).
However, epidemiological studies are often not reported for many vaccine-AEs, thus, an affirmative answer to *'Can it?'* can occasionally be obtained from individual clinical cases. If there is evidence that the vaccine caused the AE in one (or more) individual case(s) in such a way that '*Did it?'* can be strongly answered in the affirmative, then it is logical to conclude that the vaccine *can* cause the event. On the other hand, however, given a rare AE and the well-known problems of under-reporting in passive surveillance systems, the absence of convincing case reports cannot be invoked to respond in a negative way to *'Can It?'*. It is insufficient to reject a causal relationship since what has not been reported may have in fact occurred (IOM & Vaccine Safety Committee, 1994).

Will it?

'Will it?' concerns the analysis of both general and individual causality. At the general level it refers to the frequency with which a vaccine causes a specific AE, more specifically to the percentage of vaccinated who will experience the AE as a result of the vaccine administration (quantification). At the individual it refers to the probability that a certain vaccine's recipient will experience the AE due to the vaccine (IOM & Vaccine Safety Committee, 1994).
The answer to this question is estimated based on the magnitude of the *difference in risk* (*attributable risk*)[25], that depends both on the background incidence of AE (i.e., among non-vaccine participants) and on the RR of its occurrence in vaccine recipients compared to non-participants. Thus, even when RR is high, the difference in risk will be low if the event is extremely rare (IOM & Vaccine Safety Committee, 1994). Such causality assessment is essential for risk-benefit considerations because the difference in risk expresses the probability of the risk of an AE caused by the vaccine. However, *'Will it?'* causality depends on the evaluation of *'Can It?'* causality, and this means that if the evidence is insufficient to conclude that a vaccine *can* cause a given AE, then it is also insufficient to conclude *will* do it (predictions). Furthermore, when an affirmative answer to *'Can It?'* is based only on clinical cases rather than epidemiological studies, no quantitative estimate of *'Will It?'* is possible (IOM & Vaccine Safety Committee, 1994).

[24] The ratio between the rate of occurrence of the AE in vaccinated persons and the rate in otherwise comparable unvaccinated persons.
[25] The incidence of AE among vaccine recipients minus the incidence of AE among non-vaccine participants.

1.2. Causality assessment at the individual level

Although it is not easy to establish a causal relationship between an observed AEFI and a given vaccine based on a single AEFI case report (it is much easier to determine causality in population studies using aggregate analyses), the individual level of analysis is critical for (Osimani B. & Ilardo, 2022):

(i) signal detection: the identification of a possible *new* vaccine-AEFI causal relationship, (new signal, new emerging AEs or incompletely documented previously);
(ii) the collection of evidence on possible risk factors (of a clinical or personal – age, gender, etc. – nature) with consequent possible contraindications related to vaccination;
(iii) better evaluation of the benefit/harm profiles of the medical product;
(iv) the regulation of decisions of medico-legal nature where the existence of a causal link between two phenomena (the observed AEFI and a given vaccine) is an indispensable requirement to match certain diseases, or health outcomes, the recognition and attribution of legal responsibilities regarding the post-vaccination clinical course in a vaccinated individual and, in case of any damage, to compensate medical and/or financial damage following vaccination.

Individual causation analysis is about whether an exposure caused a particular event in a specific individual. It consists of diagnosing the cause of AE (ex post reconstruction, or causal diagnosis) and finding a causal explanation of the adverse outcome (*'Did it?'*).
In assessing causes in the singular case, one refers to what science, i.e., established knowledge, says to identify the causal factors involved, and then one compares the singular case with the general case to judge which factors are responsible (Rizzi, 1994). In such a process, along with the use of general causal laws to explain singular causal interactions, counterfactual and abductive reasoning intervenes: How likely would the individual under examination had been in the same current conditions, if he had not taken the pharmaceutical product? Are there factors that explain the AE better than the vaccine administration? (Osimani B. & Ilardo, 2022). These inferences are based on the clinical and subclinical conditions of the subject before and after drug administration and on general notions of (patho)physiology, genetics, immunology, etc., to identify the most plausible explanation of the particular event.
To standardize this reasoning and avoid arbitrariness, algorithms have been developed to aid in attributing causation. However, as with all algorithms, the danger of systematic distortions of the inferential process is always lurking. The current WHO algorithm for post-vaccination causation assessment is affected by such problems (Osimani B. & Ilardo, 2022) and flaws that I will describe in the next sections.
In the following section, since in addition to algorithms there are other methods for individual causal evaluation, I will deal with describing them briefly.

1.2.1. Three ways to assess individual causality in pharmacovigilance

Common methods to assess individual causality are generally classified into three categories (Berneker & Ciucci, 1982; Bierer, 2014; Lane, 1984; Lane et al., 1987), which are: (i) global introspection; (ii) construction of algorithms (branched logical trees), and (iii) Bayesian analysis.

Global introspection

The first method is the most common. It consists in the expert judgment based on previous knowledge & experience (Bierer, 2014). According to it, the evaluator tries to consider the relevant factors and to evaluate them appropriately in order to arrive at an overall decision. This is usually expressed as a "*yes*" or "*no*" response. However, it can be difficult or impossible to first possess all the relevant facts and then properly consider and weigh them all at once (Kramer, 1986). As Bierer (2014) underlines, the main challenges regard: (i) there are no standardized tools to arrive at conclusions regarding causality; (ii) this method is subjected to fallibility of human judgments (missing/misinterpretation of information).

Algorithms

The second approach regards structured algorithms presented in the form of flowcharts or questionnaires. Based on the evaluator's answers, a qualitative score is assigned to the cause effect relationship (Bierer, 2014). It is used to give a categorical probability assessment as *certain/definite*, *probable*, *possible*, or *unlikely* – they have been shown to both improve the reproducibility and validity of causality assessments, and to make such assessments more responsible (Hutchinson & Lane, 1989; IOM & Vaccine Safety Committee, 1994).
The advantage of such a method is that it is transparent and consistent, although it presents some challenges, like reduced ability to apply clinical judgment, and adherence to the scores in place of judgment with algorithms that include scoring (Bierer, 2014).

Bayesian analysis

The third approach quantifies causality. It involves the Bayes' theorem, that calculates the posterior probability of the vaccine's causality [the probability that the event was caused by the vaccine] from estimates of the prior probability [the probability that the vaccine caused the AE before observing the particular facts of the individual case – it is often based on epidemiological data, if available, and the posterior probability combines this background information with the evidence in the individual case to come up with an estimate of causation (Bierer, 2014)]. The theorem calculates a set of likelihood ratios for each relevant element of the observed case (they are constructed using information on individual cases), where each likelihood ratio is calculated by dividing the probability of observing what *actually* happened, assuming that the vaccine was

the cause, with the probability of observing the same event given the non-vaccine causality (IOM & Vaccine Safety Committee, 1994).
This method provides a direct estimate of the *'Did It?'* probability for a given case and is responsible in terms of documenting the estimates of the components that go into the calculation of posterior probability. However, such Bayesian analyses are often complicated and time-consuming, and in addition, the quantitative expression of assessor uncertainty is often highly subjective, even if based on expert advice, as the data needed to estimate the anterior likelihoods and likelihood ratios of the component may not be available (IOM & Vaccine Safety Committee, 1994).

Bierer (2014) states that *"due to problems of reproducibility and validity, no single method is universally accepted as the gold standard"* (Bierer, 2014). However, the current WHO algorithm used for individual causality assessment seems universally accepted.
Before introducing the WHO algorithm, in the next sections I will first discuss the criteria for quality of causality assessment, and then show what are the criteria for causal diagnosis of AEs.

1.2.2. Criteria for quality of causality assessment

The medical-pharmacological field on which regulatory authorities make decisions is characterized by strong uncertainty and complexity. Pharmaceutical decisions are affected by several forms of uncertainty*, "which are sharpened both by the high stakes at play and by the complexity of the epistemological procedures needed to provide the necessary information to make these decisions"* (Osimani, 2013). The WHO (2005) writes:

> "Poor quality causality assessment can lead to erroneous conclusions, crises and loss of confidence in the national immunization programme" (WHO, 2005b).

Therefore, in such a context, the quality of causality assessment is of great importance and depends on:

(i) the quality of the AEFI case report;
(ii) the effectiveness of the reporting system; and
(iii) the quality of the causality review process (WHO, 2001), more specifically, of the method used for the assessment of whether a particular vaccine is likely to cause a particular AEFI.

Regarding point (i), most case reports fail to provide sufficient details for a critical causality assessment (Agbabiaka et al., 2008). Incomplete information and therefore the loss of potentially valuable information *can make evaluation of causality difficult or impossible* (Rehan & Chopra, 2009).
Regarding point (ii), much of the evidence about individual causality comes from passive "spontaneous reporting" systems, which have been shown to have problems with both false

negative and false positive results: i.e., many of the reported cases are probably not caused by exposure to the (bio)pharmaceuticals under examination, while many events caused by (bio)pharmaceutical are not reported (under-reporting) (Faich, 1986; Tubert et al., 1992). This inevitably undermines the analysis of causality at the individual level (IOM & Vaccine Safety Committee, 1994). The well-known problem of under-reporting translates into the failure to identify (new) serious or severe AEFIs and has a strong impact on public health decisions, possibly causing an increase in morbidity and mortality among the population. Chatterjee (2011) identified the following barriers to reporting (Chatterjee, 2011):

(a) not considering the event as related to immunization;
(b) not knowing about the reporting system and process;
(c) lethargy – procrastination, lack of interest or time, inability to find the report form;
(d) fear that the report will lead to personal consequences;
(e) guilt about having caused harm and being responsible for the event;
(f) uncertainty about reporting an event when not confident about the diagnosis.

Hence, many cases are not reported. It must be said, however, that the absence of convincing case reports cannot be invoked to reject a causal relationship since what has not been reported may *actually* have occurred (IOM & Vaccine Safety Committee, 1994).
Point (iii), then, with regards to the method used for causality assessment, the tool should be valid. It should be conceived, structured, and used correctly to provide a point of view as complete, accurate, scientific, and objective as possible. Lee et al (2020) states that "*if the causality assessment is not scientific or objective, the assessment results will be inconsistent, and consequently the compensation program will no longer have credibility"* (H. Lee et al., 2020).
Moreover, according to Chatterjee it is essential to ensure that vaccine safety monitoring and causality assessment utilizes system that meets vaccine specific needs (Chatterjee, 2011).
When a vaccine-AEFI debate spills over into the public and political arena, proper assessment of causality is vital for decision-making allowing a balancing of known benefits with possible but unverified risks to protect the health of individuals (WHO, 2001; WHO-HIS-EMP, 2013).

1.2.3. Criteria for AEs causal diagnosis

First, a distinction must be made between AE and adverse reaction. The first is any new clinical phenomenon that occurs after a medicine's administration, and not necessarily an adverse response to it; the latter is a harmful and unintended response to a medicine.
In the diagnosis of an AE, the basic criteria for causality should be considered and everything in the report should be analyzed, noting what data are not present in the report (Cobert, 2013a). The basic criteria for causality are shown in **Fig.8** below.

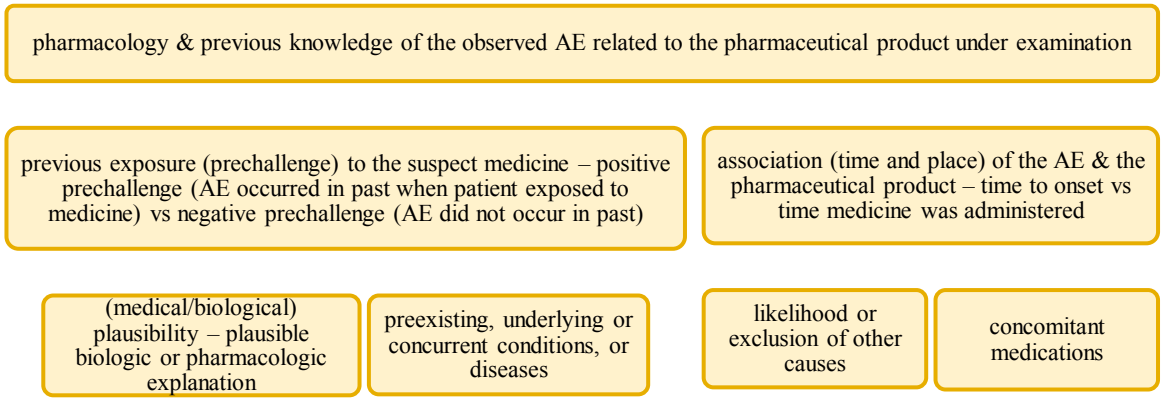

Figure 8. *Basic criteria for an AE's causal diagnosis – see (Cobert, 2013a).*

Other important factors to be considered are the following (Bierer, 2014; Cobert, 2013a):

i. patient's characteristics and past medical history by conducting appropriate physical examination and investigation;
ii. nature of the reactions during this correlation (immediate vs long term);
iii. clinical and pathological features of the events;
iv. animal toxicology data;
v. existing information about the pharmaceutical product and/or same class of medicines;
vi. possibility of drug interactions.

Moreover, while assessing causality, necessary and sufficient causes to trigger an AE, potential contribution of "inactive" ingredients and formulations need to be kept in mind together with difficulties and confounding variables such as (Bierer, 2014; Cobert, 2013a): incomplete information, quality of information on the report, availability of data; multiple drugs taken (polypharmacy), drug interactions, variability of clinical responses, diagnostic tests and procedures, intercurrent illness, underlying illness mimics AE, commonly occurring spontaneous events (e.g. nausea, vomiting, diarrhea, rash, pruritus, drowsiness, insomnia and so on).
There is also the possibility of cascade or secondary AEs/causality. I report below the example of a case of clinical practice provided by Cobert (2013a):

> "Patient takes a drug which produces anemia and has a myocardial infarct due to the anemia: Is the anemia considered an AE related to/caused by the drug? There is no clear answer.
> A 65-year-old male, obese, smoker, hypertensive, type 2 diabetic (poorly controlled) with hypercholesterolemia starts a new drug and has an inferior wall myocardial infarction 8 days after starting. Is it related to the drug?
>
> (i) his parents both smoke and have elevated cholesterol, and are 98 years old alive and fairly well;

(ii) he only took one dose and stopped because it gave him headaches, the terminal half-life is 20 minutes;
(iii) his 20-year-old dog died the day before and this was very stressful;
(iv) he worked in his garden for 5 hours the day of the attack".

This example shows that causality assessment is very tricky. The identification of a new AEFI and therefore the assessment of a causal link between a vaccine and an observed AEFI is of enormous importance but also very difficult to establish.
In the following sections I will first describe the current method used for assessing individual causality for the medicinal product and then the old system used for assessing AEFIs causality in order to highlight the differences between these systems and the WHO algorithm.

2. The method used for individual causality assessment for medicinal products (excluding vaccines) (WHO)

Causality assessment tools for AEs after drug administration (applied to drugs, small molecules with defined half-lives, temporary effects, and a defined causality window) do not translate easily into use for vaccines and AEFIs (McClenathan & Edwards, 2019). They include: Naranjo algorithm with its drug reaction probability score (Naranjo et al., 1981), Karsh and Lasagna scale (Karch & Lasagna, 1975), Kramer's algorithm (Kramer et al., 1979), Modified Kramer Method (Kramer & Lane, 1992), Roussel Uclaf Causality Assessment Model (RUCAM) algorithm (Danan & Benichou, 1993), Alden algorithm (Sassolas et al., 2010), and the World Health Organization–Uppsala Monitoring Center (WHO-UMC) system (Edwards & Aronson, 2000; Nebeker et al., 2004; UMC, 2018).
The best-known algorithms [Naranjo and Lasagna – see (Agbabiaka et al., 2008; Ralph Edwards, 2017)] and the causality assessment system developed by the World Health Organization together with the Uppsala Monitoring Centre (WHO-UMC) put causative association between an ADRs and the intake of any medicine on a 4-value probability: *certain*, *probable/likely*, *possible*, *unlikely*, as well as two situations of non-decidability: *conditional/unclassified* and *unassessable/unclassifiable* where in the first case the search for further data is encouraged, while in the second it is established that it is impossible to find further information (UMC, 2018) (see **Tab. D** in Appendix). Regarding the *certain* category a high standard *irrefutable proof* is called for, while the *probable/likely* and *possible* categories represent the balance of proof. This is the standard of proof relevant to medicine and pharmacovigilance (Puliyel et al., 2018).

The checklist is based on: (i) presence of a sufficiently close *temporal succession* between drug's administration and the appearance of the AE; (ii) *plausibility of alternative hypotheses*.[26] The plausibility of the effect with respect to the pharmacological mechanism of the medicinal product does not come into play. Since this is a "side" effect, potentially originating from alternative metabolic pathways to the one on which efficacy is based, the relative pharmacological mechanism may be completely irrelevant with respect to any adverse reactions. Excluding the plausibility of a causal connection between drug and side effect on the basis of known mechanisms related to the desired effect is methodologically unfounded procedure (Osimani B. & Ilardo, 2022).
For vaccines, *checklists* drawn up on the basis of those formulated for medicines have been used for years. However, for a decade now these have been replaced by an algorithm that shows strong elements of systematic distortion of the evaluation procedure, radically invalidating its validity and reliability – see Puliyel et al., 2018.

3. The old AEFI classification system (WHO-Brighton)

The identification of an AEFI and the evaluation of the possible causal link with a given vaccine is of enormous importance but also very difficult to establish.
To assess the AEFI's causality up to 2005, reference was made to the WHO's six-category classification in which AEs were analyzed considering the Brighton criteria following a *step-by-step* guide, characterized by the compilation of a checklist containing questions on the event under consideration (see **Tab.5**), and the classification of the causal link according to a five-value scale: *very likely/certain*, *probable*, *possible*, *unlikely*, *unrelated*, in addition to the case of non-decidability: *unclassifiable* – see **Fig.9** (WHO, 2002).

[26] For medicinal products whose administration is repeated over time (i.e., not in a single dose), treatment can also be discontinued, and administration resumed: if the disorder disappears and reappears in conjunction with the intake of the drug, the evidence of the causal link is overwhelming (Osimani B. & Ilardo, 2022).

WHO categories for causality[3]

Use step-by-step guide *(see Checklist, Section C, page 2)* to determine category.

Very likely/Certain[4]: A clinical event with a plausible time relationship to vaccine administration and which cannot be explained by concurrent disease or other drugs or chemicals.

Probable: A clinical event with a reasonable time relationship to vaccine administration; is unlikely to be attributed to concurrent disease or other drugs or chemicals.

Possible: A clinical event with a reasonable time relationship to vaccine administration, but which could also be explained by concurrent disease or other drugs or chemicals.

Unlikely: A clinical event whose time relationship to vaccine administration makes a causal connection improbable, but which could be plausibly explained by underlying disease or other drugs or chemicals.

Unrelated: A clinical event with an incompatible time relationship and which could be explained by underlying disease or other drugs or chemicals.

Unclassifiable: A clinical event with insufficient information to permit assessment and identification of the cause.

Figure 9: *The WHO-Brighton classification and the criteria for assessing the causal link between vaccine and AEFI. From: WHO. (2002).* Adverse Events Following Immunization (AEFI): Causality Assessment. *AIDE MEMOIRE.*

C. Conduct systematic standardized causality assessment using the step–by-step guide below.

☐ **1. Verify reason for reporting:** diagnosis; whether serious

☐ **2. Evaluate and assess factors**

2.1 Is this event known to be related to the vaccine? ***(Consistency of findings, strength of association.)***

2.2 What is the frequency of occurrence of this adverse event? Very common (>1/10); common (>1/100); uncommon (>1/1,000); rare (>1/10,000); very rare (<1/10,000), or not previously reported.

2.3 Are similar events known to occur with other diseases? ***(Specificity of association.)***

2.4 Is this event explainable by the biological properties of the vaccine? ***(Biological plausibility.)***

2.5 Is the vaccination-to-event interval compatible with the event? ***(Temporal relation.)***

2.6 Has the patient had similar symptoms in the past?

2.7 Is there a history of concomitant or preceding drug therapy?

2.8 Is there a history of concomitant or preceding condition?

2.9 Are there other factors that could affect the occurrence of the event?

☐ **3. Determine causality category using WHO criteria** *(see page 1)*

3.1 Is this an unknown event in relation to this vaccine?

3.2 Is this a new event?

3.3 Is there lack of sufficient data to reach a more definite conclusion?

3.4 Would the case benefit from a second review if more data became available?

3.5 Based upon answers the questions above (in Section C), in which WHO category does the case fit best? N.B. not a numerical score.

☐ **4. Prepare a brief case summary.**

☐ **5. Take action on recommendation(s) from the review.**

☐ **6. Consider the case for education purposes.**

☐ **7. Communicate findings to immunization programme staff, national regulatory authority, and others (as appropriate).**

Table 5*: Checklist for the evaluation of the causal link between vaccine and AEFI. From: WHO. (2002). Adverse Events Following Immunization (AEFI): Causality Assessment. AIDE MEMOIRE.*

This categorization was based on the standardized generic scheme developed by the WHO in collaboration with the UMC for medicinal products [see previous section (WHO-UMC, 2018)]. As can be seen in point 2 of the checklist (**Tab.5**), in a first phase of the assessment of the cause-effect association some guiding principles (or causality criteria) of Bradford Hill are examined (Bradford Hill,1965; WHO, 2001).[27]
This system was abandoned in 2013 with the revision of the criteria by the WHO and CIOMS (Council for International Organizations of Medical Sciences) and the development of the dedicated algorithm (Tozzi et al., 2013; WHO-HIS-EMP, 2013).
The reason for this choice has never been made explicit by the WHO. Before proceeding with the description of the characteristics of the algorithm and its criticalities, it is worth particular attention to retrace some of the events that led to this revision.

3.1. Moving from the old to the new system: the Quinvaxem controversy

The decision to revise the AEFI evaluation criteria followed a controversy over the safety of the pentavalent vaccine Quinvaxem (Crucell), which was introduced and administered to children in January 2008 in Sri Lanka, only to be withdrawn in April 2008 due to reports of five deaths and episodes of serious adverse events. In order to investigate these events, a WHO Panel of Experts was established and, in their report (December 2008), a modified classification of AEFIs, in which the *probable* and *possible* categories had suddenly disappeared. The deaths were then classified as follows: three as *unlikely*, one *unrelated* and the other *unclassifiable*. As Puliyel et al. (2018) point out, experts classify the three deaths in the *unlikely* category, although there is no alternative explanation capable of justifying the observed clinical event, instead of classifying them as *probable*.
In December 2009, following the government's decision to reintroduce the vaccine and reinforce the immunization program, a petition was filed in the New Delhi High Court written and signed by doctors and government political advisers in which they challenged the reasons used by the government to introduce the vaccine and also its effectiveness, claiming that data

[27] In particular: (i) *consistency of findings,* the association is confirmed by different studies (in different contexts); (ii) *strength of association*; (iii) *specificity of association*: is the event exclusively linked to the investigated phenomenon or has it verified also in conjunction with other pathological phenomena?; (iv) *biological plausibility*, the association under consideration is compatible (biologically plausible or explainable) with current scientific knowledge; (v) *temporal relationship*, the time window between administration and AEFI is sufficiently limited. Other possible indicators of causality according to the Bradford-Hill criteria are: (vi) *biological gradient/dose-response* — however, specific characteristics of the test population, routes of exposure, individual susceptibility and synergistic or antagonistic effects may make characterization of some biological gradients difficult (Fedak et al., 2015); (vii) *coherence between epidemiology and laboratory findings*, the association is compatible with available previous knowledge on observed effect and/or exposure (Dyda et al., 2018); (viii) *experimental evidence,* regarding causation it obviously provides a strong indicator of causality; (ix) *analogy*, evidence of an association between an agent similar to the one under consideration and the observed effect may strengthen the causality hypothesis; for an analysis of the epistemological foundations of the Bradford-Hill criteria and for their systematization, see (Landes et al., 2018).

from the countries where the vaccine was administered had revealed that there was no real benefit to children (Saxena et al. 2009).
In October 2010, the GACVS (Global Advisory Committee on Vaccine Safety) commissioned groups of experts from the ACCA (Advisory Committee on Causality Assessment, Canada), EU/VAESCO (Vaccine Adverse Event Surveillance & Communication of the European Union), CIOMS, and CISA (Clinical Immunization Safety Assessment, USA) to review the criteria and classification system of AEFI used until then (Tozzi et al. 2013).
In 2012 the CIOMS-WHO report was published with the collaboration of Brighton, in which new tools are provided for the investigation of AEFI (CIOMS & WHO, 2012).
Subsequently, in March 2013, the manual entitled "*Causality Assessment for an AEFI: user manual for the revised WHO classification*" was published, in which the algorithm developed *ad hoc* for vaccines was presented (WHO-HIS-EMP 2013).

4. The new system of evaluation of causality between AEFI and vaccine: the WHO-CIOMS algorithm

Regarding vaccines, in 2013 the WHO developed a dedicated method that represents the current system mainly used by regulators for causality assessment of an AEFI (WHO-HIS-EMP, 2013), and that sees its updated version in the edition published in 2019 (WHO, 2019). It is intended as a guide for a systematic and standardized global causality assessment process for individual AEFIs, performed at national and subnational level by members of the AEFI National Committee or Immunization Programme Managers. It is increasingly used by researchers and epidemiologists worldwide, in Lower Middle-Income Countries (Sebastian et al., 2019; Singh et al., 2017), but also in developed countries. It is widely utilized in Italy (Lombardi et al., 2019; Stefanizzi et al., 2019), Germany (Mentzer et al., 2018), Canada (MacDonald & Law, 2017). Moreover, it is recommended by the Brighton Collaboration Group for the analysis of vaccine safety data in pregnancy (Jones et al., 2016).
The WHO algorithm consists of four standardized parts with the following procedural order (WHO, 2019; WHO-HIS-EMP, 2013):

1. *Eligibility*. This first part is intended to determine if the AEFI case satisfies the minimum criteria for causality assessment. This means that one should be able to positively respond to questions like: Was the vaccine administered before the event occurred? What is the valid diagnosis?[28] Did the diagnosis meet a standard case definition? (i.e.,

[28] It consists in the selection of unfavorable or unintended sign, abnormal laboratory finding, symptom or disease that is thought to be causally linked to the vaccine (WHO, 2019).

the Brighton Collaboration definition, standard literature definition, national definition, or other approved definition).

2. *Checklist*. This second part comprises systematically reviewing the relevant and available information to address possible causal aspects of the AEFI. Questions here are like: Is there strong evidence for other causes? Is there a known causal association with the vaccine (vaccine product/vaccine quality) or vaccination (immunization error or immunization anxiety)? Was the event within the time window of increased association risk? Is there strong evidence against a causal association? Are there other qualifying factors for classification? – some of the question groups also consist of detailed sub-questions – see **Tab.6.**
3. *Algorithm*. This third part identifies and determine whether there is a trend suggesting causality on the basis of the information gathered in the checklist. It guides in the classification of AEFIs.
4. *Classification*. Based on algorithm, this last part consists in categorizing the entity of the AEFI association with the vaccine into four categories and then coming to a decision on causality. A case with adequate information for a causality conclusion can be classified as one of the following three categories: '*consistent* causal association with immunization', '*indeterminate*', and '*inconsistent* causal association with immunization' (coincidental); while a case without adequate information goes into the category '*unclassifiable*'.

Compared to the system previously used for attributing the vaccine-AEFI causal link, in the new system [see (Tozzi et al., 2013; WHO, 2019; WHO-HIS-EMP, 2013)] the Brighton classification is officially abandoned, and the scale turns into a dichotomous categorization: *consistent* vs. *inconsistent* (i.e., no link between the AEFI and immunization). Moreover, the category for undecidable cases is splitted into *indeterminate*[29] and *unclassifiable*[30]. In the former further investigation is encouraged, while in the latter the event is definitively archived (Osimani B. & Ilardo, 2022). Thus, the *inconsistent* category includes reactions that will not be investigated as a new signal of a causal association category. This category is used to classify a broad variety of clinical situations that in the previous system would have been classified as '*probable*' or '*unlikely*' or '*unrelated*' (Puliyel, 2018) – three different categories of three different clinical situations.

Unlike the procedure for drugs and the system previously used for vaccines, in the algorithm the following steps must be taken (see **Fig.10**):

Step I: take into account evidence pointing to *alternative explanations*;

[29] This category includes reactions that may have been caused by the vaccine, but for which the causal association has not been previously documented.

[30] This category includes events with insufficient information to allow the identification of cause and therefore causality assessment.

Step II: evaluate the plausibility of the causal link, based on a *known* association between vaccine and AE *and* temporal link (at this stage manufacturing defects, storage or administration errors or psychosomatic reactions must be excluded);

Step III: if there is no evidence of alternative explanations (*Step I*) and the association between vaccine and pathogenic effects detected is known (*Step II*), it should be evaluated whether there is strong evidence *against* causation;

Step IV: finally, the responsibility of the vaccine must be *excluded* on the basis of etiological evaluations of various types: the event could have occurred even independently of the vaccine, that is, it is a symptom of a pathological disorder, independent of the administration of the vaccine, or is attributable to risk factors (e.g. toxins) to which the subject was exposed before receiving the vaccine dose; see **Tab.6** and **Fig.10**.

Step 2: Event checklist

Check ✓ all boxes that apply — **Y: Yes N: No UK: Unknown NA: Not applicable**

I. Is there strong evidence for other causes?	**Y N UK NA**	**Remarks**
Does a clinical examination, or laboratory tests on the patient, confirm another cause?	□□□□	
II. Is there a known causal association with the vaccine or vaccination?		
Vaccine product(s)		
Is there evidence in the literature that this vaccine(s) may cause the reported event even if administered correctly?	□□□□	
Did a specific test demonstrate the causal role of the vaccine or any of the ingredients?	□□□□	
Immunization error		
Was there an error in prescribing or non-adherence to recommendations for use of the vaccine (e.g. use beyond the expiry date, wrong recipient etc.)?	□□□□	
Was the vaccine (or any of its ingredients) administered unsterile?	□□□□	
Was the vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal at the time of administration?	□□□□	
Was there an error in vaccine constitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?	□□□□	
Was there an error in vaccine handling (e.g. a break in the cold chain during transport, storage and/or immunization session etc.)?	□□□□	
Was the vaccine administered incorrectly (e.g. wrong dose, site or route of administration; wrong needle size etc.)?	□□□□	
Immunization anxiety		
Could the event have been caused by anxiety about the immunization (e.g. vasovagal, hyperventilation or stress-related disorder)?	□□□□	
II (time). If "yes" to any question in II, was the event within the time window of increased risk?		
Did the event occur within an appropriate time window after vaccine administration?	□□□□	
III. Is there strong evidence against a causal association?		
Is there strong evidence against a causal association?	□□□□	
IV. Other qualifying factors for classification		
Could the event occur independently of vaccination (background rate)?	□□□□	
Could the event be a manifestation of another health condition?	□□□□	
Did a comparable event occur after a previous dose of a similar vaccine?	□□□□	
Was there exposure to a potential risk factor or toxin prior to the event?	□□□□	
Was there acute illness prior to the event?	□□□□	
Did the event occur in the past independently of vaccination?	□□□□	
Was the patient taking any medication prior to vaccination?	□□□□	
Is there a biological plausibility that the vaccine could cause the event?	□□□□	

Table 6: *Checklist for the assessment of causality. Taken from: WHO-HIS-EMP (2013: 34-35).*

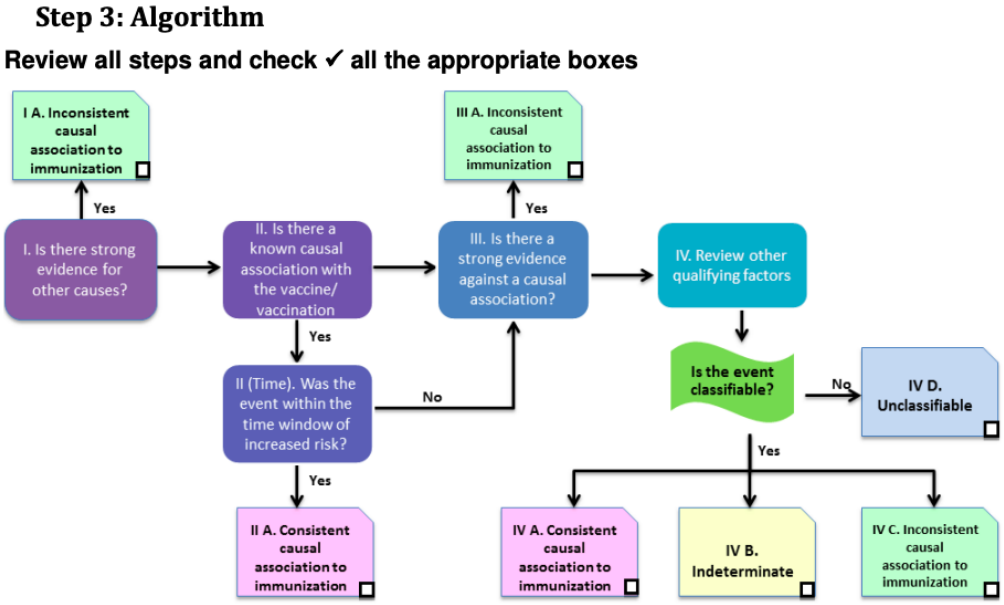

Figure 10: *Decision algorithm. Taken from: WHO-HIS-EMP (2013: 34-35)*

In the 2013 WHO Handbook in which the algorithm is presented, it is stated: "*a definite causal association or absence of association often cannot be established for an individual event […] However it is important to try to identify a possible new vaccine product-related AEFI, as well as if the event is preventable or remedial*" (WHO-HIS-EMP, 2013). However, what the algorithm achieves is exactly the opposite. As it is structured, it seems to deny the possibility that any newly observed AE may be causally related to vaccination.
Following this algorithm, it is understandable how AIFA could underestimate the reported cases. For example, in the third AIFA report we read on page 16:[31]

> "In the field of vaccine-vigilance, a specific algorithm is used, built and validated by the World Health Organization (WHO) [...] As of 26 March 2021, a total of *102 reports with a "death" outcome* were included in the National Pharmacovigilance Network, of which 2 duplicates were excluded. (...) The evaluations of the cases accompanied by detailed and complete information suggest the absence of responsibility of the vaccine in most of these, as they are often subjects with intercurrent or previous pathologies and in polytherapy, with clinical fragility, such as: cardiovascular diseases (arterial hypertension, previous AMI, heart failure, cardiomyopathy), metabolic diseases (diabetes, dyslipidemia), oncological diseases, autoimmune diseases, neurodegenerative diseases (Alzheimer's disease), respiratory and mediastinal diseases (COPD, emphysema), kidney, liver, pancreatic diseases, diseases of the lymphopoietic system (plateletopenia, coagulation defects). At the time of writing, 64% of fatal reports (No. 64) have been evaluated with the WHO algorithm and 36% have not yet been evaluated. Compared to the total number of reports with fatal outcomes, the causal link

[31] https://www.aifa.gov.it/rapporti-su-sorveglianza-dei-vaccini-covid-19.

was uncorrelated in 38% of cases, undetermined in 22% and unclassifiable due to lack of information necessary for the application of the algorithm in 3%. *The causal link can be correlated in only 1 report*."

Determining whether there is a *consistent* causal association between a given vaccine and an observed AEFI is not easy. There are very few or in any case very rare AEFIs that can be classified as certainly (or most likely) associated with a given vaccine in an individual [e.g., idiopathic thrombocytopenic purpura (ITP) was causally associated with MMR (measles-mumps-rubella) vaccination (Miller et al., 2001)]. This difficulty is due to the complexity of the analysis context in which the algorithm operates, and to the fact that, as it is currently structured, it seems to underestimate this complexity.

For this reason, the WHO algorithm has been criticized from both a conceptual and methodological point of view (Bellavite, 2020; H. Lee et al., 2020; Osimani B. & Ilardo, 2022; Puliyel et al., 2018).

The available scientific evidence is often insufficient to conclude that the association between the observed AE and the vaccine administration is real, but also insufficient confidently to rule out a link, and the systematic study of such situations can be complex for several reasons, such as the occurrence of the effects many years after vaccination, etc. However, the algorithm express itself in absolutist way by excluding vaccine-AEFI link on the sole basis of one evidence (e.g., evidence of other cause(s) at *Step I*) and not considering the possibility of long-term effects. The mechanisms underlying vaccines action in inducing an immune response are complex.

Moreover, most AEFIs are multifactorial pathologies where a multiplicity of factors of various kinds (exogenous and endogenous) are present, interact in complex ways precipitating the AE and/or acting as cofactors (Bellavite, 2020), and vary from one individual to another. However, the algorithm seems to not to consider these aspects by underestimating the role of multifactorial causation, interacting causality, and vaccine-person interactions.

The errors mentioned above increase the likelihood of false negatives, thus decreasing the accuracy of the tool. I will discuss in more detail all the criticalities that the algorithm presents in Chapter V.

In the next chapter I will address the issue of understanding the complex mechanisms associated with AEFIs by making use of the medical-pharmacological literature.

CHAPTER III

1. Biocomplexity in the occurrence of AEFIs

The WHO algorithm for causality assessment of AEFIs may be overly simple and may not do justice the complexity of biological systems and the possibility of multifactorial causation, that is, complex disease causation, complexity of the immune response (including the genesis of autoimmunity), the role of genetic variants and of the microbiome in the modulation of immune reactions (Bellavite, 2020).

The WHO states that *"vaccines are undoubtedly the most complex medical products to develop"* (WHO, 2022c) and EMA states that *"there must be evidence to demonstrate that the benefit in terms of improvement of the immune response has been achieved without an undue increase in local and systemic adverse reactions*" (EMA, 2005).

Vaccines are biological product with the great benefit for being very important and necessary for the prevention of many serious infectious diseases (prophylaxis), but they also bring with them the potential risk of being responsible for the manifestation of equally serious, although often rare, pathologies. Beyond well-documented vaccine reactions, vaccines could be responsible for serious health problems where the available scientific evidence may be insufficient to conclude that the association is real, but also insufficient to rule out a link. As WHO points out, the systematic study of these conditions is made difficult by the fact that the frequency of a true reaction can be extremely low, the effects could be more or less mild, and the effects could occur many years after vaccination (WHO, 2013). It should be noted that many effects are rare, and that effects that appear mild/harmless *prima facie* (as temporary) may indicate the onset of diseases, such as auto-immune ones, whose clinical manifestation will emerge at the clinical level after some time.

AEs may emerge from three types of phenomena, namely (Osimani B. & Ilardo, 2022):

1. The same biomolecular mechanism that produces the expected effect is also responsible for the harmful effect (e.g., inhibition of the production of prostaglandins of antirheumatic drugs can induce gastric ulcer at the same time, as prostaglandins protect the mucous membranes of the stomach).
2. The pharmaceutical product binds to more or less unknown off-target receptors, triggering metabolic cascades that interfere with the (sub)cellular mechanisms of organs or systems putatively not affected by the known pharmacological action.
3. The pharmaceutical product generates a systemic response of the organism and/or interactions at different levels of the organism.

These phenomena are linked to different causal processes: i.e., positive or negative feedback mechanisms, homeostasis phenomena, back-up mechanisms replacing those that are eventually inhibited by the drug [see (Joffe, 2011)]. In the context of these complex systems and sub-

systems of functioning of the organism, (bio)pharmaceuticals can have paradoxical effects (e.g., producing, at least in some individuals, the exact opposite of what would be expected) or bi-directional [e.g., producing an effect and its opposite, in different individuals, or in the same individual in different circumstances (Aronson & Hauben, 2006; S. W. Smith et al., 2012)] and effects that mimic the symptoms of the pathology and that for this reason are not identified as such.

In general, the harmful effects of a (bio)pharmaceutical product are highly variable and are characterized by cumulative effects and mechanisms of causal interaction (Osimani B. & Ilardo, 2022).

In the analysis of AEFIs it's also crucial to take into account: (i) the heterogeneous nature of vaccines, that is, different technology [live-attenuated, inactivated, subunit (recombinant, polysaccharide, and conjugate), toxoid, viral vector, mRNA] and composition of each vaccine both for the constituents that provoke the immune response and for the presence of different adjuvants, excipients, preservatives and so on; and (ii) the mechanism through which a vaccine induce a response by the immune system. The stimulation of the immune system by vaccines involves a complex interaction between vaccine antigens, adjuvant (if present), antigen-presenting cells, lymphocytes, and multiple immune mediators (cytokines), and the various processes involved can induce an excessive or distorted inflammatory and immune response, resulting in the occurrence of inflammatory and immune pathologies – complex (multifactorial) diseases (Bellavite, 2020).

Although serious immune-mediated AEs are generally rare and less common with the vaccine than with true infection, it is very important that they are carefully examined and evaluated for their potential causality. It is also essential that AEFI's frequency is quantified, and the mechanism associated with vaccine is studied – investigation of whether AEFI has a biologically plausible mechanism (McClenathan & Edwards, 2019).

For the treatment/prevention of diseases many fields of investigation are using precision medicine, that considers individual variability in genes, environment, and lifestyle for each person (F. S. Collins & Varmus, 2015).

1.1. AEFIs: definition and classification

An Adverse Event Following Immunization (AEFI) may be defined as *"a medical incident that takes place after an immunization, causes concern and is believed to be caused by the immunization"* (Budhiraja & Akinapelli, 2010). The CIOMS defines an AEFI as "*any untoward medical occurrence which follows immunization, and which does not necessarily have a causal relationship with the usage of the vaccine"* (CIOMS, 2012).

An AEFI may be classified according to its frequency as (CIOMS & WHO, 2012):

a) *very common* ($\geq \frac{1}{10}; \geq 10\%$);
b) *common* (frequent) ($\geq \frac{1}{100}\ and\ < \frac{1}{10}; \geq 1\%\ and\ < 10\%$);

c) *uncommon* (infrequent) $\geq \frac{1}{1,000}$ and $< \frac{1}{100}; \geq 0.1\%$ and $< 1\%$);

d) *rare* ($\geq \frac{1}{10,000} and$ $< \frac{1}{1,000}; \geq 0.01\%$ and $< 0.1\%$);

e) *very rare* ($< \frac{1}{10,000}; < 0.01\%$).

The identification of rare (occurring in 0.01% to less than 0.1% of immunized individuals) and very rare (occurring in <0.01% of individuals) AEs is insufficient at the time of vaccine licensing and more information will be needed for which AEFI surveillance has to be strengthened.

It is possible to distinguish two types of vaccine adverse reactions according to their severity as follows (Autret-Leca et al., 2006):

i. *minor*: usually occur within a few hours of injection, resolve after short period of time and pose little danger, local (including pain, swelling or redness at the site of injection), systemic (including fever, malaise, muscle pain, headache or loss of appetite);
ii. *severe*: usually do not result in long-term problems, are rarely life threatening, can be disabling, and include seizures and allergic reactions caused by the body's reaction to a particular component in a vaccine [e.g., antigen (live, killed, purified, inactivated toxin), stabilizers, adjuvant, preservatives, antibiotics].

An AEFI is considered *serious* if it results in death or in persistent/significant incapacity or in disability/substantial disruption of the ability to conduct normal life functions (e.g., paralysis), or if it is life-threatening, or requires inpatient hospitalization or prolongation of existing hospitalization (e.g., encephalopathy, seizures, aseptic meningitis) (European Medicines Agency & Heads of Medicine Agencies, 2017).

An AEFI can be any unfavorable or unintended sign, abnormal laboratory findings, symptoms or diseases, manifesting excessive biological stress caused by an extraneous material or an attenuated live virus. It may be causally related to the vaccine due to its contents being defective or contaminated because of preparation or storage inaccuracies, or administration errors (e.g., accidental intravenous injection – injection near a nerve plexus, or delivery of aluminum into the skin instead of muscle) (Bellavite, 2020). The WHO classifies AEFIs according to the causes of the event into the following five categories (CIOMS & WHO, 2012; WHO, 2020):

1) *vaccine product related reaction*: AEFI caused or precipitated by vaccine due to one or more of its intrinsic properties (e.g., external limb swelling following DTP vaccination).
2) *vaccine quality defect-related reaction*: AEFI caused or precipitated by vaccine due to one or more of its quality defects including the administration device provided by the manufacturer (e.g., failure by the manufacturer to completely inactivate a lot of inactivated polio vaccine leading to cases of paralytic polio). For new vaccines platforms, the knowledge of potential vaccine quality defects might be insufficient at the time of vaccine licensing and more information will be needed; the rapid scaling up

of vaccine production poses additional potential risks and identification of the exact substance causing the event is needed.

3) *immunization error-related reaction*: AEFI caused by inappropriate vaccine handling, prescribing, or administration and thus by its nature is preventable (e.g., transmission of infection due to contaminated multidose vial, bacterial abscess, severe local reaction, high fever or sepsis, BCG lymphadenitis, toxic shock syndrome, clusters[32] of AEFI).
4) *immunization anxiety-related reaction*: AEFI arising from anxiety about the immunization (e.g., vasovagal syncope in an adolescent following vaccination). A larger number of immunization anxiety-related reactions are anticipated due to numerous factors including older age groups, the different vaccinating environments, the novelty of the vaccines and their administration modalities.
5) *coincidental event*: AEFI caused by something other than the vaccine, immunization error or anxiety but where a temporal association with immunization exists [e.g., fever that occurs after vaccination (temporal association) but is caused by malaria since malarial parasite has been isolated from blood].

It is also possible to distinguish two types of vaccine adverse reactions based on the involvement of one component of the vaccine rather than another:

i. *specific*: if related to the antigen of a live attenuated virus vaccine (e.g., lymphocyte meningitis after anti-mumps vaccine);
ii. *non-specific*: if related to a component different from the antigen (e.g., aluminum hydroxide involved in the "macrophagic myofasciitis", allergic reactions to neomycin, latex, egg, or gelatin).

If the AE is caused by a vaccine adjuvant or excipient, rather than by its active component, it might spuriously influence the specificity of the association between vaccine and AE (WHO, 2001).
Most of vaccines' severe AEFIs are related to the vaccine action involving an innate immune response linked to the early biological defenses to injected matter, and a more antigen-specific response, linked to the adaptive immune defenses (Bellavite, 2020).
Understanding the complex mechanism underlying AEFI involves immunological, immunopathological and pharmacological considerations.

[32] A cluster of AEFIs is two or more cases of the same adverse event related in time, place or vaccine administered (WHO, 2004).

2. Immunological considerations

In many cases an AEFI occurs as an excessive or distorted inflammatory or immune response that can degenerate giving lethal outcomes[33], or may concern the onset of irreversible pathologies. Vaccines have nonspecific effects that upregulate or reduce both the innate and adaptive immune systems (Higgins et al., 2016).
Understanding how the immune system works in helping protect the body from infection clarifies how and why reactions to the vaccine occur (WHO, 2013).
The way the immune system responds to bacteria/viruses is very complex and has two complementary components: innate and adaptive immunity.

2.1. Innate immunity

Innate (or nonspecific) immunity is the immunity you were born with. It is rapid (minutes/hours), responds in the same way each time a new pathogen is encountered, is not antigen specific, and has no immunologic memory. Innate immunity includes anatomic (skin and mucous membrane), physiologic (temperature, low pH, and chemical mediators), endocytic and phagocytic, and inflammatory defensive barriers. It acts by identifying and destroying pathogens from the body and by neutralizing toxins produced by certain bacteria (Marshall et al., 2018). Thanks to pattern recognition receptors (PRRs) immune cells can detect and respond quickly to a wide range of pathogens that share common structures (e.g., pathogen associated molecular patterns, PAMPs), and recruit to sites of infection and inflammation through the production of chemokines and cytokines [e.g., tumor necrosis factor (TNF), interleukin 1 (IL-1) and interleukin 6 (IL-6)]. The latter activate local cellular response to infection and mobilize many defense mechanisms throughout the body – their dysregulated production is associated with inflammatory or autoimmune diseases (Marshall et al., 2018). Part of the innate immunity is the complement system. When it is activated (biochemical cascade) pathogens became susceptible to phagocytosis, a process by which immune cells [e.g., macrophages, neutrophils, dendritic cells, mast cells, eosinophils, basophils, natural killers (NKs), innate lymphoid cells] swallow and kill them, and which can activate the adaptive immune response through the mobilization and activation of antigen-presenting cells (APCs).

2.2. Adaptive immunity

The adaptive immune system develops to protect us from pathogens present in our individual environment. Adaptive (or acquired/specific) immunity develops over time, it is antigen-

[33] One of the main causes of morbidity and mortality worldwide are unfavorable clinical events caused by immune and non-immune mechanisms (Parida, 2013).

dependent, antigen-specific and has immunologic memory. The immune system recognizes specific antigens from bacteria and viruses and produces pathogen-specific immunological effector pathways which eliminate the pathogen (Marshall et al., 2018). During the primary immune response to the first encounter with a specific intruding pathogen, memory cells develop, replicate, and prepare the body to a second innate immune response. This kind of cells, by recognizing antigens on pathogens they have encountered previously, trigger a faster and more effective immune response than the first exposure, and confer lasting (often lifetime) immunity to that pathogen (Bonilla & Oettgen, 2010; WHO, 2013). The secondary adaptive immune response can clear pathogens before any damage occurs.
The cells involved in the adaptive immune response are lymphocytes (i.e., a type of white blood cell, belonging to the leukocyte family), more specifically:

1) *T cells*: they mature in the thymus and can differentiate into three different cell types (i.e., helper T cells, cytotoxic T cells, and suppressor T cells); and
2) *B cells*: they mature in bone marrow and some of which can differentiate into activated plasma cells that help to fight the pathogen by releasing antibodies (i.e., protective proteins, also called immunoglobulins[34]).

These cells fight the pathogen infection in two ways: B cells play a major role in the humoral (or antibody-mediated) immune response, while T cells in the cell-mediated immune response – see **Fig.11.**

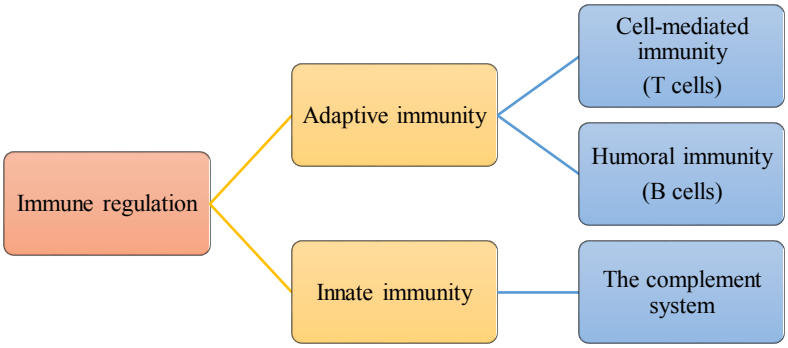

Figure 11*: Immune regulation.*

2.2.1. Humoral immunity

In humoral immunity, the mature, activated B cells secrete antigen-specific antibodies that help to neutralize extracellular pathogens. Antibodies can also attach to infected cells, but they cannot destroy host cells on their own.
A naïve B cell produces a surface-bound form of antibody, known as immunoglobulin, whose exposed antigen binding site can detect potential pathogens. When an antigen corresponding to the antigen binding site binds to a naïve B cell, a differentiation process occurs that leads to the

[34]Class of glycoproteins with high molecular weight.

generation of memory B cells and effector B cells, which produce the same antigen-specific molecules as the naïve B cell (Dornell, 2022). Thanks to the B cell antigen-binding receptor, the activated memory B cell recognizes and binds to a specific antigen, which is internalized and transformed into peptides. The activation of the helper T cells by MHC class II receptors, which secrete cytokines (e.g., IL-6, help B-cells, etc.), helps the proliferation and differentiation of the B cell into an antibody-secreting plasma cell (Janeway et al., 2001; Marshall et al., 2018). The secreted antibodies (i.e., IgA, IgD, IgE, IgG[35] and IgM) can (Janeway et al., 2001):

i. inhibit the cytotoxic effects or infectivity of the pathogen by binding to it (neutralization);
ii. coat the pathogen by allowing accessory cells that recognize the Fc portions of antibody arrays to ingest and kill the pathogen (opsonization);
iii. activate the complement cascade, where complement proteins can greatly enhance opsonization and can directly kill some bacterial cells.

In sum, antibodies bind to the antigen on the surface of the pathogen, signaling it for destruction through complement activation, promotion of opsonin phagocytosis and elimination of the pathogen by immune effector cells. Then, antigen-antibody complexes are eliminated from the complement cell cascade (Bonilla & Oettgen, 2010; Marshall et al., 2018).
IgA, IgD, IgE, IgG and IgM have different biological functions and recognize and neutralize specific pathogens (Schroeder & Cavacini, 2010), but are usually unable to eliminate a virus once infection has occurred (Marshall et al., 2018). In this case, cell-mediated immune mechanisms come into play.

2.2.2. T cell-mediated immunity

Cell-mediated immunity is directed mainly to viruses that survive in phagocytes and those that infect non-phagocytic cells, therefore to the elimination of virus-infected cells, but also of cancer-cells or cells infected by fungi or intracellular bacteria. Moreover, it can play an important role in transplant rejection (Marshall et al., 2018).
Cell-mediated immunity doesn't protect the organism with the involvement of antibodies, but it is primarily driven by T-cells, macrophages, and the release of cytokines. T-cells recognize intracellular target antigens thanks to APCs containing membrane-bound MHC class I proteins and the binding with the antigen lead to the activation of naïve T cells that maturate and differentiate into helper T cells [e.g., $CD4^+$ release cytokines that can damage the target cell directly or help activate killer T cells and macrophages] or into killer T cells [e.g., $CD8^+$ (or cytotoxic T cells) directly cause the lysis of target cells] (Dornell, 2022).
In sum, cell-mediated immunity implies (Bonilla & Oettgen, 2010):

[35] They can be divided into structurally distinct subclasses with different abilities to fix complement, act as opsonin, etc.

i. activation of antigen-specific cytotoxic T cells that recognize infected cells and induce their apoptosis by showing foreign antigens or derived peptides on their surface;
ii. activation of macrophages and NK cells, allowing them to destroy intracellular pathogens;
iii. stimulation of cytokine (e.g., IFNγ) production that mediates the effective immune response.

2.3. Passive *vs* Active immunity & Natural *vs* Artificially acquired immunity

There are two main mechanisms for acquiring immunity, *active* or *passive*.
Passive immunity refers to the transfer of active humoral immunity, in the form of "ready-made" antibodies, from one individual to another. This kind of immunity (Marshall et al., 2018):

(i) is immediate,
(ii) lasts for a relatively short period (only for a few weeks or months),
(iii) can occur naturally (e.g., by transplacental transfer of maternal antibodies to the developing fetus), *or*
(iv) can be artificially induced (e.g., by injecting exogenous antibodies that are usually manufactured for this purpose and that are targeted at a specific pathogen or toxin).

Artificially acquired immunity is used when there is a high risk of infection and insufficient time for the body to develop its own immune response, or to reduce symptoms of chronic or immunosuppressive diseases (Marshall et al., 2018).
Active immunity refers to the production of antibodies against a specific antigen or pathogen after exposure to the antigen. This kind of immunity (Marshall et al., 2018):

(i) takes time (usually weeks) to develop,
(ii) can be natural (i.e., acquired through natural infection with a microbe) and last a lifetime, *or*
(iii) can be vaccine-induced [i.e., attenuated (weakened) pathogens, inactivated organisms or specific proteins or carbohydrates known to induce immunity] and last a long time.

Effective active immunization often requires the use of adjuvants that improve the immune system's ability to respond to antigen injection (Marshall et al., 2018).

2.4. Pre-existing cross-reactive immunity

When high serotype-specific and highly neutralizing antibody titers are produced, the host is protected against future reinfection and the disease is mild or asymptomatic; conversely, when

pre-existing antibodies are cross-reactive and non-neutralizing or with a narrow neutralizing spectrum, hosts may not be sterile protected or host protection may be limited to the serotype of previous viral infections and allow persistence of new mutant viruses (Jia et al., 2022; Warter et al., 2012).

For most cases, pre-existing cross-reactive immunity result from: (i) a primary infection with a virus that sequentially resembles a secondary heterologous infectious agent, or (ii) previous vaccination (Boes, 2000; Jia et al., 2022; Warter et al., 2012), or (iii) exposures to certain commensal gut bacteria, such as pre-existing antibodies against HIV-1 gp41 (Liao et al., 2011; Williams et al., 2015). Commensal bacteria represent important sources of cross-reactive antibodies (Jia et al., 2022) – see autoimmune diseases caused by cross-reactivity between microbial and self-antigens (Rose, 2017; Zitvogel et al., 2016).

Pre-existing antibodies may affect host immune responses in case of infection or vaccination (Cobey & Hensley, 2017; Zimmermann & Curtis, 2019). An example of known cross reactivity is that between Japanese encephalitis (JE) virus antibody and yellow fever (YF) vaccine. However, the knowledge on how cross-reactive antibodies affect vaccination outcome is limited[36]. It is supposed that cross-reactive antibodies could impact the antibody response to the vaccine at the time of vaccination in a concentration-dependent manner, altering both vaccine uptake and the innate immune response by APCs (Low et al., 2015).

Cross-reactive B and T cells may have (Murray et al., 2022):

a. *Beneficial effects*:
   - Cross-reactive T cells can be generated through T-cell triggering from high-homology epitopes, which then cross-react with high avidity during a secondary heterologous infection and can block pathogenicity by preventing invasive infection or can accelerate the rate of viral clearance by forming a "secondary-like" memory immune response with a greater magnitude of B cell help and T cell responses.[37]
   - Cross-reactive memory B cells and antibodies can be produced in epitopes of high similarity between a primary and a secondary heterologous infection; cross-reactive B cells specific for highly conserved epitopes can then continue to generate a rapid, high-function memory-like response to heterologous infection, with the secretion of cross-neutralizing antibodies that can prevent viral entry into cells.[38]

b. *Harmful effects*:
   - Cross-reactive T cells can be generated in epitopes of relatively low homology and adversely affect a secondary infection with heterologous agents by prevailing in

[36] The effect of pre-existing cross-reactive antibodies has been widely studied for influenza infections (Auladell et al., 2019; Cobey & Hensley, 2017; A. Zhang et al., 2019) and flaviviruses (Andrade et al., 2019; St John & Rathore, 2019). Some studies showed that pre-existing antibodies shape booster immune responses against influenza (Dugan et al., 2020; A. Zhang et al., 2019).

[37] For these cross-reactive mechanisms see coronavirus infections (Kundu et al., 2022; Loyal et al., 2023; Mateus et al., 2023; Swadling et al., 2022).

[38] For these cross-reactive mechanisms see for example studies on coronavirus infections (Kundu et al., 2022; Morgenlander et al., 2021), influenza infection (McCarthy et al., 2018) and vaccination (Galli et al., 2009).

secondary infection response, competing for presented antigen, and interrupting the generation of high-avidity de novo T cell responses; cross-reactive CD8+ T cells can bind with low-affinity epitope from the secondary infectious agent, leading to the production of pro-inflammatory cytokines [interferon-γ (IFNγ), tumor necrosis factor-α (TNFα)] without the induction of cytolytic effector functions (degranulation), resulting in immunopathology and reducing viral clearance.[39]

- Cross-reactive B cells can be generated in epitopes of low homology and hinder responses to a secondary heterologous infection by distorting the response to antibodies with higher avidity for the initial infectious agent, reducing the production of de novo antibody responses.[40]
- Low-avidity cross-reactive antibodies or low levels of high-avidity cross-reactive antibodies that cannot neutralize a secondary heterologous infection may bind to virus and aid viral entry into cells through Fc-receptor-mediated endocytosis, the so-called antibody-dependent enhancement (ADE).[41]

3. Immunopathological considerations

Defects in the adaptive and innate immune system can lead to immunopathological conditions, including hypersensitivity reactions, autoimmune diseases, and immunodeficiencies.

3.1 Hypersensitivity reactions

Hypersensitivity reactions are undesirable, exaggerated, or inappropriate, responses produced by the immune system in response to an antigen or allergen (Marshall et al., 2018; Vaillant et al., 2022), and may be classified into four categories (Gell & Coombs, 1963; Rajan, 2003):

i. Immediate: *Type I* (or Anaphylactic Response).
ii. Cytotoxic or antibody-dependent: *Type II* (or Cytotoxic-Mediated Response).
iii. Immune complex disease*: Type III*.
iv. Delayed type: *Type IV*.

[39] For these cross-reactive mechanisms see for example flavivirus infection studies (Duangchinda et al., 2010; Mongkolsapaya et al., 2003, 2006; Screaton et al., 2015; Welsh et al., 2010).

[40] For these cross-reactive mechanisms see for example common cold coronaviruses and SARS-CoV-2 (McNaughton et al., 2022) and influenza virus studies (A. Zhang et al., 2019).

[41] For antibody-dependent enhancement mechanism see for example flavivirus infection (Goncalvez et al., 2007; Pierson et al., 2007).

Type I – the most common type – is an allergic reaction caused by re-exposure to a specific type of antigen (allergen) and is mediated by IgE antibodies. IgE bind to receptors on the surface of tissue mast cells and blood basophils (which contain histamine granules), causing them to sensitize. The subsequent exposure to the same allergen cross-links the bound IgE on sensitized cells resulting in activation of mast cells and their degranulation and secretion of histamine, platelet-activating factor (PAF), leukotrienes (e.g., LTC4) and prostaglandins (e.g., PGD2) (active mediators), causing vasodilation, vascular leak, contraction of the smooth muscles of the surrounding tissue, and inflammation [induced by enzymes such as tryptase causes tissue damage and tumor necrosis factor (TNF)] (Marshall et al., 2018; Vaillant et al., 2022).[42] The most severe form of allergic reaction is anaphylaxis, in which mast cells suddenly release a large amount of histamine and subsequently leukotrienes (e.g., intense bronchospasm, laryngeal edema, cyanosis, hypotension and shock may be present).

Type II is rare, takes 2 to 24 hours to develop and is mediated by IgG and IgM antibodies. Immunoglobulins damage cells by binding to molecules on the patient's cell surface and triggering phagocytosis or forming complexes that activate the complement system, leading to opsonization, red blood cell agglutination, cell lysis and death (Marshall et al., 2018; Vaillant et al., 2022).[43]

Type III can take days, or even weeks, to develop. It is also mediated by IgM and IgG antibodies, which bind to soluble proteins (rather than cell surface molecules) forming antigen-antibody complexes, leading to activation of the complement system, followed by neutrophil influx, inflammation and degranulation of mast cells – the complement releases chemotactic agents that attract neutrophils and cause inflammation and tissue damage (Marshall et al., 2018; Vaillant et al., 2022).[44]

Type IV – the second most common type – is cell-mediated, antibody-independent and usually take 2 or more days to develop. It is caused by overstimulation of T cells and monocytes/macrophages leading to the release of cytokines that cause inflammation, cell death and tissue damage [e.g., skin response to poison ivy (Marshall et al., 2018)].

[42] Examples include bronchial asthma (Vandervoort, 2018), allergic rhinitis (Shamji et al., 2019), allergic dermatitis (Son et al., 2018), food allergy (Koike et al., 2018), allergic conjunctivitis (Fauquert, 2019), atopic eczema (Dou et al., 2019), drug allergy (Blumenthal et al., 2019), anaphylactic shock (K. Y. Wang et al., 2019).

[43] Examples include immune thrombocytopenia (E. Lee et al., 2019), autoimmune hemolytic anemia (Li et al., 2019), autoimmune neutropenia (Vaillant & Zito, 2022), alloimmune HDFN or erythroblastosis fetalis (Leonard et al., 2019; Nassar & Wehbe, 2022), Goodpasture syndrome (Berends-De Vries et al., 2017; DeVrieze & Hurley, 2022), myasthenia gravis (Jastrzębska et al., 2019), pemphigus (Buonavoglia et al., 2019; M. S. Evans et al., 2019).

[44] Examples include systemic lupus erythematosus (SLE) (Kuhn & Landmann, 2022), serum sickness (Owczarczyk-Saczonek et al., 2019), Arthus reaction (Gershwin, 2018; Ghazavi & Johnston, 2011), reactive arthritis (Cheeti et al., 2022).

3.2. Autoimmunity

Autoimmunity involves the loss of normal immune homeostasis such that the body produces an abnormal response to its own tissue (Marshall et al., 2018). Some antibodies and T lymphocytes direct themselves against the normal components of the body (autoantigens) and for this reason are called autoantibodies and self-reactive T cells (JHU, 2023).[45]

It is hypothesized that autoimmunity results from: (i) an alteration in a body tissue so that it is no longer recognized as "self" and is therefore attacked, or (ii) a failure or disruption of the mechanisms normally responsible for maintaining the self-tolerance of B cells, T cells or both – see (Charles A Janeway et al., 2001). A disruption of the usual control process occurs, whereby these lymphocytes, which are generally suppressed, are capable to bypass suppression and, together with autoantibodies, cause pathological and/or functional damage to the organ/tissue containing the target autoantigen (inflammation) (Marshall et al., 2018). Thus, autoimmune diseases (AiDs) develop, i.e.: chronic conditions characterized by hyperactive immune responses against self (abnormal immune reactions) (Gokuladhas et al., 2021).

The exact mechanisms by which such alterations and abnormalities occur are not fully understood. However, we know that bacteria, viruses, toxins and certain drugs can play a role in triggering an autoimmune process in someone who has a genetic predisposition to develop the disease, and it is assumed that the inflammation induced by these agents somehow causes the body to "sensitize" (autoimmune reaction) in the tissues involved (Autoimmune Association, 2023).

AiDs arise from complex interactions between polygenic[46] and environmental risk factors, so they are generally classified as "complex heterogeneous diseases" factors (Gokuladhas et al., 2021; Marson et al., 2015; Vyse & Todd, 1996).

In addition, they may be classified into: (i) organ-specific and (ii) systemic (or non-organ-specific) (Castro & Gourley, 2010). In the first type the autoimmune process is directed primarily against a particular organ or tissue[47]. In the second type the autoimmune process is widely spread throughout the body, so autoantigens are identified in almost all cell types in the body, and pathological damage involves many different organs and tissues[48].

Inflammation

Poorly regulated inflammatory responses and tissue damage due to inflammation are often immunopathological features (Marshall et al., 2018). Inflammation is a process of normal

[45] Autoantibodies and autoreactive T cells may be present in individuals who have no clinical evidence of autoimmune disease – see new types of immunotherapy-based cancer treatment (JHU, 2023).

[46] Thousands of single nucleotide polymorphisms (SNPs) associated with different AiDs have been identified (Gokuladhas et al., 2021).

[47] Examples include Hashimoto's thyroiditis and Graves' disease (thyroid gland), pernicious anemia (stomach), Addison's disease (adrenal glands), type 1 diabetes mellitus (pancreas) (IDDM), vitiligo (skin), multiple sclerosis (brain, spinal cord, central nervous system), idiopathic thrombocytopenia purpura (platelet), etc.

[48] Examples include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), dermatomyositis, etc.

response to infection and is necessary to rid the body of the pathogen, but, if it becomes uncontrolled, it can lead to chronic inflammatory diseases (e.g., RA, psoriasis, inflammatory bowel disease, asthma, etc.). In the pathogenesis and in the prevention of immunocomplex diseases, the complement works as a mediator, having a protective effect when it works in moderation against pathogens and at the same time promoting inflammation that, if not kept under control, can cause damage.
Important elements in the inflammatory process are the overproduction of inflammatory cytokines (e.g., TNF, IL-1, IL-6) and the recruitment of inflammatory cells (e.g., neutrophils and monocytes) due to chemokines' action. Recruited and activated immune cells produce additional mediators that induce changes in vascular permeability and pain sensitivity (Marshall et al., 2018).

3.3. Immunodeficiency

Immunodeficiency is a state in which the elements of the immune system (lymphocytes, phagocytes, and the complement) are compromised or absent and therefore the immune system fails to fight infectious diseases (Vaillant & Qurie, 2022). It can be specific or non-specific, that is, it can concern B and T cell abnormalities or abnormalities of non-specific components.
Immunodeficiency conditions can be of two types (Marshall et al., 2018; Vaillant & Qurie, 2022):

(v) *Primary*, resulting from a primary, congenital or hereditary, defect that may affect innate or acquired immune function by inhibition of selected immune cells or pathways and is subdivided into varieties that cause:
- *T-cell deficiency*: e.g., hyper-immunoglobulin M syndrome, characterized by high levels of IgM, defects in other immunoglobulins, defects in the gene encoding the CD40 ligand on T lymphocytes, impaired cooperation of B and T lymphocytes in the immune response; the inability of the B cell to interact with CD40 results in the inability of the B cell to switch from IgM production to other classes of antibodies (Yazdani et al., 2019).[49]
- *B-cell deficiency*: e.g., X-linked agammaglobulinemia, due to a mutation in a gene on the X chromosome, causing no B cells and very low levels of or no antibodies (Hernandez-Trujillo et al., 2014).
- *both T-cell and B-cell deficiency:* e.g., severe combined immunodeficiency disease (SCID), characterized by failure of early stem cells to differentiate into T and B lymphocytes, deficiency of the interleukin-2 receptor, defective genes encoding

[49] See also DiGeorge syndrome (or congenital thymic aplasia), interleukin-12 receptor deficiency, and chronic mucocutaneous candidiasis.

ZAP-70, Janus kinase 3, and the genes involved in the DNA recombination of immune cells receptors RAG1 and RAG2 (Chinn & Shearer, 2015).[50]

- *complement deficiency*: e.g., hereditary angioedema – C1 inhibitor deficiency (Kirschfink & Mollnes, 2003).[51]
- *phagocyte deficiency*: e.g., chronic granulomatous disease (CGD), characterized by a defective NADPH that interferes with the intracellular ability of neutrophils to kill engulfed bacteria species.[52]
- *immunoglobulin A deficiency*, that results in a low level of one type of antibody, usually IgA, but levels of other immunoglobulins are normal (Moschese et al., 2019).

(vi) *Secondary*, resulting from a secondary, or acquired cause, such as viral/bacterial infections, malnutrition, autoimmunity, or treatment with immunosuppression-inducing drugs [see e.g., acquired immunodeficiency syndrome (AIDS), caused by the human immunodeficiency virus (HIV), which directly infects helper T cells and indirectly alters other immune system responses (Chinen & Shearer, 2010; Notarangelo, 2010)].

4. Pharmacological considerations

Vaccines are used to prevent diseases caused by pathogenic microbes such as bacteria (i.e., single-celled life forms that can reproduce quickly on their own) or viruses (i.e., ultramicroscopic infectious agents that replicate only inside the cells of living hosts and cannot reproduce on their own).
Different types of vaccines work in different ways to protect the body, but with all kinds of vaccines, the body is left with a supply of memory cells (T and B lymphocytes) that will remember how to fight that virus in the future (CDC, 2021).

4.1. Heterogeneity of vaccines

A vaccine is a biological product that improves immunity to a given disease. Vaccines are a heterogeneous group of biological medicinal products intended for the prevention of communicable and non-communicable infectious diseases, containing selected antigens capable of inducing a specific immune response to pathogens or substances produced by them,

[50] See also Wiskott-Aldrich syndrome, immunodeficiency with ataxia-telangiectasia, and Major Histocompatibility Complex deficiency.
[51] See also recurrent infections (C3 deficiency, deficiency of membrane attack complex – MAC), and C2 or C4 deficiency secondary to autoimmunity.
[52] See also leukocyte adhesion deficiency syndrome.

which are relevant in the pathogenesis of the disease (WHO, 2013). Each vaccine combination of antigen, adjuvant and excipients is unique (Tavares Da Silva et al., 2015).
Vaccines can be classified according to the antigen used in their preparation; those recommended globally fall into six main types of antigens, as you can see in **Tab.7**:

Live attenuated (LAV)	Tuberculosis (BCG), Oral polio vaccine (OPV), Measles, Rotavirus, Yellow fever, Varicella-zoster virus (VZV), Seasonal influenza (nasal spray)
Inactivated whole-cell (killed antigen)	Whole-cell pertussis (wP), inactivated poliovirus (IPV), Hepatitis A, Seasonal influenza (injectable), COVID-19 vaccines.
Subunit (purified antigen)	Protein based: Acellular pertussis (aP), Hepatitis B; Human papillomavirus (HPV); Polysaccaride based: Meningococcal and Pneumococcal polysaccharide vaccines; Conjugate: Haemophilus influenzae type b (Hib), Pneumococcal (PCV-7, PCV-10, PCV-13), Meningococcal A.
Toxoid (inactivated toxins)	• Tetanus toxoid (TT), Diphteria toxoid (DT and Td).
Viral vector vaccine	• Zaire Ebola virus (rVSV-ZEBOV).
Nucleic acid vaccine	• RNA vaccines, DNA vaccines, COVID-19 vaccines.

Table 7*: Vaccines classification.*

Live Attenuated Vaccines (LAVs)

Many vaccines are made from the virus itself, weakened or killed, which causes antibodies to bind to and kill a live virus. Available since 1950, Live Attenuated Vaccines (LAVs) are antigenic preparations of attenuated pathogenic agents (bacteria or viruses). They contain pathogens modified to be of greatly reduced, disease-free or very mild virulence, which stimulate an excellent strong and long-lasting immune response in just 1 or 2 doses (they may not be suitable for those who are immunocompromised) (Physiopedia, 2022). Live microorganisms provide continuous antigenic stimulation, giving sufficient time for memory cell production (A. J. Pollard & Bijker, 2021). In the case of viruses or intracellular microorganisms in which cell-mediated immunity is usually desired, attenuated pathogens can replicate within host cells.
The fact that LAVs contains living organisms raises some safety and stability issues.

Inactivated Whole-Cell Vaccines (Killed Antigen)

Inactivated whole cell vaccines consist of microorganisms (e.g., viruses, bacteria, other) that have been killed through physical (heat or radiation) or chemical processes. They are considered more stable than LAVs and the fact that they do not contain live components makes them free of the risk of inducing the disease against which they are administered. However, usually the protection they provide is not as strong as live vaccines. They may not always induce an immune response, and the response may not be long-lasting, so they may require several doses over time (Physiopedia, 2022; A. J. Pollard & Bijker, 2021).

Subunit Vaccines (Purified Antigen)

Subunit vaccines are safer and more stable than LAVs, and, like inactivated whole cell vaccines, do not contain live components of the pathogen, but differ from them in that they contain only the antigenic parts of the pathogen, which are necessary to elicit a protective immune response. Rather than introducing a whole cell (inactivated/attenuated) vaccine into an immune system, a fragment of the pathogen (e.g., its protein, sugar, or casing around the antigen) is introduced to elicit an appropriate immune response (Physiopedia, 2022). The subunit used must be chosen carefully because not all components of a pathogen represent beneficial immunological targets (Merriam-Webster, 2022). The antigenic properties of the various potential subunits of a pathogen must be examined in detail to determine which combinations will produce an effective immune response within the correct pathway, but there is no guarantee that immunological memory will form correctly.

This type of vaccine gives a strong immune response, can be administered to anyone who needs it and may require boosters for continued protection (A. J. Pollard & Bijker, 2021). Just like the previous ones, since they do not contain live components, they are considered safe.

Within this category it is possible to distinguish *protein-based vaccines*, *polysaccharides*, and *conjugates vaccines*.

Protein-based vaccines present an antigen to the immune system without viral particles, using a specific, isolated protein of the pathogen. Some examples include acellular pertussis (aP) vaccines and hepatitis B (HepB) vaccines. The former contains inactivated pertussis toxin (protein) and may contain one or more other bacterial components – the pertussis toxin is detoxified by treatment with a chemical substance or using molecular genetic techniques. The latter are composed of the hepatitis B virus surface antigen, or HBsAg, which is a protein produced by the hepatitis B virus. Recombinant technology is used that produces HBsAg without requiring purified human plasma from infected individuals, which increases the vaccines' safety by excluding the risk of potential contamination of human plasma [an example are human papillomavirus vaccines (HPV), which consist of recombinant viral vaccine proteins containing highly purified virus-like particles]. However, the potential risk is that the isolated proteins, if denatured, can bind to antibodies other than the pathogen protein (Physiopedia, 2022; A. J. Pollard & Bijker, 2021). Among the COVID-19 vaccines[53] approved or authorized for use there are protein-based subunit vaccines (Novavax), that contain the spike protein of the SARS-CoV-2 virus (CDC, 2021).

Polysaccharide vaccines create a response against molecules in the pathogen capsule, which are small and often not very immunogenic. Some bacteria are protected by a polysaccharide capsule, which helps them evade human defense systems when infecting. They tend not to be effective in infants and young children (under 18-24 months), and to induce only short-term immunity (e.g., a slow immune response, a slow increase in antibody levels, no immune memory) (Physiopedia, 2022; A. J. Pollard & Bijker, 2021).

[53] The following COVID-19 vaccines have been granted conditional marketing authorisation for use in the EU: Comirnaty (by BioNTech and Pfizer), Spikevax (by Moderna Biotech Spain SL), Vaxzevria (by AstraZeneca AB), COVID-19 Vaccine Janssen (by Janssen-Cilag International NV), Nuvaxovid (by Novavax CZ) (ECDC, 2022b).

Conjugate subunit vaccines, such as polysaccharide vaccines, create a response against molecules in the pathogenic capsule, but, unlike them, benefit from a technology that binds the polysaccharide to a carrier protein that can induce a long-term protective response, even in infants. Therefore, they may prevent bacterial infections for which polysaccharide vaccines are ineffective in those most at risk (infants) or provide only short-term protection. Moreover, they are considered safe since there are no known adverse reactions associated with them (Physiopedia, 2022; A. J. Pollard & Bijker, 2021).

Toxoid vaccines

Toxoid vaccines use the toxin produced by some bacteria, that is rendered harmless in the form of a toxoid, as an antigen to elicit an immune response targeted not at the bacterium but at the toxin (largely responsible for the symptoms of the disease). To increase the immune response, the toxoid is adsorbed to aluminum or calcium salts, which act as adjuvants, and it is possible that boosters are needed for a continuous immune protection (Merriam-Webster, 2022).
These vaccines are stable, as they are less susceptible to changes in temperature, humidity, and light. They are not highly immunogenic and can trigger very rare local and systemic reactions. They are considered safe because: (i) they cannot cause the disease they prevent, (ii) there is no possibility of reversion to virulence, and (iii) vaccine antigens are not actively multiplying and do not spread to unimmunized individuals (Physiopedia, 2022; A. J. Pollard & Bijker, 2021). [54]

Viral vector vaccines

Viral vector vaccines represent a relatively new technology. They use a modified version of a different virus as a vector to provide instructions to cells to stimulate an immune response; they deliver one or more pathogen genes encoding a target antigen with an unrelated engineered virus (e.g., adenovirus) (Physiopedia, 2022). When administered, genes are expressed in host cells and stimulated to generate the pathogenic-specific antigen that is exposed to the immune system to stimulate an antibody and cell-mediated immune response.
Studies have focused on viral vector vaccines against diseases such as Zika, influenza and HIV. Viral vector vaccines were used against Ebola and SARS-CoV-2 viruses[55]. They have also been studied for gene therapy, cancer treatment and molecular biology research (CDC, 2021).

[54] Tetanus toxoid vaccine should be inoculated to all women of childbearing potential, both during pregnancy and outside it, to protect themselves and their newborns (WHO, 2013), and might be recommended for wound management in a pregnant woman if [greater than or equal to] 5 years have elapsed (Merriam-Webster, 2022).
[55] See Oxford-AstraZeneca COVID-19 vaccine which uses a non-replicating viral vector called ChAdOx1, and Johnson & Johnson Janssen COVID-19 Vaccine (CDC, 2022; Mayo Clinic, 2022; A. J. Pollard & Bijker, 2021).

Nucleic acid vaccines

Nucleic acid (DNA or RNA) vaccines are preparations that use the genetic material [e.g., a strand of synthesized messenger RNA (mRNA)] of a disease-causing virus/bacterium to stimulate an immune response.
mRNA vaccines use mRNA inside a lipid membrane created in a laboratory. It enters the cell cytoplasm, translates it into the antigen protein and instruct human tissue cells to produce a pathogen-specific protein (an antigenic substance, e.g., spike protein), which will be recognized by the human immune system as a foreign body, thus triggering an antibody and cell-mediated immune response. The mRNA lasts a few days and then is naturally broken down and removed from the body (Merriam-Webster, 2022; Physiopedia, 2022).
DNA vaccines are currently in development, while mRNA technique has been studied for influenza, Zika, rabies and cytomegalovirus (CMV), and in the field of cancer research to trigger the immune system to target specific cancer cells (CDC, 2021). Several mRNA vaccines have been used for the prevention of COVID-19 as part of the WHO Emergency Use Listing (EUL) procedure[56] (CDC, 2022a; Mayo Clinic, 2022; Pollard & Bijker, 2021).
There is a debate in considering mRNA vaccines as conventional vaccines because of pharmacological differences. If mRNA vaccines were like conventional vaccines, after intramuscular injection most of the dose should remain in the muscle and the rest should drain through the lymphatic system, to then be captured by antigen-presenting cells and B cells and finally be completely eliminated in a few tens of hours at most (Bahl et al., 2017; Lindsay et al., 2019). These products should not show any relevant systemic disposition. Moreover, the resulting pathogen-specific protein (e.g., spike protein) is expected to remain attached to the surface of cells and not be released into the blood and tissues to meet ACE2[57] receptors with the possibility of causing organ damage (Cosentino et al., 2022).
However, some studies have shown and discussed the opposite (Appelbaum et al., 2022; Baumeier et al., 2022; Cosentino & Marino, 2022; Magen et al., 2022; Ogata et al., 2022; Patterson et al., 2022; Röltgen et al., 2022; Trougakos et al., 2022; Yamamoto et al., 2022). There is a possible link between inappropriate S protein expression in susceptible tissues and subsequent tissue damage, whereby COVID-19-mRNA-vaccine-induced S protein appears to play a role in AEFIs (Cosentino et al., 2022). One of the explanations of AEFIs could be that mRNA vaccines induce excessive production of protein S in certain individuals, for too long and/or in wrong tissues and organs, and this event is currently unpredictable, since systemic biodistribution and disposition of the COVID-19 mRNA vaccine have never been studied so far (Cosentino et al., 2022).
Moreover, it must be said that conventional vaccines contain antigens, which represent their active component and exert their effect by acting on endogenous targets (the immune system

[56] See Spikevax COVID-19 Vaccine by Moderna Biotech and Comirnaty COVID-19 Vaccine by Pfizer-BioNTech (CDC, 2022a; Mayo Clinic, 2022; Pollard & Bijker, 2021).
[57] Angiotensin-Converting Enzyme 2 is a peptidase existing both in soluble and membrane-bound forms that metabolizes angiotensin II vasoconstrictor in angiotensin vasodilator (1-7). If it is in membrane-bound form it is expressed in many organs including the gastrointestinal tract, kidney and heart.

cells), while mRNA vaccines do not contain antigens but the mRNA molecule, which is not able to trigger anti-virus immune responses unless is translated by endogenous cellular metabolism into an active portion (Cosentino et al., 2022). COVID-19 mRNA vaccines, for example, contain active SARS-CoV-2 S protein mRNA which is an active ingredient but also a prodrug[58], that by intracellular translation determines the endogenous production of the viral S protein (Cosentino et al., 2022). Both vaccine-derived SARS-CoV-2 S protein mRNA and the resulting S protein show complex pharmacology and undergo systemic arrangement (Cosentino et al., 2022). Vaccine-induced S protein binds to ACE2 and may act as a possible trigger for platelet aggregation, thrombosis, inflammation, hypertension, and other cardiovascular diseases (Angeli et al., 2021, 2022).

4.2. Monovalent, polyvalent and combination vaccines

Vaccines can be classified according to their composition into monovalent and polyvalent. A monovalent vaccine contains a single strain of a single antigen – e.g., the measles vaccine, hepatitis B vaccine). A polyvalent vaccine contains two or more strains or serotypes of the same antigen – e.g., the oral polio vaccine (OPV) (WHO, 2013).
Combination vaccines consist of two or more antigens in the same preparation, each of them can prevent different diseases or protect against multiple strains of infectious agents that cause the same disease (e.g., DTP vaccine, combining diphtheria-tetanus-pertussis antigens).
There is no evidence that the administration of combined antigens overwhelms the immune system, increasing the risk of adverse reactions, however it is very important that these types of vaccines are thoroughly tested before their use in immunization programs because: (i) adjuvants may reduce the activity of one antigen and excessively increase the reactivity of another antigen; and (ii) there may also be interactions with other components of the vaccine such as buffers, stabilizers, and preservatives (WHO, 2013).

4.3. Vaccines components

Vaccines are mixtures of substances where each component adds a potential risk of an adverse reaction. Vaccines' components include antigens, stabilizers, adjuvants, antibiotics, and preservatives (see **Fig.12**), which may also contain residual by-products from the production process (A. J. Pollard & Bijker, 2021). Adjuvants (e.g., aluminum salts) and conjugated proteins are present in some vaccines to improve immune response to vaccine antigens, most often in

[58]A prodrug is defined as "a pharmacologically inactive substance that is converted in the body (as by enzymatic action) into a pharmacologically active drug" (Merriam-Webster Dictionary, 2022). Prodrugs lack the pharmacological activity of their active parts but may contribute to the overall safety and toxicity profile of the pharmaceutical product, which is why they are usually evaluated in the overall evaluation of the medicine (Cosentino et al., 2022; K. M. Wu & Farrelly, 2007).

killed vaccine. Antibiotics, stabilizers, and preservatives serve to reduce contamination during the production process and maintain their effectiveness during transport and storage (WHO, 2013). Cases of allergy to any of these components may occur (Eldred et al., 2006; Mitkus et al., 2013).
The WHO points out that *"knowing precisely what is in each vaccine can be helpful when investigating AEFI and for choosing alternative products for those who have allergies or have had an AE known or suspected to be related to a vaccine component"* (WHO, 2013).

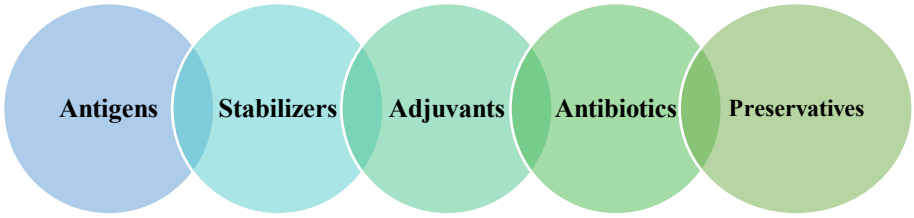

Figure 12*: Vaccines' components.*

Antigens

Antigens are the components derived from the structure of pathogenic organisms, which, recognized as foreign by the immune system, trigger a protective immune response to the vaccine. As we have seen, vaccines are prepared with different types of antigens, using different scientific methods (e.g., attenuation, activation, recombination of DNA technology, etc.) (WHO, 2013).

Stabilizers

Stabilizers are used to keep the vaccine effective after manufacturing during storage. Among them are magnesium chloride MgCl2 (oral polio vaccine), magnesium sulfate MgSO4 (measles), lactose-sorbitol, sorbitol-gelatin, etc.
The stability of vaccines is essential and the factors that influence it are the temperature, acidity, or alkalinity of the vaccine (pH). Hydrolysis and aggregation of protein and carbohydrate molecules can render bacterial vaccines unstable, and instability can cause loss of antigenicity and decreased LAV infectivity (WHO, 2013).

Adjuvants

Adjuvants are a highly heterogeneous group of compounds with one or more mechanisms of action, with in common the ability to increase the body's response to vaccine antigens by stimulating the production of antibodies (Tavares Da Silva et al., 2015; WHO, 2013). However, only a few adjuvants are used routinely in licensed vaccines (e.g., aluminum salts) (A. J. Pollard & Bijker, 2021).

As we previously discussed, after exposure to a pathogen (or vaccine), there is an initial innate immune response that identifies the pathogen and triggers a series of rapid but non-specific pathways that direct the actions of the secondary adaptive response. The pathogen's identification initiates the release of cytokines, complement and chemokines from effector cells, which, together with APCs, are responsible for crosstalk between innate and adaptive immune cells and determine the nature and extent of the adaptive immune response.

An adjuvant interacts primarily with the innate immune response and, by modulating it, can: (i) influence the downstream immune phenotype, improving the quantity and quality of the downstream adaptive immune response, and (ii) contribute to the duration of the immune response to the vaccine antigen, and consequently the efficacy of the vaccine (Coffman et al., 2010; Tavares Da Silva et al., 2015).

Adjuvants are highly variable in terms of how they affect the immune system and how severe the adverse reaction they cause, due to the resulting overactivation of the immune system (WHO, 2013). Among the potential risks of adjuvanted vaccines are severe local and/or systemic reactogenicity, systemic inflammation, and rare AE such as autoimmune disease (Tavares Da Silva et al., 2015). For example, aluminum adjuvant in vaccines can produce chronic neuropathology in genetically susceptible individuals by several mechanisms (Morris et al., 2017).

Understanding the mechanism of action of the adjuvant can provide worthwhile information on its role in the vaccine' safety profile, supporting safety assessment. For instance, the characterization of biochemical and hematological markers can identify relationships between AEs, genetic disposition, and molecular and cellular responses of individual patients (WHO, 2013). The identification of molecular responses and cell populations directly activated by the adjuvant can show whether or not there is a biologically plausible mechanism by which a vaccine/adjuvant could cause a particular AE.

Antibiotics

Antibiotics (e.g., neomycin, kanamycin, streptomycin) are used to prevent bacterial contamination of the tissue culture cells in which the viruses are grown during the manufacturing process. Only traces of antibiotics usually appear in vaccines – e.g., MMR vaccine and IPV each contain less than 25 micrograms of neomycin per dose (less than 0.000025 g) (WHO, 2013).

Preservatives

Preservatives (e.g., thiomersal, formaldehyde, phenol derivatives) are added to multidose vaccines to prevent bacterial and fungal growth. Formaldehyde is used to kill viruses or inactivate toxins during the manufacturing process and is almost all removed in vaccines by purification process. The traces that remain present in the vaccine are several hundred times less than the amount known to harm humans, even infants (WHO, 2013).

Thiomersal is commonly used in vaccines, and since it is a thiosalicylate salt of ethyl mercury (neurotoxic and nephrotoxic), it has been subject to intense safety scrutiny by the Global Advisory Committee on Vaccine Safety. To date there is no evidence of toxicity when exposed to thiomersal in vaccines – the low-level traces that may be present in a vaccine seems to have no impact on the neurological development of newborns (Institute of Medicine (US) Immunization Committee, 2001; NCIRS, 2009; WHO, 2013). Mercury is harmful after reaching a certain level in the body, and there is evidence that mercury exposure in humans is linked to markers of inflammation and autoimmunity (K. M. Pollard et al., 2019).
In people receiving a thiomersal-containing vaccine, minor reactions such as redness and swelling at the injection site may occur. Immune-mediated reactions to mercury-containing compounds are documented (Eneström & Hultman, 1995; Griem & Gleichmann, 1995; K. Pollard & Hultman, 1997), and among the manifestations there are contact allergy (i.e., delayed-type hypersensitivity), and immediate-type hypersensitivity (i.e., allergy).

4.4. Contraindications to vaccines

All vaccines are contraindicated if there is a history of a severe allergic reaction after a previous dose of vaccine or to a component of it. Vaccine antigens and components can cause allergic reactions, that can be local or systemic and can entail mild-to-severe anaphylaxis[59] or anaphylactic like responses (e.g., generalized urticaria, wheezing, breathing difficulties, swelling of the mouth and throat, shock, hypotension, etc.) (WHO, 2013). However, there is a possibility that the event will not be recognized (e.g., death can be attributed to another factor). Stone and colleagues (2019) outline several well-known mechanisms of vaccines hypersensitivity, including IgE-mediated immediate hypersensitivity reactions to vaccines or their excipients. They discuss a novel mechanism of an IgE-mediated adverse reaction to vaccinations that is unique to gelatin-containing vaccines known as galactose-alpha-1,3 galactose or "alpha-gal" hypersensitivity[60]. Moreover, they examine delayed-type hypersensitivity mechanisms and address the issue of vaccine safety in the immunocompromised (McClenathan & Edwards, 2019) – see for a detailed discussion (Stone Jr et al., 2019). This last issue is increasingly important as a growing segment of the population is immunocompromised by drugs or biologics to control their underlying disease processes.
In immunocompromised individuals (e.g., due to HIV/AIDS, congenital immune deficiencies, or drug treatments such as chemotherapy and high-dose steroids), the potential risks of vaccines must be weighed against the benefits, since they may also not respond adequately to the subunit and inactivated vaccination, and LAVs are potentially pathogenic (WHO, 2013). Individuals with compromised immune systems may not be able to eliminate attenuated pathogens in their

[59] A very rare allergic reaction, unexpected and potentially fatal if not treated adequately. Anaphylaxis should be distinguished from fainting and vasovagal syncope, as well as anxiety, which are common harmless AEs.
[60] Gelatin-containing vaccines have been shown to cause immediate-onset anaphylaxis in both adult and pediatric patients with known alpha-gal hypersensitivity (Stone et al., 2017; Stone Jr et al., 2019).

immune response, leading, for example, to prolonged infection – e.g., tuberculosis (BCG) vaccination may result in local lymphadenitis or disseminated infection. In symptomatic HIV/AIDS, LAVs (e.g., measles and yellow fever vaccines) are contraindicated (WHO, 2013). In children with asymptomatic HIV infection routine childhood BCG vaccination should not be given, but other vaccinations are not contraindicated. LAVs are contraindicated both for patients who are undergoing cancer treatment and for patients who have finished cancer treatment for less than six months.

Attenuated agents have the very rare potential to return to a pathogenic form and cause disease in vaccinated people [e.g., the very rare and serious AEs of vaccine-associated paralytic poliomyelitis (VAPP); disease-causing vaccine-derived poliovirus associated with oral polio vaccine (VDPV)]. Problems may arise if LAV is grown in a contaminated tissue culture, so it can be contaminated with other viruses, such as retro viruses with the measles vaccine.

In addition, LAVs may have a greater potential for immunization errors. For example, some are available in freeze-dried or powder form so they must be reconstituted with a specific diluent prior to administration, which carries the potential for programmatic errors if the wrong diluent is used; many require strict attention to the cold chain for the vaccine to be active and are prone to program failure when it is not adhered to.

Another reason of concern regards the use of LAVs during pregnancy. In fact, if administered to pregnant women, in theory, they may be able to cross the placenta and infect the fetus, thus representing a theoretical risk to the fetus. Although there is no evidence of risk in pregnant women from vaccination with attenuated or inactivated viruses or bacterial vaccines (and also with toxoid vaccines), they are generally contraindicated, while seasonal inactivated influenza vaccines are considered safe, and thus are recommended for all pregnant women during flu season.

4.6. How vaccines work

As we previously discussed, when a disease-causing bacterium/virus invades the human body, the immune system recognizes it as foreign, usually detecting specific protein portions of the invading organism, known as antigens.

Vaccines contain a form of the disease-causing agent, i.e., weakened or killed form of the microbe itself, or inactivated version of its toxins or protein from the microbe's surface. Once administered, a vaccine, using a harmless antigen, simulates the first contact with the pathogen by triggering a primary humoral and cellular immune response similar to that caused by natural infection, without causing disease. It presents the antigen to the immune system, allowing it to recognize the antigen as foreign and develop antibodies and memory T lymphocytes against it (CDC, 2021).

To better explain the vaccines' mechanism of action in stimulating the immune response, let's take as an example the case of a conventional vaccine with a protein antigen.

After a vaccine is injected into the muscle, the protein antigen is absorbed by dendritic cells. The latter are activated (via pattern recognition receptors, PRR) by danger signals in the

adjuvant, and are transported to the draining lymph node. Here the major histocompatibility complex (MHC) molecules[61] on the dendritic cell present vaccine protein antigen peptides resulting in activation of T cells (via their TCR receptor). They then drive the development of B cells in the lymph node resulting in maturation of the antibody response to induce different antibody isotypes. Short-lived plasma cells actively secrete antibodies specific to the vaccine protein, leading to the production of a rapid increase in serum antibody levels over the next two weeks (A. J. Pollard & Bijker, 2021). Memory B cells, which mediate immune memory, are produced, and long-lived plasma cells travel to bone marrow niches, continuing to produce antibodies for the next years (A. J. Pollard & Bijker, 2021). When the vaccinated individual is exposed to the antigen again in the future, a much stronger secondary immune response will result, destroying it before it can cause disease. CD8+ memory T cells encounter the pathogen again and proliferate rapidly, and effector CD8+ T cells help eliminate infected cells.
In addition, since the primary immune response is weaker than the secondary response, some vaccines may require two (or more) doses, simulating a subsequent infection and triggering longer-lasting antibodies and stronger response (Ginglen & Doyle, 2022).
A person capacity to respond to a vaccine, its reactogenicity and its safety profile is influenced by several factors including age (Tavares Da Silva et al., 2015). In adjuvanted vaccine antigens enhance the activation of innate immune responses in young people in a way that promotes the T cells help and the development of immune memory (Levy et al., 2004; Wood & Siegrist, 2011), but the magnitude of humoral and cell-mediated immune responses decreases with age (Tavares Da Silva et al., 2015). In the elderly, antibody responses to vaccines are slower and not as strong as those in younger people, and T-cell subpopulations are not very sensitive to vaccines, thus impairing the ability to achieve protective immunity after vaccination (Gruver et al., 2007; Panda et al., 2010).
In addition, pre-existing immunity to a specific antigen may cause lower or greater reactogenicity than re-exposure (Tavares Da Silva et al., 2015). The vaccine's safety profile is also influenced by whether the individual is immunocompromised or has underlying morbidities and/or by his/her physiological state [e.g., during pregnancy the maternal immune system presents alterations [e.g., changes in local (deciduous) and peripheral immune responses) that affect semi-allogeneic fetal tolerance (C. la Rocca et al., 2014)].

5. The complex pathogenesis of AEFIs

A vaccine may cause hyper-inflammatory or autoimmune adverse reactions, acting as a contributory cause (cofactor), together with other contributory causes (cofactors, or risk

[61] They are adaptive immune response proteins.

factors). Hyperinflammatory states or autoinflammatory syndromes, characterized by exaggerated inflammatory response, develop as multifactorial diseases (Gül, 2018; Spadaro et al., 2019). The pathogenesis of autoimmune disease is characterized by a complex interaction between genetic and environmental factors, and immune and hormonal reactions (Colafrancesco et al., 2013).
Regarding AEFIs, the WHO guidelines acknowledge that "*sometimes there are multiple factors that may precipitate the effect (event) or may function as co-factors so the side effect (event) occurs*" (WHO, 2019). This means that most vaccine induced AEFIs are diseases due to complex interactions between many different endogenous and exogenous factors.
In such a complex context, the vaccine, which constitutes one of the several factors involved in the complex pathogenesis of an AEFI, may act as:

a) A *trigger*: an agent that causes an event that would have happened sometime later anyway, and in doing so it can bring out an underlying or pre-existing condition or disease (e.g., an autoimmune condition triggered nonspecifically by the vaccine's immune stimulus). The vaccine may act by unmasking a predisposing condition (making it no longer latent) that would have led to the disease more slowly or would not even appear; both predisposing conditions and the trigger are contributing causes, with different pathogenetic mechanisms, [e.g., vaccine-induced immune thrombocytopenia in some people receiving AstraZeneca, see also (J. Reiss, 2015)].
b) A *catalyst* of a causal mechanism: anticipate the onset of an event, shortening the induction period[62] for other agents.
c) A *preventive cause* by postponing the onset of an event bringing out the induction period for another agent.
d) A *modifier* of the effect acting synergistically, that is, going to interact with several agents involved in biochemical processes causing, for example, an excessive inflammatory response (cytokine storm) that precipitated the event.

Furthermore, it must be noted that in the case of live attenuated vaccines, if, for example, the AEFI can be attributed to the pathogenesis of the attenuated vaccine microorganism and therefore not be distinguishable from the disease against which the vaccine is administered, a causal link is more plausible. In this case the identification of the attenuated vaccine microorganism in the patient's diseased tissues and/or body fluids would add weight to the causality. However, a vaccine adjuvant or excipient, rather than the vaccine's active component, may cause the AEFI by spuriously influencing the specificity of the association between vaccine and AE (WHO, 2001).
In such a context, as Bull (2007) underlines, "*for any individual case report it is rarely possible to know with a high level of certainty whether the event was caused by the product*" (Bull, 2007) or not. This is possible when the reaction is specific to the given vaccine, but an AE is rarely specific of a single medical product. Even in cases where the association of that event to the

[62] This is "*the period between causal action and disease initiation*" (Rothman, 1981), see Chapter IV.

vaccine is already known, we should always consider that each individual is unique and so is each context.

5.1. Complex diseases

When a disease is due to multiple contributing factors present in different combinations (e.g., complex genome-environment interactions) is considered complex and is defined as a disease with multifactorial etiology. Complex (multifactorial) diseases are caused by *"a combination of genetic, environmental, and lifestyle factors, most of which have not yet been identified"* (Craig, 2008). [I will define in more detail the concept of multifactorial disease in Chapter IV]. In 2002 the journal *Science* published a special issue (vol. 296, no. 5568) entirely devoted to the "puzzles of complex diseases". It included articles on the causes of diabetes and systemic lupus erythematosus, and also referred to common diseases by highlighting the challenge of trying to solve the multiple genetic, infectious and lifestyle factors and their interaction in the pathogenesis of these diseases (Bellavite, 2020).[63] Immunological, genetic, viral, drug-induced, and hormonal factors can contribute to the development of autoimmunity, and among them genetic susceptibility and environmental triggers (e.g., infections) play a major role.

5.2. Potential AEFIs induced by vaccine action involving innate immune response

Immediately after inoculation of the foreign material, a local inflammatory reaction is initiated at the injection site, mainly involving phagocytic cells, and leading to the production of cytokines by epithelial, mesenchymal and nerve cells. For example, in the case of aluminum-adjuvanted vaccines, the release of inflammatory cytokines (e.g., IL-1, IL-6, TNF-alpha) occurs a few hours after injection (T. Nakayama, 2016).
At this stage a pathological reaction may occur consisting in an excessive inflammatory reaction. It happens when local inflammatory mediators (i.e., complement, cytokines, chemotactic factors) diffuse and amplify the reaction at the systemic level, leading to general and neurological symptoms in the first hours or days later. It is pathological as it causes negative side effects that exceed those necessary to achieve the protective purposes (Bellavite, 2020). After administration of yellow fever vaccine, for example, there seems to be a strong link between increased cytokine concentration and febrile reactions, lymphadenopathy, and generalized rash (Bae et al., 2008; McKinney et al., 2006; Rock et al., 2004).
When fever exceeds a certain temperature, it is considered disease, i.e., hyperthermia. If the latter is equal to or greater than 39.5 °C is conventionally considered a serious adverse reaction

[63] Other examples of complex diseases may include kidney diseases, allergies, asthma, osteoporosis, connective tissue diseases, multiple sclerosis, scleroderma, coronary heart disease, and many more (Hunter, 2005).

to the vaccine, with the risk of causing convulsions[64], that are generally considered relatively harmless (they do not lead to organic brain damage). However, if hyperthermia and febrile seizures are long-term (Patel & Vidaurre, 2013) there is risk of developing epilepsy (Pujar et al., 2018) and the brain may suffer from inflammation-related disorders[65], respiratory distress and anoxia, which can also occur in patients with cardiovascular diseases (Bellavite, 2020). Only in extreme cases, brain degeneration and/or death can occur (Chungath & Shorvon, 2008; Crandall et al., 2019; Dlouhy et al., 2017; Hefti et al., 2016; Vestergaard et al., 2008).
We must also note that some age groups may be more susceptible to certain AEs, as in the case of the onset of febrile seizures that peaks at 18 months of age (Waruiru & Appleton, 2004). If febrile convulsions occur in these age groups after immunization, it is crucial to distinguish between a potential risk triggered by fever resulting from vaccination and those that occur randomly due to common concomitant infections (Rowhani-Rahbar et al., 2013; Tavares Da Silva et al., 2015).

5.3. Potential AEFIs induced by vaccine action involving adaptive immune response

Following the triggering of the inflammatory state, vaccine's function is the immune system activation through the presentation of the antigen by mononuclear phagocytes to lymphocytes. At this stage, pathological reactions consisting of undesirable responses due to hyper-immunization, autoimmunity, allergy, and harmful infection (the latter in case of live viruses in immunocompromised patients) may occur.
Diseases induced by hyper-immunization following the administration of vaccines are due to sensitivity to one of the vaccine's components and exacerbation of atopic or vasculitis symptoms (Bellavite, 2020) – see also (Barbaud et al., 2013; Watanabe, 2017). An example of documented hyper-immunization reactions concern those that occurred in the Italian population following repeated administration of tetanus vaccine (Gentili et al., 1993). To avoid hyper-immunization, and the associated risks, and the status of pre-existing immunity is unknown, laboratory tests should be carried out to determine the antibody titre and vaccination should be avoided if the antibody titre is high (de La Fuente et al., 2013).
Among AEFIs one of the most worrying is the triggering of autoimmune diseases (Hua et al., 2015). Manifestations of autoimmune diseases after vaccinations are often reported as case reports, case series, and experimental animal models (Ruhrman-Shahar et al., 2017; Shoenfeld et al., 2015). Vaccines have long been suspected of playing a negative role in inducing such diseases (Agmon-Levin, Arango, et al., 2014; Baker et al., 2015; Cerpa-Cruz et al., 2013; Colafrancesco et al., 2014; Guimarães et al., 2015; Haase et al., 2016; Perricone et al., 2013, 2014; Rinaldi et al., 2014; Toussirot & Bereau, 2015; Zafrir et al., 2012), and many mechanisms have been suggested that could cause autoimmunity (Benoist & Mathis, 2001; Fujinami et al.,

[64] See e.g., measles-mumps-rubella (MMR) vaccine (Demicheli et al., 2012; H. G. Lee et al., 2019), MMRV vaccine (Ma et al., 2015), DTP vaccine (Barlow et al., 2001).
[65] cell damage due to excitotoxicity or secretion of oxygen metabolites by microglia.

2006; Salemi et al., 2010; Shoenfeld et al., 2015; Wraith et al., 2003). Examples of confirmed associations between autoimmune disease and vaccinations include:

i. Guillain-Barré syndrome[66] and swine flu vaccine (Eisen & McBryde, 2009; Hurwitz et al., 1981; Juurlink et al., 2006; Langmuir, 1979; Lasky et al., 1998; Lehmann et al., 2010; Olivieri et al., 2021),
ii. immune thrombocytopenia (IT) and MMR vaccination (Beeler et al., 1996; Cines et al., 2009; Jonville-Béra et al., 1996; Miller et al., 2001; Nieminen et al., 1993),
iii. reactive arthritis and hepatitis B (Hassan & Oldham, 1994),
iv. rabies and tetanus toxoid (TTd) vaccination (Aksu et al., 2006),
v. systemic lupus erythematosus (SLE) and other autoimmune diseases and hepatitis B virus (HBV)/human papilloma virus (HPV) (Agmon-Levin et al., 2009) and anti-tetanus vaccinations (Ruhrman-Shahar et al., 2017) – see also (Bragazzi et al., 2017; B. Wang et al., 2017),
vi. dermatomyositis, type 1 diabetes mellitus and anti-phospholipid syndrome and anti-tetanus vaccination (CDC, 2010; Meyer et al., 2010).

The pathogenesis of these diseases is very complex. If we take for example SLE, it is subject to: (a) environmental factors [e.g., viruses (Segal et al., 2017), bacteria (Qiu et al., 2019), drugs (Szczech et al., 2017)], (b) genetic susceptibility [e.g., HLA polymorphism (Molineros et al., 2019; D. Santoro et al., 2010)], and (c) hormonal factors [SLE has indeed a significant prevalence in the female gender (Nusbaum et al., 2020)].
The vaccine adjuvants may increase the risk of triggering autoimmune AEs, by increasing the immunogenicity of the injected antigens (Bellavite, 2020) – see (Cerpa-Cruz et al., 2013).
Assessing the AEFI's link with autoimmune disease is difficult due to complex innate and adaptive immune responses to vaccine components that may contribute to reactogenic responses (McGarvey et al., 2014). Autoimmune diseases can be induced by vaccines components through a number of mechanisms and can be classified as (Ruhrman-Shahar et al., 2017):

a. antigen-related (molecular mimicry) or nonspecific (bystander activation) (Perricone et al., 2013);
b. adjuvant-related autoimmune/inflammatory syndrome, ASIA syndrome (Shoenfeld & Agmon-Levin, 2011);
c. preservatives (or other components) related, allergic reaction/overdose (Petrovsky & Aguilar, 2004).

Vaccine antigens can trigger both immunity against microbial antigens and autoimmunity if there is similarity between antigen protein sequences and protein sequences of body

[66] Disease in which the immune system mistakenly attacks a part of the peripheral nervous system but can also affect the central nervous system and respiratory muscles.

components or Human Leukocyte Antigen (HLA) receptors (i.e., molecular mimicry) (Colafrancesco et al., 2013; Cruz-Tapias et al., 2012; de Martino et al., 2013; Israeli et al., 2012; Rinaldi et al., 2014).
Vaccine-induced autoimmune syndrome appears to be associated with genetic predisposition, e.g., HLA-DRB1/HLA-DRB4, following exposure to additional external factors or endogenous autoimmunity triggers (Shoenfeld & Agmon-Levin, 2011; Watad et al., 2017, 2018).
The presence of aluminum adjuvant can increase local inflammatory responses and immune systemic response (Bellavite, 2020). Adjuvant aluminum particles can last a long time inside cells of the immune and nervous systems (Exley, 2020; Gherardi et al., 2016; Krewski et al., 2007; Maya et al., 2016; Mold et al., 2016; Shardlow et al., 2020; Shaw, Seneff, et al., 2014; Shaw, Li, et al., 2014; Willhite et al., 2014), remaining in lymphoid organs and even entering the brain (Crépeaux et al., 2017; Shaw et al., 2013). For example, the abnormal long-term persistence of vaccine-derived aluminum hydroxide in muscle, i.e., macrophagic myofasciitis (Gherardi et al., 2001; Rigolet et al., 2014)), is characterized by chronic fatigue syndrome (Exley et al., 2009; Santiago et al., 2015), oxidative stress on the blood (Bonnefont-Rousselot et al., 2004), cognitive dysfunction (Passeri et al., 2011; Ragunathan-Thangarajah et al., 2013), hypotonia (H. D. Müller et al., 2009), child motor retardation (Gruis et al., 2006), sensory disturbances, loss of vision and cerebellar signs (Authier et al., 2001), and alterations of cerebral circulation (van der Gucht et al., 2015).
For the possibility of these log-term effects, in the assessment of causality, the time window for autoimmune diseases should be sufficiently large (e.g., not less than 24 months) to not exclude slow-onset cases (Bellavite, 2020).
An example of vaccine's long-term effect may be the effect of the Hemophilus influenzae type b vaccine on the incidence of diabetes. It has been studied and the results showed that immunization from the age of 2 months is associated with an increased risk of diabetes (a potential chronic AE) (Eskola et al., 1990), underlining that vaccine-induced diabetes should not be considered a rare potential AE. In addition to diabetes, the incidence of many other chronic immunological diseases, including asthma, allergies, and immune-mediated cancers, has increased and in some cases may also be linked to immunization (Classen & Classen, 1999).
In extreme situations, non-live vaccines may alter adaptive immune having detrimental non-specific effects on infant health [see, e.g., the association between whole cell diphtheria-tetanus-pertussis (DTwP) vaccine with an increase in all-cause infant mortality (Aaby et al., 2018; J. Higgins et al., 2016)]. Like DTP, BCG and measles-containing vaccines (MCV) may alter T-cell and B-cell immunity (Messina et al., 2019).

5.3.1. Antibody-dependent enhancement (ADE)

Neutralizing antibodies are induced by the mechanism of action of many vaccines and prevent the pathogen entry into cells, avoiding infection. However, sometimes antibodies are unable to prevent cell entry and can increase a virus's ability to enter cells and cause disease to worsen through the antibody-dependent enhancement (ADE) mechanism (Offit, 2021).

When a vaccinated person is subsequently infected with the pathogen against which the vaccine protects, it is not necessarily ADE, but three different scenarios can occur (Offit, 2021):

1. *Mild disease*: the person may experience some mild symptoms, that last only a few (1-3) days (see e.g., many respiratory and gastrointestinal infections like influenza, COVID-19, and rotavirus) – in this case the vaccine worked.
2. *"Breakthrough" disease*: this term is usually used for vaccinated people who become more severely ill, require hospitalization, or experience untoward outcomes, such as complications (e.g., pneumonia) or death – in this case the vaccine may not have worked at all or did not induce high enough levels of immunity to effectively impede infection.
3. *ADE:* the antibodies generated by the vaccine bind to the virus and help it enter cells more easily than it would on its own, thus facilitating the infection of a greater number of cells, often causing more serious illness than if the person had not been vaccinated.

ADE can be caused by a pathogen and sometimes it is the result of vaccination. In this case the vaccine should no longer be used or should only be recommended for those who are not at risk of being affected by ADE. For example, after observing in children who had received a version of the measles vaccine (made by inactivating the measles virus using formaldehyde) the manifestation of measles infection with the development of high fever, unusual rashes and an atypical form of pneumonia, the vaccine was withdrawn from use. Those who received this version were recommended to be vaccinated again using the live and weakened vaccine against measles (in use today), which does not cause ADE (Offit, 2021). A more recent example of ADE following vaccination comes from dengue virus.[67]
Some have put forward the idea of producing vaccines based solely on unique sequences of pathogens, thus frustrating the potential risk of cross-reactivity in existing vaccine formulations, but this approach hypothesized in the theory has not yet been put into practice (Bragazzi et al., 2019; Kanduc & Shoenfeld, 2016).

5.4. Risk factors in complex AEFIs causation

As far as vaccines are concerned, the multifactorial nature of most AEFIs and the fact that severe reactions affect only a few individuals suggests in most cases vaccines are not the only

[67] In 2016, a vaccine was developed to protect against all four serotypes of the virus, with the hope that, by inducing immune responses to all four serotypes simultaneously, the vaccine could circumvent ADE-related problems following dengue virus disease. After the vaccine's administration to 800,000 children in the Philippines, and the subsequent death of some of them after encountering the dengue virus, it was hypothesized that the children had developed antibody responses that were unable to neutralize the natural virus circulating in the community. So the vaccine was recommended only for children over 9 years of age who had already been exposed to the virus (Offit, 2021).

cause of the event and further factors are necessary in the development of pathology. In general, we can distinguish:

(i) *patient-related* risk factors:
   - those that the patient *can* influence, e.g., dietary habits, alcohol intake, pro-inflammatory foods, smoking, poor or excessive hygiene, psychological status, anxiety, stress, etc.; and
   - those that the patient *cannot* influence, e.g., age, gender, genetic predisposition, immune defenses, comorbidity (coexisting pathologies within the body), intestinal microbiome disorders, liver function or kidney problems, congenital anomalies, inherited underlying disease, preexisting undiagnosed disease, etc.;

(ii) *medicine-related* risk factors: dosage, frequency, type of medicine, excipients, concomitant therapies (intake of more meds), etc.

(iii) *socially-related* dimensions: norms, beliefs and values, relationships (with family, friends and working team), physical environment such as climate, working place, social environment, economic status, etc.

Among them, crucial is the role of the microbiome and genetic susceptibility in the complex mechanisms regulating the innate and adaptive responses to immunization.

5.4.1. The role of intestinal microbiome disorders as a predisposing factor for AEFIs

Maladaptive responses of the microbiome can lead to a wide variety of chronic inflammatory and auto-immune conditions (Gil-Cruz et al., 2019; Relman, 2020). It is known, for example, that allergic diseases and autoimmune encephalitis (Gholizadeh et al., 2019) as well as multiple sclerosis (Camara-Lemarroy et al., 2018) are correlated with alterations in intestinal microbiota, increased intestinal permeability and changes in bile acid metabolism.

The gut microbiome actively affects multiple host functions, including circadian rhythmicity, nutritional responses, metabolism, and immunity (Hacquard et al., 2015; Lynch & Hsiao, 2019; Zheng et al., 2020). It is crucial in the training and development of major components of the host's innate and adaptive immune system. On the other hand, the immune system coordinates the maintenance of key features of host-microbe symbiosis (Zheng et al., 2020).

The interactions between the commensal microbiota and host immunity are complex, dynamic, and context-dependent, influencing immune homeostasis and susceptibility to infectious and inflammatory diseases (Relman, 2020; Zheng et al., 2020). Microbiome-immune interactions are involved in regulation of infection and commensal spread, in many 'non-communicable' gastrointestinal diseases[68] and extra-intestinal disorders[69].

[68] E.g., inflammatory bowel disease (IBD) (Zhang et al., 2017), celiac diseases (Valitutti et al., 2019).

[69] E.g., rheumatic arthritis (Maeda & Takeda, 2019), metabolic syndrome (Belizário et al., 2018), neurodegenerative disorder (Main & Minter, 2017), malignancy (Gopalakrishnan et al., 2018).

However, in most cases the mechanisms of these interactions are still relatively poorly defined, as well as the long-term impact that dysbiosis states of the neonatal period may have on adult immunity and the risk of immune-mediated diseases (Zheng et al., 2020). The intestinal microbiome may not be *the* trigger for disease but may contribute to systemic inflammatory reactions by propagating acute disease or causing it to transition to a chronic inflammatory state (G. C. Brown, 2019; Daulatzai, 2014; Henry et al., 2008; Relman, 2020). In a genetically susceptible host, imbalances in microbiota-immunity interactions in defined environmental settings may contribute to the pathogenesis of a multitude of immune-mediated disorders (Zheng et al., 2020).

In case of increased intestinal permeability (e.g., caused by drugs, dysmicrobism, etc.), bacterial endotoxins that can be released from the gut can interact with immune cells triggering self-reactivity, chronic inflammation, and tissue damage in genetically sensitive individuals (Gershwin, 2018; S. J. Lee & Lee, 2002). The intestinal bacterial flora alters substances that can convert into autoantigens and mistakenly trigger immune responses of the wall itself (Bellavite, 2020) – see the synergy between bacteria lipopolysaccharide (LPS) and inflammatory cytokines in neuroinflammation and neurodegeneration (Brambilla et al., 2013; G. C. Brown, 2019; S. J. Lee & Lee, 2002; Suzumura et al., 2006). Moreover, a breakdown/increase in intestinal barrier permeability and the translocation of commensal bacteria/endotoxins into non-intestinal organs could trigger various autoimmune pathways (G. C. Brown, 2019; Dehner et al., 2019; Henry et al., 2008).

After vaccination, it is possible that an alteration in intestinal microbiome, especially with the loss of endotoxins in the general circulation, increases the susceptibility to a stronger and more severe reaction to the immune stimulus aroused by the vaccine (Bellavite, 2020). Therefore, first, it is important that before administering a vaccine the healthy state of the gut in an individual is verified, and second, in the context of the evaluation of the vaccine-AEFI causal link, it is essential to consider the role of microbiome as a possible susceptibility factor of AEFI.

5.4.2. Genetic susceptibility

One individual may experience a serious adverse effect while another cannot. This is a clear indication of the important role played by the underlying susceptibility factors, which predispose or prepare an individual's complex innate or adaptive system for an overreaction or distorted reaction. As we have discussed above, the intestinal microbiome can be a predisposing factor to the development of an AEFI. In addition to this and other factors, there is an increasingly emerging knowledge of genetic susceptibility to adverse effects (Bellavite, 2020). Some people have pre-existing genetically defined conditions (e.g., congenital immunodeficiency, viral receptor and cytokine variants, epileptic tendencies, defects in detoxification inhibitors and enzymes, etc.), resulting from specific genetic variations (often inherited from a parent) (Whitaker et al., 2015b), which *contribute* to the development of an excessive vaccine reaction (disease) but *do not cause it directly*. If, for example, we consider epileptic seizures, they are genetically complex diseases and are thought to be influenced by

variations in several susceptibility genes (J. Nakayama & Arinami, 2006), including those encoding acute phase cytokines (Nur et al., 2012). The role of predisposition as cofactor in determining vaccine risk (Bellavite, 2020) is demonstrated by the fact that the risk of febrile seizures post-vaccination, for example, is greater in individuals with a prior and familial history of the disease (Gvozdenovic et al., 2018; Vestergaard et al., 2004). For example, it is known that there are two loci involved in MMR-febrile seizure association: the interferon-stimulated gene IFI44L and the CD46 measles virus receptor, which also influence the magnitude of the measles antibody response (Haralambieva et al., 2017). In addition, in case of polymorphisms, for example, the role of mutations in the SCN1A gene it is known by the fact that the risk of post-vaccine seizures is increased in patients with Dravet syndrome – a severe epileptic encephalopathy (Scheffer, 2012; Verbeek et al., 2013, 2015).

Studies show that vaccination is the trigger of the first seizure in about 50% of cases (Auvin et al., 2018). According to others, genetic or structural defects are an underlying cause of the onset of seizures in children after receiving a vaccine, which may act as a trigger[70] (Verbeek et al., 2014).

Interesting is the initiative of some researchers who have created the Ontology of Genetic Susceptibility Factors (OGSF) framework aimed at providing a guide to represent different types of genetic susceptibility factors for vaccine AEs, such as HLA alleles, SNPs, genes and gene haplotypes (He, 2016; Lin & He, 2014; Xie & He, 2017).

5.4.3. Precision medicine in understanding the mechanisms behind AEFIs

The knowledge on the genetic predisposition to certain pathologies has paved the way for predictive or personalized medicine, which analyzes and interprets the DNA of an individual with the aim of knowing his/her genetic susceptibility to developing a certain pathology (Strianese et al., 2020). Such an analysis can assess the risk for a disease to develop. In this way it is possible to implement preventive measures to reduce the risk of the onset and/or severity of the disease or delay its onset.

Many investigative fields in medicine are utilizing precision medicine (F. S. Collins & Varmus, 2015), It is defined as *"an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person"* (UC Davis Health, 2023).

When it comes to AEFIs, vaccinology needs to consider individual variation, understanding the genomics, metabolomics, proteomics, and the microbiome associated with AEFIs (Poland et al., 2013), particularly as more and more vaccines are available to prevent disease and new adjuvants become mainstream (Poland et al., 2013).

Using precision medicine technologies help in more accurately identifying and defining population cohort, through increased understanding and knowledge of the underlying causes

[70] It should be noted that live vaccines can be safely administered to children with Di George syndrome, a congenital T cell defect associated with a deletion in chromosome 22 (deletion 22q11. 2) (Azzari et al., 2005).

and biological pathways of disease (Bilkey et al., 2019). Moreover, it would allow to be more precise on dosages, boosters, and schedules by offering an approach tailored to an individual, while preventing the disease, and thus decreasing the risk of certain adverse reactions to the vaccine in an individual (McClenathan & Edwards, 2019).

In vaccinology, vaccinomics and adversomics study adverse side effects of vaccines, using immunogenomics and systems biology approaches, exploiting the tools of bioinformatics (Hagan & Pulendran, 2018; Haralambieva et al., 2019; McGarvey et al., 2014; Poland et al., 2013; Sharma et al., 2019; Whitaker et al., 2015).

CAP IV

1. Causality

Causality is a fundamental concept in all natural sciences, and medicine makes no exception. Understanding and defining causality has been a topic of debate for philosophers, scientists, academics, jurists and more. Knowing causal relationships is essential for scientific explanations, for predicting, for interventions, and for attribution of liability (J. Reiss, 2015, 2016a). Different levels of analysis address different questions regarding causality (see **Fig**.**13**).

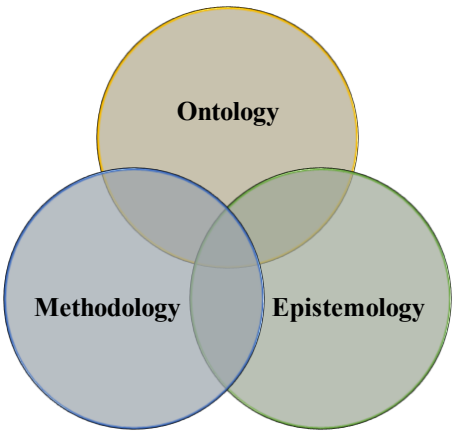

Figure 13: *Causality investigation paradigm.*

Understanding and explaining event causality implies the analysis of how cause and effect can or should be linked. This has been a primary focus of scientific and epistemological discussions over time (Palinkas, 2014; Parascandola & Weed, 2001; Salmon, 1998; Susser, 1973; Zachos & Sparos, 2004). The debates involve both the ontology and epistemology of causation.
The former concerns basic implicit assumptions in science about how the world is (Andersen et al., 2019): What is causation? What are causal relations? How is causation related to laws of nature, probability, action, and freedom of will? (Beebee et al., 2009). The second concerns what we can know about the world (Andersen et al., 2019): How causal claims can be inferred? When are correlation causal? How is causation related to perception, knowledge, and explanation? (Beebee et al., 2009). We need background knowledge and specific information to establish causal relations, but: How much background knowledge? What type of information?
The philosophical literature has identified various concepts of causality. Epistemological and methodological literature is implicitly and/or explicitly based on such concepts. Obviously, a methodology that (implicitly or explicitly) adopts any but not the other concept of causality will inevitably end up by excluding from the set of causal phenomena events and phenomena that do not meet the requirements dictated by the concept of causality underpinning it. Therefore,

from a methodological point of view it is important that the notion of *cause,* which supports causal assessment procedures, is *flexible* and *wide* enough to reliably allow the correct identification of all causal phenomena, and at the same time minimize failures to detect such phenomena when they are present.

In the present discussion, the emphasis on minimizing false negatives in the trade-off with false positives is linked to the fact we are dealing with a process of discovery (risk detection). The focus is on the failure to detect existing but yet unknown phenomena (*latent risk*), rather than on proving a specific hypothesis as in benefit assessment (*hypothesis-testing*). The two contexts, therefore, are asymmetrical epistemic situations (Osimani, 2014a, 2020; Osimani & Mignini, 2015).

A narrow notion of causality will tend to decrease the cases in which the phenomenon is considered causal, so it will tend to increase false and true negatives. *Vice versa*, a *wider* notion of cause will tend to increase false and true positives.

Now, it is clearly more efficient for a detection system not to lose signals whether positives or negatives rather than eliminating false positives. So, the optimization of efficiency for a signal detection system recommends the adoption of *flexible* tools for the identification of such signals.

In our case, this translates into a notion of causality as wide as possible. This might imply that a pluralistic approach may be advisable instead of a monistic one.

A monistic approach is one where the notion of causality is restricted to a set of few necessary/sufficient conditions for causation. A pluralistic approach to causality means that diverse notions of causality may be appropriate (in different contexts). Such an approach increases the probability of a positive causal assessment, with respect to a monistic approach.

In this chapter I will present the ontological and epistemological notions which may be considered useful for the analysis of causal assessment in risk detection context, with a particular focus on the algorithm developed by WHO. The following table (**Tab.8**) illustrates the main dimensions of causation investigated in the ontological *versus* epistemological accounts of causality.

The ontology of causality	**Causation accounts:** - The deterministic regularity concepts of causality *(sufficient cause, necessary cause, necessary and sufficient, component-sufficient)* - Probabilistic concepts of causality - Causality as counterfactual dependence (including cases of redundant causation & the definition of causation as a causal chain) - Mechanistic approach - Dispositionalism **Monocausality vs Multicausality:** - Risk factors - Rothman's multicausal model (including the concepts of *induction period and temporal latency, interactive causes and synergistic interactions)* **Types of causes & Causal relations**
The epistemology of causality	**General vs Singular causality** - *Type-level* causation (general) - *Token-level* causation (singular) - The relationship between general causation & singular causation

	Clinchers vs Vouchers **Evidence Hierarchies vs Evidential pluralism** **Singular causation assessment in the medico-legal field**

Table 8: *The ontological & epistemological philosophical notions useful for the WHO algorithm's analysis.*

In the following section I will begin by addressing the ontological question, then I will deal with the epistemological one.

2. The ontology of causality

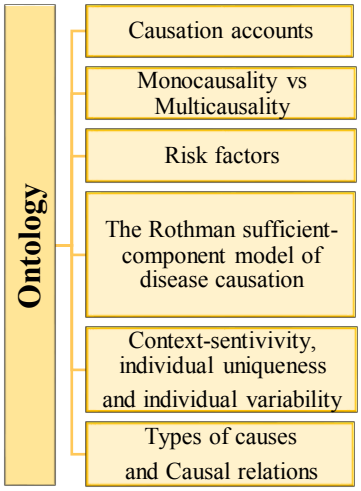

Figure 14: *The ontology of causality.*

2.1. Causation accounts

Each of the major discontinuities of philosophy of science is characterized by a new definition of causality. Asking what *cause* means and what is causality does not find a univocal answer. Many theories of causality have tried to answer this question and have done so differently. We can distinguish the following causation accounts, as relevant for the present discussion:

(i) *regularity theories*,
(ii) *probabilistic dependencies*,
(iii) *counterfactual dependencies*,
(iv) *mechanisms*, and
(v) *dispositionalism*.

These theories support diverse interpretations of causal claims (epistemological issue), thereby playing critical roles in medicine (J. Reiss, 2016a).

2.1.1. The deterministic regularity concepts of causality

Under the regularity view, causality is defined in terms of constant conjunctions of events, and it is possible to distinguish the following concepts of causes: (1) *sufficient*; (2) *necessary*; (3) *necessary and sufficient*; and (4) *component-sufficient* (INUS condition).

Sufficient cause

The concept of causality has been widely discussed as a specific relationship between two events C and E, where one has C because of E if the realization of C is *always* followed by that of E (the outcome *always follows* the cause) (D. A. Hume, 1739). Events are the relata of causal relations and are defined as event-types [i.e., kinds of event that can be instantiated in many places and times (J. Reiss, 2015)]. The causal relation is deterministic: 'C causes E' means that whenever C occurs E occurs. The criteria in the recognition of causes (which constitute a causal law) are (D. A. Hume, 1739):

(i) *contiguity in time and space* between cause C and effect E;
(ii) *temporal precedence* (C precedes E); and
(iii) regularity of the association of cause C and effect E: *constant conjunction* (strong correlation) between cause and effect, where C is cause of E only if C is *sufficient* for E.

A sufficient cause *inevitably* produces an effect. But the occurrence of such effect need not have been produced by it.
Furthermore, most causes are *not invariably* followed by their effects. This is especially valid in so-called "soft-sciences", such as sociology, economics, and medicine. Let's consider, for example, the occurrence of a certain side effect such as an anaphylactic reaction after amoxicillin intake. The drug is a sufficient cause for developing the disease. However, not everyone develops allergic reactions because of amoxicillin exposure. Diseases are complex and some people may have, for example, a genetic susceptibility to the disease, while other not. In addition, another cause Z may alternatively cause effect E, so the presence of E does not imply the prior occurrence of A. Exposure to the drug is one of many different way(s) through which an allergic reaction can occur. Allergic reactions can occur as a result of exposure to other substances such as tree pollen, grasses, mold, insect bites or bites, food, any other medicine.

Necessary cause

According to the regularity theory: (i) the same cause should *always* produce the same effect (at least under the same/similar conditions), and (ii) the same effect *never* occurs 'but from the same cause' (D. Hume, 1739). As Mackie (1965) reports, for a cause C to be *necessary* in the circumstances for the effect E, C *must always*:

(i) precede the effect E, and
(ii) be present if the effect E is present: you will *never* have E if you don't have C.

However, the presence of *C*, does not necessarily imply that *E* will occur. For example, a person must be infected with HIV before s/he can develop AIDS. HIV is a specific cause of AIDS, so HIV exposure is a necessary condition to develop the disease. However, in medicine, we know that there are also HIV-positive people who never develop the disease. The same can be said in the case of malaria or tuberculosis. A person develops malaria or tuberculosis only when exposed to *plasmodium malariae* and *mycobacterium tuberculosis*, respectively. However, not all people who have the parasite in their body develop the disease. The presence of the pathogen is necessary for the disease to occur, but it is not sufficient to trigger the pathological reaction on its own. Other adjuvant causes could be necessary, such as particular processes of the immune system of the individual or precarious hygienic-environmental factors or malnutrition, etc. Therefore, you may need more than just HIV infection for AIDS to occur. The microorganism is one of the many causal factors (or components[71]) that must be present for the disease to occur.
In the assessment of AEs following a pharmaceutical product administration in pharmacovigilance, some adverse health outcomes have causal factors without any component defined as a necessary cause. For example, in the case of fulminant hepatitis, one cannot immediately establish that the event is related to the drug, since other agents, such as hepatitis A or B viruses or cytomegalovirus may be also triggers of this kind of event (Mota & Kuchenbecker, 2017).

Necessary & Sufficient cause

The classical conception of causality assumes that all causes are deterministic. A cause C is both *sufficient and necessary* for the effect E to occur. This means that E will *never* happen without C, and E will *always* happen after C. The cause *always* leads to the outcome, and the

[71] These factors can be endogenous (e.g., a weak immune system is a potential causative factor that would facilitate the life of the plasmodium in the body by making it increasingly aggressive and leading to the development of malaria) or exogenous (climate, hygienic conditions, etc.).

outcome *never* happens without the cause. C is the cause of E if, in a perfectly stable system, any change in A induces a change in B (D. A. Hume, 1739).

cause C ↔ effect E
(Biconditional relationship)

In addition, in such a relationship, we have specificity of the cause (E can only be caused by C) and specificity of the effect (C causes E only).
Crucial limits characterize such conception of causality. These can be illustrated by analyzing the Koch's postulates. In the 19th century Charles Paul de Koch attempted to apply the classic deterministic view of causality to bio phenomena related to a large number of bacterial, viral and deficient diseases (e.g., rabies virus, cholera bacterium, malaria, tuberculosis, HIV, etc.). Such efforts resulted in the so-called Germ Theory of diseases. Koch's postulates state that (Berman, 2019; J. Reiss, 2016a; Verlato, 2022):

(i) The agent must be present in every case of disease (*necessary cause*). It must be found in all the organism suffering from the disease and should not be found in healthy organisms.
(ii) The agent must not appear in combination with any other disease (*specificity of the effect*).
(iii) The isolated agent must induce the disease in a susceptible organism (*sufficient cause*).

The application of these criteria to establish the causal pathogen-disease relationship implies that: the same cause gives the same effect. However, this is not the case. Koch himself, having found asymptomatic carriers of cholera, realized that postulate (iii) was too strong (J. Reiss, 2016a). The virus may be necessary, but it is not sufficient for the disease to develop. More specifically: (a) not all infectious diseases have good animal patterns, (b) some microorganisms that are generally harmless (e.g., Staphylococcus aureus on our skin) can cause certain individuals to develop a pathology under certain conditions. When people are exposed to a pathogen (e.g., the tuberculosis bacillus) they do not necessarily become infected.
To put it briefly, there seem to be many other factors that play a role in determining whether a particular individual becomes infected after being exposed, such as nutritional status or immune status that clearly have an impact for example in "causing" tuberculosis (MPH, 2015). However, all these other determinants are not explained by Koch's postulates.
In clinical practice the kind of situation in which a cause is *both necessary and sufficient* for the effect to occur is very rare [see e.g., the gray baby syndrome following the use of chloramphenicol (Mota & Kuchenbecker, 2017), or some genetic diseases with a specific genotype mutation].[72]

[72] For example, a gene mutation in chromosome 15q23 (HEXA gene) is associated with Tay-Sachs disease. This is a rare autosomal recessive progressive neurodegenerative condition. This disease manifests in early childhood between ages two to ten, due to deficiency of the enzyme hexosaminidase A that causes the accumulation of ganglioside GN2 in the brain) (Demir et al., 2020; Ramani & Sankaran, 2022). Everyone with the mutation will

Causal structures are not one-to-one dependencies but complex networks of dependencies. A theory that considers the multifactorial context and therefore better fits in our picture is the one developed by John Stuart Mill and then advanced by John Mackie. This considers causes in their roles as components of "causal sets".

Component-sufficient cause

In his book "System of Logic" Mill states that when we identify single events as causes, we choose one element from a complex set of conditions (Mill, 1843, 1862, 1956), where each of the members of the set is equally required to produce the effect.
John Stuart Mill points out that in nature there could be multiple reasons (causes) for the same outcome and many event-types are not regularly followed by their effects unless certain conditions are in place. Mill's criteria are the following:

(i) a cause needs helping factors to produce its effects;
(ii) effects can be produced by more than one cluster of causes,
(iii) these clusters (background conditions) may contain absences (e.g., a sedentary life, lack of physical exercise), or standing conditions (e.g., genetic predisposition), as well as positive factors (e.g., cigarette smoking);
(iv) for each effect(-type) there are alternative sets of conditions that can act as causes.

Hence, following Mill causes are neither necessary nor sufficient conditions for their effects to occur. Mackie's account of causes may be considered to follow Mill's approach in that in his account a cause A is *neither necessary nor sufficient* for the effect B (Mackie, 1965), rather it is an event that fulfils the INUS ('Insufficient but Non-redundant part of an Unnecessary but Sufficient') condition: A is an insufficient but necessary component of a minimal condition, which is unnecessary but sufficient for B to take place (Mackie, 1965, 1974). Let's consider, for example, the case of myocardial infarction. There is a multitude of factors participating in the causation of this disease and among them there are: hypertension (A), smoking (B), obesity (C), genetic susceptibility (D), lack of physical exercise (F). An INUS condition may be a combination in which these causal factors are involved: $(ABC)\vee(BDF)\vee(ADF)\Leftrightarrow E$; the effect E can be caused by different causal sets: (ABC) or (ADF) or (BDF) (Osimani, 2020).

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eventually develop Tay-Sachs, and no one without the mutation will ever have it (Ramani & Sankaran, 2022). Similarly, an inherited defect in a single gene (the Huntington's gene) induces Huntington's disease (a rare inherited disease that causes progressive degeneration of nerve cells in the brain), so that no one who has the gene escapes the disease, and no one with the disease does not have the mutated gene. However, in both cases within the time window from the presence in the body of the gene mutation/defect to the pathology's manifestation in the individual, other causal factors may intervene, interfering and preventing the onset of the disease. An extreme situation may be the case in which an individual with a specific genotype mutation dies before the pathology occurs (premature death). Here, the presence of gene mutation remains at the potential level. We can say that the genetic factor may not be sufficient in itself for the development of the disease, whose development depends also on the context.

In the health sciences, a modern version of the regularity view based on Mackie's archetypal is the so-called sufficient-component model formalized by Rothman, which is widely used in epidemiology, and especially for the study of diseases of multifactorial nature. As Zachos and Sparos (2004) underline, the basic difference between Mackie's idea and Rothman's model is that the former refers *directly* to deterministic laws, whereas the latter refers only *indirectly* to those laws. To put it briefly, according to Rothman: (i) the cause is an event that alone, or in conjunction with other events, causes a disease; (ii) the minimal set of components which inevitably causes the disease is 'the sufficient cause'; (iii) each component of such sets is a 'component cause' (Rothman, 1976, 2012a, 2012b; Rothman & Greenland, 2005).

Mackie's INUS conditions theory is considered a major theory of causation suitable for unravelling causes of disease (Osimani, 2020), however, it presents some problematic aspects. First, the theory doesn't distinguish between genuine causes[73] and 'epiphenomena'[74] (Mackie, 1974; J. Reiss, 2015). Second, sometimes, even if a scientist finds a number of factors sufficient for the development of the disease (e.g., a complete knowledge of the patient's habits, family history, and so on), s/he cannot predict *with certainty* whether, for example, a smoker will develop lung cancer, but at the same time, it would not be wise to exclude smoking as a cause just because no such a complete set has been found. As Reiss (2015) points out, in such a situation even if there is no knowledge of the complete set many factors are accepted as *bona fide* causes.

In addition, Mackie's theory is a deterministic approach to the concept of causation. Determinism means here that in 100% of cases when you have a sufficient causal set (say XZY) you have the effect E. This implies exact reproducibility of the event and reduction/absence/explanation of variability[75]. However, there are events whose variability cannot be reduced/explained, i.e.: probabilistic events. In medicine, diseases generally have multiple sets of causes which do not invariably induce a given effect. In some cases, one of the causal factors can play a prominent role, overshadowing other factors and giving the impression of a deterministic event (e.g., germs in infectious diseases, poisons in intoxications, etc.), while in others the disease seems to be more of a probabilistic event (e.g., tumors, autoimmune diseases, etc.). The sufficient-component notion of causation attempts to explain probabilistic events (e.g., smoking as a cause of lung cancer) via unknown component causes (unknown deterministic variables are supposed to be present) (Parascandola & Weed, 2001). However, in such a complex context, a cause may not be an INUS condition, rather it may only increase the

[73] A *genuine cause* obtains on account of a *direct causal relation* of the form: 'X→Y' (a cause is immediately followed by the final event).

[74] These are events that are the result of a common cause. This is the situation of a *causal fork*: a third variable Z causes both X and Y ('Z → X', 'Z → Y'), and Z is a common cause (Reiss, 2015). If we have 'X ← Z → Y', X and Y are correlated but do not have any causal relationship.

[75] In the environment of an experiment, variability can be reduced (sometimes almost to zero) by controlling the experimental conditions. Instead, in case of natural events for which the conditions can be investigated but not controlled, the variability can only be explained (e.g., Newton's theory accurately predicts and explains the orbits of the planets).

probability of its effects (J. Reiss, 2015). Another view of causal laws is indeed offered under the probabilistic account.

2.1.2. Probabilistic concepts of causality

There are several probabilistic theories of causality. However, they all agree on the idea of a probability-changing requirement: a cause is a factor that increases (or changes) the probability of its effect but may be *neither necessary nor sufficient* for its occurrence (Cartwright, 1979; Eells, 1991; Lagiou et al., 2005; Parascandola & Weed, 2001). The probabilistic approach introduces the notion of causality as a *probable conjunction* (Suppes, 1970), abandoning the idea of causality as a constant conjunction.
Suppes (1970) states that (sets of) causes may be not sufficient for their effects but rather they make them *more likely*. The cause *contributes* to some extent to the occurrence of the effect. Given a contributing cause A the probability of the event B is *greater* than the probability of B given not-A. So, eliminating A does not eliminate B, but reduces its probability.
According to many a probabilistic definition of causation is more consistent with scientific and public health goals (Kleinbaum et al., 1991; Kramer, 1988; Parascandola & Weed, 2001; J. Reiss, 2015, 2016a).
A conceptual question may arise from the idea that a cause raises the probability of its effect in a causal homogeneous population[76] (Lagiou et al., 2005), that is: Does a cause increase the probability in *all* causal homogeneous populations, in *some* populations, or on *average*? (Reiss, 2016a). Nancy Cartwright and Eells talk about a very strong requirement, that is: *contextual unanimity*. Only those factors that raise the probability in *all* causal homogenous populations[77] can be considered causes (Cartwright, 1979; Eells, 1991). A slightly weaker version of this requirement states that causal factors raise the probability of the effect in *some* populations but do not lower it in any (Skyrms, 1980). Then, if we investigate biomedical practice, we can say that, if there is, e.g., a gene that makes some people immune to vinyl chloride, then the substance should not be considered carcinogenic even if it increases the probability of cancer for most people (Reiss, 2016a). John Dupré, by doing such kind of considerations, focuses on average probability increases, according to which only those factors that increase the probability of their effects on *average* should be called causes (Dupré, 1984).
Average causal effects are what RCTs establish. However, as Reiss (2016a) underlines, whether a factor can be considered cause depends on the *actual* distribution of factors in a population: a treatment that is effective on average can be harmful to some (J. Reiss, 2016a). If the effect is different, it may mean that either something was different in the cause or in the background conditions, so if two (or more) patients with the same disease get different effects from the same treatment, there must be some *causal relevant difference* between them (E. Rocca & Anjum,

[77] "A population is said to be causally homogenous whenever there is no variation among the causes of an outcome of interest in the population. If sex is a causally relevant factor, a causally homogenous population is one in which every member is a woman or one in which every member is a man, etc." (J. Reiss, 2015).

2020a). Here, the issue concerns the heterogeneity that characterize the various subgroups in the population, and statistical approaches cannot uncover all causally relevant information (Anjum et al., 2020). Hence, epistemologically speaking, the decisions that derives from the recourse to such a notion of cause are misleading for those subpopulations whose members are harmed by the treatment.
Moreover, it is still debated about how to move from the detection of correlation to the affirmation that there is a causal relationship.
The probabilistic notion of causation presents the following problematic and challenging aspects (Campaner, 2009; J. Reiss, 2015):

a) causal relationships are asymmetric (if X is the cause of Y, then Y is not the cause of X), while the statistical ones are symmetric (if P (B | A) > P (B | ~A), then P (A | B) > P (A| ~ B). For example, you are *more likely* to be affected by an allergy in the presence of grass pollination, and pollination is *more likely* to be present if there is allergy, so the relationship of statistical significance is maintained in both directions while the causal relevance goes in only one direction;
b) difficulty in determining whether A is relevant in relation to B and how it is, so determining whether or not it is necessary for the alleged cause to increase the probability of the effect occurring;
c) difficulties in precisely defining the reference class[78] of the analysis.

2.1.3. Causality as counterfactual dependence

According to Lewis, a cause is something that makes a difference, and the difference it makes must be a difference from what would have happened without it (Lewis, 1973b, 1986b). According to the concept of difference-making 'a cause makes a difference to whether its effect obtains: without it, the effect would not have obtained'[79] (Hall, 2004; D. A. Hume, 1739; Kment, 2010; Lewis, 1973a; J. Reiss, 2015). The important role of the causes as difference-makers is attested by the fact that our causal judgments are often guided by counterfactuals (Lewis, 1973b).
C and E are two distinct actual events, where E causally depends on *C* if and only if (Lewis, 1973b, 1986b):

[78] Reference class is "a class of events or objects to which a probability or frequency refers" (Bandolier, 2022). The reference class problem "is usually regarded as one specifically for the frequentist interpretation of probability" and "arises when we want to assign a probability to a proposition (or sentence, or event) X, which may be classified in various ways, yet its probability can change depending on how it is classified" (Hájek, 2007). As Cheng (2009) points out: "statistical inferences depend critically on how people, events, or things are classified. As there is (purportedly) no principle for privileging certain categories over others, statistics become manipulable, undermining the very objectivity and certainty that make statistical evidence valuable and attractive to legal actors" (Cheng, 2009).
[79] On this definition of cause Mill based his method of difference applied in controlled experiments (Mill, 1874, 1956).

(i) if it were the case that C occurs, then it would be the case that E occurs, and
(ii) if it were the case that C does not occur, then it would be the case that E does not occur.

The counterfactual is a conditional in the form: "If it were the case that C, then it would also be the case that E" (C □→ E). In the claim 'event C caused event E', the conditional counterfactual is: 'if C had not happened, E would not have happened' or, probabilistically, 'if C had not happened, E would have had a *lower probability* of happening', where both C and E describe singular (or *token* or actual) causation and where C is its antecedent and E is its consequent (Lewis, 1973a; J. Reiss, 2015).
Lewis indeed aims to model singular causation, *deterministic* in mold and accompanied by a possible world semantics, rather than causal laws (J. Reiss, 2015).
There have been many discussions over time that have questioned the adequacy of Lewis analysis of causality in terms of counterfactuals.
First, there may be several possible ways of interpreting counterfactuals, and among them some can give rise to spurious non-causal dependencies between events (J. Reiss, 2015). Suppose, for example, that events *C* and *E* are effects of a common cause *D*. One is naturally led to the reason that there must be a causal dependence between *C* and *E*, so the counterfactual is:

(i) if *C* had not occurred, then *D* would not have occurred *(backtracking counterfactual)*, and
(ii) if *D* had not occurred, *E* had not occurred.

However, point (i) should not be used in the assessment of causal dependence, as it can lead to counterexamples and erroneous causal judgments. *Not-backtracking counterfactuals* should instead be used.
Second, according to many, when two or more causes compete in their bringing about an effect (so when several alternative events compete to cause and effect) such a counterfactual theory of causation fails because of problems with cases of *redundant causation* (e.g., overdetermination) (C. Hitchcock, 2003, 2013; J. Reiss, 2015). This means that *actual causes* do *not always* make a difference to the effect (i.e., when there is another factor that would have caused the effect had it not been for the functioning of the actual cause). In such a context, Reiss (2015) underlines that factors can be causally relevant to an outcome without being the *true* cause.
Since the reasoning behind this sort of circumstances bears several analogies to causality assessment for AEFIs, I present below the contribution of philosophical literature.

2.1.3.1. Overdetermination

Lewis distinguishes cases of symmetrical overdetermination from cases of preemption. The former are cases in which two processes terminate in the effect, with neither process preempting

the other (Donnan, 2018; J. Reiss, 2015). Let's consider for example a situation in which a patient (P) receives two concurrent medicines, respectively B and C, and then develops a severe adverse health outcome (E). In probabilistic terms, in cases of overdetermination, a cause does not increase the probability of the effect because the effect will happen anyway, so there is *no actual correlation* between the cause and the effect (Donnan, 2018; J. Reiss, 2015; Williamson, 2019).[80] In cases of overdetermination, performing a counterfactual analysis of the type '*but for* A, would B not have occurred?' (i.e., the *but-for-test*[81]) fails to detect genuine causes (Stevens, 2007).
This type of situation may also occur in context of the AEFI's causal analysis, and it is therefore essential to take it properly into account.

2.1.3.2. Preemption & Causation as a causal chain

Counterfactual considerations have been challenged also by cases of preemption. Preemption is sort of opposite to overdetermination. Overdetermination is the case of two or more causes independently able to produce the same effect. Instead, in the case of preemption we have one cause interrupting the course of events which would have led to the effect that it causes being produced by another cause [see also (Andreas & Günther, 2021; Dyrkolbotn, 2017; Hall, 2004; Lewis, 1986a, 1986b)].
For example, let's suppose that there is a terrorist attack and two terrorists from different viewpoints shoot at a politician at short distance. According to standard counterfactual reasoning one cannot say that any of the terrorists is the cause of the death of the politician because the politician would have died from the shoot of the other terrorist (*causal redundancy*).
The case of preemption can be exemplified by a terrorist shooting at the politician and the intervention of a truck passing by, which interrupts the trajectory of the bullet towards a target therefore saving his life. In this case, although the politician is still alive, one cannot say that the terrorist is not liable at least of attempted murder. The fact that the truck interrupted that bullet trajectory does not exempt the terrorist from his responsibility because if the bullet had not been interrupted by the truck, the natural course of the event would have led to the death of the politician. In this case the truck is a preempting cause, that is, something which interrupt the course of the event of another causal phenomenon.
Lewis developed a theory of preemptive causation that allows to justifiably allocate causal responsibility in the face of preemption, by drawing on the notion of causal chain (Lewis, 1986a).

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[80] Even in cases of asymmetrical overdetermination, where you have a major cause (in the sense that it is sufficient by itself to cause the harm) joined by one (or more) minor cause(s) [i.e., cause(s) that is not sufficient to cause the harm, either individually or jointly with the other minor causes] there is *no actual correlation* between the cause and the effect (M. Moore, 2003).
[81] This is the *condicio sine qua non* (c.s.q.n.) theory (the traditional conditionalist theory, also known as the theory of equivalence of causes or natural causality) elaborated by the German criminalist Von Buri and known in the Anglo-Saxon legal systems as *but for test* (Franceschetti, 2017; Rossi, 2000) used for legal liability.

A medical example may illustrate the point. Let's suppose that a person with breast cancer is administered with a vaccine and after three weeks s/he dies of heart failure. By drawing on the theory of preemption one would say that although the person would have died anyway because of cancer still the vaccine is the *actual* cause whereas the cancer is only a *potential* cause of death which has not been recognized because the heart failure produced by the vaccine preempted the neoplasia to further develop and lead to the death of the patient. So, the fatality is entirely inscribable to the vaccine even if the neoplasia could have potentially led to death at a later stage. As we will see in Chapter V the WHO algorithm instead treats *actual* and *potential* cause on a par, and wrongly applies a counterfactual reasoning which absolve the actual cause from its responsibility on the ground of the potential effect that the potential cause would have produced.

As we will propose in Chapter V, a distinction between actual and potential cause in line with the preemptive theory of causation is required in order to properly address this sort of cases.

The distinction between potential and actual cause has been emphasized in the philosophical literature precisely in connection with biological phenomena, such as the analysis of genetic vs other kinds of processes in biology [see e.g., (Waters, 2007; Woodward, 2002, 2004)]. Waters (2007), in particular, insists that in a context where multiple causes are present, such causes are not ontologically the same [i.e., 'the fallacy of parity arguments' (Waters, 2007)], but some causes are *actual difference makers* while others are not (regardless of epistemic context). He stressed an ontological difference between being a cause and being the actual cause: the former only entails that a factor is a potential difference maker, while the latter that it is the actual difference maker (Waters, 2007). Analogously, some causal factors are more salient (triggers) in particular cases than others (background conditions), and as such the former would count as causes.

These epistemological distinctions will reveal to be crucial in addressing the implications of multicausality in individual causality assessment.

2.1.4. Mechanistic approach

The mechanistic approach is strongly linked with *scientific explanation.* There are many different mechanistic theories (see e.g., W. Salmon; S. Glennan; W. Bechtel; R. Richardson; A. Abrahamsen; Fr. Machamer; L. Darden; C. Craver; J. Bogen, and others) focusing on different notion of mechanisms and diverse goals and scopes of causal inference in the sciences. They share a fundamental characteristic that I describe as follows:

(i) a risk factor A is cause of a medical outcome B if, and only if, A *produces* the outcome B by a mechanism of the appropriate kind.

Some mechanistic approaches are specifically aimed at explaining the biological mechanisms of diseases. Among them, for example, W. Bechtel and A. Abrahamsen have turned to the explanation of the functioning of cardiac and cellular metabolism (Bechtel & Abrahamsen,

2005; Bechtel & Richardson, 1993), while Peter Machamer, Lindley Darden and Carl Craver developed the 'dualistic theory' which is used in the field biology and neuroscience (Machamer et al., 2000). The *intrinsic dynamism of mechanisms* is emphasized with the introduction of two notions, that of activity and that of entity (and property of entities). The former is what produces change, while the latter is what is involved in the activities (Machamer, 2004; Machamer et al., 2000). These are the main points: (i) the activities have a primary causal nature; (ii) entities must be appropriately located, structured and oriented, and the activities in which they are involved must have specific rhythm, duration, order; (iii) mechanisms are structured on several levels, hierarchically organized and their interlevel and intra-level characteristics can be analyzed (Campaner, 2006, 2009).

These types of approaches are very important because in medicine understanding a disease means characterizing its symptoms, detecting its possible cause(s), experimentally identifying the *actual cause(s)* and showing the mechanism by which the cause(s) produce the disease.

Mechanistic language is pervasive in the field of biomedical research. Let's think about mechanisms of diseases (e.g., mechanisms of heart failure, cardiovascular disease, migraine, obesity, complications of diabetes, etc.), drugs and treatments/surgical interventions (e.g., deep brain stimulation (DBS), percutaneous coronary intervention, etc.) (Campaner, 2011).

Mechanistic terms are also used to indicate pathologies that remain mysterious. For example, the mechanism of disease is sometimes a label for a pathology that is largely unknown and that researchers are trying to discover, and in many cases, it is the final goal of the investigation, something that needs to be further studied (Campaner, 2011) (e.g. the development of peripartum cardiomyopathy or Paget's disease or the mechanisms linking infertility and congenital malformation).

Moreover, it must be said that not all the mechanisms underlying diseases are known and/or easy to be identified, and if it were, many of them will probably never be fully known or will only be partially known.

The knowledge of causal mechanisms is crucial to understanding causality. Gillies argues that we need mechanistic knowledge not only to establish causal hypotheses about the cause of illness, but also to develop an appropriate treatment and for evaluating the safety of a treatment (Gillies, 2018).

A particularly relevant mechanistic approach to causality for the present discussion is the so-called "*dispositionalism*" (Anjum, 2020). According to *dispositionalism*, the mechanism is a complex and contextual phenomenon and causality is potential (i.e., cause X has a tendency to cause Y). A particular individual or entity has a pre-disposition to determine the event, so there is a *high probability* that *this* cause *produces* the effect. These concepts are particularly useful for the context of individual causality assessment of AEFI since most AEFIs are multifactorial diseases, each individual has specific and different characteristics (dispositions), and vaccines may have the tendency of causing a given AE. In a person with a (genetic or acquired) predisposing factor, this factor may cause the AEFI (e.g., abnormal immune response) with the intervention of the vaccine (a vaccine may trigger autoimmunity).

2.1.5. Causal dispositionalism

Causal dispositionalism understands causes as complex, intrinsic, tendential and context-sensitive phenomena (E. Rocca et al., 2020). According to dispositionalists, since clinical practice deals with the individual patient (who is particular and unique), one should start from the particular and unique situation of the individual case to understand causality (Anjum, 2020). This perspective supports the idea that far from being a problem, heterogeneity and anomalous cases represent an epistemological advantage for causal investigation (Anjum & Rocca, 2020). According to Anjum (2020) causal singularism[82], mutual manifestation[83], and interference[84] must be emphasized.

Causal dispositionalism is an ontological framework with an impact on practice in which causes are defined as dispositions (Anjum, 2020). It was first introduced by Mumford and Anjum (Mumford & Anjum, 2010), who then developed the so-called vector model to model causality in the single case (Mumford & Anjum, 2011).

A disposition refers to a property, what something can do (e.g., 'aspirin has a capacity to (causally) relieve headache') (E. Rocca & Anjum, 2020b). The focus is on the intrinsic causal powers, abilities (Mumford, 1998) or stable capacities [as Cartwright (1989) call them], dispositions, or properties of a thing or of a system, that is, on the causal mechanism, interactions, and dynamics at work – detailed causal understanding of *why* and *how* something might or might not happen is sought (E. Rocca & Anjum, 2020b). More precisely, as Anjum (2020) points out:

(i) A disposition is a type of property[85], that can exist unmanifested (e.g., a substance is toxic even when it is not harming anyone);
(ii) causality usually happens when dispositions manifest themselves (e.g., a fertile woman becomes pregnant, toxic arsenic kills, etc.); thus
(iii) the dispositional property is a cause, and the manifestation is an effect;
(iv) the 'proof' of a disposition's existence in something or someone lies in its manifestation; but there are dispositions that we simply cannot know of until they are manifested, and perhaps not even then (e.g., a person might have early-stage cancer without manifesting any observable symptoms, but the causal process has nevertheless started). Thus, a disposition is not a mere possibility, rather it is a potentiality that comes out into the world as a real possibility in the properties of things (Anjum, 2020).

[82] This is the ontological view that causality happens in the unique particular context (Anjum, 2020), thus suggesting that there might never be two identical causal situations in practice (Anjum et al., 2020).

[83] This means that, for a manifestation to occur, there must always be at least two powers working together to bring it about; they may operate in pairs, interactions of greater adicity are also possible as well as interactions involving more than two powers. In such a context it makes no sense to consider one power as the operational power and the other as the one that simply stimulated or triggered it (Carruth, 2020; Mumford & Anjum, 2011).

[84] For causation there is always the possibility of interference I, which would prevent the effect E. There are two variety of interference that applies to natural causal processes and are subtractive or additive (Mumford & Anjum, 2011).

[85] E.g., fragility, flammability, toxicity, fertility, etc.

All causal processes are intrinsic and specific, and effects occur in the individual as the result of multiple dispositions, many of which are unique to that individual (Anjum, 2020).
Each person has a unique set of dispositions, which affect how we react to medicines, and a manifestation is the result of multiple dispositions working together (E. Rocca, 2020).
Hume and the neo-Humeans (e.g., Lewis, Psillos and Beebee) are skeptical about dispositions, as they believe our knowledge of them is inferred from what we have already observed elsewhere. For example, we think that a particular glass of wine is *actually* fragile, because we have seen other wine glasses break from a very small impact elsewhere (Anjum, 2020). However, dispositionalists argue that dispositions (Anjum, 2020; E. Rocca & Anjum, 2020b):

(i) *are plausibly real* because, even if they are not directly observable, they can explain what actually happens – the principles underlying the behavior of things (e.g., observing in a person that the arteries are clogged with arterial plaques one might see that they are disposed to reduce blood flow and therefore to heart attack and stroke); thus,
(ii) *"could reveal the direction in which the situation is heading: what tends to be"* (Anjum e Mumford 2018a) and have a *degree of tendency*, which can range from very weak to very strong (e.g., something can be more or less toxic, and so on);
(iii) are useful both to make prognoses for illness and recovery, and to make the correct diagnosis (i.e., you must choose the right treatment that aims at the right disposition: headache can be a manifestation of a series of diseases, it can be caused for example by stress or a brain tumor, so the treatment should reflect this difference);
(iv) are *intrinsic* properties that:
    - belong to a particular individual or entity or process (it cannot be said that a drug works if it does not have an intrinsic property to produce its effect), or
    - emerge at the group level, that is: a number of dispositions are present, none of them are intrinsic to the individual, but rather emerge as a result of interactions with others – see also (Anjum & Mumford, 2018; E. Rocca & Anjum, 2020a). For example, if we consider a fertile woman that becomes pregnant, this manifestation is a result of multiple dispositions working together: i.e., manifestation partners for pregnancy (e.g., a fertile man's sperm, the correct balance of hormones in the uterus, etc.);
    - can exist unmanifested and gives its bearer a power, ability, or causal capacity (e.g., a person may have a disposition towards a disease that never manifests itself).

A tendency/disposition that is *statistically weak*, such as, for example, the tendency of oral contraception to produce thrombosis, in some individuals, *could be very strong and in any case*, however it cannot manifest itself alone or in isolation: causal production is a matter of complex interaction of multiple dispositions, many of which are represented by the background conditions (E. Rocca & Anjum, 2020b).
According to dispositionalism, causality is complex, since it requires the interaction of one or more mutual manifestation partners (Anjum, 2020)*:*

i. Mutual manifestation partners are a pair or set of dispositions that working in interaction with each other can produce an effect that otherwise neither they couldn't do on their own.
ii. Each of the manifestation partners are not treated as *the* cause and others as background conditions, rather all contextual factors that contributes to producing the effect are considered causes of the effect in virtue of their own dispositions.
iii. Some of the dispositions might be necessary for the effect, while others might be triggers.

As Rocca et al. (2020) underline, if, for example, we have the hallucinogenic drug N, N-dimethyltryptamine, it is inactive when ingested, but once combined with a trigger (e.g., beta-carbolines) it becomes bioavailable. On a dispositionalist view, both these substances should count as causes of the hallucinogenic effect (E. Rocca et al., 2020) – see also (Waters, 2007).
Furthermore, given that the effect is the result of the complex interaction of different dispositions, the causal process will be highly context-sensitive. As Rocca and Anjum (2020b) points out, *"what a disposition does in one context, together with a certain combination of mutual manifestation partners, will be different from what it does in another combination"*. It is therefore important to understand the causal mechanisms, to know more about the dispositions of the patient who will interact with the treatment, as well as to examine the dispositions of the treatment, since they *"will tell us how the treatment works in the body, but also how the various dispositions of the patient might interact with the treatment"* (E. Rocca & Anjum, 2020b).
In sum, causality is the result of the interaction of multiple dispositions and if we want to establish the causal link between an intervention *I* and an effect *E* in dispositionalist terms, it will mean trying to establish whether *I* has intrinsic properties (or dispositions), which, in combination with others, can possibly produce *E* (Rocca & Anjum, 2020b). I summarized the key features of dispositionalism in **Fig.15** below.

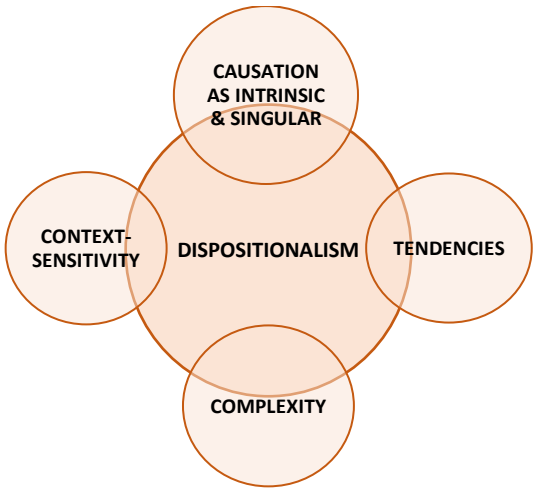

Figure 15*:Key features of dispositionalism.*

In the following section I will describe the vector model, since I think it could be useful if adopted in the WHO algorithm (Mumford & Anjum, 2011). This model represents that causality occurs in the only particular context and is a way to describe the quality of a causal situation (it does not serve to measure and quantify it) (Anjum, 2020). This is exactly the context of analysis in which the WHO algorithm operates.

2.1.5.1. The vector model

In "Dispositions and the Unique Patient", Anjum (2020) describes the vector model that serves to represent the individual patient with his/her chronic condition (e.g., irritable bowel syndrome) – see **Fig.16**. The vertical line represents the current situation, on a quality space between two outcomes: F (e.g., lack of gastrointestinal symptoms) and G (e.g., continuous symptoms); while vectors represent the dispositions that are in place simultaneously and contribute to one of these results (Anjum, 2020). Two important features of dispositions are their *degree of strength* and *direction*.
The length of the vector, as well as the type of disposition represented by it, varies from one individual to another.
In Anjum's system vectors are assigned a qualitative meaning: it does not reflect a numerical/statistical trend of how often the effect occurs in a particular population (Anjum, 2020).

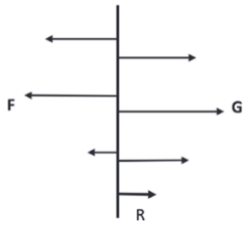

Figure 16: *Vector model. From* (Anjum, 2020)

For example, if the consumption of fatty meals disposes a given patient to gastrointestinal symptoms to a greater extent than the consumption of salt or sugar, this should be reflected in the length of the related vectors.
In addition to the dispositions that induce individuals towards the onset of symptoms (or manifestations), one should also include those dispositions that eliminate the symptoms (e.g., regular exercise or a good night's sleep) (Anjum, 2020). Then, the resulting vector R shows whether the overall trend disposes towards F or G, and how much. The length and direction of the vector should be based on what is the case of a particular individual at a given time (Anjum, 2020). Here, general scientific knowledge can only serve to suggest what causal dispositions might be at play in the case of this particular patient: e.g., we know that the symptoms could be caused by the type of diet, cardiovascular conditions, and so on.

In addition, it must be noted that different dispositions may compose in a simple additive way or may interact in a nonlinear way and produce a *synergistic effect* (i.e., the total effect is greater than the sum of the individual factors), or an *antagonistic effect* (i.e., the total effect is smaller than the sum of the individual factors) (Anjum, 2020)[86].
The vector model allows to illustrate the following features of causality (Anjum, 2020):

(i) *subtractive causal interference*: the effect can be interfered with by removing a vector disposing toward the effect (**Fig.17A);**
(ii) *additive causal interference*: the effect can be interfered with by adding a vector disposing away from the effect (**Fig. 17B);**
(iii) *different degrees of tendency*: a disposition has a tendency towards its manifestation with a certain degree or intensity, so each disposition comes in various strengths (**Fig.17C);**
(iv) *threshold effect(s)/tip-ping point(s)*: it is a stage in the causal process where something conspicuous happens that we might be particularly interested in bringing about or preventing (**Fig. 17D).**

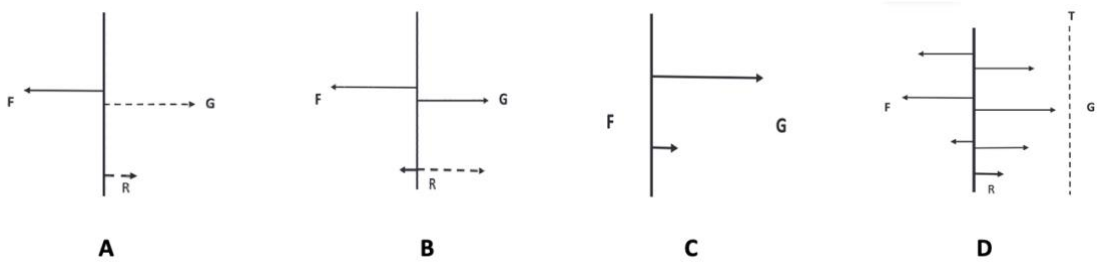

Figure 17: **A** Subtractive interference. **B** Additive interference. **C** Dispositions with different strength of tendency. **D** A threshold effect T. From (Anjum, 2020).

Particularly important for the purposes of the evaluation of AEs manifested in an individual following vaccination, are points (i) and (ii). Let's take again a patient with gastrointestinal symptoms. Such symptoms can be counteracted *subtractively*, by reducing the intake of alcohol, sugar or processed foods, or *additively*, using probiotic supplements to improve the complexity of the intestinal microbiota (Anjum, 2020).
Understanding the dispositions involved and the causal mechanisms by which they interacted to produce (or inhibit) the effect is particularly important to predict whether there are risks associated with the use of a given intervention. Side-effects are often rare, but they indicate dispositions in the patient that were able to causally interact with the medicine (Anjum, 2020)

[86] As Reiss (2016b) reports, these concepts had previously been offered by Mill through the presentation of two models to explain how factors combine, namely: (i) mechanical: *causes combine additively* (the contribution from different factors affecting an outcome simply add up); and (ii) chemical: *causal factors interact*: they combine interactively (J. Reiss, 2016b). The result of their interaction is different from the mere sum of their contributors (it may even be something totally different from the effects that would be expected from each of them: e.g., in pharmacology).

– see also (E. Rocca et al., 2019, 2020). Most medical treatments are cases of additive interference[87]. Causal processes can therefore be counteracted, subtractively or additively, and this means that even when the effect generally results from the cause, it is possible to have the cause along with some interfering agent that prevents the effect from happening (Anjum, 2020).
Regarding point (iii), Anjum (2020) gives the example of a person taking oral contraception, that has a *very strong disposition* to prevent ovulation, but also a *very weak disposition* to produce thrombosis. According to dispositionalism, even if the thrombosis-drug correlation seems very weak statistically, it must count as causality because there is something in the intervention (an intrinsic disposition) that contributes to the outcome (thrombosis), to a stronger or weaker degree in combination with the proper manifestation partners (Anjum, 2020).
Regarding point (iv) Anjum (2020) specifies that the threshold effect could be the point at which a disposition manifests itself (such as the phase during an illness in which a symptom occurs) and adds that the threshold is useful because it can help show if a patient is closer to the threshold of the disease. In this case, *a small change in the cause could result in a big change in the effect*, and the same change might not make a difference to another person who is in a more robust state of health. What triggers a disease is therefore not always the main cause of the disease but could simply be the "straw that broke the camel's back" (Anjum, 2020) (the vector model allows us to illustrate this).
As Edwards (2018) writes, real-life causality is usually multifactorial and complex, and pharmacovigilance concerns data from complex health systems in which multiple interconnected factors evolve, and dispositionalism is applicable to complex data. This approach considers the innate characteristics (dispositions) of the medicinal product [i.e., its various pharmacological actions (pharmacodynamics), its distribution in the body (pharmacokinetics), and its interactions with other drugs] and the exposed patient [i.e., specific susceptibilities (e.g., genetics, age, sex); physiological state (e.g., body weight or pregnancy); co-morbidities, drug-drug interactions; social and environmental factors] (Edwards, 2018).
Hence, as Anjum and Rocca (2020) suggest, dispositionalism should be considered for medicine, public health, and in particular pharmacovigilance. I believe that thinking of causes as dispositions may be of great help in the context of the individual causal analysis of AEFIs, because it can help in reducing the likelihood of false negatives and positives, thus leading to a positive causal assessment.

2.1.6. Towards a pluralistic approach to causation

Each account of causation often diverges on ontological issues (Tooley, 2009) and, as we have seen, is subject to counterexamples and/or limitations and critical aspects. As Williamson points out, such monistic theories of causality present difficulties and inadequacies in explaining the epistemology of causality (Williamson, 2006).

[87] This can be used when subtractive interference is not possible or sufficient to reduce the pathological phenomenon (Anjum, 2020).

Some philosophers have, thus, developed pluralistic notions of causality. Hall (2004) defines causation by combining two types of monistic accounts. Two events can be in a type of causal relationship that can be explained by a difference-making analysis, or they can be in a completely different type of causal relationship that can be explained by means of production (e.g., Salmon's causal process theory, or Glennan's mechanistic theory, etc.) (Hall, 2004).
According to Williamson (2006), an analysis of causality in terms of just one of the indicators of causal relationships *will fail to capture its whole, rather multifarious, notion* (Williamson, 2006). A multifaceted concept that considers the wide range of indicators is needed.
Schaffner points out that it is necessary to trace and intersect the various notions of causality to constitute a valid causal analysis for biology and medicine (Schaffner, 1993). The idea that causal assessment should be based on combination of causality accounts is dominant in contemporary philosophical debate [see (Campaner, 2009; Campaner & Galavotti, 2007; Cartwright, 1999, 2004, 2007a; de Vreese, 2006; Galavotti, 2008; Godfrey-Smith, 2009; C. Hitchcock, 2003, 2007a; Parkkinen et al., 2018; Psillos, 2006; Russo & Williamson, 2007b, 2007a; Stapleton, 2008; Weber, 2007) and others].
In our context a *pluralistic approach* favors the adoption of a wider notion of causality, rather than the adoption of specific monistic definitions. Any method used for the assessment of a causal link that embraces only one concept of cause to establish the existence of a relationship will simply tend to increase both false negatives and positives.
Higher flexibility in what is considered to be causal increases the chance of capturing more phenomena and is therefore more advisable in a context of signal detection, such as the one we are dealing with.

2.2. Monocausality vs Multicausality

Besides the adoption of different notion of causality, one should also consider the fact, especially in medicine, causal phenomena are rarely monocausal (e.g., genetic ones, in particular of chromosomal type). Most of the times, diseases are the result of multiple contributing factors (multicausality). Researchers increasingly consider pathologies in complex '*webs*' of causality (MPH, 2015).
In general, defining a cause-effect relationship is not easy (Kramer & Lane, 1992), even more so in the context of complex systems such as those dealt with by the biomedical sciences, in which living organisms and their possible pathological modifications (diseases) constitute the summit of complexity in nature (Bellavite & Zatti, 1996). While in other sciences (e.g., physics) the laws governing the norm are studied, in medicine, especially in treating the patient, the focus is rather on deviation from the norm (e.g., pathophysiology).
Monocausal theories assume that a disease is motivated by at least a single cause, i.e., *the* cause (Mota & Kuchenbecker, 2017; J. Reiss, 2016a; Verlato, 2022). In this case the disease is defined as 'specific'. One cause is sufficient/necessary to explain the event. In this case we can also speak of a determining cause of the disease (deterministic view), for which the pathology is

defined as mono-factorial. The pathology is therefore generated by a cause capable of provoking by itself all the events that always lead to the appearance of the pathology [e.g., monogenic hereditary diseases (sickle cell anemia, cystic fibrosis, Duchenne muscular dystrophy, etc.), resection of a large vessel that causes hemorrhagic shock or ingestion of a high dose in a single intake of a poison, etc.].

In most of the cases health outcomes (pathologies) are multifactorial. Multicausal theories allow for multiple causal factors to underpin a disease etiology. According to the concept of multifactorial disease etiology, a disease (or pathological event) has more than one cause (multicausality), so much so as to speak of a causal complex or constellation of causes. When the disease is the effect of several causes, it is defined as 'non-specific'. Chronic diseases (e.g., cancers, type 2 diabetes, cardiovascular illnesses, autoimmune diseases, etc.) are considered good examples of 'multifactorial models of disease'. According to this view the causal basis of many diseases is too complex to identify single necessary/sufficient causes (Stegenga, 2018).

The disease is the consequence of a more or less complex interaction of different factors that act simultaneously or in succession on the organism. The disease is the result of interaction and balance between multiple contributing and intermediate factors (Fedak et al., 2015) present in different combinations (e.g., complex genome-environment interactions).

Living systems are characterized by dynamic stability due to a balance of interactions between multiple systems at multiple levels (e.g., gene, protein, pathways, subcellular, cellular, tissue, organs, systems) (Noble, 2002). A deviation from this balance leads to disease. In considering the biology of cancer, Bertolaso and Dupré state that, since different processes are involved in the development and physiological maintenance of the organism, understanding these interactions, the interdependence of processes, helps to unravel the complexity of the biological processes underlying cancer (Bertolaso & Dupré, 2018) – see also (Bertolaso, 2016).

In such a context, the question 'what is *the* cause of the observed pathological phenomenon?' may have no single answer. If causation may be described from the perspective of the distinction between necessary and sufficient cause (Kramer, 1988) p. 256), on the other hand, a cause can also be multifactorial, in which case it is *neither necessary nor sufficient* for a given individual (Palinkas, 2014; Rizzi & Pedersen, 1992; Rothman et al., 2008).

As we have already discussed, in the philosophical literature Mill was the first philosopher to admit and insist on the complexity and the plurality of causes. In his approach, a cause is a set of jointly sufficient conditions required to produce the effect, and there may be several independent causes of the effect so that the effect may be produced by one cause and sometimes by another. For example, coronary heart disease has smoking among its causes, but can also be brought about by a variety of (set of) conditions such as obesity, unhealthy lifestyle habits [e.g., carrying out a sedentary life), the intake of certain pharmacological drugs like Vioxx (Rofecoxib), diabetes, hypercholesterolemia, hypertension, familiarity (genes), and so on].

As we have seen in Chapter III, most AEFIs are multifactorial pathologies (e.g., hypersensitivity reactions, autoimmune diseases). They do not come from a *unique* cause but can be induced by more than one causal mechanism, each possibly involving the presence of multiple causes (or risk factors) of various kinds (exogenous and endogenous) that jointly interact in a complex way (Bellavite et al., 2020; Rothman, 2012b; Rothman & Greenland,

2005). As we will see the WHO algorithm adopts a monocausal view on causation and is therefore inappropriate to adequately address the challenges posed by individual causal assessment of AEFIs.
The concept of multifactorial disease etiology (multicausality) allows to explicitly recognize the different roles of co-causes, or risk factors. Co-causal relationships can be essential for the onset of the disease or aggravate the existing disease by intensifying its manifestations, prolong its course, delay its healing, accelerate its evolution, favor the appearance of complications, or anticipate the unfortunate outcome.

2.2.1. Multiplicity of causes (risk factors) and their possible categorization

Risk factors may be exogenous *(extrinsic factors)* and/or endogenous *(intrinsic factors)*. The latter are internal causes of the system (organisms), such as alterations of the genetic heritage or congenital malformations, while the former are causes external to the system such as:

i. *infectious factors*: viruses, bacteria, protozoa, etc.,
ii. *chemical substances*: taken under medical prescription or voluntarily, substance abuse, exposure to environmental pollution, occupational hazards or chemicals used in agriculture, food industry, etc.,
iii. *physical factors*: radiant energy (ionizing radiation, UV rays), kinetic energy (various traumas), thermal energy (burns, hyper- and hypothermia), electrical energy (discharges electric, electrocution).

In the presence of endogenous factors, originating from the organism, whether physiological or pathological, we speak of endogenous causality, while in presence of exogenous factors (causes), that come from the outside world, we speak of exogenous causality (Little, 2023).
Co-causes can be categorized as *predisposing or adjuvant intrinsic (individual, organic) factors*, and/or *predisposing extrinsic (environmental) factors*, which favor the onset and evolution of a pathology increasing the susceptibility of an organism to get sick (WHO, 2009; Zhou & Rupa, 2018).
Predisposing intrinsic factors are genetic factors: genes that regulate the probability of occurrence of certain diseases in a given individual. This is the so-called genetic susceptibility or hereditary predisposition (familiarity), for which the cause of the disease is not inherited but the risk of developing it is increased with regard to average susceptibility in the population (e.g., autoimmune diseases, inflammatory diseases, allergies, some neoplasms, etc.).
Adjuvant intrinsic factors include age, sex, previous or concomitant diseases, hormone levels like estrogens or glucocorticoids levels (e.g., high levels of cortisol can increase blood pressure, increase blood sugar, downregulate the immune system – T and B –), and so on.
Predisposing extrinsic (environmental) factors can be:

(i) *nutritional conditions*: e.g., protidic-energetic malnutrition and vitamin deficiency with consequent defective immune response/infections, or exaggerated caloric intake/obesity that can lead to hypertension, musculoskeletal diseases;
(ii) *work activity*: e.g., exposure to particular toxic agents may increase the risk of developing certain pathologies;
(iii) *lifestyles/behavioral habits*: e.g., smoking, alcohol consumption, use of illicit substances;
(iv) *sexual habits*: e.g., sexual promiscuity (occasional unprotected intercourse with different partners) increases the risk of infections by particular pathogens, such as HIV, HPV, candida, herpes, gonococcus, treponema, trichomonas.

External factors are causes that contribute to the development of the disease and can be combined with internal genetic features, pathogenic elements and physiological causes into effective causal complexes (Rizzi, 1994).
Vaccines are exogenous factors, where their stimulation of the immune system involves a complex interaction between its components, antigen-presenting cells, lymphocytes, multiple immune mediators (cytokines), and the various processes involved can induce an excessive or distorted inflammatory and immune response, depending on the context.

2.2.2. Context-sensitivity, individual variability & individual uniqueness

Any analysis of causality is strongly dependent on the specific context: causation is highly context sensitive. Context sensitivity means that the effect is the result of the joint interaction of various causes (Osimani, 2020). When it is said that a cause is context-sensitive it means that one cause in one context produces one effect while in another context it may produce another effect depending on the situation.
The concept of context-sensitivity is essential in the clinical setting. Along this line some philosophers emphasize individual uniqueness and phenomenology (Anjum et al., 2020; Broom, 2020; Engebretsen, 2020; Kirkengen, 2020; M. Loughlin et al., 2018). Among the various approaches to the notion of causality that account for multicausal phenomena, dispositionalism is particularly useful in addressing the implications of multicausality in individual causality assessment. According to dispositionalism (Anjum, 2020):

(i) the same disposition might tend to produce different effects;
(ii) the effects are produced not by single but by multiple dispositions, thus
(iii) the same causal intervention does *not always* produce the same effect;
(iv) different contexts will give different effects,
(v) two contexts are never exactly the same.

Therefore, as Anjum (2020) underlines, all patients *differ* from each other in some dispositions, so:

1. each patient will represent a unique set of mutual manifestation partners for a treatment, so a patient will be a different mutual manifestation partner for treatment than another patient;
2. even if the treatment works as expected in both patients (i.e., it has the same disposition in both) the two patients may get different side effects, or the treatment may work with different strength or momentum in each of them; thus,
3. the manifestation of a disposition may be different in different contexts without the disposition of the intervention (i.e., the pharmaceutical product) being different: this is why the same cause does not always have the same effect.

Each individual can be conceived as a unique and complex system consisting of possible combinations of different (risk) factors (or variables) at different levels (e.g., molecular, cellular, organic), which jointly contribute to the effect in presence of the investigated cause (Osimani, 2020), and vary from individual to individual (mutual causality).
We are far from a perfectly stable system, the investigator finds himself having to search for causes by selecting them from a dynamic and continuous train of events (Rizzi, 1994). As Osimani (2020) points out:

> "Human beings are not gas molecules; their reactions to the same treatment may be largely dependent on contingent factors (variation of individual response in different circumstances: intrasubject, or individual variation), and on various systematic mediating and interacting causes. Mediators and moderators may (and generally do) act jointly and at different organ levels (genetic/genomic, proteomic, cellular), and also emerge dynamically within one's own clinical history and social environment. Mediators and moderators may also non-additively contribute to modulating the causal effect through joint interaction" (Osimani, 2020).

Individual uniqueness and individual variability must be emphasized by focusing to the whole patient experiencing the condition (Anjum et al., 2020). In clinical practice there are no two people with the same diagnosis of disease who have exactly the same characteristics. The fact that each patient is unique from a medical point of view (with different genetics, life habits, history, etc.) indicates that it is unlikely that there are ever two identical causal situations in clinical practice. If an AE occurs in one patient which is not statistically supported or which is not observed in other patients, this cannot exclude the possibility of causation in that patient.
From a dispositionalist point of view, causal uniqueness is typical of causality and as such should be the default expectation in any causal assessment (Anjum, 2020). Causal inquiry begins from understanding the complexity of the patient's context, which represents an indispensable source of (causally relevant) medical evidence. His/her uniquenesss, including medical data, condition, and narrative, are fundamental elements to generate causal hypotheses about the complex situation and all the dispositions that influence the medical condition (Anjum & Rocca, 2020).

Context-sensitivity, individual uniqueness, and *individual variability* make individual causation analysis highly complex and characterized by strong uncertainty. When causes are highly context-sensitive, as they are in the context of causality assessment of AEFIs, a plurality of causality methods/accounts is necessary to diagnose causality.
A way to formalize the context-sensitive nature of causation is provided by Mackie and has been formalized by Rothman in his model of multifactorial causation.

2.2.3. The Rothman sufficient-component model of disease causation

The complexity of the pathogenesis of disease(s) is well underlined by the representation of causes in causal networks (or causal complexes or pies), the so-called sufficient-component model of disease causation proposed by Ken Rothman. This is a general model of causation that sheds light on several important principles of causation, also useful for the individual level of analysis (Rothman, 2012). The model is ontologically deterministic in the form of a report of minimal sufficiency and becomes epistemologically probabilistic as we do not know all the factors involved in a causal complex (Rothman & Greenland, 2005).
By embracing the INUS account, Rothman's model allows to uncover causes of an event E by removing from a set of sufficient conditions for E all those conditions not essential to its entailment (Strevens, 2003). According to Rothman:

i. causes are *neither necessary nor sufficient* to produce disease (Rothman & Greenland, 2005);
ii. causes are insufficient components of sufficient causal complexes (Rothman, 1976). [A sufficient cause is not a single factor, but a complete causal mechanism (i.e., a minimal set of factors and circumstances that, if present in a given individual, will "inevitably produce disease")];
iii. each single causal factor belongs to a set of conditions sufficient for the occurrence of the pathology and neither of them is cause of the relevant effect, though their combination is a cause;
iv. multiple contributing causal factors may act together (*'act in concert'*) to produce a health outcome, so that without each component in place the disease would not have occurred *at that specific time* (Rothman & Greenland, 2005);
v. different individuals will have different sets of individual components that combine to produce a sufficient cause (MPH, 2015).
vi. we can remove a cause C from any number of different conditions sufficient for E and check if E still occurs.

In the graphical representation of the model (see **Fig.18**), each causal pie represents a causal mechanism for a given disease – a set of *interacting causal components* (Rothman & Greenland, 2005). There are multiple mechanisms that cause any type of disease. In the three below, the disease (the coronary artery disease) may result from a variety of different 'sufficient causes'.

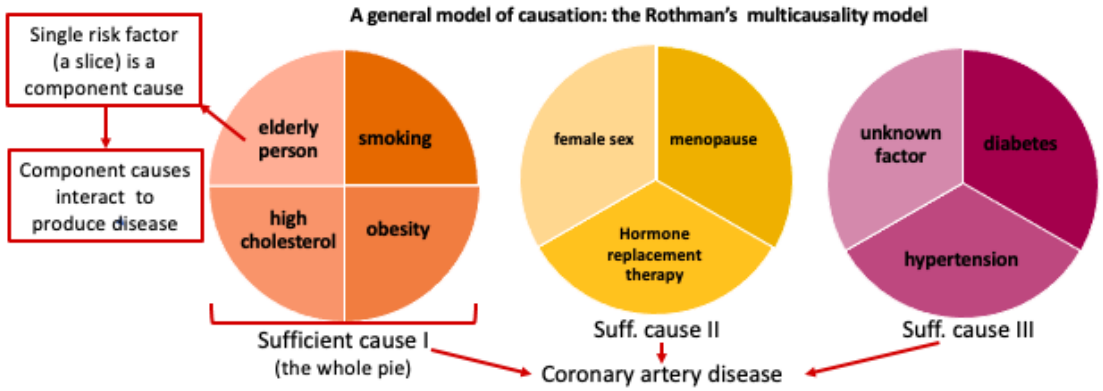

Figure 18*: An example of a general model of causation: the Rothman's multicausality model.*

Each individual case of disease occurs through a single mechanism (or sufficient cause). A given causal mechanism (the whole pie) requires the *joint interacting action of many component factors* (each slice of the pie). Each component cause is an event or a condition that plays a necessary role in the occurrence of some cases of a given disease. For example, in the first pie chart in **Fig.18**, we have the risk factor 'smoking' together with other risk factors including old age, obesity and hypercholesterolemia, where all of them play a causal role in coronary artery disease. Some component causes may act in many different causal mechanisms. According to the first pie the presence of the four component causes is sufficient to produce coronary artery disease in the given individual. If any one of these components were absent, coronary artery disease would not occur. However, the *sufficient cause I* is only one way in which coronary artery disease could occur – *"Different individuals will have different sets of individual components that combine to produce a sufficient cause"* (MPH, 2015). The *sufficient cause I* is one possible cause, and there may be many other sufficient sets for coronary artery disease (see for instance *pie II* and *III*). Some components might be shared among different sufficient causes. Suppose, for example, that the *sufficient causes II* and *III* both contain female sex: this would mean that women are at an even increased risk of coronary artery disease. If a given component is present in all sets, this implies that it is a necessary condition for effect to occur.

The multicausal model developed by Rothman can be very useful for individual causal analysis of AEFI as it underlines the complexity of disease pathogenesis and allows to develop multiple causal hypotheses on the causality of the disease.

If we apply Rothman's model to the context of the WHO algorithm, we may have, for example, the following case: a person (i) receives vaccine X, (ii) manifests AEFI after a plausible time interval, (iii) has a pre-existing disease and (iv) had not had a negative health outcome up to that point. The AEFI may have been a coincidental event (Stephan et al., 2020) or there must have been a causal component (or causal factor) alone insufficient but necessary for the event to occur in that specific individual in that specific moment. The fact that the causal factor is defined as *insufficient* means that other component causes must interact with it to produce the disease and that blocking any of them could result in prevention of some cases of the disease (Rothman & Greenland, 2005). The fact that a causal component is identified as *necessary*

means that it plays a necessary role in the occurrence of the AE in that specific case (obviously it is not necessary in an absolute sense as that same event could have occurred also due to other causes and at a different time). At the level of individual causality, however, it is not possible to identify the necessary cause that explains the occurrence of a single case of the disease, but the idea of being able to identify a non-redundant component in the network of causes that caused the AE makes sense. In an individual, more than one causal complex could be hypothesized to explain the event by combining in a different way all the identified causal factors and considering the unknown ones that may have contributed. The idea of the multiplicity of causal networks or causal complexes implies that while a disease is well defined from a clinical point of view (e.g., lung cancer), the causative agents are classified according to a polythetic classification: e.g., lung cancer cases are not all characterized by the same factors but have in common a partial overlap of causes.
In addition, the sufficient component model allows to consider the following notions, useful in the specific context of an individual AEFI causal analysis: *induction period, temporal latency* and *catalyst and preventive causes* (Rothman et al., 2008).

2.2.3.1. Induction period, Temporal latency & Catalyst and Preventive causes

The *induction period* is *"the period between causal action and disease initiation"* (Rothman, 1981). If we consider the example of a person who is born with a genetic predisposition (causal component factor A) to lung cancer, the risk of lung cancer can be influenced by many component factors. At the age of 20 the disease has not yet manifested itself, but the person begins to smoke (B) and is exposed to air pollution (C) (MPH, 2015). At the age of 50 mutations appear (D). Once A, B, C and D have all turned up, the disease initiates. The induction period for A is 50 years, while the induction period for B and C is 30 years, for D is 0 years. Disease is inevitable once a causal mechanism is complete, but may not be immediately manifest, because (MPH, 2015):

i. it may take time to become manifest: *temporal latency* (the time between disease initiation and disease manifestation/detection) (Rothman, 1981),
ii. it might be fortuitously cured before becoming manifest,
iii. death from other causes might intervene.

Some agents may have a causal action able to shorten the induction time of other agents and other agents may be able to postpone the onset of an event bringing out the induction period for another agent (catalyst and preventive cause respectively). Let's assume, for example, that exposure to factor A leads to event E after an average interval of 8 years, and exposure to medicine B may reduce this interval to 2 years. According to Rothman, it is not sufficient to argue that E would have occurred anyway, and therefore that B is not a cause of its manifestation. Since the time of the event is part of the definition of an event, we may argue that E would not have occurred at that time. This is the reason why *"we consider any agent that*

acts as a catalyst of a causal mechanism, shortening the induction period for other agents, as a cause" and *"any agent that postpones the onset of an event, bringing out the induction period for another agent, a preventive causal factor"* (Rothman, 2012).
Rothman's model is just one way to consider the multiplicity of factors involved in the development of a health outcome [other ways include counterfactual models and directed acyclic graphs (Alexander et al., 2015)]. However, as we will see in the next chapter, because of its usefulness in unravelling causes of disease (multicausality analysis), its ability in highlighting interacting causality, catalyst and preventive causes, induction period, and temporal latency, it is particularly adequate to analyze causality assessment of AEFIs in individuals.

3.3. Types of causes and Causal relations

In the case of the individual causal assessment of AEFIs, in addition to the aforementioned issues (multicausality, Rothman's model), it is important to consider also different types of causal influence that the WHO algorithm takes into account only in some steps of the procedure in a rather arbitrary way. For example, the contributing role of preexisting pathologies is considered as a reason to exclude the responsibility of vaccines in causing AEFIs in the first step of the algorithm. If someone affected by thrombophilia is hit by venous thrombosis after immunization, the preexisting pathology allows the exclusion of the vaccine responsibility in causing the thrombosis and the algorithm stops here.
Other types of causal influence not adequately taken into account by the WHO algorithm are contributory cause, indirect, mediating, modifying, moderating cause(s), hasteners and delayers. In the following I elaborate on this.

Contributory cause (CC): partial cause

The definition of contributory cause (CC) stems directly from multicausal approaches to causality. If effects are the result of multiple causes, then each of them may be considered to contribute to the outcome, without necessarily determining it. When neither of the causes is sufficient to bring about the effect, then each of them is considered a CC.
According to this definition, a cause that contributes to the production of the effect is *partly* responsible for the effect, and in turn the effect is *partly* dependent on this cause. CC is indeed a *partial cause* (Scheffler, 2003), and as such it merely raises the probability of the effect.
The notion of CC is particularly important in our context, since it is indispensable in distributing responsibility of harm after vaccination, among different possible contributing factors.
Considering multicausality a cause X may not be a necessary nor a sufficient condition for an effect Y (Mackie, 1965), but it contributes in some way to the effect. Here the definition of a contributory cause (CC). A cause is CC when it is not sufficient to bring about the event Y,

since other causes are also needed for the effect to occur, but it helps in some way to bring it about. If CC was sufficient, the other causes would not count as causes.
In contrast to this concept is the notion of *full cause*, which is the sum of all partial causes. A full cause is the conjunction of all possible causal complexes for the effect (Mackie, 1965). In practice it concerns all the possible explanatory hypotheses for the event, each including different combinations of the causal factors present in the individual (known and not) and therefore also different mechanisms that may have led to the event.
A CC may act in several ways: by aggravating a preexisting condition (pathology) or by intensifying its manifestations, prolonging its course, delaying its healing, accelerating its evolution, favoring the appearance of complications or anticipating the unfortunate outcome. Potential contributing factors include *mediators*, but also (genetic, environmental, stochastic, etc.) *modifiers* that contribute to the occurrence of the effect without being directly linked to it.
To introduce these two types of causes, it is first necessary to distinguish between *direct* and *indirect* causation.

Direct (immediate) vs indirect (mediated) causality

Another distinction, which will reveal to be relevant in our analysis of the WHO algorithm for AEFI's causality assessment, regards *direct* and *indirect* causality. *Direct* causality refers to the concatenation of effects represented by a regular and continuous series of phenomena, such that the final event can be traced back to the original cause. The causal influence of one event on another is *direct* (Spohn, 1990). Instead, if (new) co-causal factors are inserted leading to a different event (intermediate event) we are in presence of *indirect* causality. Thus, we can further differentiate between *immediate* causality and *mediated* causality. The former is when a cause is immediately followed by the final event, while when the influence of the first cause on the final effect of a concatenation is mediated by other events in between (intermediate event), we are in presence of *mediated* causality (Spohn, 1990) – see **Fig.19.**
Therefore, a cause can be indirect and unknown (Bierer, 2014), i.e.: intervening/mediating, moderating (Koeske, 1992; Kramer, 1988; Susser, 1973). If for example we have a causal chain like this: X → Z → Y, the node X is a cause of Y, but it affects Y through Z, so although there is a causal link between X and Y, this is an indirect causal relationship (Z is a intervening/mediating variable) – see also (Pearl, 2009). We have a one-directional causal chain with an indirect causal link from X to Y (Leng et al., 2020).

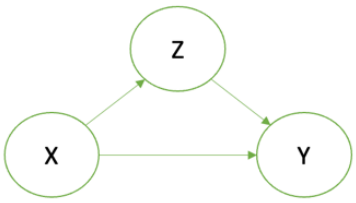

Figure 19: Example of a mediator (Z). Z lies on the causal path from X to Y; the path X→Z→Y contributes to the total effect of X on Y; X causally influences Y.

Causal factors which contribute to the effect without being directly linked to it include *mediators,* but also *modifiers*.
A situation in which we are in presence of a modifier is when an effect Y may fail to directly follow its cause X because the intervening factor Z prevents it from doing so by modifying the timing (or modalities) of the outcome Y (J. Reiss, 2015). Thus, effect modification occurs when Z intervene by modifying the causal relationship between X and Y. An intervening factor is independent of the original event and occurs in time between the original event and the resulting damage. Potential effect modifiers may be conceptualized by using current knowledge, prior experience and the investigation of questions like "For exposure E, disease D, and factor X (potential effect modifier): is there a link between E and D? Is it *biologically plausible* that the link between E and D differs for levels of X?" (PSU, 2022).
A contributory factor may also be defined as a *moderator* when it amplifies or weakens the effect between X and Y. For example, this is the case when the effect of one factor changes intensity at various levels of the other factor, e.g., in presence of hypoxia the negative chronotropic effect of vagal stimulation increases (leading to deceased heart rate). This is an example of quantitative interaction. Another case may be when the effect of one factor becomes opposite (increase *vs* decrease) in the various levels of the other factor such as acetylcholine, administered to an isolated artery, that determines vasodilation (decrease in blood pressure) if the endothelium is intact, or vasoconstriction (increase in blood pressure) if the endothelium has been removed. This is an example of qualitative interaction.
Considering all the above, as Corraini et al. state, *effect modification*, *interaction*, and *mediation* although conceptually different are potentially interdependent notions (Corraini et al., 2017).
Faced with a pathological manifestation of a multifactorial nature (AEFI), different types of causes and causal relationships should be considered by the investigator to avoid an erroneous rejection of the vaccine-AEFI causal link hypothesis, which leads to an increase in the likelihood of false negatives. If all available types of causes and causal relationships were considered in the causal procedure underlying the WHO algorithm, its reliability would considerably increase.

Hasteners & delayers

A special type of interactive factors is called hasteners, or delayers – depending on their action. The former makes the effect occur earlier and is typically preempting cause of what it hastens, while the latter makes the effect occurs later and typically blocks a would-be preempting cause of what it delays (Touborg, 2018).
In typical cases we usually judge that hasteners are causes of what they hasten, and delayers are not causes of what they delay; while in atypical cases we intuitively judge that a hastener is *not* a cause of the event it hastens and a delayer is a cause of the event it delays (Schaffer, 2005; Touborg, 2018). According to Rothman any cause of death corresponds to a mere hastener (Rothman et al., 2008).
Let's consider the following case study to illustrate the point.

> Natalie Morton (UK) died (event Y), after receiving Human papillomavirus (HPV) vaccine (cause Z). In a first moment, given the temporal relationship and the apparent state of health of the girl, the authorities stated that the vaccine was responsible for her death. However, later the autopsy detected the presence of a preexisting pathology within her body, a malignant chest tumor in an advanced stage (cause X), the tumor had heavily infiltrated her heart. In presence of this alternative explanation to the death, authorities stated as follows: "The medical evidence suggests the vaccine was not a contributing factor in her death" because, given the severe condition of the tumor, the death of the girl would have occurred *sooner or later* (Bowcott, 2009; WHO, 2019).

However, although Z did not directly cause Y, it may have acted by modifying the timing or modalities of Y, for example by triggering biochemical mechanisms in the body that anticipated the event. If one makes this kind of consideration(s), it can be argued that the death could have happened a little earlier because of Z. If the effect would not have happened just when it did happen, but a cause just made a tiny contribution, such cause is a *hastener* (or *delayer)*.

3. The epistemology of causality

Understanding causality, defining what causes are, how we can find them and how to identify a causal relationship are at the core of pharmacovigilance and medical practice (patient safety). When referring to causes of disease (or adverse health outcomes), the targets of investigation vary depending on the context. A clinician, for example, is mainly engaged in researching the causes of disease-manifestations in the patient to treat him/her; the medical student is more inclined towards general causal relationships; a scientist is looking for causal relationships in the attempt to establish or confirm a causal link *"somewhere in the train of events that lead to a disease"* (Rizzi, 1994).

These goals are achieved by explicitly or implicitly adopting different views on the kind of evidence which is needed to justify causal inference.

The following section is devoted to illustrating such issues with a particular focus on the distinction between singular and general causality and on the evidential requirements currently established by the scientific community for the assessment of causal claims in medicine (see **Fig.20**).

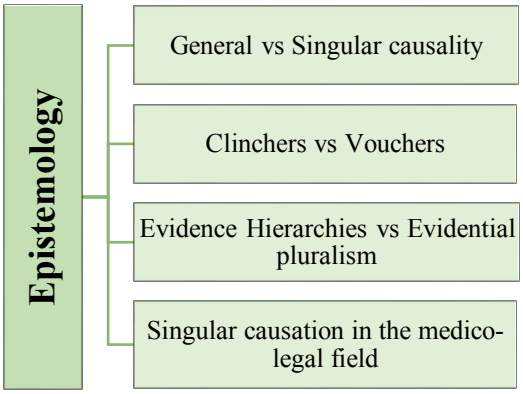

Figure 20: *The epistemology of causality.*

3.1. General vs Singular causality

In the medical context causality assessment can be implemented by (Dragulinescu, 2012):

(i) the epidemiological study of frequencies at population level, and/or
(ii) pathophysiological evaluations in laboratories at microstructural level, and/or
(iii) medical diagnoses (e.g., 'this case of renal failure was caused by aspirin intoxication').

Data from points (i) and (ii) are used to infer causal laws (or general causal statements: e.g., general causal knowledge of the nature of human physiology) which, depending on the type of evidence, can be probabilistic (e.g., 'smoking causes cancer with such-and-such probabilities') or deterministic (e.g., 'aspirin ingestion greater than 5 g/day induces an inflammatory response in renal interstitial tissues') (Dragulinescu, 2012). Epidemiological evidence is usually used to formulate probabilistic causal laws, while microstructural laboratory evaluations serve for laws without exception entering the black-box (mechanisms).
General 'causal laws' are used in medical diagnoses to draw singular causal conclusions about a particular organism.
Hence, causal explanations entail reference to and discernment between singular and general causality (Rizzi & Pedersen, 1992). [Between causes that relate to the singular case and the straightforward allegation that a certain, regularly occurring relation is a cause-effect connection, i.e., such-and-such is a cause of this type of event (population-based, general causality) (Mackie, 1965, 1974; Rizzi, 1994; Rizzi & Pedersen, 1992; Wulff et al., 1986)]. Some philosophers have contributed to the causation debate in this regard and to the understanding of causal concepts – among them see for instance (Halpern & Kleiman-Weiner, 2018; C. Hitchcock, 2007b; C. R. Hitchcock, 1995; Pearl, 2000; Woodward, 2004).
Stressing such discernment is of paramount importance to causal reasoning in medicine where *singular causality* can be described as a relationship between a concrete sequence of causally related events in the specific patient [the individual event, a particular object or entity in the

sequence is called *token* (Russo & Williamson, 2011; Williamson, 2013)], while *general causality* means various categories of causal relationships between the types of events, as in the etiology of a disease[88] (Rizzi & Pedersen, 1992).
The causal analysis can therefore take place on two different levels:

1. *Token-level*: analyzes individual events. Individual causality refers to events that *actually* happened. The focus is on the individual in whom a health outcome has already occurred aiming to explain 'what *did* happen' ('retrodictive' causality*, ex-post* reconstruction).
2. *Type-level*: analyzes population event. General causality relates to the laws of coverage, that indicate which antecedents *can* produce certain events, and are therefore eligible, to make predictions about the succession of events (Summerer, 2013) ('predictive' causality, *ex-ante* perspective). The focus here is on 'potential' causal propositions for populations.

General causal claims are central to scientific inquiry and play an important role in prediction and control (Pearl, 2000, 2009; Woodward, 2004), but also serve as basic knowledge needed to address issues of actual causation. Actual causal claims play also a crucial role in science, especially in interpreting empirical findings to support general causal theories, and are fundamental in practical and social contexts, especially those involving explanation and attribution of responsibility (D. A. Lagnado et al., 2013).
In the following sections I will first describe *type-level* causation and then I will move on *token-level* causation, which is the focus of my argumentation. Then I will discuss the relation between token and type level causation.

3.1.1. Type-level causality (general)

In the field of biomedical and social research, scholars often seek to establish causal laws, that is general statements of the form: *'X causes Y'* (e.g., 'smoking causes cardiovascular disease'), where both X and Y refer to type-level events that can be instantiated multiple times. Social scientific generalizations like these may serve to explain the occurrence of an event, to predict a future event and to give advice (Cartwright, 1994; Hempel & Oppenheim, 1948; Roberts, 2004).
Type-level causality relates to the existence of a causal law that indicates a regular and repeatable connection between phenomena. General causal relations can obtain repeatedly, since they are true properties, event-types, or variables, rather than individual (token) events. Event-types can be described as types of objects or entities (Russo & Williamson, 2011;

88 Rizzi & Pedersen (1992) reported the following example: "'cranial fracture with dural laceration leads to meningitis' is a statement of general causality between event types. It means that if an event is of the type 'cranial fracture with dural laceration', then it will be highly likely to cause 'meningitis' in the individual person, who has acquired cranial fracture with dural laceration".

Williamson, 2013), or as *"classes or categories of events that are referred to under a common descriptive label"* (Rizzi & Pedersen, 1992) or as *"universals, having appropriate tokens as instances"* (Scheffler, 2003).
Causal claims operating on this level are like 'smoking causes lung cancer', 'exercise prevents cardiovascular disease', 'preparation X may cause bone-marrow depression' (Rizzi & Pedersen, 1992) or 'paracetamol calms the febrile state'. Some claims can be generally true even if they have some exceptions, some general claims will be lawful truths, others not (Grinfeld et al., 2020).
General causal relations between event types appear under idealized conditions, e.g., in laboratory set-ups, or experiments such as controlled trials (RCTs), where *ceteris paribus* conditions can be controlled (Wulff, 1981).
In the *ex-ante* perspective (prognosis), the causal knowledge based on scientific laws serves to represent a probable or seriously possible future outcome, allowing to *predict* an event of the type that has occurred (Summerer, 2013). In this context predictions should be formulated in terms of *certainty* or *high probability* (Hart & Honoré, 1985; Summerer, 2013).

3.1.2. Token-level causality (singular)

Individual level causation, or 'token' or 'actual causation[89]', holds between token events in a particular concrete case. Causal inferences operating on the toke-level are like 'Robert's smoking caused him to develop lung cancer' (Grinfeld et al., 2020; C. R. Hitchcock, 1995) or 'swallowing *this* paracetamol pill calmed *this* febrile state' (J. Reiss, 2015).
At the *token-level* one applies the general causal law to the specific concrete case and provides a *causal explanation* of the concrete event, that should be endowed with adequate explanatory force (Hart & Honoré, 1985; Summerer, 2013). The analysis consists in the identification of an antecedent theoretically suitable to determine an effect similar to the actual one, and then goes on to define if that specific antecedent has intervened in the causation (exclusively or combined with other factors) of that specific effect. One identifies a token event through established concepts (scientific laws – general causality). For example, as Rizzi and Pedersen report, the concrete event 'patient X has developed meningitis at time t', falls under the concept 'a person suffering from meningitis', that defines an event type (Rizzi & Pedersen, 1992). In other words, one searches the general case (or reference case[90]) and compares the singular case to it, in order to explain causal relationships in the singular case (Rizzi, 1994; Rizzi & Pedersen, 1992).

[89] The term has been used extensively in the tort law literature [see e.g., (Wright, 1985)], and became firmly established in the philosophical lexicon with Pearl (2000) (Baumgartner & Glynn, 2013).
[90] The reference case is defined by Rizzi and Pedersen as: "*a catalogue which serves as a guideline for the causal search, and from which are drawn causes, complexes, and effective causal relations. […] The reference case may be framed as the comprehensive proposition of causal factors and connections, all of which are duly possible or potentially competent of producing the effect, which includes a demarcation of the proper causal field"* (Rizzi & Pedersen, 1992). The latter represents *"the way we conceptualize the time-space context within which the causal*

While the use of universal causal laws is necessary to predict future events with certainty or high probability, for the *ex-post* perspective of singular causal explanation it is not sufficient to grasp the meaning of a given antecedent. [It is useless to reiterate the limits of a deterministic and strictly nomological-deductive causal explanation[91] since it is not able to clarify the causal link with respect to the single event]. Questions like these may arise: How likely would it have been that the individual was in the same condition as today, if he had not taken the (bio)pharmaceutical product? Are there factors that explain the adverse event better than an explanation based on vaccine administration? Such inferences are based on the clinical and subclinical condition of the subject before and after the administration of the (bio)pharmaceutical product and on general notions of (patho-)physiology, genetics, immunology, and so on, in order to identify the most plausible explanation of the particular event (Osimani B. & Ilardo, 2022).

In the view of an *ex-post* reconstruction (causal diagnosis), the imputation of a concrete event, while requiring reference to scientific laws, takes place on the basis of counterfactual judgment and therefore of the comparison between real course and hypothetical course (Hart & Honoré, 1985; Summerer, 2013). The decisive moment of confirmation of the causal hypothesis provided by scientific laws, namely the passage from the sufficient condition to the necessary one, is guaranteed by the imputation formula of the *conditio sine qua non* (*c.s.q.n.*), based precisely on mental elimination and counterfactual judgment which allow to arrive at a judgment endowed with *logical probability* through the exclusion of alternative causes (Summerer, 2013). Counterfactual is a hypothetical reasoning characteristic of induction and critical proof (logic).

Therefore, as Summerer (2013) points out, according to this conception, scientific laws serve (on a general and generalizing level) to make predictions, while the *c.s.q.n.* aims (on a concrete and individualizing level) at the reconstruction of a causal relationship and the explanation of an event. In this context the rational credibility of the explanation is decisive (Summerer, 2013). Today causality is ascertained through the conditionalistic theory (*c.s.q.n.*) with the corrective of subsumption under scientific laws. Individual causal assessment makes use of epidemiological content and strength, universal and frequentist laws (inductive/Bayesian approach - probabilities and statistics), exclusion of alternative causes, abductive and counterfactual reasoning (Casali, 2010).

3.1.3. The relationship between general causation and singular causation

The link between general and singular causality is object of vivacious debates in philosophy of science (S. R. Smith, 2007). We can however distinguish between two lines of thought, namely (S. Glennan, 2011):

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relations take place" (Rizzi & Pedersen, 1992) and the significance of a single causal factor for the outcome (e.g., meningitis) is judged according to it.

[91] In a nomological-deductive model for a scientific explanation, explanation is intended in terms of deduction from "laws of nature", from a "causal law".

(i) the *generalist view* which holds that the veracity of individual causal claims is subscribed to by general causal laws: singular causal relations obtain because they are instances of a general causal regularity (or law);
(ii) the *singularist view* which states that singular causal relations can obtain even if they are not instances of causal regularities (or laws), and it is singular causal relations that make general causal statements (or causal generalizations) true, since the latter do nothing but properly describe a pattern of singular instances of causally related events.

Among those who embrace the singularist view, the most discussed were Ducasse and Anscombe.
Ducasse (1926) argues that it is sufficient that a particular event has occurred only once for the cause to be defined, and thus it is not necessary to imply the assumption that the same (or a similar) event has ever occurred before (Ducasse, 1926). According to Ducasse, *causation is perceived rather than inferred* (Ducasse, 1965).
Anscombe argues that true singular causal claims do *not* describe instantiations of universal regularities (Anscombe, 1981). Causality consists in deriving an effect from its causes and an analysis in terms of necessity or universality does not tell us that effects derive from their causes (Anscombe, 1971). She holds the conceptual priority of singular causal concepts over the general concept of cause. This is based on the rejection of the thesis according to which the perception of a causal relationship derives from or is originally connected to the concepts of necessity, universality, law, and prediction: the causes of an event are often known, although it is not known if there is a general law of connection, and, in many cases it is much easier to identify with almost certainty the causes of an event already realized than to make a prediction about future effects of a cause (Anscombe, 1971; Santoni de Sio, 2008). Thus, it is not true that our knowledge of causal relationships can *only* come from the observation of regularities, but causality can be perceived directly (Anscombe, 1981; Gijsbers, 2021; Sosa & Tooley, 1993) and can be observed in the individual case (Anscombe, 1971; Ducasse, 1926, 1965, 1968).
If so, causation must be present in the single observed cause-and-effect pair, and thus the truth of the individual causal statement is independent of obtaining any universal regularity (Gijsbers, 2021; Sosa & Tooley, 1993).[92]
Lewis and Humphreys suggest first trying to analyze singular causal claims in terms of the probability of a single case, and then trying to understand general causal claims as generalizations about singular causal claims (Humphreys, 1989; Lewis, 1986a). However, they do not tell us how the general causal claims relate to singular causal claims (Carroll, 1991; C.

[92] Gijsbers talks about the existence of 'a thick causal experience' that the regularity theory cannot explain (Gijsbers, 2021). For 'a thick causal experience' he means *"an experiential episode of a subject that prima facie justifies belief in a statement of the form 'c caused e' without relying on belief in a causal regularity linking events of types C and E (where c is an event of type C and e an event of type E)"* (Gijsbers, 2021). According to Gijsbers, 'a thick causal experience' must be local in an epistemic sense, i.e., *"the experience must be such that knowledge of distant events cannot adversely affect its ability to justify the local causal claim"*. Such a local causal experience can play its justifying role regardless of what we learn about distant events (Gijsbers, 2021).

R. Hitchcock, 1995). The general causal statement 'smoking causes lung cancer' is true because it generalizes about true singular causal claims (e.g., Martha's smoke caused her cancer, John's smoke causes him cancer, and so on), however in probabilistic causal generalizations it is too strong to assume that every instance of the singular causal relationship obtain: not everyone who smokes gets lung cancer (S. Glennan, 2011). Indeed, general causal claims are association of aggregated data: Marta smoke & Marta dies; Peter smoke & Peter died; John smoke & John died; X smoke & X died.

According to Hitchcock, X is a cause of Y if X increases the likelihood of Y (compared to a certain alternative Z, and across a sufficient range of background contexts), but from this it follows nothing strictly about actual events X and Y (e.g., "it is possible that smoking increases the probability of lung cancer even though in a certain population all and only non-smokers develop lung cancer") (C. R. Hitchcock, 1995). In contrast, singular causal claims entail that the events X and Y *occur*: the claim "David's smoking caused him to develop lung cancer" would not be true unless "David smoked and David developed lung cancer" (C. R. Hitchcock, 1995). Therefore, as Hitchcock (1995) states:

> "…if general causal claims could be analyzed in terms of singular causal claims, general causal claims should have implications about the instantiation of the event-types named. By modus tollens, claims of general causation cannot be reduced to claims of singular causation".

According to Scheffler *"token causation is ontologically and methodologically prior to natural laws and type causation"* (Scheffler, 2003).

Weber argues that neither the individual case is reducible to the generic nor the generic is reducible to the individual case, rather, each level must be analyzed independently. The causal relationships of a single case must be analyzed in one way, and generic relationships in another (Weber, 2007).

Russo and Williamson, basing their argument on the analysis of causal inference in the case of autopsy, argue that inferences are neither universally *top-down* nor universally *bottom-up*, but instead a mixture of the two (Russo & Williamson, 2011).

Top-down means that epistemic access to causal relations flows from the generic level (the *top*) to the single case level (the *bottom*) (Russo & Williamson, 2011). To infer, for example, that exposure to medicinal product X is a cause of the occurrence of adverse event Y in person P, we first learn that exposure to medicinal product X is a cause of the occurrence of event Y from repeated observations of particular exposures and particular events together with theoretical knowledge about the underlying mechanism. Then this generic causal claim is particularized to the individual case by applying further evidence that exposure to drug X produced event Y, along with any further knowledge regarding the mechanism involved in that particular case (Russo & Williamson, 2011).

Bottom-up reflects the vision of those who maintain that causal relations are directly perceivable (Anscombe, 1971; Ducasse, 1926, 1965, 1968). Epistemic access to causal relations flows from the individual level (the *bottom*) to the generic one (the *top*) (Russo & Williamson, 2011). If

we consider for example the mechanistic causality approach, here causal relations are analyzed in terms of physical processes manifesting conserved quantities[93], or of connections in complex-systems mechanisms[94], or of dispositional capacities in the setting of a nomological machine[95], linking token cases. Single-case causal relations are analyzed[96], and a generic causal relation can be considered as a generalization of underlying single-case relations (Russo & Williamson, 2011).

According to Russo and Williamson, if, for example, the physician must determine that Marta's heart attack was a cause of her death, s/he needs evidence both that there is 'a viable biological mechanism linking heart attack and death' and that the heart attack made a difference to her death.

Glennan (2011) expresses himself in favor of the singularist view of causal relations, but contrary to Russo and Williamson he argues that 'a viable biological mechanism linking heart attack and death' is a generic explanation of a mechanism, and not all heart attacks cause death. The fact that heart attacks on some occasions are linked through a physiological mechanism to a person's death makes heart attack a *prima facie* candidate for the cause of a particular death. But to establish heart attack as the cause of Marta's death, it would have to be shown that it made a difference in the specific case. The fact that the heart attack caused Marta's death depends on the details of the adverse event, the state of the person's other vital systems, and the place, time and circumstances of the event. It should also be shown that if Martha had not had a heart attack, she would not have died, so if, e.g., Marta suffered from sepsis and sepsis caused a failure of several organs including the heart, and that, given all these conditions, the heart attack did not make a difference to Marta's death (S. Glennan, 2011).

Glennan argues that a singularist view of causation is well supported by the mechanical approach because it suggests that: (i) causal interactions are mediated by mechanisms, and mechanisms are specific systems of interacting parts, where these interactions happen at a particular place and time, and (ii) generalizations are generalizations on the behavior of mechanisms, and are true *"because mechanisms do or would behave in the way described on actual or hypothetical occasions"* (S. Glennan, 2011).

Glennan's account is particularly relevant in the present context since it provides the essential guiding principles for the establishment of individual cases of AEFIs.

3.2. Clinching method vs Vouching methods for causal inference in medicine

In addition to various approaches to causation, one should consider that also the notion of evidence and the requirements assigned to evidence in scientific inference are object of a vivacious debate in the philosophical and methodological literature. Cartwright, for example,

[93] See (Dowe, 2000; Salmon, 1998)
[94] See (S. S. Glennan, 1996)
[95] See (Cartwright, 1999)
[96] See (Cartwright, 1989)

makes a rough distinction between *clinching* methods and *vouching* methods (Cartwright, 2007b).

Clinching methods require *conclusive* (irrefutable) evidence for warranting a causal conclusion: evidence that 'clinches' the conclusion (Cartwright, 2007b). In medicine experimental evidence (mainly randomized controlled trials, RCTs) is considered as such (i.e., *strong* evidence). In fact, clinchers are elitist since they *value evidence for the degree to which they exclude random and systematic error* (Osimani, 2020). This kind of approach deductively forces its conclusions and deliver an acceptance/rejection verdict on the hypothesis under investigation based on *modus tollens* reasoning (i.e., *hypothesis testing*) (Osimani, 2020).

In Evidence Based Medicine (EBM), for example, evidence is put to test before entering the court (Osimani, 2020). Clinical decisions should be evidence based, and in EBM "causally relevant evidence is taken to be statistical and population-based, generated from large clinical studies" (Anjum et al., 2020). RCTs are considered the gold standard for establishing causality (J. H. Howick, 2011) because, thanks to their experimental design, and if well conducted, they are best at isolating a causal factor from potentially confounding factors and seeing if it makes a statistical difference in the outcome (Anjum et al., 2020). These methods were developed to test the efficacy of pharmaceutical products and with the aim of basing the care of individuals in general knowledge of which is the most effective intervention in a studied population (Rocca & Anjum, 2020a). The focus is on false positives. For the need to control for confounders, they make use of strict inclusion and exclusion criteria for recruiting the participants. However, while these controlled conditions increase the reliability of the experimental results and the confidence that the observed outcome is due to the tested intervention, this limits the external validity of the study (Anjum et al., 2020). Anjum et al. (2020) note that in the face of chronic and/or elderly patients, and/or pregnant women or even children, it is not obvious that the clinical trials results apply *directly* with respect to dosage, efficacy and/or safety. This means that while evidence-based policy is well informed about what is happening in the study population, causally relevant information about the unique local context is ignored or lost (Cartwright & Hardie, 2012).

In addition, it is doubtful that the methods for evaluating the efficacy of treatments are equally effective in assessing the causal relationships between pharmaceutical products and suspected AEs, especially because we are dealing with unintended and unwanted consequences of interventions (Osimani, 2014b).

Some epidemiologists [see e.g., (Papanikolaou et al., 2006; Vandenbroucke, 2008)] have recognized the distinctive virtues and weaknesses of randomization in efficacy vs. safety assessment. According to Rudén & Hansson (2008) the focus of research in risk detection is on false negatives, rather than on false positives (Hansson & Rudén, 2008). Therefore, focusing and relying only on methods that have been developed to test efficacy may result in neglecting relevant issues when it comes to safety (Osimani, 2014a). As Osimani (2014a) points out, the exclusive use of RCTs to justify causal claims is wrong both for the type of information they provide and for the type of information they are unable to incorporate or account for (Osimani, 2014b).

In contrast to clinching methods, there are *vouchers*. These are methods whose results cannot force any conclusion, but only suggest or support it *more or less strongly* (Osimani, 2020; Osimani & Mignini, 2015). These methods 'merely vouch' for their conclusions (Cartwright, 2007b): they do not definitively refute/prove a given hypothesis, but rather aim to provide a way to assess the *degree of plausibility* of a given hypothesis given a set of data (i.e., graded judgment) and, possibly, to measure it probabilistically. A voucher doesn't require conclusive evidence but evidence that can help make a case for a conclusion (i.e., evidence that 'speaks' of a causal relationship), and that can be *combined* with evidence of different kinds from other methods to secure the conclusion of causality (Cartwright, 2007a, 2007b). They are flexible enough to incorporate several and different types of evidence in the inferential framework (Osimani, 2020).

This type of approach admits a plurality of causal indicators (e.g., signals at the molecular level, at the epidemiological level, etc.) to infer causality. A type of evidence, which if taken individually would not be sufficient to allow any significant inference, could be gathered and jointly support a given hypothesis, strongly indicating the hypothesis of a causal association between the pharmaceutical event and the observed AE, without nevertheless being conclusive (Landes et al., 2018; Osimani & Mignini, 2015). This is a particularly appropriate approach when causes are highly context-sensitive (such in biology or the social sciences). Those who are mainly concerned by these aspects and, more generally, by defeasibility of scientific inferences are opponents of the EBM, who advocate a pluralist methodology (Osimani, 2020). They are opposed to giving RCTs a privileged role in establishing causality and to consider difference-making necessary/sufficient to establish causality, but neither statistical evidence, nor evidence on mechanisms supporting it are *per se* sufficient to establish causation, rather they are both necessary (Osimani, 2020) – see also (Anjum & Mumford, 2018; Clarke et al., 2014; Osimani, 2013; Russo & Williamson, 2007a).

The emphasis on evidence hierarchies that strongly favor RCTs over other types of evidence and the regulator's relative dependence on such standards, however, compromises the efficient use of heterogeneous evidence (Osimani, 2014a). This, if applied to the context of the WHO algorithm, translates into the increase in the likelihood of false negatives.

3.3. Evidence Hierarchies vs Evidential pluralism

The current evidence-based paradigm holds that the best evidence of causation comes firstly from the randomized experimental designs (RCTs) and secondly from controlled observational studies, thus underestimating the role of evidence coming from the individual patient, which is thus considered non-strong and non-causal (Rocca, 2020) – see **Fig.21.** RCTs are considered the gold standard level of evidence and as such they provide *strong evidence*, in contrast with e.g., anecdotal studies which are said to provide *weak evidence*.

Strong evidence is defined as that type of evidence which provides direct proof of the truth of a causal claim. Examples include experimental evidence, repeatable and with consistent results

[high-quality scientific studies: experimental evidence, produced by studies such as RCTs, or other experimental clinical trials (non-randomized, or randomized and uncontrolled), meta-analysis of RCTs, etc.; and observational evidence, produced by epidemiological studies (or analytical observational clinical trials – cohort, case-control –, etc.)].
Weak evidence is a type of evidence that is consistent with a causal statement but does not exclude other (contradictory) claims. An example is anecdotal or circumstantial evidence, based on the assumption that two coexisting factors are linked even though alternative explanations have not been explored (this is used for generating hypotheses which can then be tested with experimental evidence).

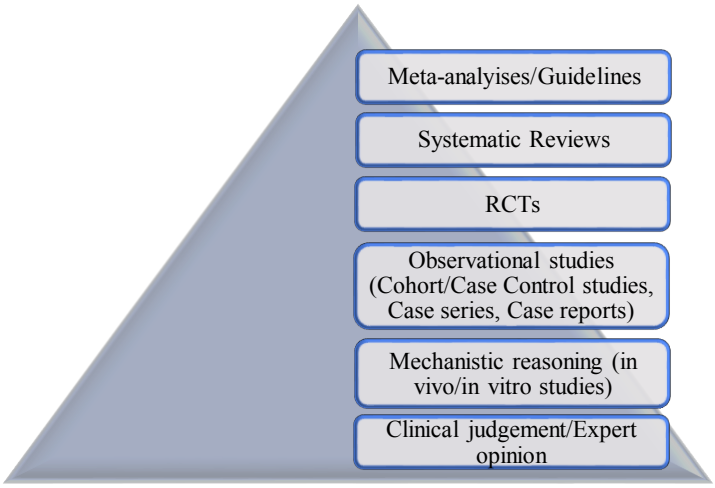

Figure 21: *Evidence Hierarchies: the order of importance increases from the bottom up.*

Since our knowledge of pathophysiological mechanisms is at any given time incomplete, and may be also wrong (J. H. Howick, 2011), there is this tendency to emphasize population-based statistical evidence over mechanistic knowledge to determine whether an intervention works.
However, many clinicians and philosophers of medicine have expressed perplexities with respect to this paradigm, by arguing that statistical approaches cannot uncover all causally relevant information (Anjum et al., 2020). Moreover, correlations produced by population studies are not necessarily causal. According to some philosophers, in order both to establish whether the correlation is causal or not and to find out how an intervention works, knowing the mechanism(s) by which the cause brings about the effect is necessary [see in this regard the Russo-Williamson epistemic theory (EBM+) (Russo & Williamson, 2007) where both statistical evidence and evidence of mechanisms are necessary to establish causality]. Causal relationships can be established only if the theoretical knowledge coming from the laboratory and clinical science is also used (Anjum et al., 2020).
However, by requiring multiple criteria to be jointly satisfied in order to establish causation, this sort of pluralism goes in the direction of the one allocated by Cartwright with her plea for a vouching approach. Instead, the spirit of Cartwright's appeal to vouching methods is one where different sorts of possibly inconclusive items of evidence can independently contribute to increase or decrease the degree of support of a given causal claim under investigation. This

sort of approach is best suited to optimizing all available evidence in delivering a causal judgment as evidence comes in.

This is in line with the conception in medicine that a variety of different types of evidence is helpful in determining whether an observed correlation is causal, i.e., evidential pluralism. This interest is even more justified if we are in the context of collecting, analyzing and evaluating evidence on pharmaceutical safety. AEs represent a particularly vulnerable issue for the health system and a crucial ethical problem for decisions regarding (bio)pharmaceutical products (Osimani, 2014b).

Many have addressed the issue of safety evaluation in pharmacology with a vision of philosophical work on causality and causal inference from statistical data (Osimani, 2014a). This is mainly because current evidence standards have tended to emphasize internal validity of studies and hence randomization, ignoring alternative paths to causal assessment, such as the joint support of different types of evidence to a given hypothesis (Osimani, 2014a).

Using solely one type of evidence to support a causal relationship increases the likelihood of false negatives (failure in detecting possible causes of the observed event) (Landes et al., 2018). As Osimani (2014b) stresses, this may be detrimental to safety assessment since much of the evidence for harms comes from anecdotal reports, case series, or survey data. Anjum (2020) points out that individual reports of the same adverse reaction (aggregate cases) can indicate the possibility that drug-X caused the AE. The fact that among those who took drug-X only one patient experienced a certain AE may be evidence of causality: *"if causality happens in the particular case (ontologically), this means that each individual patient represents a valuable source of evidence (epistemologically), also for causality"* (Anjum, 2020).

The above-mentioned "lower level" evidence is ever more considered a valid source of information that contributes to assessing the risk profile of medications (Benson & Hartz, 2000; Golder et al., 2011; Hauben & Aronson, 2007; J. Howick et al., 2009; Osimani, 2014a).

Along experimental evidence would be more appropriate to consider other and different kinds of evidence to support and strengthen a causal hypothesis [see (Krieger & Smith, 2016; J. Reiss, 2009, 2012). Therefore, the integration of information coming from different sources of safety signals such as spontaneous case reports, literature, data-mining, pharmaco-epidemiological studies, post-marketing trials, drug utilization studies, non-clinical studies, late-breaking information, etc., should be adopted to perform an accurate causality assessment avoiding an increase in the likelihood of false negatives (Osimani, 2014b).

Some philosophers of science have suggested the adoption of a pluralistic approach to causal inference together with an inductive rather than hypothetico-deductive inferential paradigm (Landes et al., 2018). Osimani and Mignini (2015) argue that inductivist approaches, like Bayesian Hypothesis confirmation, fare better than hypothetico-deductive ones (EBM) in causality assessment and scientific inference in pharmacology, especially when dealing with harms (Osimani & Mignini, 2015). Bayesian methods are flexible in terms of the type of evidence which can be considered, and also allow to use evidence vouchers, useful for decisions in the field of uncertainty. An interesting and useful application of a Bayesian approach in medicine and pharmacology is represented by E-Synthesis, a methodological tool for aggregating multiple types of evidence (e.g., cell-data, clinical-data, epidemiological studies,

etc.) *to jointly contribute to hypothesis confirmation* (Osimani, 2020), i.e., the assessment of causal link between pharmaceuticals and AEs in probabilistic terms. More specifically, it consists in a Bayesian epistemic network, which formalizes scientific inference probabilistically (Osimani, 2020): it *"uses probabilistic knowledge about statistical models in order to output a probabilistic estimate that a given individual might be affected by a given ADR"* (de Pretis et al., 2019) and *"has the virtue of being able to be adapted to various theoretical stances on causality (counterfactual vs. process theories vs. regularity vs. inferentialist theories of causality)"* (Osimani, 2020).

3.4. Singular causation assessment in the medico-legal field

In the regulation of decision of medico-legal nature the existence of a causal link between two phenomena is an indispensable requirement for the recognition of liability and insurance or compensation benefits. The causal link represents the etiological link between a given event, whether it originates from a human action or the natural course of events, and the occurrence of a certain consequence relevant to the legal system (Monateri & Gianti, 2016).
In the pharmaceutical domain practice, causality assessment is the process of finding out if the pharmaceutical product is responsible for causing the observed damage/adverse health outcome to the patient.
The concept of causal responsibility plays a major role in the legal domain since it is a necessary condition for the attribution of the agent's legal, and moral responsibility (Grinfeld et al., 2020; Hart & Honoré, 1985; D. Lagnado & Gerstenberg, 2017; M. S. Moore, 2009; Santoni de Sio, 2008; Tadros, 2005; Usher, 2018). The concept of causal responsibility is typically grounded in the notion of token causation (Grinfeld et al., 2020). The purpose of the lawyer is to make causal statements about particulars, that is to establish that on some particular occasion some particular event was the effect (or consequence) of some other particular event (Hart & Honoré, 1985). This process does not involve the formulation of laws, but rather the application of generalizations already known or accepted as true to particular concrete cases.
Judgments of causal and legal responsibility are graded (Grinfeld et al., 2020). This implies that some causes are treated as stronger than others (O'Neill et al., 2022) and that more responsibility is usually given to an agent for a given effect when the latter is a direct result of its action, rather than when it is the result of a long causal chain (Brickman et al., 1975; Hilton et al., 2010; D. Lagnado & Channon, 2008; McClure et al., 2007; Spellman, 1997).
In forensic science different medico-legal criteria are used in the evaluation of the causal relationship (Zappaterra, 2018). The criteria developed in medical literature for establishing individual causal claims reflects the considerations advanced by philosophers. This more or less directly support the revision of the WHO algorithm (see **Tab.9**).

Medico-legal criteria	Description
Criterion of scientific possibility	This should be analyzed preliminarily, representing the first step of the counterfactual reasoning. In relation to the many peculiarities of the individual cases, reference is made to scientific laws (coverage laws). On this basis a preliminary possibility of admissibility of the link or its exclusion can be reached, where it is scientifically impossible that the hypothesized action may have played a causal role, even with the support of any competing factors. In the event of a possible or probable link, the other evaluation criteria are considered for a possible judgment of certainty or a higher degree of probability.
Chronological criterion	This consists in judging whether or not the time interval elapsed between the harmful action and the appearance of the first manifestations of a given disease is compatible with the existence of a causal link. There may be immediate, mediated or late links.
Topographic criterion	This concerns the verification of the correspondence between the anatomical region affected by the harmful action and the site of the disease onset. There may be a direct, indirect and backlash relationship (e.g., embolism).
Criterion of qualitative &quantitative efficiency	This *assesses whether the damaging agent is qualitatively and quantitatively sufficient to cause the damage.*
Etiological criterion (or harmful eligibility)	A proportionality between cause and effect is sought and a compatibility between the nature of the harmful action and the species of the damage occurred, between the dose or force applied and the magnitude of the effects found. Eligibility can be absolute (the cause is sufficient) or relative (co-causes are needed).
Criterion of phenomenal continuity	This verifies, in logical and chronological succession, the clinical manifestations (symptoms) of the harmful cause, taking into account, not only the characteristics of the course of the induced pathology, but also the connotations of any pathogenic causal factors that intervene or overlap with the usual clinical framework
Criterion of statistical probability	This can provide data in favor of causal hypothesis, but alone does not appear sufficient to constitute proof of the existence of the causal link. It can be used to refute or support a hypothesis or the conclusive judgment of a probabilistic type.
Criterion for excluding other causes	This is of substantial importance to verify whether causes other than that on whose etiological role it is necessary to investigate are possible of being proposed in the determinism of the event. An accurate analytical procedure of each available element must be conducted to see if the pathological picture observed can be explained etiogenetically in a way different from that reported or hypothesized. In the case of multiple hypotheses, the aim is to highlight whether a factor, even if apparently scarcely significant, may have played a competing role with the pathological pre-existences in the determinism of more striking implications.
Circumstantial & clinical anamnestic criterion	The examination of circumstantial data (characteristics of place, time, etc.) and the accurate collection of the description of disorders and clinical manifestations accused can confirm or deny a possible causal link.
Anatomical-pathological criterion	The ascertainment of the cause of death at the time of examination or autopsy is sometimes a fundamental element and by itself probative, other times it is negative or doubtful.

Table 9. *Medico-legal criteria in the evaluation of the causal relationship* (Zappaterra, 2018).

The medical-forensic field consider situations in which there is a cause versus many co-causes. A cause (or efficient cause) is defined as the antecedent *necessary and sufficient* to produce the effect, while co-causes are those factors that intervene in determining a phenomenon (others modify the final outcome in a chained sequence), that otherwise would be not achievable in absence of one or more (pre-existing, simultaneous or supervening) co-causes – see Art. 41 of the Italian Code of Criminal law[97] (Cod. Pen. Art. 41, 1930).

The analysis of individual causality consists in: (a) the identification of an antecedent theoretically suitable to determine an effect similar to that concretized, and (b) determining if that precise antecedent has necessarily intervened in the causation (exclusive or combined) of that precise effect. Here we make use of the following tools: epidemiological content and force of the laws of coverage (universal/frequentist laws), exclusion of alternative causes and counterfactual reasoning (e.g., 'What would have happened if the commissive antecedent had not really occurred?') (Casali, 2010).

The legal field resorts to the so-called theory of scientific causality (Concas, 2017; Franceschetti, 2017; Lebiu G. et al, 2017). The particular event must be explained on the basis of general laws of coverage, which in some cases are universal (i.e., an event is *always* accompanied by another event), in others can be only statistical[98] (i.e., a certain event is accompanied by another event in a high percentage of cases: the event is only probable, albeit to a considerable extent) (Rossi, 2000). The latter explain the causal link only in a certain number of percentages of cases. In the case in which there is no satisfactory knowledge on the mechanism of the phenomenon, the statistical explanation *may help* to lead to the identification of a penally relevant causal link, on the basis of the evidence gathered (Rossi, 2000).

The establishment of the causal link by the judge therefore implies the recourse (in most cases) to statistical laws, and has a probabilistic character (Rossi, 2000). The use of the terminology 'possibility of existence of causal link' is an important aid in the definition of the causal link, and it is done according to the following scale: *impossible*, *unlikely*, *possible*, *highly possible* and *certain*. The validity of the link from the legal side will exist exclusively in the last two cases (Lebiu G. et al, 2017). For example: patient X is given therapy D, in 40/50/90% of cases the patient is saved, in 1/60% etc. s/he is not saved; to explain the causal link only those laws that explain a particularly high percentage of cases close to 90/99% can be used. Thus, the action of an agent is cause of the observed event when, according to the best science (universal, scientific laws, and statistical laws) and experience of that historical moment, the event is a

[97] Art.41 regulates cases in which the event is the result of several different causal factors, by stating that: "*The presence of pre-existing or simultaneous or supervening causes, even though independent of the act or omission of the offender, shall not exclude a causal relationship between his act or omission and the event"* (Cass. Pen. Sec. IV no. 3922, 2021; Criminal Code. Art.41, n.d.). It affirms the unsuitability of co-causes to break the causal link between the agent's conduct and the event (Rossi, 2000). However, since the production of the event is not always connected in a linear way to the agent's conduct but it can be the result of a plurality of factors (antecedent, concomitant or subsequent)**,** which can affect the cause-effect mechanism (Lebiu G. et al. 2017), the legislator added a second comma according to which the co-causes "s*hall exclude the causal relationship when they were in themselves sufficient to bring about the event*."

[98] This is the most frequent case since it is practically impossible to find as many universal laws as there are the conditions involved in the production of an event.

certain or highly probable consequence of the agent's action, since without it the event would not have occurred (Franceschetti, 2017).
However, even if we have a law that explains 99% of cases, in the concrete real case a problem arises: the single case submitted to the knowledge of the judge can be that case 1 in 100 (1/100) that is not explained by the law that instead explains 99% of cases, and it is precisely for this reason that we cannot use the abstract percentage of the law to conclude about causality in in single case. Thus, *we must not use statistical probability* (i.e., the abstract percentage number of cases), *but we must lower the law in the concrete case*.

3.4.1. The requirement of logical probability

The causal link is explained by procedural certainty, i.e., ″beyond any reasonable doubt″ (BARD)[99] (Art. 5 Legge n. 46, 2006). This principle is equivalent to ″a high degree of rational credibility, which exists even if the alternative hypotheses, although abstractly formulable, have nevertheless remained without adequate confirmation in the procedural results and extraneous to the natural order of things and normal human rationality″ (Giglio & Radi, 2022).
Through the Franzese sentence of the Criminal United Sections (Cass. Pen. Sec. Unite n.30328, 2002), the requirement of 'a degree of probability close to certainty' is replaced by 'a degree of probability close to 100'. The sentence establishes the usability of causal laws with a much lower probability coefficient if they are supported by other evidence that can corroborate their validity (Brocardi, 2022). To establish and justify the existence of a given probability as to whether or not there is a hypothetical causal link, the concept of logical probability is therefore used.
As Marani (2014) points out, statistical probability of verifiability of the event in a given specific case alone is not sufficient to assert responsibility for the event to the agent's conduct. Rather, in the first place, a causal explanation of the event, abstractly applicable to the specific case, is hypothesized based on a sufficiently valid statistical or universal law of coverage. Then, it is necessary to verify, through a judgment of high logical probability, the reliability, *in practice*, of the causal explanation hypothesized (Marani, 2014). This happens on the basis of the procedural evidence, that, if the commissive conduct supposed due to the event was not completed, and excluding the interference of alternative causal courses, the event, with a high degree of rational credibility, would not have occurred, or would have occurred much later, or would have had less harmful intensity (Marani, 2014).
The judge, therefore, will have to evaluate on a case-by-case basis the existence and incidence of other factors, according to common logic (Brocardi, 2022). This is the so-called logical-scientific probability theory (Monateri & Gianti, 2016).
To better understand the difference between statistical probability and logical probability let's consider, for example, the case of a sexual HIV infection with a very low probability, e.g., a probability of 5% in cases of a woman who has suffered sexual violence by a man with HIV

[99] BARD establishes the need for a *high degree of probability* of guilt – see (Art. 5 Law no. 46, 2006).

virus. Now, if the woman dies from HIV, the event is attributable to the conduct of sexual violence perpetrated by the carrier of HIV. If we were to look at the statistical probability, we would have to deny the causal link because we would have to say that the statistical data associate 5% of cases, it is not a certainty close to 100, and therefore we would have to deny the causal link. The logical probability, on the other hand, means applying this law in the concrete case and if in the concrete case it is ascertained that the woman has never had any other sexual relationship with anyone, has not had blood transfusion, has not come into contact with blood, this speaks for. However, if it is ascertained that there have been no other potential sources of transmission of the HIV virus, in this case even the law that explains a low number of cases in the concrete case will explain the causal link BARD and therefore there will be a certainty, which is not a statistical certainty of the law but an *evidential certainty*, that of the individual process. This means applying the law from an abstract dimension to a dimension of procedural certainty.

Analogical considerations hold in medical liability. If, for example, a wrong therapy is followed by death 40% of the times, this does not mean that in the individual case the probability of a causal link between the death of a patient and the medica error is 40%. If there are no other causal factors that explain the death event acquired at the process, it means that the judge will say that the case constitutes one of those 40 cases that are covered by the abstract law.

Therefore, one should not look at statistical probability, at the law that explains an abstract number of cases, but at logical probability, which means obtaining certainty from a procedural point of view. This means affirming that the conduct was the cause of the event 'beyond any reasonable doubt' and that there are no further causal factors of explanations of the event.

The causal link, therefore, must be investigated according to a counterfactual analysis capable of leading to a high logical probability and a rational and scientific credibility of the fact (Brocardi, 2022; Lebiu G. et al, 2017). Logical probability does not define the causal link in and of itself, but rather the criterion by which to proceed with the evidential determination of that link, which must make it possible to base a conviction on the point with a high degree of rational credibility (Marani, 2014). In such a context, causal laws provide a statement relating to the connection between certain types of phenomena and, through it, the necessary argumentative basis for the application of the conditional counterfactual formula which is indispensable (Hart & Honoré, 1985; Summerer, 2013).

CAP V

1. The WHO algorithm for individual causality assessment of AEFIs: an epistemological analysis

As Rocca et al. (2019) point out, the practical challenges that pharmacovigilance must face, specifically how to ascertain, collect, confirm, and communicate the best evidence to aid clinical choice for individual patients, derives in part from profound key issues regarding the epistemology of pharmacovigilance (E. Rocca et al., 2019). In such a context, the recourse to a plurality of methods and theories and their integration with different sources of evidence is necessary.

In pharmacovigilance the current tool widely used worldwide for individual causality assessment of AEFIs is the 2019 WHO algorithm (developed in 2013) – see Chapter II. The main opposing voices (Bellavite et al., 2020; H. Lee et al., 2020; Osimani B. & Ilardo, 2022; Puliyel et al., 2018) questioned its validity, stating that the algorithm presents some criticalities leading to the non-recognition of the vaccine's responsibility in having caused the AEFI.

Given what discussed in Chapters III and IV, the aim of this chapter is to highlight and investigate the WHO algorithm's criticalities underlining the flaws that characterize it both from a conceptual and a methodological point of view. The criticisms already reported in the relevant literature will constitute the starting point of my analysis.

I will start from a critical description of the algorithm with its mandatory sequential *steps* (WHO, 2019). I will proceed by identifying from time to time the aspects considered problematic.

Using the tools provided by the philosophical literature on causality (ontological, epistemological, and methodological, see Chapter IV) and by embracing both a multi-causal and an evidential pluralistic approach, I will stress the necessity to support/enhance/modify the pharmacological and immune-pathological evaluations discussed in Chapter III (i.e., complexity underlying vaccines' mechanism of action in relation to the AEFIs' manifestation, complexity of biological systems and of vaccine-person interactions, and so on), which highlights the need for a multi-factorial approach.

In addition, and above all, the epistemological analysis will prove to be fundamental in the qualitative evaluation of the causal link(s) underlying the algorithm's functioning and their adequate categorization, and for an overall evaluation of the algorithm as it is conceived and methodologically structured.

2. Critical description of the WHO algorithm

As can be seen from the diagram in **Fig.22,** if the first question is answered affirmatively (i.e., that there is an alternative explanation – e.g., a preexisting/concomitant pathology or genetic susceptibility or congenital anomalies, and so on) the analysis procedure is immediately interrupted by classifying the AEFI as *inconsistent*. This leads to the *a priori* exclusion of the AEFI-vaccine causal link without other indicators being considered. For example, the WHO manual reports the case of death of a teenager girl who had been administered the human papilloma virus (HPV) vaccine, in which the vaccine's responsibility was excluded on the sole basis of the evidence produced by autopsy examination that had found the presence of a malignant mediastinal tumor.
Moreover, this exclusion occurs without temporality being considered, except in the second part of *Step II*. It is then a very limited interval of time: this prevents the detection of reactions, even very serious ones (such as autoimmune reactions), which can arise even after weeks or months (Bellavite, 2020) – long-term effects are not considered.

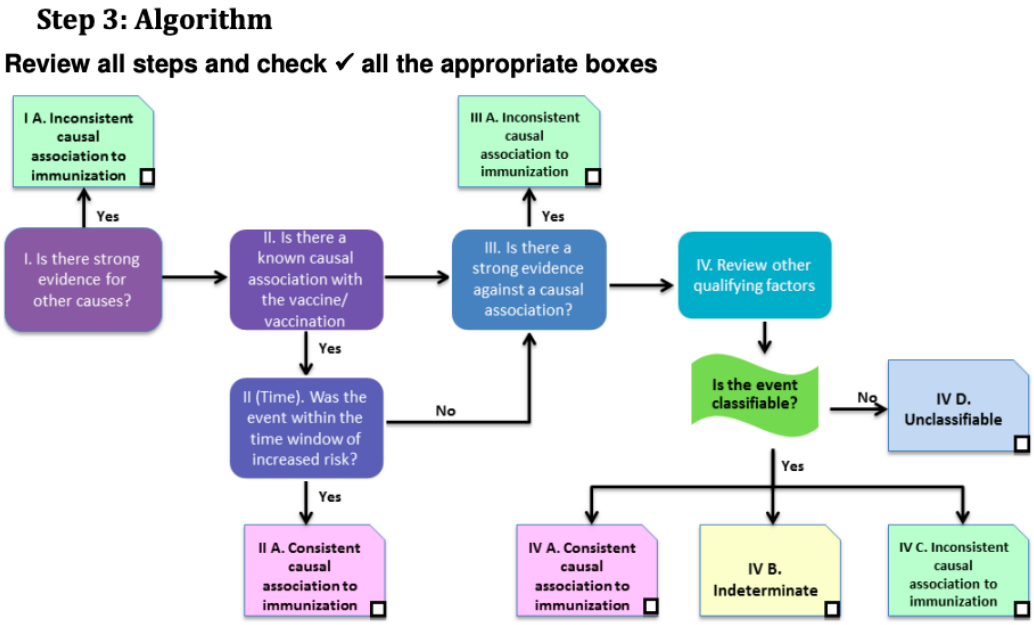

Figure 22*: The 2013 WHO decision algorithm. Taken from: WHO (2013: 34-35)*

Only those reactions already previously recognized as associated with the vaccine under examination *and* that occurred within an "appropriate" time interval (causality criteria) will be able to overcome the entire *Step II* and therefore to be classified as *consistent.*
Then, the transition from *Step II* to *Step III* is possible only if:

(i) there is no evidence for other causes *and* the reaction has been previously recognized as associated with the vaccine *and* the answer to the temporal question is negative, or
(ii) there is no evidence for other causes *and* the reaction has *not* been previously recognized as associated with the vaccine (the time question will be bypassed automatically).

In *Step III* it is necessary to verify whether there is evidence *against* the vaccine-AEFI causal link. As in *Step I*, the algorithm appears to require evidence to rule out the vaccine-AEFI causal link instead of proving it. It represents another exclusion criterion related to evidence published in literature that rejects a statistically significant association between the disease and previous vaccinations (i.e., epidemiological studies). Evidence at the population level is directly used for assessing causality at the individual level. Thus, the possible lack of evidence in literature would lead to the exclusion of vaccine-AEFI causal link, even if in that particular case there is biological plausibility and a plausible time interval for a consistent association.
Such a rigid use of the exclusion criteria applied to *Step I* and *Step III* (respectively the "other cause" for AEFI and the negative evidence in literature for the vaccine-AEFI causal link) can lead to evaluation errors or questionable interpretations (especially if the clinical situation or autopsy is not clear and decisive). For example, any concomitant pathology may be considered as *the* cause of AEFI, without considering the possible interaction between this pathology and the effect of the vaccine as a possible contributory cause of AEFI (most of which are multifactorial diseases) (Bellavite, 2020).
The assessor then moves to *Step IV* only if there is no evidence of other causes *and*:

Option a:
- the reaction has previously been recognized as vaccine-associated, *and*
- the response to the time question is negative, *and*
- there is no strong evidence *against* a causal association.

Option b:
- the reaction has *not* previously been recognized as vaccine-associated, *and*
- there is no strong evidence *against* a causal association.

In this last step, if the event is considered classifiable but does not meet case definitions[100] it is classified as *inconsistent*. This means that an AEFI not yet previously recognized as such, but potentially categorizable as *indeterminate*, therefore subject to further investigation, is instead filed as not linked to the vaccine (Puliyel et al., 2018).
In addition, it must be noted that *Step IV* is repetitive, as it asks again about alternative explanations for the AEFI (e.g., acute illness, other pre-existing health conditions or exposure to a potential risk factor or toxin, and concurrent medication). However, unlike *Step I*, it looks for a pre-existing pathology as a contributing factor that may have precipitated the event. This means that a pre-existing pathology should no longer be considered *the* cause (i.e., the unique explanation for the AEFI), but one of its possible causal factors. The potential role of contributing causes, therefore, is not totally ignored, but it is almost impossible or very difficult to get at this point of the analysis without the vaccine being excluded in the previous stages (see

[100] It means that it does not fall within the standard definitions established by the Brighton Collaboration, recognized and adopted internationally, concerning events already previously identified after vaccination; e.g., the definition of encephalitis as a possible pathological inflammatory manifestation of the central nervous system (CNS), temporally associated with administration of vaccines.

also Puliyel, 2018). Therefore, one could ask: Why does the algorithm repeat the same question posed in *Step I* to *Step IV*? Why did it not consider "the other cause" at *Step I* as one of the possible causes involved in the manifestation of AEFI?

Moreover, it is important to note that each AEFI has distinct characteristics and therefore, depending on the type of AEFI, different factors and different types of evidence with different strength may be required for causality assessment. However, the current WHO system doesn't provide specific causality assessment guidelines for individual types of AEFI (it provides general guidelines for all types of AEFI), which would be of great help to conduct more accurate causality assessments – see (H. Lee et al., 2020).

Looking at the algorithm as it is structured it is clear that, unlike the previous system that favored the identification of AEFIs as it admitted a plurality of causal indicators (see Chapter II), *independently sufficient* to increase the probability of causation, the current system has stiffened the procedure by dichotomizing it in a binary scale (*consistent/inconsistent*) in which much of the information is lost due to the requirements *jointly necessary* to classify the link as *consistent* (Osimani B. & Ilardo, 2022). This procedure obviously tends to increase the number of false negatives.

In the most recent version (WHO, 2019), the checklist has been revised with the addition of an additional question on *vaccine product* and a new section, the one on *vaccine quality* (see **Tab. E** in Appendix), and, since the algorithm proceeds by criteria jointly necessary for causal attribution, the greater the number of questions, the higher the probability that the causal link will fall into the *inconsistent* or *unclassifiable* categories (Osimani B. & Ilardo, 2022).

The revised AEFI classification scheme appears to be designed to deny the possibility of a new vaccination related AEFI and it can be seen as a violation of the precautionary principle[101] – see (Puliyel et al., 2018). The latter indeed dictates that when an activity raises threats of harm to the environment or human health (i.e., where there is evidence of risk), *"even if some cause and effect relationships are not fully established scientifically"*, precautionary measures (e.g., withdrawal of the pharmaceutical product from the market or suspension of the vaccination campaign to certain population's subgroups) should be taken until complete scientific evidence is available – see European Union law (EUR-Lex, 2002b, 2002a) and Chapter II.

In the 2013 WHO Handbook in which the algorithm is presented, it is stated: "*a definite causal association or absence of association often cannot be established for an individual event […] However it is important to try to identify a possible new vaccine product-related AEFI, as well as if the event is preventable or remedial*" (WHO-HIS-EMP, 2013). However, as we have seen, what the algorithm achieves is exactly the opposite.

In sum, the WHO algorithm as it is structured is subject to strong biases of the inferential process (Osimani B. & Ilardo, 2022), and with its application it seems difficult, if not impossible, to recognize a causal vaccine-AEFI link in a single case. Looking at the algorithm and considering the topics covered in the previous chapters, what needs to be asked, and what

[101] It is one of the fundamental principles of the European Union that governs policies relating to the environment, health and food safety, whose characteristic is the prevention of risks in the face of scientific uncertainty. See also (Osimani, 2013).

I will address in the following sections, is what the algorithm implies and does not (but should) imply at the level of:

1. Ontological conception of causality: what conception of causality do the WHO guidelines imply?
2. Epistemological approach to causal inference: what conception of epistemological justification do the WHO guidelines imply?
3. Methodology: what methodology do the WHO guidelines adopt?

And again, what are the criticalities and ambiguities that characterize the WHO algorithm?

3. What the current algorithm implies: causality assessment criteria

In this section I will list and discuss what from my point of view the algorithm seems to imply first at the level of causal ontology, and then from the levels of epistemology and methodology – see **Fig.23**.

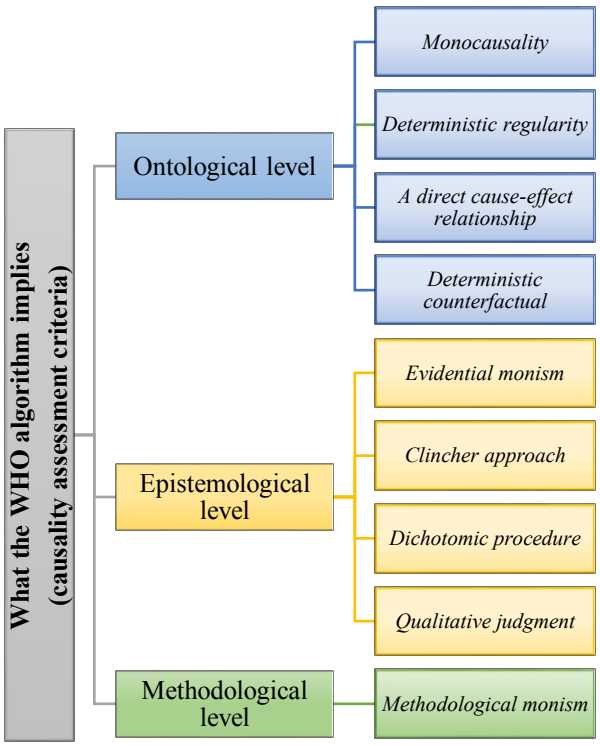

Figure 23: *What the algorithm implies at the ontological, epistemological and methodological levels of causality.*

3.1. Ontological level

3.1.1. Monocausality

The concept of causality that the algorithm seems to adopt is monocausal: it looks for a single (*unique*) cause for the disease, i.e., *the* cause (see *Step I*). One cause (or a risk factor alone) is necessary/sufficient to explain the AE – i.e., one-to-one causal association (X→Y) (see Chapter IV). According to this view, the disease is defined as monofactorial and not as a complex and variable constellation of signs/symptoms with multiple factors underpinning its etiology (i.e., multifactoriality). In the medical sciences the former case tends to be rare, while the latter is the standard. By defining the pathological manifestation (e.g., the AEFI) as monofactorial, the algorithm underestimates the role of contributing causes (e.g., mediators).

As we discussed in Chapter IV (see Mackie, Rothman) the causal basis of many diseases is too complex to identify a single necessary/sufficient cause (Stegenga, 2018). In general, cases of a single and well-defined etiology (e.g., genetic anomalies or infectious diseases) are rare, and anyway they find fertile ground in relation to other factors (Rothman & Greenland, 2005).

In clinical medical practice most health outcomes, including AEFIs, are pathological manifestations with multifactorial etiology (see Chapter III): they do not come from an *exclusive* cause but can be motivated by more than one causal mechanism, each involving the presence of multiple causes (or risk factors) of various kinds (exogenous and endogenous) that jointly interact in a complex way either precipitating the AE or by acting as cofactors[102] (Bellavite et al., 2020; Rothman, 2012b; Rothman & Greenland, 2005). The complexity of the pathogenesis of the disease is well underlined by the representation of causes in causal networks or in causal complexes such as those proposed by Rothman (mainly used in epidemiology – general level of causality) (Mackie, 1974; Rothman, 1976; Rothman & Greenland, 2005) – see Chapter IV.

For a context as complex as that of individual vaccine-AEFI causal link analysis, however, such a monocausal approach is not good. The algorithm appears too simplistic for a context as complex as that of AEFI, especially when compared with the WHO-UMC system for ADR and the old WHO-Brighton system for AEFI. In these systems, in fact, where even if an alternative explanation is available, a causal association with drug/vaccine is still considered "possible"[103], and where it is recognized that the two causes could work synergistically (Puliyel et al., 2018) [e.g., genetic susceptibility factors and other individual susceptibility factors that make one susceptible to developing an AEFI (Berkovic et al., 2006; Soriano et al., 2015)].

Multifactoriality, therefore, should be considered as a necessary element in the causal 'diagnosis' of AEFIs, and if so, since an effect can ontologically depend on many causes, and

[102] Co-causes may act as difference-makers or may be involved in a chain of reactions in which interactions between causes lead to the effect.

[103] The old system was in line with John Mill's theory that in nature there may be multiple reasons (causes) for the same outcome, and, if there are two possible causes at the same time, one of them could be the causal factor.

even different mechanisms of causality, an entity like *the* cause may simply not exist (Scheffler, 2003).

3.1.2. Deterministic regularity

A view of causality that underpins the algorithm can be close to that of regularity that presuppose causation to be deterministic (see Chapter IV). Causality is interpreted as a deterministic causal regularity: if X causes Y, then X must *always* be followed by Y (i.e., constant conjunction). Thus, whenever X occurs, Y occurs (A→B, asymmetric relation), and X is cause of Y if it is a sufficient/necessary condition for Y in a two-way relationship (A↔B). For instance, if we claim that "H1N1 vaccine causes Guillain Barré Syndrome (GBS)" it means that (IOM & Vaccine Safety Committee, 1994):

(1) all people immunized with H1N1 vaccine will develop GBS – i.e., if *all* recipients of H1N1 vaccine develop the disease, H1N1 vaccine is a sufficient cause of GBS;
(2) all cases of GBS are caused by exposure to H1N1 vaccine – i.e., H1N1 vaccine is a necessary cause of GBS if the disease occurs only among the recipients of H1N1 vaccine.

However, as I pointed out in the previous section and in Chapters III and IV, in medicine this view seems to be too simple, since many diseases are complex (i.e., multifactorial). Causal structures are not one-to-one dependencies but complex networks of dependencies. For many causes supposedly necessary for each effect there are several alternative causes, and for many conditions where a sufficient cause is believed to have been found, an exception can be found, and in most cases those factors identified as sufficient to produce the effect are sufficient only in the context of the background conditions that are assumed to be in place.
Causality should therefore not be expressed in the form 'if X then *always* Y'. To say that *not always* a cause is *invariably* followed by its effect (e.g., smoking *not always* causes cancer, and there are cases of cancer in people who do not smoke), but that *sometimes* X leads to Y and sometimes you will have Y without having X, means that a cause is *neither necessary nor sufficient* for Y, and the constant conjunction becomes a *possible* conjunction (see Chapter IV). Returning to the previous example, therefore, a third point should be added, namely:

(3) is there at least one person whose GBS has been caused or will be caused by H1N1 vaccine? – i.e., H1N1 vaccine is a cause neither necessary nor sufficient; it is a putative cause.

In most AEFIs a clinical cause may not be either necessary or sufficient for a given individual (Palinkas, 2014), but must be contributory (or partial). In such a context there is no answer to the question "what is *the* cause of the observed pathological phenomenon?". Since there is not just one possible cause, but several, each cause cannot be considered *per se* necessary/sufficient

(deterministic) to determine the disease (Puliyel, 2018; Bellavite, 2020), but rather probabilistic (see Chapter IV) – see **Fig.24.** A contributory cause may increase the probability of developing AEFI; thus, given A, the probability of AEFI is greater than the probability of AEFI given not-A, so eliminating A you can reduce the risk of AEFI.

necessary cause	•If disease Y manifests, then cause X must have preceded it; without X, the disease Y never develop
sufficient cause	•If cause X occurs, then disease Y will also occur; in presence of X the disease Y always develops
contributory cause	•If cause X occurs, the probability of disease Y increases.

Figure 24: *Necessary, sufficient, and contributory causes.*

However, in the algorithm the distinction between deterministic and probabilistic causality is not sufficiently clear. By embracing a deterministic regularity conception of causality, the algorithm falls pray of Hume's fallacy, according to which causality exists only if A is sufficient in itself for B.
In this way, the possible co-causal role of vaccines in multifactorial diseases (see Chapter III) is underestimated along with that of genetic susceptibility (or pre-existing disease) which, as a co-cause, would no longer be sufficient on its own for AEFI (see Mackie, Chapter IV). The vaccine may have contributed concretely to AEFI, e.g., to precipitate encephalopathy in patients susceptible due to genetic factors (Soriano et al., 2015).
In line with the application of a probabilistic notion of cause at the individual level of causality assessment in the case of multifactorial diseases is also the Italian Cassation Court with the Franzese judgment[104].

3.1.3. A direct cause-effect relationship

The WHO algorithm defined the term causal association as *"a causal-effect relationship between causal factor and disease without factor intervening in processes"* (WHO, 2019). It means that there is a clear, *immediate* connection between the events.
In practice, here the algorithm is talking about causes as a chain of events (see Lewis, Chapter IV) looking for a *direct* cause-effect relationship. A direct cause, in fact, leads to the outcome in an unbroken chain or train of events, and the connection is *immediate* in the sense that the cause proximately resulted in the final event (i.e., proximate cause) (see Chapter IV) –it is the

[104] "[…] the presence of a risk factor is not in itself sufficient to ascertain the causal link with the individual occupational disease. It may be used to indicate mere potential, for the purposes of general causality, or to indicate the suitability, the general capacity of a substance to cause disease. But it cannot serve individual causality or to identify the link that binds a precise activity to a single harmful event" (Cass. Civ. Sec. Lav. n. 8078, 2016).

closest cause to the final event in a chain of events, it is basically the last cause resulting in the final event.[105]

However, the vaccine is almost never a *direct* cause of the event, and it is not even said that it is *immediate*. In human biology, cases of direct causation are very rare, because of the existence of intermediate steps in any causal process. AEs may be influenced by one or more intervening factors (e.g., predisposing, enabling, precipitating factors, and so on) that indirectly cause them – see Chapter IV. Causal relationships may consist in indirect effects (non-linear interactions): the relationship between a cause and its effect is mediated/moderated by one or more factors that contribute to the occurrence of the effect without being directly linked to it (i.e., contributing causes).

Moreover, it is not certain that the AE is *immediate*, but it could occur with a certain *temporal latency* with respect to the 'event cause' – see Rothman, Chapter IV.

At *Step I*, if, for example, a person is administered with vaccine Z and then the adverse event Y (e.g., death) occurs, and a genetic predisposition X is found, which would inevitably lead to Y in a time t_{10}, the fact that the algorithm defines X *the* cause of Y means that the X-Y causal relationship is considered direct. It implies that the potential role of Z (or other possible causes) as intervening factor(s) in the processes that leads from X to Y is ignored. The vaccine, for example, could have intervened as an intermediary factor that increases the likelihood of developing Y or that anticipates the manifestation of Y to a time t_5 by shortening the induction period of X[106] – see Rothman, Chapter IV. In this case the X-Y causal relationship would be indirect, and not direct as the algorithm defines it, and consequently it would no longer be possible to consider X as *the* (direct) cause.

By adopting the above new definition of causal association, the algorithm tends to underestimate the presence of different type of causal relationships and the mechanism by which they are mediated, thus also ignoring the counterfactual 'whether death would have occurred at that time (i.e., t_5), if it had not been caused by the vaccine' – see also Puliyel et al. (2018).

By underestimating interacting causalities, the algorithm classifies a causal association as *inconsistent* when there is another cause and as *undetermined* when the vaccine may be a cause but there is no evidence that it is *the* cause (Bellavite, 2020). Thus, many AEs in which the vaccine may have played a role as a co-cause remain unrecognized. For example, the contribution of vaccine in precipitating encephalopathy in patients who are susceptible on account of genetic factors, as well as sudden death after vaccination of an infant with pre-existing heart disease, might not be considered as causally related to the vaccine (Bellavite, 2020).

[105] In contrast, the underlying (or ultimate) cause is the first cause, that set the other in motion resulting in a series of events, each one causing the next. It is remote from its putative effect in a causal chain, it ultimately resulted in the final event.

[106] The vaccine can also help in aggravating a pre-existing pathology (reinforcing factor).

3.1.4. Deterministic counterfactual

In the algorithm the counterfactual understanding of causality seems applied in a deterministic and monocausal way. At *Step I*, for example, assuming that the other cause (e.g., pre-existing pathology) may not be necessary for AEFI, but at the same time may be sufficient for it, one wonders if AEFI would have occurred in person X if it had not been for the pre-existing pathology (one wonders if it made the difference) (see Lewis, Chapter IV). The assessors therefore ask: '*but for'* the existence of the pre-existing pathology (i.e., if the pre-existing pathology was not present), would AEFI have occurred in person X? Or, in other words: would AEFI have occurred in any case in person X without the existence of the pre-existing pathology? if person X had not had the pre-existing pathology would AEFI have occurred?
This counterfactual, also known as the 'but-for-test' (or *sine qua non)*, works under the assumption of determinism. The presence of the pre-existing pathology would mean the absence of the link of AEFI with any other causes in person X. The answer given by the algorithm is that the AEFI would not have happened *but for* the pre-existing pathology. The latter is indeed considered *the* cause of AEFI (i.e., it is necessary for it, it is the factor without which the event could not occur). It is not asked whether AEFI *could* have occurred anyway in person X due to the vaccine without the pre-existing condition.
However, at the individual level, the counterfactual is based first on the patient's medical record, and then on hypothetical assessments based on well-known general laws, which should all be instantiated in the individual case. The event may be the product of non-necessitating and indeterministic cause(s). The pre-existing pathology, as well as the vaccine, are nothing more than one cause (a risk factor) among multiple causes involved in the occurrence of AEFI in person X.
The pre-existing pathology could be a background condition and the vaccine a trigger. In situations where there are multiple causes for the event (including situations of overdetermination), the "but for the test" is unworkable. Each cause is a potential cause of the event, so there is no certainty as to which one *actually* caused AEFI. It is difficult to determine a single factor responsible for the outcome. This implies that, if according to the general laws we know that the pre-existing pathology may cause the observed AEFI, it is not said that in the specific individual X it has *actually* caused AEFI. Causation is potential: the pre-existing pathology *usually* causes AEFI, it is a putative cause.
Therefore, the query may be whether the putative cause contributed materially to the outcome (David et al., 2005), but it is equally difficult to analyze the contribution of each individual cause to the entire harmful event and to determine which factor is more responsible and to what extent, due to the possibility of too many "but-for" causes. [In such cases the jurisprudence makes use of "joint and several liability" (tort law), i.e.: all the factors involved in causing the event are considered independently responsible for it].
Given that an AEFI is complexly determined and given the underlying uncertainty about what is that *actually* led to the event in person X, only a qualitative probabilistic answer to a question "what would have happened if" could be possible. Therefore, in *Step I*, if there is evidence of other causes, one should ask: '*did* the risk made by 'the other cause' *probably* cause AEFI in

person X? If person X had not taken the vaccine, *how likely* is it that AEFI would have occurred at that particular time due to the presence of the pre-existing pathology? Would AEFI have had a *higher* or *lower probability* of occurring?'

3.2. Epistemological level

3.2.1. Evidential monism

The epistemological approach to causal inference that seems dominant in the algorithm is that of evidential monism (see Chapter IV): only one type of evidence is required to justify causation at each Step.
For example, in *Step II* only evidence of other causes is used to exclude the vaccine-AEFI causal link, while in *Step III* only *strong* evidence against a causal association is used. In *Step III*, the use of the term *strong* recalls to the concept of "*strength*" of causal association, that is a Hill's causality criterion used in epidemiology, corresponding to *probabilistic dependence* causality indicator (see Landes et al., 2018). The type of evidence requested by the algorithm to justify its conclusions here is epidemiological (experimental[107] or observational) evidence [see page. 5, 23 and 32 (WHO, 2019)]. If in fact for the algorithm causality is regularity (ontological level), it is quite obvious that it tends to seek regularity to infer causality (epistemological).
However, using solely one type of evidence to support a causal relationship increases the likelihood of false negatives (failure in detecting possible causes of the observed event) (Landes et al., 2018). This problem justifies the need to adopt a sort of evidential pluralism. Along experimental evidence would be more appropriate to consider other and different kinds of evidence, that could be combined in order to support a causal hypothesis and strengthen it [see (Krieger & Smith, 2016; J. Reiss, 2009, 2012)].

3.2.2. Clincher approach

The algorithm seems structured like a *clincher* method. This approach requires *conclusive* (irrefutable) evidence for warranting a causal conclusion: evidence that 'clinches' the conclusion (i.e., the causal relationship), rather than merely 'vouches for' it (Cartwright, 2007b) – see Chapter IV. In medicine clinical experimental evidence (mainly RCTs – the gold standard level of evidence –, see Chapter IV) is considered as such (i.e., *strong* evidence). Thus, if you don't have it anything less than this is not accepted as evidence. (Hence the problem of the admissibility of evidence in the algorithm that I will discuss later on).

[107] Experimental evidence produced by studies such as RCTs – or other experimental clinical trials (non-randomized, or randomized and uncontrolled) –, meta-analysis of RCTs, etc.

Clinchers deductively force their conclusions, thus, as such, the algorithm, accepts/rejects the causal hypothesis on the sole basis of statistical evidence (i.e., *hypothesis testing*): H entails E, your evidence contradicts E, hence you may infer that H is not the case (Osimani, 2014c) – i.e., *modus tollens*:

$$\begin{array}{l} H \rightarrow E \\ \neg E \\ \hline \neg H \end{array}.$$

In *Step III*, the algorithm focuses on correlative (or difference-making) evidence alone [i.e., on causal association studies, epidemiological (experimental or observational) studies] and uses this evidence to exclude the vaccine as cause of AEFI [see page. 5, 23 and 32 (WHO, 2019)]. However, such an approach is epistemologically and methodologically wrong. Difference-making (or correlation) evidence may often not be sufficient by itself to prove causation. Correlation (or statistical association) does not imply causation: "correlation is (...) neither necessary nor sufficient for causation" [(J. Reiss, 2009),p. 24]. Despite this, the algorithm is justifying its conclusions on the basis of this type of evidence, that is evidence of treatment efficacy. Clinchers have indeed been developed to test the efficacy, they are *not useful* in case of AEs to pharmaceuticals (context in which the algorithm operates), and even more so in case of an individual analysis. In fact, RCTs:

(i) focus on false positives, thus missing relevant issues when it comes to causal indications regarding AEs – risk detection research should focus on false negatives (Osimani, 2014b) (i.e., on the problem of failing to see causality, cases where the vaccine is not a cause of AEFI, when in fact it is). This is important because RCTs study a limited number of treated patients, which may not be enough to detect a rare but serious adverse effect of treatment. It means that, since this type of error is a function of the statistical power of the study, a large sample size would be required to detect rare and serious AEs;

(ii) are carried out on homogeneous groups of people selected according to pre-established inclusion criteria and studied under controlled conditions, for which the evidence produced provides evidence referring to subjects *similar* to the one under examination, thus limiting external validity. The evidence is limited to situations that are homogeneous to those in which it has been demonstrated, but not all situations where an event can occur are the same. Men are not all genetically and biologically equal so that what benefits one can hurt another and *vice versa*. The physiological 'mechanism' at work may not always be the same. The population studied is very different from the real-life treated population, making it difficult and problematic to directly apply clinical trial results to routine clinical practice cases in relation to dosage, efficacy, or even safety (Anjum et al., 2020) – the issue of external validity. Therefore, evidence from RCTs (although perfectly valid internally) must be extended to the target population with great caution (Osimani, 2014c);

(iii) provide information (understanding) of what works but not of what doesn't work – the fact that an intervention works does not mean that there is a guarantee that it actually makes people better and that there are no possible harmful effects – understanding how the intervention works (i.e., the underlying processes) is crucial in protecting people against possible vaccines' serious adverse effect;
(iv) investigate a limited number of factors, thus failing to embrace the concept of multifactorial disease's etiologies (Rizzi & Pedersen, 1992) – most AEFIs are pathological manifestations of multifactual nature (see Chapter III).

Given what has been said so far, it follows that clincher methods are inadequate for the purpose of minimizing harms of health interventions. The application of a clinching approach (including the underlying hypothetico-deductive reasoning) in case of individual AEFIs' assessment is scientifically and methodologically wrong, causing a decrease of accuracy of the tool by raising false negatives.
Despite this, the algorithm, while being aimed at an analysis of adverse events to vaccines, was structured according to the clincher methodology. This choice, although debatable, is not very surprising, as the evidence on which clinical decisions are mainly based, and which are therefore considered causally relevant, are statistical and population-based evidence (generated by large clinical trials) (Anjum et al., 2020), and also because, in the regulatory field, the guidelines for the approval, suspension and withdrawal of drugs are strongly based on *hypothesis testing* (Osimani, 2014a).
However, in evaluating harms, you generally do not start with a specific hypothesis and then collect evidence to test it, but rather the reverse: you observe and collect evidence, which you are called on to explain in some way (Osimani, 2014b). In contrast to clincher, another type of approach, in my view, may be better suited to the context of analysis of AEFI. This method, called *voucher*, 'merely vouch' for its conclusions – see Chapter IV. It doesn't require conclusive evidence but evidence that can help make a case for a conclusion (i.e., evidence that 'speaks' of a causal relationship), and that can be *combined* with evidence of different kinds from other methods to secure the conclusion of causality (Cartwright, 2007a, 2007b). Single pieces of heterogeneous evidence, which if taken individually would not be sufficient to allow any significant inference, could be accumulated (over time) and jointly support a given hypothesis, strongly indicating the hypothesis of a causal association between the pharmaceutical event and the observed AE, without nevertheless being conclusive (Landes et al., 2018; Osimani & Mignini, 2015).

3.2.3. Dichotomic procedure

The current algorithm tends to establish the causal link in a rigidly dichotomic way. The algorithm is set up as a categorical causal assessment, i.e.: it accepts/rejects the hypothesis under investigation (hypothesis falsification) in a dichotomist way (i.e., black or white, yes or no, consistent or inconsistent, etc.) without degrees in-between (Osimani, 2020; Osimani &

Mignini, 2015). The algorithm becomes a binary method that needs precisely clinching evidence otherwise it fails to make the inferential shot. Everything else is classified as *indeterminate*. Therefore, there will be many more *indeterminate* cases in a dichotomous approach than in a graded one. In the context of AEFIs, if a lot of cases go into the *indeterminate* category this inevitably leads to losing a lot of information.
It is therefore necessary that the algorithm turns into a probabilistic causal evaluation tool, which no longer requires a clear-cut rejection or acceptance of the investigated hypotheses (Landes et al., 2018; Osimani & Mignini, 2015).

3.2.4. Qualitative judgment

The algorithm accumulates the evidence in a qualitative way, that is, it gives a non-numerical judgment, which therefore takes place on the basis of personal observation by the assessor. It assigns a qualitative value to the causal vaccine-AEFI link, i.e., 'consistent' or 'inconsistent'.
Expressing oneself in qualitative terms allows the professional identity of clinicians (with its experience) to play an important role in the process of causal evaluation, which, in my opinion, makes this mode of judgment correct. A qualitative judgment is more useful than a quantitative one in cases where there is no previous knowledge on the fact under examination, which means there is little or no available data on it. However, in dealing with uncertain situations, qualitative judgment should open up many more possibilities than a *dichotomous* response.
The reasoning around the causal link should be based on the ground of probabilistic causality understood in qualitatively terms according to logical probability – high degree of logical probability (see Chapter IV).

3.3. Methodological level

3.3.1. Methodological monism

From the epistemological analysis it emerges that the algorithm tends to adopt methodological monism in assessing individual causality, preferring to focus on population-based evidence (i.e., what is known about *"Can it?"*, general causation) [page 10 (WHO, 2019)].
The 2019 WHO manual states that *"the evidence of a link between a vaccine as a potential cause and a specific event is derived from epidemiological studies"* [see page 5 (WHO, 2019)], that may be experimental (mainly RCTs) and/or observational. In practice, the algorithm refers to hierarchies of evidence. *Step III* privileges the use of *"Cochrane reviews, GACVS reviews, systematic reviews, etc."* [see (WHO, 2019), p. 32] to conclude the rejection of a causal vaccine-AEFI relationship.

As we have already discussed the design of RCTs is considered to provide the *strongest* scientific evidence (i.e., necessary/sufficient) related to a causal vaccine-AEFI association. However, as we discussed in the epistemological section, while such studies are generally accepted as the most scientifically valid assessment of causal relationships, most are often too small to contribute useful evidence related to a vaccine-AEFI association. Many of the AEs are in fact so rare that even large multicenter randomized trials would be too small to detect them. As already mentioned, it is essential to base the causal judgment considering also, and simultaneously, single clinical cases, case series and uncontrolled observational studies. It is therefore necessary to gather different type of evidence and evidence from different sources (methodological pluralism).

If we look at *Step II* one may argue that the algorithm shows a pluralistic evidential approach by focusing both on difference-making evidence (i.e., association studies) and mechanistic evidence (i.e., basic science studies, mechanistic knowledge – Hill's *biological plausibility* criterion) (Landes et al., 2018). The algorithm first looks for a *known* association between the vaccine and the observed AEFI [see page 25 (WHO, 2019)], and then, if "*the Can it? question has no clear "yes" or "no" answer, biological plausibility may provide support for or against vaccine causality"* [see page 11 (WHO, 2019)]. However, things are not exactly as they seem. The 2019 WHO guidelines, in fact, specify that *"evidence regarding biological plausibility can never prove causality"* and that *"it can be invoked only when a laboratory finding or a symptom/sign are consistent with the natural history and physiopathology of the infection or antigen"* (WHO, 2019).

I will discuss the problem of underestimating biological plausibility later on. What is important to underline here is that with the first statement the algorithm explicitly gives little value to mechanistic approaches (studies on biological mechanisms) and at the same time with the second one, it greatly limits their use by the assessor. Consequently, a higher value is automatically given to experimental approaches (i.e., difference-making evidence), thus confirming the adoption of an evidential monistic approach, and excluding other valid approaches (i.e., lower-level (weak) evidence, e.g., anecdotal evidence). This may be particularly detrimental as much of the evidence for harm comes from anecdotal reports or case series (Osimani & Mignini, 2015)

Moreover, as we have discussed in the previous sections, because of their limits and their inadequacy to be applied in an individual case, experimental studies cannot be considered in such an absolutist way as the main and only source of valid evidence to justify causation.

The above confirms the need for the algorithm to adopt a pluralistic evidential approach and that, in doing so, it should integrate lower-level evidence with higher-level one (i.e., methodological pluralism).

4. What the current algorithm should imply: causality assessment criteria

In this section I will list and discuss what from my point of view the algorithm should imply first at the level of causal ontology, and then at the level of epistemology and methodology – see **Fig.25**.

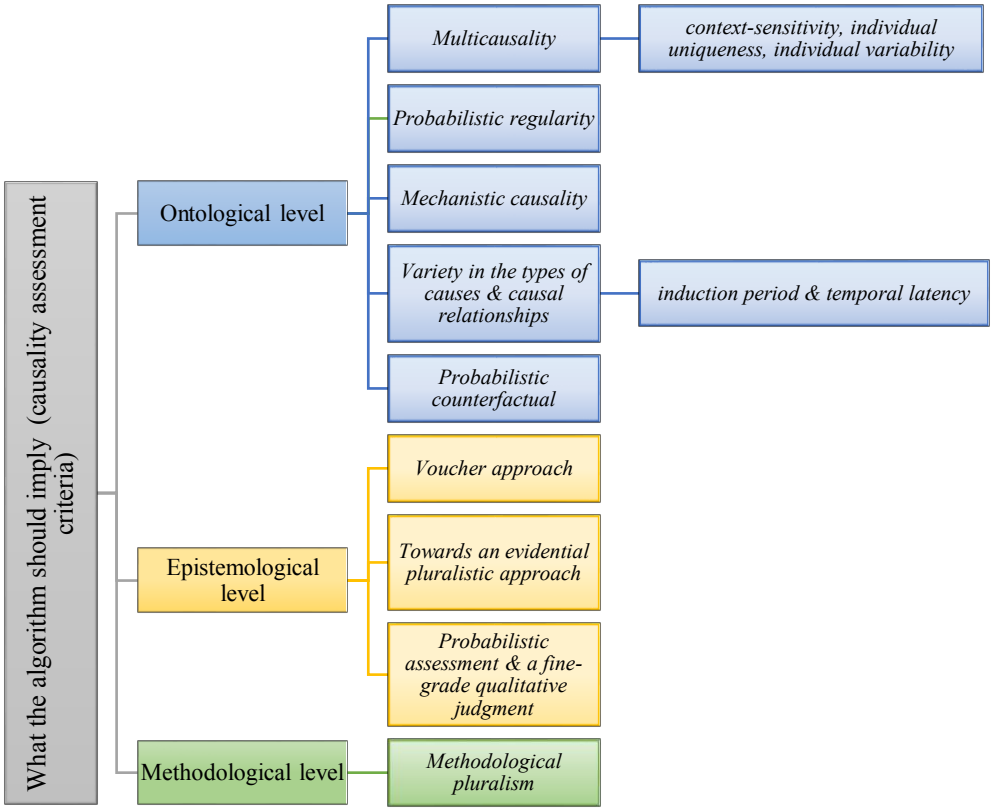

Figure 25: *What the current algorithm should imply (causality assessment criteria) at the levels of causal ontology, epistemology, and methodology.*

4.1. Ontological level

4.1.1. Multicausality, context-sensitivity, individual uniqueness, and individual variability

As discussed in Chapter IV, causality may be best conceived within a pluralistic frame.
In *Step I* of the algorithm the fact that if there is an alternative explanation for AEFI (or if another factor is involved) the possible vaccine-AEFI causal link is rejected clearly indicates that multifactoriality is not considered. If it had been considered, the 'other cause' would not be sufficient to exclude other factors and the vaccine could be considered as a co-cause in a set of causes, each of which may play a role in causing the event.

It is essential to distinguish between what we can define as AND causality, OR causality and interactive causality. In the first case, two causes contribute to the event in the sense that both are necessary for the event to occur (if you do not have both the event does not manifest). In the second case, it is sufficient that one of the two causes is present for the AEFI to occur (each cause is *per se* sufficient). In the third case we are faced with multicausality for which two (or more causes) interact synergistically (reinforcing each other) to produce the event. Here the causes are not necessary for the event, but if both are present the probability that the event will occur in that individual at that time and with that intensity increases.
However, the algorithm doesn't do such distinctions, focusing only to the OR case (i.e., the presence of the preexisting pathology is *sufficient* for the AEFI to occur). Given the multifactorial nature of AEFIs and the other cases mentioned above, this should not be the case.
Moreover, all the above suggest that further elements need to be considered, namely: (i) any analysis of causality is highly dependent on the specific context (context-sensitivity); (ii) each individual constitutes in itself a unique and complex dynamic system: each person is different from another one (individual uniqueness); and (iii) risk factors vary from individual to individual (individual variability, mutual causality) (see Chapter IV).
In the case of vaccines, it is crucial to stress that we are in a situation in which the treatments under investigation are high context sensitive. The vaccine-person interaction(s) are important: the vaccine can lead to the AEFI by interacting with one or more different components present in the individual [factors that are different from person to person: e.g., other drugs (polypharmacy), predisposing genetic factors, ongoing inflammatory processes due to pre-existing pathologies, immune system, metabolic pathways, etc.].
The mechanism of action of the (bio)pharmaceutical product is studied and it is, in a certain sense, an objective fact, but how it works in every single person is uncertain.
In the medical sciences, every clinical case is never the same as another one. It is therefore important that causal analysis focuses on the whole patient experiencing the condition (Anjum et al., 2020).
In individuals with the same manifestation of disease, the disease may progress differently, the impact of a certain risk factor for that disease is experienced differently from person to person, the same treatment can have opposite effects on different individuals (i.e., it can have beneficial effects for some while for others it can be poisoning), etc.
C*ontext-sensitivity*, *individual uniqueness,* and *individual variability* make individual causation analysis highly complex and characterized by strong uncertainty which further supports the need to make judgments according to a probability scale (such as those proposed in the old system – see Chapter II).
Although they are crucial elements to consider in an analysis of causality at the individual level and in which AEFI is multifactorial, the algorithm seems to take none of these concepts into account. In fact, if we look at the algorithm (especially at *Step I*), as it has been conceived and structured, it does not seem to do justice to:

i. The complex nature and variety of many reactions to vaccines (e.g., inflammatory and immune pathologies induced by vaccine) – complex disease causation.

ii. Complex mechanisms regulating immune responses.
iii. The role of:
    a. Predisposing conditions (genetic or acquired factors) in modulating immune response. In medicine, it is known that a predisposing factor produces a susceptibility or disposition (a genetic predisposition and/or a variation in genes, such as particular polymorphisms) in the person to a disease without *actually* causing it. In other words, genetic susceptibility, contributes to the development of a disease but does not directly cause it.
    b. Alteration of the microbiome and of the intestinal barrier that may contribute to autoimmune or systemic inflammatory reactions by interacting with immune cells.
iv. The role of other risk factors, endogenous (gender, age, etc.) and/or exogenous (viruses, bacteria, drugs, habits, environment, etc.) in contributing to the occurrence of the AEFI in the individual.

If these complexities, conditions, multiplicity of risk factors, contributing and interacting causalities were properly and carefully considered and analyzed, it would be quite plausible to conclude that a vaccine may play a co-causal role, by contributing to precipitate an AEFI in a predisposed individual. In inflammatory and immune system diseases, interaction with underlying pre-existing diseases is the rule, so it is easy to do errors in causal evaluation using the algorithm as it is currently set.
The WHO algorithm should also include the interdependence factors of all risk factors before decreeing a vaccine-AEFI non-correlation. It should be seen if all the other causes were not a risk factor in the encounter with the vaccine that may have acted worsening the situation.
In this context, two philosophical approaches can be of great help to establish causality: one in which interacting causal factors leading to the event should all count as causes (dispositionalism, Chapter IV), and/or one that distinguishes between factors that are context-related (background conditions) and factors that are more salient (triggers), and that would count as causes (see Waters, Chapter IV).

4.1.2. Probabilistic regularity

The concept of cause that, in my opinion, the algorithm should embrace is that of probabilistic regularity, and not deterministic.
The probabilistic approach abandons the idea of causality as a constant conjunction in favor of causality as a probable conjunction. Causal relationships are accompanied by probabilistic dependencies: if X causes Y, the presence of X increases (or decreases) the probability of Y occurring (see Chapter IV).
Approaching causality in probabilistic terms accounts for both multifactoriality (see Mackie, Rothman), and dispositionalism.
Since most AEFIs are multifactorial, due to multiple contributing causal factors present in different combinations (some of which will be known but others will be unknown), and

regarding the possibility that vaccines may act as co-causes in determining AEFI (see Chapter III), there is not only one possible causality, but several, and each should be evaluated in the context given by probability (Edwards, 2012). The purpose cannot be to identify *the* determining cause, rather it would be better to resort to the concept of probabilistic causality, which deals better with cases of multiple causality, compared to deterministic ones.
According to dispositionalism (see Chapter IV), causality is potential (i.e., cause X has a tendency to cause Y). Every causative factor is potential: e.g., in an individual with a (genetic or acquired) predisposing factor, this factor may cause the AEFI (e.g., abnormal immune response) with the intervention of the vaccine. A vaccine may accelerate or reinforce abnormal reaction or trigger it (a vaccine may trigger autoimmunity). Moreover, dispositionalism emphasizes the processual nature of a manifestation, i.e.: it is produced by two or more mutual disposition partners acting together, where a disposition is a thing's property (causal power) towards manifestation, and the power is for the whole process (causal chain) that lead to the final event.

4.1.3. Mechanistic causality

The existence of different possible causal mechanisms that may have led to AEFI indicates that a mechanistic concept of causality should also be considered.
A contributory cause (e.g., the vaccine) may be involved in a chain (or web) of reactions in which interactions between causes lead to the effect (see Chapter IV).
With the concept of causality as regularity we see a black box regularity from A to B while with the concept of cause consisting of mechanisms, we enter the black box. A causal mechanism in fact explains what is going on between the intervention (e.g., the vaccine) and the outcome (e.g., the AEFI), i.e., the processes or pathways through which an outcome is brought into being.

4.1.4. Variety in the types of causes and causal relationships, induction period and temporal latency

In a complex context such as that of AEFIs, where they are the result of the interaction and balance between multiple contributing factors and intermediate factors, it is not possible to rely only on a *direct* cause-effect relationship (Fedak et al., 2015).
However, the algorithm underestimates the role of interacting causation and more generally seems not to consider the types of causes and causal structures. But doing so is important for trying to define what kind of cause the vaccine may be (e.g., direct cause, indirect cause, contributing cause, interacting, mediating or moderating cause, and so on) and the type of causal relationship in which it is involved (see Chapter IV), and consequently attribute to it the degree of probability with which it may have contributed to the occurrence of the AEFI in the patient.
The vaccine as a contributing cause, for example, can act by aggravating a pre-existing condition (pathology) or intensifying its manifestations, prolonging its course, delaying its

healing, accelerating its evolution, favoring the appearance of complications, or anticipating their unfortunate outcome.
Furthermore, focusing on a unique cause responsible for the event, the algorithm does not count for phenomena of redundant causation. For example, when an event is determined by multiple causes acting in concert to produce it, it may be a case of overdetermination (see Chapter IV). This could be the case with AEFIs, but the algorithm seems not to take this into account. For example, if without the disease the person would have died from the vaccine and without the vaccine would have died from the disease at the same time then there would be perfect overdetermination.
The WHO algorithm does not distinguish any of this, being very simplistic. In sum, it does not imply but should imply:

i. Cases of redundant causation (preemption/overdetermination).
ii. Indirect cases.
iii. Contributory, interacting causes (mediating, moderating/modifying), including cases of synergistic interaction vs additional effect.
iv. Intervening cause that anticipates the event [e.g., the disease leads to the effect in a time equal to 10 years (t_{10}) the vaccine arrives and anticipates, accelerates and/or intensifies the pre-existing madness for which you die of disease and vaccine. Without vaccine it would have been at t_{10}, with the vaccine at t_5], or that postpone it.
v. Temporal latency and induction period (see Rothman, Chapter IV).

The WHO algorithm does not distinguish any of the types of causes and causal relations above. It is very simplistic. However, there are so many possibilities, and each cannot be treated in the same way. What needs to be asked is how do we formalize multifactoriality in the individual case? Case by case we should see, for example, the vaccine in what kind of causal structure it can be (causal models). With the proposal that I'll make in the last section of this chapter, I intend to provide a tool that can distinguish them and treat them adequately.

4.1.5. Probabilistic counterfactual

The ascertainment of individual causality involves counterfactual and abductive reasoning. These inferences are based on clinical and subclinical conditions of the patient before and after administration of the vaccine and on general notions of pathophysiology, genetics, immunology, and so on, in order to identify the most plausible explanation of the event manifested in the individual (Osimani B. & Ilardo, 2022).
Given the multifactorial nature of AEFIs (including cases of redundant causation – see Chapter IV), we know that a causal factor does not exclude other causal factors, and different types of causal relationships may be present. Given the individual context of analysis, we must also consider the context sensitive nature of vaccines, individual variability, and uniqueness. Consequently, in the algorithm, in order to categorize the AEFIs, a counterfactual reasoning

like the following should be applied: if the co-cause X (e.g., vaccine) had not been present, how much would have been the probability that the effect would have occurred in the individual at that particular moment? The counterfactual must be probabilistic exactly because of multifactorial nature of AEFIs.
In the algorithm, as we have seen, the counterfactual is placed instead, and erroneously, in a deterministic way, and the time factor (e.g., long-term effect) is not considered.

4.2. Epistemological level

4.2.1. Voucher approach

In the algorithm, conclusive evidence is needed to infer the vaccine-AEFI causal link, while a voucher approach is satisfied with evidence that is not necessarily conclusive (see Chapter IV). According to a voucher approach, for example, basic scientific evidence (e.g., experiments on molecules at the cellular level – mechanistic knowledge) cannot serve as conclusive evidence to say that the medicine causes the AE. These are laboratory-level studies, so you know that the drug acts that way at that level, but then at the clinical level it could take pathways in an individual's body that you do not know. So, such evidence would only serve as a causality indicator, in the sense that it indicates that there *can* be causality and not that there is causality in an absolutist way.
This type of approach admits a plurality of causal indicators (e.g., signals at the molecular level, at the epidemiological level, etc.) *independently sufficient* to infer causality (e.g., mechanisms *OR* probabilities). There may be available many types of indicators, which, jointly or separately, support the causal claim that X caused Y (Osimani & Mignini, 2015), and you might also have multiple types of evidence. For example, in addition to evidence coming from population studies, Cartwright talked about four types of direct evidence that can speak in favor of individualized singular causal claims, namely: (i) presence of required support factors (i.e., other factors without which the cause could not be expected to produce this effect – moderator variables); (ii) presence of expectable intermediate steps (mediator variables); symptoms of causation (i.e., of the putative causes acting to produce the effect); and (iii) characteristics of the effect (Cartwright, 2017).
If the algorithm were conceived epistemologically as a voucher, then multiple indicators of causality could be considered simultaneously [e.g., biological plausibility (mechanistic knowledge) + strength of the association (probabilistic dependence) + specificity (difference-making) + counterfactual dependence + temporality] by *cumulatively contributing* to support the causal association.
When you have more indicators of causality you do not express yourself in a dichotomous way (i.e., yes/no), but in degrees, that may be expressed in quantitative terms (e.g., you can ask yourself: how much is the probability that A caused B, from 0 to 10 or from 0 to 100?) or

qualitative terms (i.e., using a graded scale like: very likely, possible, probable, etc.). The hypotheses of the causal association therefore should be assessed in a probabilistic fashion [i.e., assessment of the degree of plausibility of a given hypothesis given a set of data – see (Osimani & Mignini, 2015)].
For example, in presence of an AE (e.g., death of a patient after vaccine administration), a physician will first recognize the presence of both a (generic) difference-making connection and a (generic) mechanistic connection to death (that explains the difference-making relation), applying this generic medical knowledge to the single case under examination. Counterfactual judgment is applied consisting in the comparison between real course and hypothetical course (Hart & Honoré, 1985; Summerer, 2013), but is not sufficient to assess the causal link in the specific case. It should also be essential:

(i) to seek evidence of a biological mechanism able to explain the vaccine-person interaction, and then
(ii) to show that the vaccine makes a difference in *this* case, namely that had the person not received the vaccine, s/he would not have died (i.e., probabilistic counterfactual: if the person had not received the vaccine what would have been the person's probability to die?).

It therefore seems necessary to suggest converting the method on which the algorithm is currently based (i.e., clincher) to a method that adopts (Landes et al., 2018):

(i) a pluralist approach to causal inference, allowing to consider all available knowledge integrating it with incoming data (different types of evidence)[108]; and
(ii) an inductive (e.g., Bayesian methods of Hypothesis confirmation) and explanatory reasoning (i.e., abductive: inference to the best explanation/Peircean abduction) to infer causality, rather than the hypothetico-deductive inferential paradigm underpinning current practices.

As Osimani & Mignini (2015) have pointed out, in the field of causal assessment and scientific inference in pharmacology, vouchers fare better than hypothetic-deductive ones (e.g., EBM) when dealing with harms.
This is because they are methods whose results cannot force any conclusion, but only suggest or support it more or less strongly; they (Osimani, 2020; Osimani & Mignini, 2015):

(i) do not definitively refute/prove a given hypothesis, rather aim to provide a way to assess the *degree of plausibility* of a given hypothesis given a set of data (i.e., graded judgment) and, possibly, to measure it probabilistically;

[108] Vouchers appeal to the *Principle of Total Evidence*, as "an essential desideratum in non-monotonic reasoning, as opposed to the hypothetico-deductive paradigm" (Osimani, 2020) – see Chapter IV.

(ii) are *flexible* enough to incorporate new possibly conflicting evidence in the inferential framework, without necessary eliminating old beliefs;
(iii) are particularly appropriate when causes are *highly context-sensitive* (e.g., in biology, social sciences, etc.).

Context sensitivity means the joint interaction of various causes in determining a given effect and modulating its intensity (Osimani, 2020) (see Chapter IV). Saying that a cause is context-sensitive means that one cause in one context causes one effect while in another context it may cause another effect depending on the situation. This implies that you may have evidence of causality in one context while in another not (e.g., a study in elderly where evidence of causality emerges *vs* study in children in which no evidence of causality emerges) with the consequent doubt whether it is causality or not. Using a voucher approach you can say, for example, that it *could* be causality only in the elderly and not in children (i.e., more *flexibility*), while with a clincher you must express yourself in absolutist terms (yes/no) and therefore be certain.
In addition, it must be noted that crucial information on causal interaction comes from detailed case series, or from basic science (molecular studies; in vitro or in silico tests), rather than from experimental studies alone. The former, in fact, may contribute to a greater extent to the identification of specific subclasses in which the effect follows the treatment to a greater or lesser extent (Osimani, 2020), while the latter is evidence on whether (and to *what* extent) there is a causal link between two phenomena.
A voucher approach, compared to a clincher, allows you to consider all the available evidence together to say that a causal link can exist in that specific context.

4.2.2. Towards an evidential pluralistic approach

As we have discussed, the algorithm tends to show a clinching approach. The algorithm in fact, as we have seen in the section on its description, requires specific causality criteria (and certain types of evidence) *jointly necessary* to classify the link as *consistent* (from *Step II* onwards) – i.e., *AND* structure [see also (Osimani B. & Ilardo, 2022)]. It does so in one of the two following possible pathways:

1) Step I: *You must have no evidence of other causes* that explains the event[109]

AND

Step IIA: *The causal link must be known*[110]

AND

[109] The question posed in *Step I* recalls to Hill's specificity criterion [see (WHO, 2005a)] – difference making causality indicator (Landes et al., 2018).
[110] The question posed in *Step IIA* recalls to the following Hill's criteria: consistency, strength, and biological plausibility (WHO, 2005a) – i.e., respectively inferential patterns, probabilistic dependence, and mechanistic knowledge causality indicators (Landes et al., 2018).

Step IIB*: Time link must be plausible*[111]

2) Step I*: You must have no evidence of other causes* that explain the event;

AND

Step IIA: *The causal link must be known*

AND

Step III*: You must not have strong evidence against causation*[112]

AND

Step IV*:* if the AEFI considered classifiable, *the event must meet case definitions*.

Given the above, we could say that the algorithm can be defined at a pluralistic but deterministic epistemological level: it requires all the types of evidence listed above to infer that there is the AEFI-vaccine causal link. This means that until you have them all you cannot say that the vaccine is responsible for the damage. This procedure obviously tends to increase the number of false negatives.

This type of approach finds a parallel with the legal field. Think of a court case in which the judge has to establish the guilt of a defendant and conclude that s/he is guilty requires that the evidence to be produced must be proof 1 *AND* proof 2 *AND* proof 3. Because of the lack of only one of the three the defendant would not be convicted. This procedure makes it very likely that the accused will not be convicted when s/he may be guilty. This means that the likelihood of false negatives increases.

It is therefore more difficult to establish the vaccine's responsibility if the method necessarily requires proof 1 *AND* proof 2 *AND* proof 3, compared to a method that allows proof 1 *OR* proof 2 *OR* proof 3.

What I'm talking about is a pluralistic approach of evidence of the type 'you can have this or that kind of evidence, and/or you can put it together'. You can accumulate evidence that alone may not be sufficient but together it is, and you can take various types of evidence in a probabilistic way.

According to this view, pluralism should not be seen as a requirement, but as an opportunity: if you have more, the better.

The algorithm was developed to avoid any kind of arbitrariness, but for this purpose, it increases false negatives. This kind of pluralistic approach allows us freedom in choosing the type of evidence to justify our conclusions, and in giving us the possibility to have all kinds of evidence, thus reducing the number of false negatives.

[111] At *Step IIB* the causality indicator is temporality.

[112] The question posed in Step III recalls to Hill's strength criterion (WHO, 2005a) – i.e., probabilistic dependence (Landes et al., 2018).

4.2.3. Probabilistic assessment & a fine-grade qualitative judgment

If we consider that most AEFIs are multifactorial, it would be 'natural' to consider a graded notion. In the legal field, actual judgments of causal and legal liability in such contexts are graded (Grinfeld et al., 2020; D. A. Lagnado et al., 2013).
Medicine is not an exact science; it is therefore affected by uncertainty. Moreover, the evidence for causal relationships in medicine is complex and fragmentary. Consequently, there are rare cases in which we can have conclusive evidence on an investigated hypothesis. All other cases would remain unresolved, and we would lose a lot of information if we limited ourselves to using only conclusive evidence. Therefore, to optimize the use of all available evidence, only probabilistic and graduated approaches remain.
In the case of AEFI using only conclusive evidence inevitably leads to losing a lot of info. For example, for every available evidence the dichotomous approach will simply classify them as *consistent* or *inconsistent*; consequently, whenever evidence is considered *inconsistent*, it can never more contribute to supporting the hypothesis of causality.
The probabilistic approach, being more "nuanced", will tend to include much more info, thus giving more accuracy to the tool. With the dichotomous approach the probability associated with causation will be *systematically biased downwards*.
How we assess causality should therefore be probabilistic and fine-graded.

4.3. Methodological level

4.3.1. Methodological pluralism

This aspect overlaps with the epistemological one. In fact, as I have already said, the algorithm justifies the causal link on the basis of evidence hierarchies, which however is very rigid and, as we have discussed, has problems.
The algorithm mainly bases its conclusions on evidence produced by experimental epidemiological studies, showing a preference towards this type of studies over others.
Less strict criteria should be used to allow evidence from different types of studies, even those considered low-level evidence. One should not ask whether it is better clinical trial (randomized trial) or epidemiological study or basic sciences, but all of them (quantitative, qualitative, observational, experimental etc.) are useful to establish causality. Those studies labeled as weak-level evidence may give an important contribution to individual causal analysis.

5. Critical aspects

5.1. The requirement of *strong* causation at *Step I*

The requirement of *strong* causality recalls to the concept of *strength* of causal association, which has a probabilistic meaning. The algorithm, however, underestimates the distinction between *strong* causation and *weak* causation, thus failing to attribute to the concept of *strength* the right (i.e., probabilistic) meaning.
At *Step I*, in fact, since 'the other cause' is one of the many contributing causes (or risk factors) involved in the AEFI, we cannot speak of a *strong* association between the AEFI and the detected pre-existing pathology rather than a *weak* association. The concept of *strength* should therefore be reconsidered.
It is known that vaccines can lead to abnormal reactions to stimuli in conditions of individual (genetic or acquired) susceptibility, so one could say that the subject affected by the adverse outcome was a carrier of predisposing factors (genetic or acquired) that were strong enough to cause the disease with the intervention of the vaccine.

5.2. A partial cause is not *the* cause

At *Step I,* in case in the person a preexisting pathology (or a genetic predisposition or anomaly) is detected, the algorithm excludes in absolutist terms the vaccine as a possible cause of AEFI stating that *the* cause of AEFI in the individual is, for example, the pre-existing pathology.
In a multifactorial context such as that of AEFI, in which other causal factors are present and operating, the pre-existing pathology is nothing more than one of the multiple causes involved, it is therefore a partial cause, and as such cannot be considered *the* cause. A partial cause (or contributory cause) in fact merely raises the probability of the effect, but it is nevertheless a cause.
The algorithm not only defines a partial cause as *the* cause, but also bases its judgment of exclusion of the vaccine-AEFI causal link on a partial cause.
In light of what has been said so far, this constitutes an error from the ontological and epistemological point of view.
In a context where we can distinguish more than one factors that can be pointed to as contributing to the effect and that can be relevant to it, it is reasonable to deal with incomplete, partial causes (Scheffler, 2003), but in their totality. Whether you consider the vaccine or any other cause (e.g., the preexisting pathology) it is obvious that they are embedded in a set of cofactors that enable them to produce AEFI. So, it is all the more pointless to speak about *the* cause. Whenever we aim at identifying possible causal factors for the AEFI, one should cope with the idea that *no* cause in medicine stands alone (see Mackie, Rothman, Chapter IV).

5.3. The problem of considering causality assessment as a *differential diagnosis*

The 2019 WHO user manual states that:

> "In doing causality assessment on an individual case report, it must be remembered that in essence one is conducting a differential diagnosis" [(WHO, 2019), page 7]
>
> "It is important to recognize that causality assessment of an AEFI in an individual patient is an exercise in medical differential diagnosis. A good clinician does not diagnose diabetes or coronary artery disease on the basis of conflicting or vague information. In the same way, an AEFI should not be causally linked to a vaccine without adequate information" [(WHO, 2019), page 34].
>
> "The algorithm aims to be a roadmap for decision-making of the reviewers, but it *does not*, and *should not*, *take away* the expert and *deductive logical process* inherent in linking a diagnosis to its potential cause" [(WHO, 2019), p.35].

A differential diagnosis is not necessarily about causality. Let's take the following example. The differential diagnosis process of an unconscious patient requires the doctor to resort to the Magnetic Resonance Imaging (MRI) that shows a brain hemorrhage, thus allowing the diagnosis of hemorrhage (Gots, 2005). Whether it occurred because the patient was taking a specific medication, or whether it was due to uncontrolled hypertension, or whether it resulted from a congenital aneurysm or a blow to the head is not part of the differential process. However, sometimes during the diagnostic process it can happen that if, for example, a significant elevated carboxy hemoglobin (COHbg) (e.g., 50%) is found in the patient, a diagnosis of carbon monoxide poisoning is made (Gots, 2005). In this case the diagnosis necessarily leads to a causal attribution, i.e.: poisoning by carbon monoxide. But this does not mean that a differential diagnosis determines causality.
Here follows the consideration that the algorithm does not concern the AEFI's diagnosis, which is expected at a stage prior to the causality assessment (i.e., *Eligibility* section), rather you are conducting causality assessment of the observed AEFI, that is you are trying to determine what caused the event.
However, the current WHO algorithm imposes an epistemological procedure, similar to a sort of *differential* diagnosis, where one proceeds through a process of exclusion of an alternative hypothesis (one or more co-causes) until the identification of *the* cause (see *Step I*). A similar approach is questionable in a '*causal* diagnosis' of an AEFI where the excluded hypothesis (e.g., vaccine) may be co-causally responsible for the AEFI's occurrence.
The algorithm, instead, should proceed by evaluating all the available causes to consider the contribution of each of them to the outcome under investigation.

5.4. The fallacy of shifting of the *burden of proof*

In the causal imputation of the AEFI the algorithm is influenced by strong bias in the dimension of the *burden of proof* (Osimani B. & Ilardo, 2022).
The algorithm in fact holds the task of assessing whether AEFI may be causally imputated to the vaccine, thus if the vaccine is responsible. The algorithm should therefore '*prove* the fact' by providing *sufficient* evidence to justify the claim that the vaccine caused the AEFI.
However, the algorithm instead of providing evidence that *proves* the vaccine's guilty/liability and therefore justifies a favorable conclusion on the causal vaccine-AEFI link, it presents opposite evidence: i.e., evidence that *disproves* the vaccine's guilty/liability (thus proving its innocence) and therefore justifies a negative conclusion on the vaccine-AEFI causal link.
In practice we could say that the algorithm defends the claim that this vaccine caused the observed AEFI in this person in a fallacious way by shifting the burden of proof, by requiring evidence that there is *no* causal correlation between this vaccine and the observed AEFI in this person – see *Step III*. At *Step I* the evidence presented and used to disprove the vaccine's liability is evidence that proves that another fact can explain the event alternatively to the vaccine.
At *Step II* the shift of the burden of proof occurs by another fallacy: the so-called fallacy of argument from ignorance. *Step II* is the only one in which "positive" evidence is sought to prove the fact. However, as we saw in the section where we described the algorithm, such research is based on *known knowledge* (information in the literature and scientific basic research that can confirm the vaccine-AEFI causal link). Beyond those vaccine reactions that are well documented[113], for others (the AEFI is 'new' and/or rare and/or the vaccine is new) the available scientific evidence is often insufficient to conclude that the association is real, but also insufficient to confidently rule out a link.
However, in absence of evidence of a vaccine-AEFI causal association the algorithm asserts the veracity of the claim 'the vaccine is not the cause of the AEFI in this person' based on the lack of evidence to the contrary. It means that, since there is no evidence against this claim, this claim is true: since there is no evidence that the vaccine is the cause of AEFI, the vaccine is not the cause of AEFI. We cannot say that the claim 'the vaccine is not the cause of the AEFI in this person' is true because we don't know that it's not. With this conclusion, the algorithm does not classify the AEFI as *consistent* and moves to *Step III* in which evidence *against* the vaccine-AEFI causal association is sought (i.e., evidence that in a certain sense justifies the negative conclusion of the previous step and that is again population-base evidence).
However, lack of evidence of causal correlation is not evidence of lack of causation.
The fact that population level studies present objective standards (such as P-values, confidence intervals and relative risks) may convey the false feeling that the judgment on the causal link resulting from their use is entirely objective. The algorithm falls into this error by allowing the exclusion of the causal link on their basis. However, one can almost never be sure of rejecting a causal relationship on the sole basis of such studies because even the largest epidemiological

[113] For example, postvaccine central nervous system disease, such as encephalitis or encephalomyelitis, may occur after smallpox vaccine administration.

studies have insufficient statistical power to detect extremely rare causes of an adverse outcome, even more so at the individual level.
In the absence of epidemiological studies that favor the acceptance of a vaccine-AEFI causal link, the algorithm should proceed by considering also other types of evidence (such as evidence from individual clinical cases and case series), to infer about a vaccine-AEFI causal link.
The algorithm, set up as it is, despite the aim of objectivity in making a causal judgment, tends to be biased against the assignment of causal responsibility to the vaccine.

5.5. Algorithm *lacks* granularity

Compared to the 2005 WHO-Brighton system, the current algorithm results less flexible. It has a dichotomous scale and an "*AND* (∧)" structure, i.e., each criterion is necessary to move on to the next step and to conclude about a causal-link. The old system had a greater graduality (six scale values), and an "*OR* (∨)" structure, i.e., none of the indicators of causality was necessary in an absolute sense, but the higher they were the greater the probability that there was a link.
With the "*OR* (∨)" structure, the vaccine-AEFI causal link is not excluded if for example:

i. the clinical AE has a reasonable temporal relationship with the administration of the vaccine and at the same time is unlikely to be attributed to a concomitant disease or to the intake of a drug;
   OR
ii. the clinical AE has a reasonable temporal relationship with the administration of the vaccine but can also be explained by a concomitant disease or by taking a drug.

In case (i) the vaccine-AEFI causal link would be categorized as *probable,* while in case (ii) it would be categorized as *possible***.**
With the "*AND (*∧)" structure the scale is impoverished and becomes dichotomous. Furthermore, more stringent criteria for causality assessment have been introduced to reach the conclusion of a *consistent* vaccine-AEFI causal association (otherwise the conclusion falls into the *inconsistent* category). To exacerbate the problem, the list of conditions for assigning a positive causal assessment has been further extended. The more the criteria that need to be satisfied for a link to be considered causal, the greater the probability that the link falls within the *inconsistent* or *unclassifiable* category.

5.6. The problem of underestimating evidence of *biological plausibility*

Sources of evidence for causality assessment include biological plausibility. In *Step II* the mechanistic evidence regarding plausible biological pathways from cause to effect is considered as a qualifying factor that the vaccine *may* cause the observed AE.

The *empirical* biological plausibility is the one most considered in reaching causality judgments, however vaccine-AEFIs associations can be evaluated with a certain biological plausibility also on *theoretical* bases. The former is based on the *known* effects of the natural disease against which the vaccine is administered and on the results of animal experiments and in vitro studies, while in the latter case an expert could postulate a feasible mechanism by which the vaccine *could* cause the AE on the basis of biological plausibility (IOM & Vaccine Safety Committee, 1994).

The biological plausibility of vaccine harm can be deduced from its known action: in some rare and susceptible individuals, an abnormal response to the stimulus occurs, provided by antigens and adjuvants present in the vaccine. The person in whom a vaccine harm occurs is usually predisposed through some risk (genetic or acquired) factor that alone is not sufficiently *strong* to cause disease, but, with vaccination, the organism is destabilized to the point of a pathological reaction, i.e., AEFI (Bellavite, 2020).

Importantly, one thing is to use this type of argument to assert that causality exists and quite another to use it to *deny* causality (asymmetry). Biological plausibility is circumscribed by the state of current knowledge and "it should not be used in itself to *deny* causative association" (Puliyel et al., 2018).

In the past the recognition of the association between high-titer measles vaccine with an excess of female mortality [now well-known – see (Aaby et al., 2003)] was delayed due to the absence of a biologically plausible explanation. The association of intussusception with rotavirus vaccination was accepted when a biologically plausible explanation was not available (CDC, 2011). Only later it was discovered that vaccines have non-specific effects that up-regulate or down-regulate both the innate and adaptive immune systems and this may affect the survival of children (J. P. T. Higgins et al., 2016). Therefore, in addition to non-specific beneficial aspects that a vaccine can have, there are also unexpected harmful effects that should not be overlooked simply because at the time when it is first noticed a ready explanation is not available (Puliyel et al., 2018).

In the algorithm, this is considered as *an additional piece of supporting evidence* within the question posed in *Step II*, and not as evidence capable of demonstrating causality. However, the problem is that biological plausibility is invoked *"only when a laboratory finding or symptom/sign is similar and consistent with the natural history and pathophysiology of the infection or antigen"* [page 26 (WHO, 2019)].

Other kinds of evidence, which demonstrate the existence of a mechanism and the capacity to lead from cause to effect, do not qualify, thus recognizing the experimental approach at the expense of other valid approaches, with the consequent risk of failing to detect causality in a number of cases that cause harm (Puliyel, 2018), plus increasing false negatives.

Hence, an alternative way to conceive biological plausibility as a possible support for AEFI causality assessment may consist of the following conditions: a) the same disease (or a biologically similar one) has already been described in other cases after vaccination, and b) the subject is a carrier of a greater predisposition to that particular pathology (Bellavite, 2020).

5.7. The problem of using the criterion of general causality to *exclude* vaccine's responsibility in the individual

Step II asks about 'is there a *known* causal association with the vaccine/vaccination?' (i.e., evidence in the published peer-reviewed literature – e.g., case records, laboratory records) [see page. 22 and 25 (WHO, 2019)]. *Step III* asks about "is there *strong* evidence *against* a causal association?" (i.e., body of published evidence – Cochrane reviews, GACVS reviews, systematic reviews, epidemiological studies, etc.) [see page. 23 and 32 (WHO, 2019)] – here *probabilistic dependence* is required.

Evidence at the population level is therefore used to rule out that in the particular case vaccination may have caused AEFI (Bellavite, 2020; Puliyel et al., 2018). Thus, "if there is no evidence in published peer reviewed literature that this vaccine may cause such an event" *and* "if there is a body of published evidence that rejects a statistically significant association between the disease and previous vaccinations", the vaccine-AEFI causal link is excluded.

Before the question *'Did* the vaccine given to a particular individual cause the particular event reported?' is answered, one must answer the question '*Can* the given vaccine cause a particular AE?'. At *Step II,* in fact, the questions "in this patient *did* a specific test demonstrate the causal role of the vaccine?[114]" [see page 22 and 26 (WHO, 2019)] and "in this patient, *did* the event occur within a plausible time window after vaccine administration?" [see page 23 and 27 (WHO, 2019)] are preceded by the question "is there evidence in *published peer reviewed literature* that this vaccine *may* cause such an event if administered correctly?" [see page 23 and 31 (WHO, 2019)]. Thus, *only if* there is evidence at the population level (epidemiological: experimental and/or observational) that the vaccine *can* cause the adverse event, the AEFI is classified as '*consistent* causal association with immunization' – passing *Steps II* and *III* (Puliyel, 2018). These studies are indeed considered to provide *strong* scientific evidence (i.e., necessary/sufficient).

However, as Edwards points out "any consideration of causality based only on epidemiological approaches is not logically defensible and certainly not socially acceptable", then specifying that "since adverse effects of medicines are generally rare, it is not possible to exclude drug causation in an individual by reliance on epidemiological evidence alone only to argue that the incidence is below a level determined by statistical power, of the study or studies combined" (Edwards, 2012).

This sort of studies uncovers empirical associations by statistical analysis (difference-making evidence) and, although provides important indications on the incidence of AEFI in vaccinated subjects allowing comparison with unvaccinated subjects, presents some limitation when applied at the individual level of causal analysis. First, the fact that epidemiological studies are subject to selection bias and diversity of non-randomized groups represents a very serious problem in a case of low-incidence adverse reaction (Bellavite, 2020). Second, the requirement of available epidemiological or clinical literature supporting individual causality assessment is

[114] Clinical or laboratory proof; the WHO guidelines provide the example of a case of aseptic meningitis after immunization with the Urabe mumps vaccine virus, in which isolation of the Urabe virus from cerebrospinal fluid is considered definitive evidence that it caused meningitis (WHO, 2019).

also flawed if we consider that the vaccines' safety is demonstrated in clinical trials often conducted by comparisons instead of placebos (e.g., saline 0.9% NaCl) with adjuvants[115].
In addition, it must be noted that the epidemiological literature tells us of an increased risk of a given disease among some people in the population with specific characteristics, but the risk is only a measure of how much individual probability of the disease increases (e.g., in vaccinated compared to unvaccinated), conditional on the vaccine's administration. Epidemiological evidence tells us, for example, that a toxin *can* produce an injury, but is unable to tell us that the exposure to that toxin *actually* caused that particular injury in the individual (Parascandola, 1998). Other substances are also known to being able to cause that injury, and some people exposed to same toxin may develop the injury, while others not. These considerations refer to the concepts of multifactorial nature of diseases, individual uniqueness and variability, and the context-sensitive nature of causality discussed earlier.
To apply the general knowledge derived from these studies to the individual case, it is necessary to understand whether the study is representative of the individual.
According to what has been said so far epidemiological evidence cannot be considered sufficient in itself to (dis)prove causality. It can never alone suffice as evidence that a particular exposure caused a particular outcome in a particular individual but can only help/support in assessing causality.
Singular causality questions can be aided by knowledge of general causal relationships but claims of general causality cannot be reduced to claims of singular causality. Knowing that smoking probabilistically causes lung cancer does not imply that a *specific* smoker's lung cancer was *actually* caused by his/her smoking – see (C. R. Hitchcock, 1995; Stephan et al., 2020).
Even if it is legitimate to extrapolate frequentist quantification to the individual level, in the specific case it is not known whether a certain event instantiates a certain general law, or another. For example, in an individual who has congenital heart disease and receives the vaccine and then dies, even if the individual has the pre-existing pathology, it may be that congenital cardiomyopathy was not the trigger of the AE. These general 'causal laws' can only provide a statistical contribution to the reconstruction of the causal link in the actual case (Casali, 2010), and should not be used as a *decisive criterion* in the exclusion/confirmation of the individual causal link precisely because of uncertainty regarding the laws at play in these specific circumstances.
For these methodological reasons, epidemiological evidence to assess individual causality should be used with great caution and be supplemented by circumstantial evidence regarding the specific case at stake. Such evidence may support or weaken the assumption of a causal

[115] Six clinical trials tested the safety of the HPV vaccine Gardasil. In 5 of them the control group received Aluminum Hydroxy phosphate Sulfate, while in only one of them the physiological solution was used as placebo. In the summary of the safety profile of the vaccine (available at: http://www.merck.com/product/usa/pi_circulars/g/gardasil/gardasil_pi.pdf) however, the systemic and serious adverse effects (i.e., the rate of autoimmune disorders), are evaluated comparing the group receiving Gardasil with only the group receiving aluminum (or placebo). As Bellavite (2020) underlined, by this way, any potential reactogenic effect of aluminum salts were masked.

association between the vaccine and the AEFI, thus increase or decrease confidence in a factor being causally related to the observed outcome.

5.8. The *stopping rule* and the problem of admissibility of evidence

The stopping rule concerns when you are allowed to stop the search for evidence in order to be able to affirm that the vaccine-AEFI causal link exists or not.
To stop you would need conclusive evidence about alternative. *Strong* evidence is not enough, because until one option remains possible, it deserves to be left open for further research. From an epistemological point of view, eliminating it when it is still possible amounts to set its probability to 0 without any supporting evidence for this move. In the WHO algorithm the stopping rule is determined by the algorithm itself, by how it is structured. As we have seen, general level evidence is considered by itself sufficient (i.e., *strong*) to exclude the vaccine-AEFI causal link in the individual.
This is the so-called *stopping rule problem*. It may be defined *"as the problem of when to terminate the search for causes"* (Rizzi & Pedersen, 1992). Having set up the algorithm with the *a priori* exclusion of the possible vaccine-AEFI relationship by categorizing the AEFI in the 'inconsistent' category on the sole basis of the evidence relating to an "alternative cause" aimed at explaining the event (*Step I*), interrupts the process of causal diagnosis of AEFI, and therefore of research and collection of further evidence useful to ascertain the vaccine-AEFI causal link. The reason why this process is interrupted is not acceptable since one type of evidence cannot be sufficient *per se* to establish the causal link, especially if the AEFI is a pathological manifestation on multifactorial etiology. Rather, considering also that "*causal explanations are context-specific and context-determined"* (Rizzi, 1994), the affirmative answer to the question posed in *Step I* should serve to continue to ask questions about possible other alternative explanations by *corroborating* or *downgrading* the evidence found in probabilistic terms. Only the collection of other evidence that is added to the previous one can help to confirm to a degree closer to certainty or highly probable the causal link (as does the system used for medicines).
The algorithm shows a very strict stopping rule, so if I have a specific type of evidence (e.g., *Step I*: *strong* evidence for other causes), it basically excludes the admissibility of the other ones. This choice to rely only on one type of evidence restricts the evidence that can be considered acceptable for assessing causality. The algorithm identifies and evaluates only the evidence for other cause(s) and establishes that this acts as a stopping rule as it blocks the process of search and accumulation of other evidence that can confirm or not the causal link.
But, why do we have to stop here?
The algorithm prevents the evaluator from embracing a pluralist approach and at the same time ignores the context-dependence of the evidence (i.e., the type of evidence that is considered weak evidence of causality).

In my view, the algorithm should not have a stopping rule, but an admissibility criterion as broad as possible that allows to put together 'all the available evidence' on the case under examination and to evaluate their evidential value both independently and jointly.

6. Ambiguities

6.1. The concept of '*strong* evidence'

The algorithm speaks of *strong* evidence for other causes and *strong* evidence against the causal association (respectively *Step I* and *III*), but it is not specified what is meant by *strong* evidence. The WHO points out that *"an association between vaccine administration and an adverse event is most likely to be considered strong when the evidence is based on"* (WHO, 2001):

(i) well-conducted human studies that, within a study design that is designed to test the hypothesis of such a link, determine a clear association (e.g., RCT, cohort studies, case-control studies, controlled case-series analyses).
(ii) an association that is demonstrated in more than one human study and consistent among the studies (they must have been well-conducted by different researchers in different populations, with consistent results, despite different study designs). In many cases, the demonstrable association in studies between the dose (or the number of doses administered, or both) and the presumed AE will strengthen the causal association between vaccine and AE.
(iii) a strong similarity of AE to the infection the vaccine is intended to prevent, and there is a non-random temporal relationship between vaccine's administration and AE.

To the question posed in *Step I* the algorithm specifies that a detailed medical history (e.g., Had the patient prior history of similar symptoms/pathological manifestations? Had the patient history of concomitant or preceding condition? etc..), clinical examination and/or investigations including laboratory tests in the patient (e.g., autopsy, epidemiological, clinical and laboratory profile of the case, etc.) *"may help to identify other conditions such as other diseases and congenital anomalies that could have caused the event"*(WHO, 2019).
However, the algorithm does not specify how the conclusion that, for example, the pre-existing pathology detected[116] caused the event is justified. It is not clear what it means by *strong*

116 The detection may happen by observation of medical signs (e.g., anatomical, physiological abnormalities, etc.), laboratory findings (i.e., anatomical, physiological phenomena that can be shown by laboratory diagnostic tests, including (but not limited to) chemical tests, electrocardiograms, electroencephalograms, X-rays, and so on.), etc.

evidence. Considering points (i)-(iii), we could hypothesize that the use of the term *strong* may mean that this justification takes place on the basis of general evidence (evidence hierarchies).

6.2. The requirement of a '*plausible' time window* between vaccination and AEFI's onset

In the second phase of *Step II* the algorithm requires a *plausible* time interval from vaccination to the occurrence of the AEFI in order to confirm the vaccine-AEFI causal link. The expression 'plausible' is generic and the algorithm does not specify any criteria for its definition.
For conventional vaccines this corresponds to 2-4 weeks (sometimes it can also reach 6-8 weeks, but it is very rare), since it is assumed that the effects are mainly linked to the pro-inflammatory action. However, this time frame is correct when applied to acute-onset AEFIs (e.g. hyperthermia, febrile seizures, anaphylaxis) (Bellavite, 2020), instead it is not adequate for cases of AEFIs consisting of chronic illnesses and autoimmune diseases (complex and multifactorial), for which it would be proper to consider a sufficiently large time window (e.g., 24 months) in order to not exclude slow-onset cases (Agmon-Levin, Zafrir, et al., 2014; Grimaldi-Bensouda et al., 2017; Hughes et al., 1996; Leslie et al., 2017; Tourbah et al., 1999; B. Wang et al., 2017; Yuan et al., 2016; Zafrir et al., 2012; Pulyel, 2018; Rigolet et al., 2014).
A very limited time interval prevents the detection of reactions, even very serious ones (such as autoimmune reactions), which can arise after weeks or months from the injection.
The acceptable time window for each AEFI is different.

7. Conclusions & proposal

By focusing on *monocausality* and a *direct* causal-effect relationship, the WHO algorithm tends to underestimate the presence of different type of causal relationships and the mechanisms by which they are mediated. It classifies a causal association as *inconsistent* when there is another cause and as *undetermined* when the vaccine may be a cause but there is no evidence that it is *the* cause. In this way, many AEs in which the vaccine may have played a role as a co-cause remain unrecognized. It is essential that different types of causes and causal relationships (including temporal latency and induction period) are properly recognized and considered in the algorithm.
Moreover, the use of solely one type of evidence (e.g., evidence of other causes at *Step I* or epidemiological evidence against a causal association at *Step III)* to support a causal relationship may often not be sufficient, thereby increasing the likelihood of false negatives.
In clinical practice, diagnoses are often made with degrees of certainty (Naidu, 2013). Analogously, few AEFIs can be considered to be certain or unlikely and often the role of the

vaccine in causing an AEFI cannot be demonstrated (because of the absence of specific tests, the platform is a new technology, the AEFI is rare/new/unknown, etc.).
A binary approach (yes/no; consistent/inconsistent) to causality assessment can therefore hardly adequately reflect the context and processes that characterize clinical practice. Compared to the 2005 WHO-Brighton system, the WHO algorithm has a *dichotomous procedure* (binary scale: *consistent/inconsistent*), resulting in a less flexible tool. Each criterion is necessary to move on to the next step and to conclude about a causal link. Much of the information is lost due to the requirements *jointly necessary* to classify the link as *consistent.* This procedure obviously tends to increase the number of false negatives and translates into systematic failure to detect possible causes of the observed events (Osimani B. & Ilardo, 2022).
At *Step II* the use of the criterion of '*known* association' as decisive in assessing a vaccine-AEFI causal link, tends to increase underreporting and the denial of a new possible vaccine-AEFI link would put people's health at risk.
Moreover, the lack of clarity (ambiguities) in some points of the algorithm leaves room for arbitrariness and further errors.
The high likelihood of false negatives derives from a fallacious approach at different steps and levels (i.e., ontological, epistemological and methodological levels) (see **Fig.26**). Possible revisions should therefore address the following questions:

(i) *multifactoriality* (ontological aspect). This is a necessary element in the causal analysis of AEFI since most AEFIs are pathological manifestations with multifactorial etiology, together with the context-sensitive nature of vaccine, individual uniqueness, and individual variability. These elements make individual causation analysis highly complex and characterized by strong uncertainty. In such a complex and uncertain context one can only try to determine to what extent each factor may have contributed to (increased the probability of) the effect.
(ii) *evidential pluralism* (epistemological aspect). Different types of evidence (heterogeneous evidence) should be allowed to contribute to the causality assessment. This would reduce the likelihood of false negatives thereby increasing the accuracy of the algorithm.
(iii) *voucher approach* (methodological aspect). Non-conclusive evidence should be admitted (Osimani, 2020; Osimani & Mignini, 2015), and no scientific proof/certainty required for taking action (decision-making under uncertainty: *probabilistic and fine-graded assessment)*.

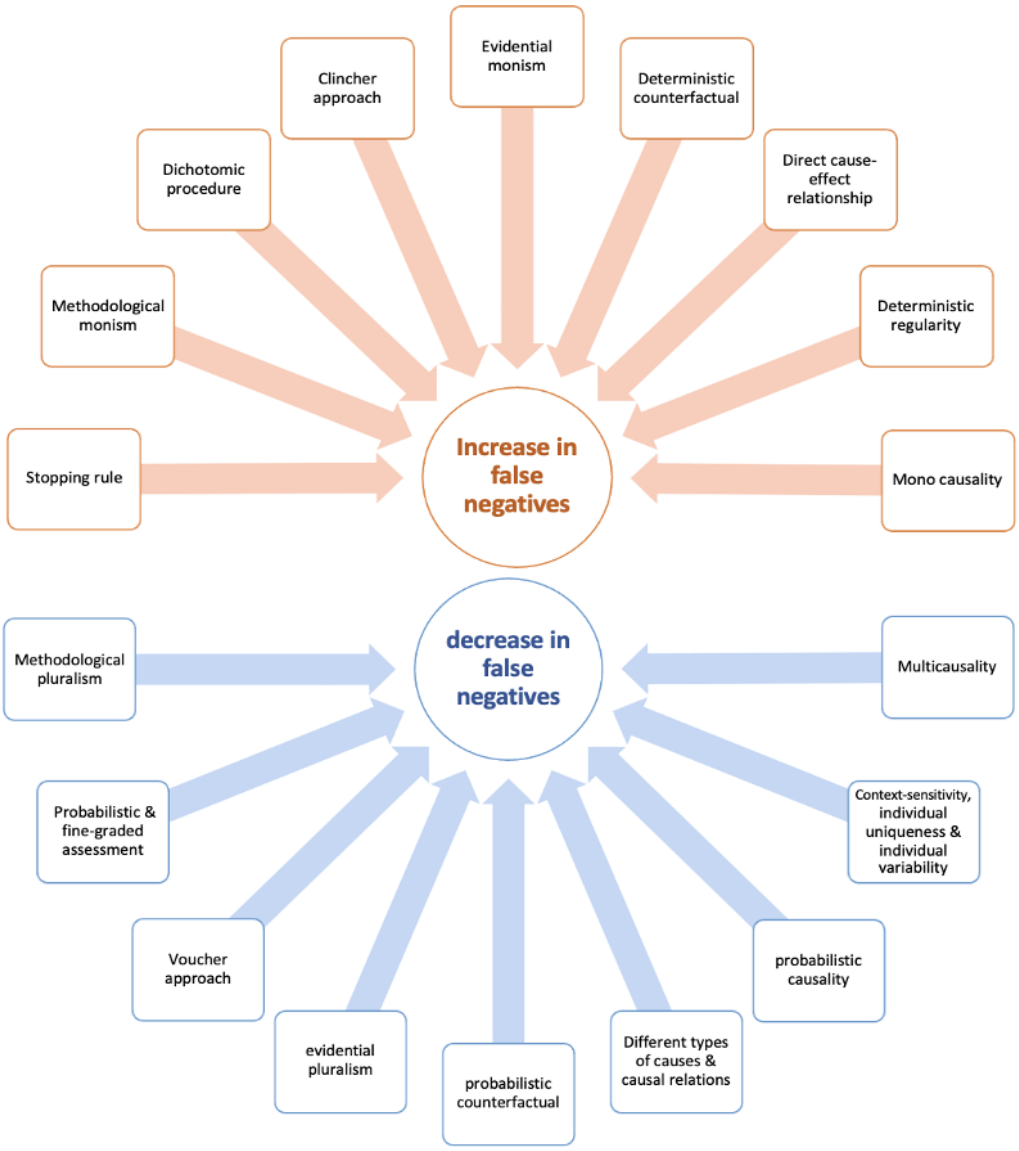

Figure 26: *Comparison between the old system and the proposed new one.*

7.1. The new algorithm: A new theoretical framework

The proposal I intend to advance is a new system that consists in the adoption of the following new theoretical framework:

THE NEW ALGORITHM: A NEW THEORETICAL FRAMEWORK			
Levels	**Causality assessment criteria**	**Rules**	**Considerations/Outcome(s)**

ONTOLOGY	***Multifactoriality***	*All* possible causes at play ***must*** be considered. No cause should be excluded. Even if an alternative explanation is available, a causal link with the vaccine must be considered possible.	The role of vaccine will not be excluded since it ***may*** be a co-cause in a set of causes, each of which ***may*** play a role in causing AEFI.
	Context sensitivity/ individual uniqueness/ individual variability	Vaccine-person interaction(s) and all interactive phenomena (e.g., synergistic) ***must*** be considered.	Vaccines effects are highly context sensitive and most AEFIs are inflammatory and immune system diseases, due to the interaction with underlying pre-existing conditions in the individual. The vaccine ***can*** lead to AEFI by interacting with one or more different components present in the individual*. Allow for the possibility that the vaccine ***may*** play a co-causal role, by contributing to precipitate AEFI in the predisposed individual.
	Probabilistic causality	Every cause increases the probability of AEFI occurring in the individual at that time and with that intensity to a greater or less extent with regard to another one. Thus, the probabilistic contribution of each cause ***must*** be considered.	Every causative factor is potential. The vaccine has a tendency to cause AEFIs. Thus, we may claim, for example, that in the individual with a (genetic or acquired) predisposing factor, this factor ***may*** cause AEFI (e.g., abnormal immune response) with the intervention of the vaccine. The vaccine's contribution raises the probability of AEFIs occurring.
	Mechanistic causality	The whole process (causal chain) or web of reactions that lead to AEFI ***must*** be considered.	Different possible causal mechanisms ***may*** lead to the AEFI (direct vs indirect). Since the vaccine may act as a co-cause, it ***may*** be involved in a chain/web of reactions in which interactions between causes lead to the AEFI.
	Variety in the types of causes & causal relationships	All possible types of causes present and causal relationships ***must*** be distinguished, considered and analyzed (direct/indirect causality; contributing; interacting; intervening; mediating/moderating/modifying) *Overdetermination/preemption* phenomena ***must*** be considered.	The AEFI ***may*** be the result of the interaction and balance between multiple co-causes and intermediate factors. Thus, the vaccine, as a co-cause, ***can*** act by aggravating a pre-existing condition or intensifying its manifestations, prolonging its course, delaying its healing, accelerating its evolution, favoring the appearance of complications, or anticipating their unfortunate outcome. AEFI ***may*** be a case of an *overdetermination/preemption* phenomenon, and the vaccine ***may*** be one of the causes involved.

	Induction period & temporal latency	Time frame ***must*** be considered. Restricted time intervals *should not* be used as reasons to exclude causation. Or, they should be sufficiently long to accommodate medium-to-long term AEFIs.	Even if the AEFI is a condition that manifests itself as a long-term effect, the vaccine ***can*** be a cause of it.
	Probabilistic counterfactual	Because of the multifactorial nature of AEFIs, a probabilistic counterfactual ***must*** be applied.	*Did* the risk made by 'the other cause' ***probably*** cause AEFI in the individual? If the individual had not taken the vaccine, ***how likely*** is it that AEFI would have occurred at that particular time due to the presence of 'the other cause'? Would AEFI have had a ***higher*** **or** ***lower probability*** of occurring?'
EPISTEMOLOGY	***Voucher approach***	Each piece of evidence (also non conclusive) ***must*** be considered, serving as a causality indicator.	Any piece of evidence (e.g., evidence coming from laboratory-level studies) can indicate that there ***can*** be causality. A vaccine-AEFI causal link ***may*** be inductively inferred with evidence that is not necessarily conclusive, and a plurality of causality indicators ***can*** be considered simultaneously to s*upport* or *suggest* the existence of the causal link. So, one ***can*** infer that there ***can*** be causality in the individual under examination (although this could not be the case in another individual).
	Evidential pluralism	All available heterogeneous evidence ***must*** be considered.	All the available evidence and different types of evidence ***must*** be considered simultaneously to *support* or *suggest* the existence of the vaccine-AEFI causal link. One type of evidence or another ***can*** be used, and/or they ***can*** be put together; evidence that alone may not be sufficient, but together it is, ***can*** be accumulated, and various types of evidence in a probabilistic way ***can*** be taken.
	Probabilistic assessment & a fine-grade qualitative judgment	A probabilistic fine-graded qualitative assessment ***must*** be applied.	Every available evidence is classified according to a probabilistic fine-graded qualitative scale. This ***can*** contribute to support the hypothesis of causality.
METHODOLOGY	***Methodological pluralism***	Different sources of evidence ***must*** be considered.	Weak-level evidence studies ***may*** give an important contribution to individual causal analysis, together with strong-level evidence studies.
*Factors that are different from person to person: e.g., other drugs (polypharmacy), predisposing genetic factors, ongoing inflammatory processes due to pre-existing pathologies, immune system, metabolic pathways, etc.).			

Table 10: *A new theoretical framework for individual causality assessment of AEFIs.*

As for the old one, the proposed algorithm presents precise criteria and 'rules' to guarantee a standardization of the procedure, but unlike the previous one it is conceived and structured differently from the ontological, epistemological and methodological point of view.
From the application of the above-listed criteria (see **Tab.10**), the investigator will be able to collect in a *flexible* and *extensive* way a varied and complete amount of information that will allow the generation of many possible causal hypotheses to explain the AEFI (complex '*webs*' of causality or causal complexes like those of Rothman), and the identification of the *most plausible* explanations. All this will convey in the categorization expressed in a fine-graded probability scale: *degree of probability close to certainty*.
Given the context of analysis characterized by complexity and high uncertainty, it is not possible 'to seek' irrefutable high-level evidence and express oneself in terms of absolute certainty, rather one should express in terms of a very high degree of certainty (in probabilistic terms) about the existence of the causal relationship. Since it is difficult to quantify the contribution of each co-cause, it would be appropriate to express it in qualitative terms: *very likely, probable (more likely), possible (less likely), unlikely*.
Since this is *not* a dichotomous procedure and there is *not* a mandatory path in which a step with the relative criterion/criteria precludes the passage to the next, the probability of reaching a 'positive' causal assessment increases. In the new algorithm a specific type of evidence is *not* required to justify the existence of a causal link, and the criteria are *not jointly necessary* to achieve a 'positive' categorization of the vaccine-AEFI causal link. According to this view, pluralism is an opportunity: you can have (inconclusive) evidence 1 *OR* 2 *OR* 3, and/or all of them: if you have more, and the more probative, the higher the probability of a causal link between AEFI and vaccination.
This kind of pluralistic approach allows (indeed, mandate) that each available item of evidence is considered in order to justify one's conclusions, thereby reducing the number of false negatives.
The graphical archetypal of the new algorithm is represented in **Fig.27** and the categorization according to a fine-graded probability scale is offered in **Tab.11** below.

Category	Description
Very likely	This category includes those AEFIs for which there is a suitable time frame* and for which, both referring to general laws and using abductive and inductive reasoning, the association with the vaccine is *very likely*. The vaccine played a causal role in triggering the event in the individual, so that without the vaccine it is highly probable that AEFI would not have occurred in the individual at that particular time and/or with that intensity even in presence of another cause [e.g., pre-existing disease, congenital anomaly, drug(s) intake, etc.]. In this case the AEFI is very unlikely to be explained by 'other cause(s)'. This category may also include those situations in which you have two/more causes that contributed to the event in the sense that both/all are (or are suspected to be) necessary for the event to occur at that time in the individual (if you do not have both/all the event does not manifest in the person in that moment). The vaccine-AEFI link should be considered *very likely* associated with the vaccine even in the presence of other co-cause(s), to the extent that the AEFI would not have occurred at that particular time in the individual with the mere presence of 'the other cause(s)'. Also, the vaccine's presence was necessary.

	Regarding the responsibility to be attributed to a cause for AEFI in the medico-legal setting, the same degree of responsibility should be given to each causal factor [e.g., the vaccine, the preexisting pathology, and (if present) others] as without each of them it is very likely that AEFI would not have occurred in the person at that time. It means that in case of economic compensation and, for example, in the presence of two causes both necessary for the event to occur, the role of the vaccine of having caused AEFI must be recognized at 50% (if the causes are 3, it will be recognized at 33, 33%, and so on) – if each caused AEFI with the same force.
Probable (more likely)	This category includes those AEFIs for which there is a suitable time frame* and for which, both referring to general laws and using abductive and inductive reasoning, the association with the vaccine is *probable.* The vaccine played a co-causal role in triggering the event in the individual, so that without the vaccine it is *more likely* that AEFI would not have occurred in the individual at that particular time and/or with that intensity in presence of another cause. Other cause(s) in this case may also explain the event but are *less* likely. Therefore, if we have cause A (e.g., the vaccine) and cause B (e.g., the preexisting pathology) that have contributed to AEFI, we could say that the vaccine played a co-causal role in triggering the event in the individual. Furthermore, with the vaccine it is *more likely* that AEFI would have occurred in the individual at that particular time and/or with that intensity in presence of another cause (e.g., pre-existing disease). In the legal field, the presence of multiple causes for the effect, more responsibility is usually given to an agent for a given effect when it is a direct result of its action rather than when it results in the end of a long causal chain (Brickman et al., 1975; Hilton et al., 2010; D. Lagnado & Channon, 2008; McClure et al., 2007; Spellman, 1997), – see Chapter IV. This could be an interesting cue to modify the algorithm in the following direction. In presence of, for example, vaccine and pre-existing disease as co-causes, both responsible for the event, one could give *greater responsibility* to one factor rather than the other depending on whether it is a proximate cause or not. In this way, two (or more) causes would be recognized for the same event and the responsibility of the other cause (i.e., the *less responsible* one) in having caused the event would not be excluded *a priori.* Following Waters (2007), those causal factors which are more salient (triggers) in the particular case than others (background conditions) would count as causes.
Possible (less likely)	This category includes those AEFIs for which there is a suitable time frame* and for which, both referring to general laws and using abductive and inductive reasoning, the association with the vaccine is *possible.* The vaccine played a co-causal role in triggering the event in the individual, so that without the vaccine it is *less likely* that AEFI would have occurred in the individual at that particular time and/or with that intensity in presence of another cause (e.g., pre-existing disease). Other cause(s) in this case could also explain the event and are *more likely*.
Unlikely	This category includes those AEFIs for which there is an improbable time frame* and for which, both referring to general laws and using abductive and inductive reasoning, the association with the vaccine is *unlikely.* Other cause(s) in this case could also explain the event and are *very likely*.
Unrelated/ coincidental	This category includes those AEFIs for which there is an incompatible time frame* and for which, both referring to general laws and using abductive and inductive reasoning, the association with the vaccine is *unrelated or coincidental.* Other cause(s) are sufficient by themselves to explain the AEFI; it was demonstrated that 'the other cause(s)' are independent of a possible synergistic interaction with the effects of the vaccine itself on the immune responses (Bellavite, 2020).
Unassessable/ unclassifiable	The info reported is insufficient/inadequate to classify the AEFI.
***Time frame:** must be established in relation to the type of AEFI; it is less relevant for development of autoimmune/degenerative diseases.	

Table 11: *Classification of the vaccine-AEFI causal link.*

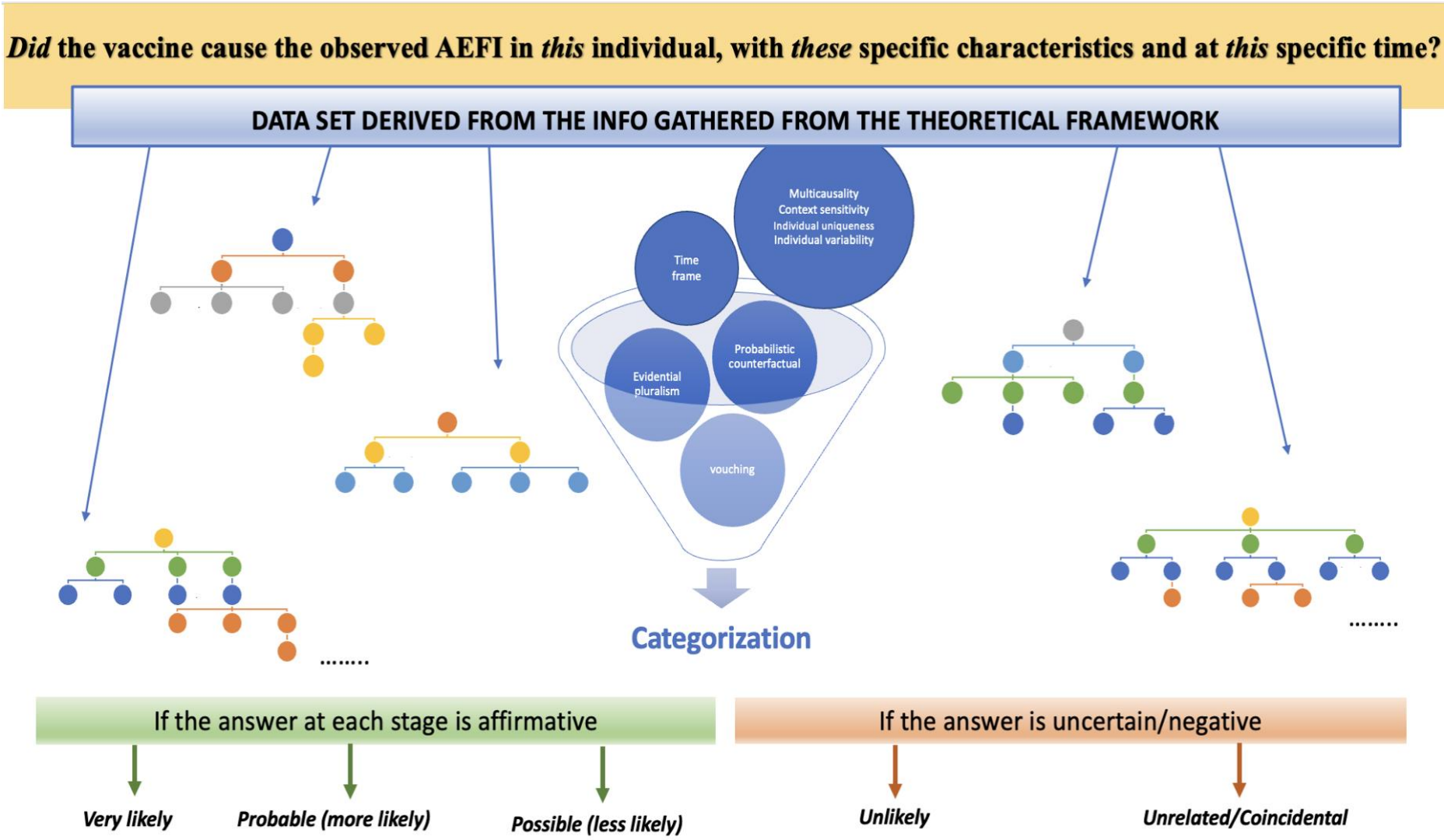

Figure 27. *The new algorithm for individual causality assessment of AEFIs.*

The proposed theoretical framework would result in an important improvement of the system since it would bring the following advantages:

i. Greater *inclusiveness* and *flexibility* to the system: the use of a single piece of evidence does not preclude the admissibility of the next one, as it happens in the current algorithm in which the order of the questions and the obligation to respect this order of categorization preestablishes an admissibility filter invalidating the procedure.
ii. Emphasis on the multifactorial nature of AEFIs and their context sensitivity, as well as the roles played by individual uniqueness and individual variability in the occurrence of AEFIs. Individual causality assessment is modelled as a highly complex activity, characterised by strong uncertainty.
iii. Adoption of a *dynamic* approach to causality, by embracing the dispositionalist theory (Anjium and Mumford, 2018). On the dispositionalist view, everything that contributes to producing the effect are causes (Anjium, 2020). The dispositionalist approach has important methodological implications that should be considered in this context.
iv. Adoption of the criterion of counterfactual dependence (e.g., How likely would it be that this person would have died if he had not taken the vaccine?) by reasoning in qualitative probabilistic terms according to logical probability [high degree of logical probability].
v. Development of a *comprehensive* and *exhaustive* analysis of the AEFI, allowing for the *generation of several hypotheses* related to the causal vaccine-AEFI link.

The joint combination of i-v increases the chance to detect safety signals and therefore *increase the accuracy* of the instrument.
In the following section I will present a case study to show how the reasoning and conclusions would be different with the application of the new proposed algorithm.

7.2. Case study: the new practical framework

The following case shows how the new algorithm works.

Case study

> Marta is 34 years old and is administered with the non-replicating viral vector vaccine based on the adenovirus ChAdOx1 (AstraZeneca) (*causal factor A*) to prevent the onset of complications due to exposure to the SARS-CoV-2 virus.
> Marta suffers from type 1 diabetes without complications (*causal factor B*) and is on estroprogestin therapy (*causal factor C*) because of polycystic ovary. She doesn't know to be affected by thrombophilia (*causal factor D*).

10 days after immunization Marta develops cerebral venous thrombosis and then dies (the suspected AEFI).

If we apply the new proposed algorithm to this case study, we proceed as follows.

Adoption of causality assessment criteria

First, we should assume that, since most AEFIs are multifactorial in nature, the vaccine may have acted as contributory cause (CC). Considering its intrinsic properties, we know it may have the *tendency* of causing certain AEs (see dispositionalism and causal laws – Chapters III and IV) and the occurrence of such events in certain individuals rather than in others suggests considering context-sensitivity, individual uniqueness and individual variability (see Chapter IV).
Then, in this specific case we refer to the following *causal scientific laws*:

(i) *Causal factor B (Cf-B)*: diabetes.
Various studies confirm that people with diabetes are likely to suffer from cardiovascular diseases twice as much as non-diabetic patients. This is because diabetes has a thrombophilic diathesis that is potentially responsible for a state of thrombophilia, a pathology that induces an increased risk of thrombus formation. In addition, the hyperglycemia that characterizes diabetic pathology also seems to play a central role in thrombophilia.

(ii) *Causal factor D (Cf-D)*: thrombophilia.
Thrombophilia can be acquired or due to genetic factors of blood clotting (genetic predisposition, Factor V Leiden mutation or Factor II mutation G20210A in heterozygosity, deficiency of natural coagulation inhibitors, prothrombin 20210). Most cases of thrombosis of the cerebral venous sinus are due to hypercoagulability (i.e., thrombophilia), a common condition present in 5-6% of the general population (Mannucci & Franchini, 2015). It can therefore be expected that about 5,000-6,000 people per 100,000 subjects vaccinated with Vaxzevria are carriers of these coagulation abnormalities (AIFA, 2021).

(iii) *Causal factor C (Cf-C)*: estroprogestin therapy.
Estroprogestin therappy is a risk factor for venous thrombosis. It is known that these drugs increase the risk of venous thromboembolism by about 4 times in women (O. Wu et al., 2005).
Thus, the absolute annual risk of having an episode of venous thromboembolism for a woman aged <40 years, heterozygous for the PV Leiden mutation and taking an estroprogestin preparation, is in the order of 0.4% (Middeldorp, 2011).

(iv) *Interaction between Cf-C and Cf-D*: congenital thrombophilia increases the risk of thrombosis, in combination with estroprogestin therapy.

(v) *Causal factor A/suspected CC (Cf-A/CC)*: vaccine.
Vaccines are known to induce a response by the immune system which involves antigens, adjuvant (if present), antigen-presenting cells, lymphocytes, and multiple immune mediators (cytokines). This response may lead to an excessive or distorted inflammatory reaction that can lead to hyperimmune phenomena (see Chapter III). It is known that vaccines can trigger immune thrombocytopenia with thrombosis, of which a very serious manifestation is cerebral venous thrombosis. Going into the specific of the vaccine under examination, this contains an adenovirus (rendered harmless) used as a "shuttle" to transport the genetic material of Sars-CoV-2 into the cells, which stimulates the cells to produce antibodies, and a sequence called SP (signal peptide) used to best express the genetic material of the coronavirus that could stimulate an excessive immune response.

Consideration(s)/outcome(s)

In this case, the person status presents comorbidities, and the thrombotic event could have occurred through various pathways (of which most likely some are unknown), namely:

(i) The event would still have occurred without the vaccine because it was due to diabetes.

OR

(ii) The event would still have occurred without the vaccine because it was due to the intake of estroprogestin drug in the presence of congenital thrombophilia.

OR

(iii) The event would still have occurred without the vaccine because it could have occurred independently of diabetes and ongoing therapy.

OR

(iv) The event would still have occurred without the vaccine because of complex interactions between all the other causal factors present.

OR

(v) The presence of vaccine may have increased the probability of the disease in that individual. The question is: Is the probability that the event occurred due to the presence of the vaccine greater than the probability that the event would have occurred without the vaccine? Did the vaccine contribute to the occurrence of the event which otherwise would not have occurred or would have occurred later in time or would have occurred at a lower intensity?

Now, we consider the various hypotheses in which the vaccine may have contributed to the AEFI.

Reasoning on the possible co-causal role of the vaccine in having contributed to AEFI

In light of the above considerations, one should investigate whether the vaccine may have contributed to AEFI, for example, by acting as:

a) a *modifier* of the effect acting synergistically: it interacted with several agents (those involved in the biochemical processes concerning diabetes and genetic thrombophilia) causing an excessive inflammatory response (cytokine storm) that precipitated the event.

OR

b) a *trigger*: it unmasked the genetic predisposition to the formation of thrombi (thrombophilia), by stimulating a specific reaction that led to the formation of thrombi;

more specifically, as

c) a *catalyst* of a causal mechanism: it anticipates the onset of the event, shortening the induction period for other causal factors (e.g., thrombophilia + estroprogestin therapy).

OR

d) a *preventive cause*: it acted by postponing the onset of the event, bringing out the induction period for another causal factor (e.g., thrombophilia).

Looking at the case study, we could distinguish three possible cases:

i) The effect wouldn't have happened without Cf-A/CC (vaccine), but also not without one or more co-morbidities.

OR

ii) The effect would (or might) have happened anyway, Cf-A/CC just increased the probability.

OR

iii) The effect would not have happened just when it did happen, but Cf-A/CC just made a 'tiny' contribution. If the person has several co-morbidities, about to die, and s/he is administered with Cf-A/CC, it may happen that this pushes him/her over the edge. This means that it contributed, but minimally so: the vaccine acted as a hastener/preempting cause (it makes the effect occur earlier).

Classification

If the vaccine is recognized as a possible CC, as such it must be held accountable to the AEFI, and therefore considering the type of information collected, the causal vaccine-AEFI link could

fall into one of the following categories: *very likely, probable (more likely) or possible (less likely), unlikely*.
Only if the other cause(s) is independent of a possible synergistic interaction with the effects of the vaccine on the immune responses, the vaccine-AEFI causal link is classified as *unrelated/coincidental*.
Different considerations and conclusions would have been obtained if we had applied the WHO algorithm to the case study.

7.3. Difference(s) with the WHO algorithm

Considering the case study above, if we now apply the WHO algorithm, the following considerations and conclusions follows:

(i) The tool is characterized by a mandatory path and the first question is aimed at *excluding causation* in a *dichotomous way* on the sole basis of evidence of alternative cause(s) able to explain AEFI. It should therefore follow that the causal vaccine-AEFI association is classified *a priori* as *inconsistent,* due to the presence of 'the other cause(s)', i.e., diabetes, thrombophilia, estroprogestin therapy. The excluded hypothesis (the vaccine) may be co-causally responsible for the AEFI's occurrence.
(ii) The multifactoriality nature of AEFI (i.e., venous thrombosis) is not appropriately considered or ignored altogether. The research is aimed at detecting *the* (unique) cause of AEFI: in our case it is 'the other cause'. There is no question about the possible co-causal role of the vaccine. The concepts of vaccine-person interactions, context sensitivity, individual variability, individual uniqueness, and the possibility that there are different types of causes and causal relationships present in the manifestation of AEFI is not considered (appropriately).
(i) Due to the stopping rule, the classification procedure is exhausted at the first step because of the sole evidence of 'other cause(s)'.

As Chandler (2019) points out, the current surveillance systems for vaccines are designed to detect pretty common AEs, well characterized from a nosocomial point of view, and to provide a population risk estimate. However, this is not enough to promptly assess the benefit-risk profile of innovative (and therefore unpredictable) pharmaceutical technologies nor to outline the different risk profiles determined by demographic factors, (sub)clinical, genetic, or other (Osimani B. & Ilardo, 2022). Chandler suggests a multidisciplinary approach oriented to scientific and investigative deepening (Chandler, 2019), which makes use of all the tools available for the collection, analysis, and synthesis of data, including *machine learning* and *knowledge retrieval* techniques on the one hand and systemic immunology and vaccinology on the other (Osimani B. & Ilardo, 2022) – see also (Blumenthal et al., 2021; Campbell-Tofte et al., 2019; Sobolev et al., 2016), and BIOVACSAFE initiative (Lewis et al. 2015). More

proactive solutions to optimize all the information that can help anticipate and prevent the risk of adverse reactions have been proposed by the scientific literature [see for instance (de Pretis et al., 2019; Inácio et al., 2017; Osimani, 2020; Ribeiro-Vaz et al., 2016)].

It is crucial that health care professionals (vaccinators) and authorities become aware of the algorithm' methodological issues to update vaccine surveillance policies and clinical practice, and to restore the necessary trust between society and political and health institutions (Osimani B. & Ilardo, 2022).

The proposed new algorithm may be a useful and decisive contribution to the problem of false negatives that affect the current system. This would constitute a valuable theoretical and practical tool for policymakers and legal officers to address the complex procedure of individual causality assessment of AEFIs. Hopefully, this will contribute in making individual causal assessment of AEFIs more reliable and accurate.

Conclusions

The concept of causality is of cardinal importance in health research, clinical practice, in the implementation of public health policies and in the medico-legal setting. Knowing causal relationships is crucial for scientific explanations of past events, for predicting future events, for interventions to determine or modify the results, and for attribution of liability (J. Reiss, 2015, 2016). This consideration becomes even more relevant when it comes to vaccines and their safety, as they are biological preparations that are administered to *healthy* subjects (IOM & Vaccine Safety Committee, 1994; WHO 2001; WHO-HIS-EMP 2013). An increasing number of recent cases contributed to draw higher attention to the problem of the AEFIs evaluation process and the reasons why the causal link ends up being almost always excluded.
The reasoning behind such process is standardized and systematized by the application of the 2019 version of the WHO AEFI algorithm (developed in 2013) (Chapter II). Despite its generalized use worldwide, increasing cases of serious and sometimes lethal AEFIs systematically valued as non-correlated to vaccines, have led to questioning its validity. The main opposing voices (Bellavite et al., 2020; H. Lee et al., 2020; Osimani B. & Ilardo, 2022; Puliyel et al., 2018) state that the algorithm presents some criticalities leading to the non-recognition of the vaccine's responsibility in having caused the AEFI. This is because, as it is conceived and structured, the algorithm seems to underestimate the complexity of the analysis context in which it operates.
The WHO algorithm seems not to do justice to the complexity of biological systems and the possibility of multifactorial causation – complex disease causation, complexity of the immune response (including the genesis of autoimmunity), complexity underlying vaccines' mechanism of action in inducing immune responses in relation to the AEFIs' manifestation, the role of genetic variants and of the microbiome in the modulation of immune reactions, complexity of vaccine-person interactions, and so on (see Chapter III). *Multifactoriality* is a necessary element in the causal diagnosis of AEFIs, since most AEFIs are multifactorial pathological manifestations. They occur as excessive or distorted inflammatory or immune responses that can degenerate to lethal outcomes or may concern the onset of irreversible pathologies (see Chapter III). These complexities highlight the need for a multi-factorial approach.
Moreover, understanding and explaining event causality implies the analysis of how cause and effect can and should be linked and this has been a primary focus of scientific and epistemological discussion over time. Philosophical literature has identified various concepts of causality (ontology). Epistemological and methodological literature is implicitly and/or explicitly based on such concepts (see Chapter IV).
Obviously, a methodology that (implicitly or explicitly) adopts any but not the other concept of causality will inevitably end up by excluding from the set of causal phenomena events and phenomena that do not meet the requirements dictated by the concept of causality underpinning it. A narrow notion of causality will tend to shrink the set of cases, in which the phenomena are considered causal, so it will tend to increase false and true negatives. Therefore, from a methodological point of view it is important that the notion of *cause,* which supports causal

assessment procedures, is *flexible* and *wide* enough to reliably allow the correct identification of all causal phenomena, and at the same time minimize failures to detect such phenomena when they are present. This implies the adoption of a pluralistic approach instead of a monistic one.

Multicausality and the individual analysis context also underline the need to consider *context-sensitivity*, *individual uniqueness,* and *individual variability*, that make individual causation analysis highly complex and characterized by strong uncertainty (see Chapter IV). In such a complex context, it is crucial to recognize the role of interacting causation and the presence of different the types of causes and causal structures.

The WHO algorithm establishes the causal link in a rigidly deterministic way and excludes *a priori* the possible co-causal role played by the vaccine in the occurrence of the AEFI as contributing cause. This approach, by imposing an epistemological procedure similar to a sort of differential (causal) diagnosis, tends to lead towards the identification of a single *direct* cause (*the* cause) – the disease is thus defined as monocausal –, underestimating the role of interacting, mediating and moderating causes.

The WHO algorithm focuses on *monocausality* and on a *direct* causal-effect relationship, thus tending to underestimate the presence of different types of causal relationships and the mechanisms by which they are mediated. It classifies a causal association as *inconsistent,* when another candidate cause can be associated with the AEFI, and as *undetermined* when the vaccine may be a cause but there is no evidence that it is *the* cause (Bellavite, 2020).

The WHO algorithm is characterized by a mandatory sequence of Steps. The first question is aimed at *excluding causation* in a *dichotomous way* on the sole basis of evidence of alternative cause(s) able to explain AEFI. However, the excluded hypothesis (the vaccine) may be co-causally responsible for the AEFI's occurrence. In this way, many AEs in which the vaccine may have played a role as a co-cause remain unrecognized or are attributed to other factors only.

If the above-mentioned complexities, conditions, multiplicity of risk factors, contributing and interacting causalities were properly and carefully considered and analyzed, it would be quite plausible to conclude that a vaccine may play a co-causal role, by contributing to precipitate an AEFI in a predisposed individual. The WHO algorithm should also include the interdependence factors of all risk factors before decreeing a vaccine-AEFI non-correlation. It should be seen if all the other causes were not a risk factor in the encounter with the vaccine that may have acted worsening the situation. In this context, two philosophical approaches can be of great help to establish causality: one in which interacting causal factors leading to the event should all count as causes (dispositionalism, Chapter IV), and/or one that distinguishes between factors that are context-related (background conditions) and factors that are more salient (triggers), and that would count as causes (Waters, Chapter IV). A vaccine may accelerate or reinforce an abnormal reaction or trigger it.

In addition, the WHO algorithm has a *dichotomous procedure* (binary scale: *consistent/inconsistent*), which can hardly adequately reflect the context and processes that characterize clinical practice, thus resulting less flexible. Moreover, it has an "*AND (∧)" structure*, which makes the algorithm more rigid (i.e., each criterion is necessary to move on to

the next step and to conclude about a causal link). Much of the information is lost due to the requirements *jointly necessary* to classify the link as *consistent.* This procedure obviously tends to increase the number of false negatives. This translates into the failure in detecting possible causes of the observed event (Osimani B. & Ilardo, 2022). More specifically, at *Step II* the use of the criterion of '*known* association' as decisive in assessing a vaccine-AEFI causal link, tends to increase underreporting and the denial of a new possible vaccine-AEFI link would put people's health at risk.

Moreover, the use of solely one type of evidence to support a causal relationship may often not be sufficient, increasing the likelihood of false negatives (see Chapter IV), and also the lack of clarity (ambiguities) in some points of the algorithm leaves room for arbitrariness and further errors.

All the above justifies the need to consider a more *flexible* approach, which allows for non-conclusive evidence (Osimani, 2020; Osimani & Mignini, 2015), does not require any scientific proof/certainty for taking action (decision-making under uncertainty), and allows to gather and consider more and different types of evidence (all heterogeneous evidence: *evidential pluralism).*

The minimization of false negatives may derive from changes to be made at these steps and at different levels. Using the tools provided by the philosophical literature on causality (see Chapter IV), and embracing both a multi-causal, vouching and evidential pluralistic approach, I stressed the necessity to revise the current WHO algorithm.

I proposed a new theoretical framework, that is characterized by (i) new ontological and epistemological criteria, (ii) a new methodological structure, and (iii) a 'new' categorization (new compared to the current system).

The proposed alternative allows the investigator to collect evidence in a *flexible* and *extensive* way. This will allow the generation of many possible causal hypotheses able to explain the AEFI (complex '*webs*' of causality or causal complexes like those of Rothman) and then the identification of the *most plausible* explanation. All this will convey in the categorization expressed in a fine-graded probability scale: *very likely, probable (more likely), possible (less likely), unlikely*. This kind of classification will tend to include much more info, thus reducing false negatives.

The goal of reducing (false) negatives naturally trades off with the goal of reducing (false) positives. Hence, one may object that the net accuracy of the instrument is not increased by the algorithm. However, this should be considered in the context of risk vs. benefit assessment. In the case of AEFIs, we are dealing with risk detection, hence with the problem of latent risks, yet unknown and unthought by the scientific community. Hence the focus is on false negatives. This contrasts with the context of hypothesis testing, that is a situation where an intended (and therefore known) causal relationship is tested, in order to verify its validity — benefit assessment (Osimani, 2020). The costs of false negatives and false positives are different in the two settings, and the algorithm should take this into account (Osimani & Ilardo, 2022).

Moreover, the new proposed algorithm is *not* a dichotomous procedure and there is *not* a mandatory path in which a Step with the relative criterion/criteria precludes the passage to the next. This implies an increase in the probability of reaching a 'positive' causal assessment. In

the new algorithm *no* specific type of evidence is required to justify the existence of a causal link, and criteria for causality assessment are *not jointly necessary* to achieve a 'positive' categorization of the vaccine-AEFI causal link. According to this view, pluralism is an opportunity: you can have (inconclusive) evidence 1 *OR* 2 *OR* 3, and/or all of them: if you have more, and the more probative, the higher the probability of a causal link between AEFI and vaccination.
The proposed theoretical framework would result in an important improvement to the system since it would bring the following advantages:

i. Greater *inclusiveness* and *flexibility* to the system: the use of a single piece of evidence does not preclude the admissibility of the next one, as it happens in the current algorithm in which the order of the questions and the obligation to respect this order of categorization preestablishes an admissibility filter invalidating the procedure.
ii. Emphasis on the multifactorial nature of AEFIs and their context sensitivity, as well as the roles played by individual uniqueness and individual variability in the occurrence of AEFIs. Individual causality assessment is modelled as a highly complex activity, characterised by strong uncertainty.
iii. Adoption of a *dynamic* approach to causality, by embracing the dispositionalist theory (Anjium and Mumford, 2018). On the dispositionalist view, everything that contributes to producing the effect are causes (Anjium, 2020). The dispositionalist approach has important methodological implications that should be considered in this context.
iv. Adoption of the criterion of counterfactual dependence (e.g., How likely would it be that this person would have died if he had not taken the vaccine?) by reasoning in qualitative probabilistic terms according to logical probability [high degree of logical probability].
v. Development of a *comprehensive* and *exhaustive* analysis of the AEFI, allowing for the *generation of several hypotheses* related to the causal vaccine-AEFI link.

The joint combination of i-v increases the chance to detect safety signals and therefore *increase the accuracy* of the instrument.
The proposed new algorithm may be a useful and decisive contribution to the problem of false negatives that affect the current system. This would constitute a valuable theoretical and practical tool for policymakers and legal officers to address the complex procedure of individual causality assessment of AEFIs. Hopefully, this will contribute in making individual causal assessment of AEFIs more reliable and accurate.

Appendix

Table A. Historical overview of major vaccine discoveries between the 19th and 20th centuries.

Date	*Event*
1880	Emil Adolf von Behring (1854–1917), considered among the most important founders of immunology, discovered the vaccine against diphtheria and tetanus, introducing the concept of antitoxins (despite the wide spread of the vaccine, even today these diseases have not been completely eradicated).
1885	The research of Louis Pasteur (1822–1895) led to the antidote for two bacterial infections, anthrax, and rabies. His discovery revolutionized the study of infectious diseases, i.e., the use of artificially 'weakened' bacteria in the laboratory to attenuate their aggressiveness and thus reduce the possibility of violent responses of the organism.
1908	Albert Calmette and Camille Guérin, who were working at the Institut Pasteur de Lille (France), developed the Bacillus Calmette-Guérin (BCG) tuberculosis vaccine to protect against tuberculosis (first administered to a person in 1921).
1955	Jonas Salk (1914–1995) introduced the 'inactivated' vaccine against polio (with intramuscular administration) and decided to not patent it so that it could be available to everyone.
1957	Albert Sabin (1906–1993) developed another vaccine with different characteristics, namely 'live-attenuated oral polio vaccine' (OPV), that turned out to be the most widespread vaccine against polio. In the same line of Salk, Sabin did not patent the vaccine, and promoted scientific collaboration by facilitating the development and distribution of vaccines (Hotez, 2021). Moreover, he donated his viral strains free of charge to the Soviet scientist Mikhail Chumakov, which allowed vaccine development also in the USSR. In this way it was possible to implement a worldwide vaccination campaign.
1971	Maurice Hilleman developed the MMR vaccine (trivalent vaccine against measles, mumps, and rubella).

Table B. Historical overview of WHO's global strategies to address epidemics/epidemics.

Date	*Event*
1949	Alexander Langmuir (the chief epidemiologist of the US-CDC) designed a highly successful national disease reporting system and created the Epidemic Intelligence Service, building on U.S. experience of malaria and polio eradication programs (Calain, 2007).
1955	Marcolino Candau (WHO's Brazilian director general) managed WHO's campaign of malaria eradication, followed by attempts to eradicate smallpox worldwide (the Soviet Union and Cuba provided 25 million and 2 million doses of freeze-dried vaccine, respectively).
1959	The World Health Assembly committed itself to a global smallpox eradication program (Brown et al., 2006).
1960s	Vaccination was made much cheaper, easier, and more effective thanks to technical improvements like the introduction of jet injectors and bifurcated needles.
1967	WHO launched the Intensive Smallpox Eradication Programme (ISEP) with the support of the world's most powerful players.

1968	Review of essential elements of global public health surveillance (including WHO's role as a coordinating body) during the 21st World Health Assembly (WHO, 1968).
1974	WHO launched the Expanded Programme on Immunization (EPI) (Brown et al., 2006), thanks to which new vaccines have become available [e.g., Hepatitis B, rotavirus, Hemophilus influenzae type b (Hib), pneumococcal vaccines, human papillomavirus (HPV), recommended for global use; e.g., yellow fever, typhoid conjugate, Ebola, recommended in countries where disease burden data indicate they should be used (WHO, 2013).
1995	- Adoption of two resolutions calling for a revision of International Health Regulation (IHR). - Establishment of a comprehensive programme to tackle new, emerging, and re-emerging infectious diseases (WHO, 1995a). - Foundation within the WHO of a new unit, i.e., the Division of Emerging Viral and Bacterial Diseases Surveillance and Control (WHO, 1995b), later renamed the Epidemic and Pandemic alert and Response (EPR) and Communicable diseases Surveillance and Response (CSR) departments (Calain, 2007).
2000	CSR supported the creation of a Global Epidemic Alert and Response Network (GOARN) to coordinate the technical resources involved worldwide in the fight against epidemic diseases (Enserink, 2004).
2003	- With the emergence of SARS, thanks to GOARN, WHO coordinated the international response to the epidemic (limiting the international spread of SARS). - Revision of the existing IHR (approved in 2005 by the 61st World Health Assembly).
2007	The new IHR text entered into force as an instrument of international law binding on all 194 member countries. It gave the WHO Director-General the power to determine whether an event represents a health emergency of international concern – i.e., Public Health Emergency of International Concern (PHEIC) (Missoni et al., 2019).

Table C. Aspects of medicines regulation in Europe that fall within the competence of NRAs (EMA, 2020b).

Aspects of medicines regulation in Europe that fall within the competence of NRAs
Assessment of the initial application for marketing authorization for all medicines in EU (most of the medicines available are authorized at national level).
Assessment of applications for authorization of clinical trials (EMA plays a key role in ensuring that the standards of good clinical practice are applied in cooperation with Member States and manages a database of clinical trials carried out in EU).
Evaluation and regulation of medical devices (EMA is involved in the assessment of certain categories of medical devices).
Evaluation of food supplements and cosmetics.
Decision making or obtaining information on the price or availability of medicines, which takes place within the country's national health system.
Control of advertising of non-prescription medicinal products (it is mainly carried out on a self-regulated basis by sectoral bodies, supported by the statutory role of NRAs in the Member States).
The monitoring or obtaining information on pharmaceutical patents, which take place through national patent offices or through a centralized process at the European Patent Office.

Development of treatment guidelines (national governments or health authorities of individual EU Member States draw up guidelines for decisions regarding diagnosis, management, and treatment in specific areas of health care).
Development of laws on medicines, which are drafted by the EC (that also develops EU policies in the field of human or veterinary medicines and public health), and then adopted by the European Parliament, together with the Council of the European Union.
Granting of marketing authorizations (the legal decision to grant, suspend or revoke a marketing authorization for any medicinal product falls within the competence of the EC for centrally authorized products and the national competent authorities of the EU Member States for nationally authorized products).

Table D*:* The WHO-UMC system for standardized case causality assessment. From: (UMC, 2018)

Causality term	Assessment criteria*
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable/ Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional/ Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

*All points should be reasonably complied with

Table E. Checklist for the assessment of causality. Taken from: WHO (2019: 71-72).

	Y	N	UK	NA	Remarks
I. Is there strong evidence for other causes?					
1. In this patient, does the medical history, clinical examination and/or investigations, **confirm** another cause for the event?	☐	☐	☑	☐	Dengue is suspected but not confirmed. (Platelets ↓, TWBC ↓, liver ++). But X ray, Culture, IgM and virus isolation not done
II. Is there a known causal association with the vaccine or vaccination?					
Vaccine product					
1. Is there evidence in published peer reviewed literature that this vaccine may cause such an event if administered correctly?	☐	☑	☐	☐	
2. Is there a biological plausibility that this vaccine could cause such an event?	☐	☑	☐	☐	
3. In this patient, did a specific test demonstrate the causal role of the vaccine ?	☐	☑	☐	☐	
Vaccine quality					
4. Could the vaccine given to this patient have a quality defect or is substandard or falsified?	☐	☑	☐	☐	As per investigation report
Immunization error					
5. In this patient, was there an error in prescribing or non-adherence to recommendations for use of the vaccine (e.g. use beyond the expiry date, wrong recipient etc.)?	☐	☑	☐	☐	As per investigation report
6. In this patient, was the vaccine (or diluent) administered in an unsterile manner?	☐	☑	☐	☐	As per investigation report
7. In this patient, was the vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal when administered?	☐	☐	☑	☐	
8. When this patient was vaccinated, was there an error in vaccine constitution/ preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?	☐	☑	☐	☐	As per investigation report
9. In this patient, was there an error in vaccine handling (e.g. a break in the cold chain during transport, storage and/or immunization session etc.)?	☐	☑	☐	☐	As per investigation report
10. In this patient, was the vaccine administered incorrectly (e.g. wrong dose, site or route of administration; wrong needle size etc.)?	☐	☑	☐	☐	As per investigation report
Immunization anxiety (Immunization stress related responses - ISRR)					
11. In this patient, could this event be a stress response triggered by immunization (e.g. acute stress response, vasovagal reaction, hyperventilation dissociative neurological symptom reaction etc.)?	☐	☑	☐	☐	
II (time): Was the event in section II within the time window of increased risk (i.e. "Yes" response to questions from II 1 to II 11 above)					
12. In this patient, did the event occur within a plausible time window after vaccine administration?	☐	☐	☐	☑	Because there are no, "Yes" responses to questions in II
III. Is there strong evidence against a causal association?					
1. Is there a body of published evidence (systematic reviews, GACVS reviews, Cochrane reviews etc.) **against** a causal association between the vaccine and the event?	☐	☑	☐	☐	
IV. Other qualifying factors for classification					
1. In this patient, did such an event occur in the past after administration of a similar vaccine?	☐	☐	☐	☑	
2. In this patient, did such an event occur in the past independent of vaccination?	☐	☐	☑	☐	
3. Could the current event have occurred in this patient without vaccination (background rate)?	☑	☐	☐	☐	In this situation, it is possible that sepsis could be a complication of the respiratory tract infection
4. Did this patient have an illness, pre-existing condition or risk factor that could have contributed to the event?	☑	☐	☐	☐	Fever one week prior to immunization
5. Was this patient taking any medication prior to the vaccination?	☐	☑	☐	☐	
6. Was this patient exposed to a potential factor (other than vaccine) prior to the event (e.g. allergen, drug, herbal product etc.)?	☑	☐	☐	☐	Other infections, (unconfirmed)

Note: Y: Yes; N: No; UK: Unknown; NA: Not applicable.

Bibliography

Aaby, P., Jensen, H., Samb, B., Cisse, B., Sodemann, M., Jakobsen, M., Poulsen, A., Rodrigues, A., Lisse, I. M., Simondon, F., & Whittle, H. (2003). Differences in female-male mortality after high-titre measles vaccine and association with subsequent vaccination with diphtheria-tetanus-pertussis and inactivated poliovirus: reanalysis of West African studies. *Lancet (London, England)*, *361*(9376), 2183–2188. https://doi.org/10.1016/S0140-6736(03)13771-3

Aaby, P., Mogensen, S. W., Rodrigues, A., & Benn, C. S. (2018). Evidence of Increase in Mortality After the Introduction of Diphtheria–Tetanus–Pertussis Vaccine to Children Aged 6–35 Months in Guinea-Bissau: A Time for Reflection? *Frontiers in Public Health*, *6*. https://doi.org/10.3389/FPUBH.2018.00079/FULL

Abeysinghe, S. (2017). Contesting a Pandemic: The WHO and the Council of Europe. *Science as Culture*, *26*(2), 161–184. https://doi.org/10.1080/09505431.2016.1212825

Agbabiaka, T. B., Savović, J., Harris, R., & Ernst, E. (2008). The development of a tool to assess the quality of case reports of adverse events. *International Journal of Risk and Safety in Medicine*, *20*, 123–133. https://doi.org/10.3233/JRS-2008-0435

Agmon-Levin, N., Arango, M. T., Kivity, S., Katzav, A., Gilburd, B., Blank, M., Tomer, N., Volkov, A., Barshack, I., Chapman, J., & Shoenfeld, Y. (2014). Immunization with hepatitis B vaccine accelerates SLE-like disease in a murine model. *Journal of Autoimmunity*, *54*, 21–32. https://doi.org/10.1016/J.JAUT.2014.06.006

Agmon-Levin, N., Zafrir, Y., Kivity, S., Balofsky, A., Amital, H., & Shoenfeld, Y. (2014). Chronic fatigue syndrome and fibromyalgia following immunization with the hepatitis B vaccine: another angle of the "autoimmune (auto-inflammatory) syndrome induced by adjuvants" (ASIA). *Immunologic Research*, *60*(2–3), 376–383. https://doi.org/10.1007/S12026-014-8604-2

Agmon-Levin, N., Zafrir, Y., Paz, Z., Shilton, T., Zandman-Goddard, G., & Shoenfeld, Y. (2009). Ten cases of systemic lupus erythematosus related to hepatitis B vaccine. *Lupus*, *18*(13), 1192–1197. https://doi.org/10.1177/0961203309345732

AIFA. (2012). *La nuova legislazione di farmacovigilanza*. Agenzia Italiana Del Farmaco. https://www.aifa.gov.it/-/la-nuova-legislazione-di-farmacovigilanza

AIFA. (2019). *Piano di attività per l'anno 2019* . Agenzia Italiana Del Farmaco. https://www.aifa.gov.it/documents/20142/648668/piano_attivit%C3%A0_2019.pdf

AIFA. (2021). *Complicanze tromboemboliche post-vaccinazione anti-COVID-19 con Vaxzevria (ChAdOx1 nCov-19, AstraZeneca) o con COVID-19 Vaccine Janssen (Ad.26. COV2.S, Johnson & Johnson)*. https://www.aifa.gov.it/documents/20142/1289678/Documento_esperti_coagulazione.pdf

AIFA. (2022a). *Mission e valori*. Agenzia Italiana Del Farmaco. https://www.aifa.gov.it/web/guest/mission

AIFA. (2022b). *Organizzazione*. Agenzia Italiana Del Farmaco. https://www.aifa.gov.it/web/guest/organizzazione1

Aksu, K., Keser, G., & Doganavsargil, E. (2006). Reactive arthritis following tetanus and rabies vaccinations. *Rheumatology International*, *27*(2), 209–210. https://doi.org/10.1007/S00296-006-0185-5

Alexander, L. K., Lopes, B., Ricchetti-Masterson, K., & Yeatts, K. B. (2015). Causality. In *ERIC Notebook* (pp. 1–5). UNC CH Department of Epidemiology. https://sph.unc.edu/wp-content/uploads/sites/112/2015/07/nciph_ERIC15.pdf

Al-Worafi, Y. M. (2020). Pharmacovigilance. In *Drug Safety in Developing Countries: Achievements and Challenges* (pp. 34–35). Academic Press Elsevier Inc.

Andersen, F., Anjum, R. L., & Rocca, E. (2019). Philosophical bias is the one bias that science cannot avoid. *ELife*, *8*, e44929. https://doi.org/10.7554/eLife.44929

Andrade, P., Gimblet-Ochieng, C., Modirian, F., Collins, M., Cárdenas, M., Katzelnick, L. C., Montoya, M., Michlmayr, D., Kuan, G., Balmaseda, A., Coloma, J., de Silva, A. M., & Harris, E. (2019).

Impact of pre-existing dengue immunity on human antibody and memory B cell responses to Zika. *Nature Communications*, *10*(1). https://doi.org/10.1038/S41467-019-08845-3

Andreas, H., & Günther, M. (2021). Difference-Making Causation. *The Journal of Philosophy*, *118*, 670–681.

Angeli, F., Reboldi, G., Trapasso, M., Zappa, M., Spanevello, A., & Verdecchia, P. (2022). COVID-19, vaccines and deficiency of ACE2 and other angiotensinases. Closing the loop on the "Spike effect." *European Journal of Internal Medicine*, *103*, 23–28. https://doi.org/10.1016/J.EJIM.2022.06.015

Angeli, F., Spanevello, A., Reboldi, G., Visca, D., & Verdecchia, P. (2021). SARS-CoV-2 vaccines: Lights and shadows. *European Journal of Internal Medicine*, *88*, 1–8. https://doi.org/10.1016/J.EJIM.2021.04.019

Anjum, R. L. (2020). Dispositions and The Unique Patient. In Rani Lill Anjum, Samantha Copeland, & Elena Rocca (Eds.), *Rethinking Causality, Complexity and Evidence for the Unique Patient: A CauseHealth Resource for Healthcare Professionals and the Clinical Encounter* (pp. 1–241). Springer International Publishing. https://doi.org/10.1007/978-3-030-41239-5_2

Anjum, R. L., Copeland, S., Rocca, E., Broom, B., Edwards, I. R., Mohn Engebretsen, K., Kerry, R., Kirkengen, A. L., Lindstad, T. G., Low, M., Hagen, K. B., & Price, C. (2020). *Rethinking Causality, Complexity and Evidence for the Unique Patient: A CauseHealth Resource for Healthcare Professionals and the Clinical Encounter* (Eds.). Springer International Publishing. https://doi.org/10.1007/978-3-030-41239-5

Anjum, R. L., & Mumford, S. (2018). Emergence and Demergence. *Philosophical and Scientific Perspectives on Downward Causation*, 92–109. https://doi.org/10.4324/9781315638577-6/EMERGENCE-DEMERGENCE-RANI-LILL-ANJUM-STEPHEN-MUMFORD

Anjum, R. L., & Rocca, E. (2020). When a Cause Cannot Be Found. In R. L. Anjum, S. Copeland, & E. Rocca (Eds.), *Rethinking Causality, Complexity and Evidence for the Unique Patient: A CauseHealth Resource for Healthcare Professionals and the Clinical Encounter* (pp. 55–74). Springer International Publishing. https://doi.org/10.1007/978-3-030-41239-5_4

Anscombe, G. E. M. (1971). Causality and Determination. In *Causation*. Cambridge University Press.

Anscombe, G. E. M. (1981). Causality and Determination. In *Metaphysics and the Philosophy of Mind: Collected Philosophical Papers* (Vol. 2, pp. 133–147). Basil Blackwell.

Appelbaum, J., Arnold, D. M., Kelton, J. G., Gernsheimer, T., Jevtic, S. D., Ivetic, N., Smith, J. W., & Nazy, I. (2022). SARS-CoV-2 spike-dependent platelet activation in COVID-19 vaccine-induced thrombocytopenia. *Blood Advances*, *6*(7), 2250–2253. https://doi.org/10.1182/BLOODADVANCES.2021005050

Aronson, J. K., & Hauben, M. (2006). Anecdotes that provide definitive evidence. *BMJ (Clinical Research Ed.)*, *333*(7581), 1267–1269. https://doi.org/10.1136/BMJ.39036.666389.94

Art. 5 Legge n. 46. (2006, February 22). *Modifiche al codice di procedura penale, in materia di inappellabilità delle sentenze di proscioglimento*. https://www.parlamento.it/parlam/leggi/06046l.htm

Auladell, M., Jia, X., Hensen, L., Chua, B., Fox, A., Nguyen, T. H. O., Doherty, P. C., & Kedzierska, K. (2019). Recalling the Future: Immunological Memory Toward Unpredictable Influenza Viruses. *Frontiers in Immunology*, *10*(JUL). https://doi.org/10.3389/FIMMU.2019.01400

Authier, F. J., Cherin, P., Creange, A., Bonnotte, B., Ferrer, X., Abdelmoumni, A., Ranoux, D., Pelletier, J., Figarella-Branger, D., Granel, B., Maisonobe, T., Coquet, M., Degos, J. D., & Gherardi, R. K. (2001). Central nervous system disease in patients with macrophagic myofasciitis. *Brain : A Journal of Neurology*, *124*(Pt 5), 974–983. https://doi.org/10.1093/BRAIN/124.5.974

Autoimmune Association. (2023). *What is autoimmunity?* Autoimmune Association. https://autoimmune.org/resource-center/about-autoimmunity/

Autret-Leca, E., Bensouda-Grimaldi, L., Jonville-Béra, A. P., & Beau-Salinas, F. (2006). [Pharmacovigilance of vaccines]. *Archives de Pediatrie : Organe Officiel de La Societe Francaise de Pediatrie*, *13*(2), 175–180. https://doi.org/10.1016/J.ARCPED.2005.10.020

Auvin, S., Jeljeli, M., Desnous, B., Soussi-Yanicostas, N., Dournaud, P., & Sterkers, G. (2018). Altered vaccine-induced immunity in children with Dravet syndrome. *Epilepsia*, *59*(4), e45–e50. https://doi.org/10.1111/EPI.14038

Azzari, C., Gambineri, E., Resti, M., Moriondo, M., Betti, L., Saldias, L. R., Gelli, A. M. G., & Vierucci, A. (2005). Safety and immunogenicity of measles-mumps-rubella vaccine in children with congenital immunodeficiency (DiGeorge syndrome). *Vaccine*, *23*(14), 1668–1671. https://doi.org/10.1016/J.VACCINE.2004.10.005

Bae, H. G., Domingo, C., Tenorio, A., de Ory, F., Muñoz, J., Weber, P., Teuwen, D. E., & Niedrig, M. (2008). Immune response during adverse events after 17D-derived yellow fever vaccination in Europe. *The Journal of Infectious Diseases*, *197*(11), 1577–1584. https://doi.org/10.1086/587844

Bahl, K., Senn, J. J., Yuzhakov, O., Bulychev, A., Brito, L. A., Hassett, K. J., Laska, M. E., Smith, M., Almarsson, Ö., Thompson, J., Ribeiro, A. (Mick), Watson, M., Zaks, T., & Ciaramella, G. (2017). Preclinical and Clinical Demonstration of Immunogenicity by mRNA Vaccines against H10N8 and H7N9 Influenza Viruses. *Molecular Therapy : The Journal of the American Society of Gene Therapy*, *25*(6), 1316–1327. https://doi.org/10.1016/J.YMTHE.2017.03.035

Baker, B., Eça Guimarães, L., Tomljenovic, L., Agmon-Levin, N., & Shoenfeld, Y. (2015). The safety of human papilloma virus-blockers and the risk of triggering autoimmune diseases. *Expert Opinion on Drug Safety*, *14*(9), 1387–1394. https://doi.org/10.1517/14740338.2015.1073710

Bandolier. (2022). *Reference class*. Bandolier: "Evidence Based Thinking about Health Care." http://www.bandolier.org.uk/booth/glossary/refclas.html

Barbaud, A., Deschildre, A., Waton, J., Raison-Peyron, N., & Tréchot, P. (2013). Hypersensitivity and vaccines: an update. *European Journal of Dermatology : EJD*, *23*(2), 135–141. https://doi.org/10.1684/EJD.2012.1842

Barlow, W. E., Davis, R. L., Glasser, J. W., Rhodes, P. H., Thompson, R. S., Mullooly, J. P., Black, S. B., Shinefield, H. R., Ward, J. I., Marcy, S. M., DeStefano, F., Immanuel, V., Pearson, J. A., Vadheim, C. M., Rebolledo, V., Christakis, D., Benson, P. J., Lewis, N., & Chen, R. T. (2001). The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine. *The New England Journal of Medicine*, *345*(9), 656–661. https://doi.org/10.1056/NEJMOA003077

Baumeier, C., Aleshcheva, G., Harms, D., Gross, U., Hamm, C., Assmus, B., Westenfeld, R., Kelm, M., Rammos, S., Wenzel, P., Münzel, T., Elsässer, A., Gailani, M., Perings, C., Bourakkadi, A., Flesch, M., Kempf, T., Bauersachs, J., Escher, F., & Schultheiss, H. P. (2022). Intramyocardial Inflammation after COVID-19 Vaccination: An Endomyocardial Biopsy-Proven Case Series. *International Journal of Molecular Sciences*, *23*(13). https://doi.org/10.3390/IJMS23136940

Baumgartner, M., & Glynn, L. (2013). Introduction to Special Issue on "Actual Causation." *Erkenn*, *78*, 1–8. https://doi.org/10.1007/s10670-013-9441-8

Bechtel, W., & Abrahamsen, A. (2005). Explanation: a mechanist alternative. In C. Craver & L. Darden (Eds.), *Special Issue: "Mechanisms in Biology"* (ed., Vol. 36, pp. 421–441). Studies in History and Philosophy of Biological and Biomedical Sciences. https://doi.org/10.1016/j.shpsc.2005.03.010

Bechtel, W., & Richardson, R. C. (1993). Discovering complexity: Decomposition and localization as strategies in scientific research. *Princeton University Press*.

Beebee, H., Hitchcock, C., & Menzies, P. (2009). The Oxford Handbook of Causation. *The Oxford Handbook of Causation*, 1–816. https://doi.org/10.1093/OXFORDHB/9780199279739.001.0001

Beeler, J., Varricchio, F., & Wise, R. (1996). Thrombocytopenia after immunization with measles vaccines: review of the vaccine adverse events reporting system (1990 to 1994). *The Pediatric Infectious Disease Journal*, *15*(1), 88–90. https://doi.org/10.1097/00006454-199601000-00020

Belizário, J. E., Faintuch, J., & Garay-Malpartida, M. (2018). Gut Microbiome Dysbiosis and Immunometabolism: New Frontiers for Treatment of Metabolic Diseases. *Mediators of Inflammation*, *2018*. https://doi.org/10.1155/2018/2037838

Bellavite, P. (2020). *Causality assessment of adverse events following immunization: the problem of multifactorial pathology [version 2; peer review: 3 approved, 1 approved with reservations]*. https://doi.org/10.12688/f1000research.22600.1

Bellavite, P., Puliyel, J., Keele, C. E., Monitoring, U., & Chandler, R. (2020). *Open Peer Review Causality assessment of adverse events following immunization: the problem of multifactorial pathology [version 2; peer review: 3 approved, 1 approved with reservations]*. https://doi.org/10.12688/f1000research.22600.1

Beninger, P. (2018). Pharmacovigilance: An Overview. *Clinical Therapeutics*, *40*(12), 1991–2004. https://doi.org/10.1016/J.CLINTHERA.2018.07.012

Benoist, C., & Mathis, D. (2001). Autoimmunity provoked by infection: how good is the case for T cell epitope mimicry? *Nature Immunology*, *2*(9), 797–801. https://doi.org/10.1038/NI0901-797

Benson, K., & Hartz, A. J. (2000). A Comparison of Observational Studies and Randomized, Controlled Trials. *New England Journal of Medicine*, *342*(25), 1878–1886. https://doi.org/10.1056/NEJM200006223422506

Berends-De Vries, T., Boerma, S., Doornabal, J., Dikkeschei, B., Stegeman, C., & Veneman, T. (2017). Goodpasture's Syndrome with Negative Anti-glomerular Basement Membrane Antibodies. *European Journal of Case Reports in Internal Medicine*, *4*(8). https://doi.org/10.12890/2017_000687

Berkman, P. A. (2020). Science diplomacy and its engine of informed decisionmaking: Operating through our global pandemic with humanity. *The Hague Journal of Diplomacy*, *15*(3), 435–450. https://doi.org/10.1163/1871191X-BJA10034

Berkovic, S. F., Harkin, L., McMahon, J. M., Pelekanos, J. T., Zuberi, S. M., Wirrell, E. C., Gill, D. S., Iona, X., Mulley, J. C., & Scheffer, I. E. (2006). De-novo mutations of the sodium channel gene SCN1A in alleged vaccine encephalopathy: a retrospective study. *The Lancet. Neurology*, *5*(6), 488–492. https://doi.org/10.1016/S1474-4422(06)70446-X

Berman, J. J. (2019). Changing how we think about infectious diseases. *Taxonomic Guide to Infectious Diseases*, 321–365. https://doi.org/10.1016/B978-0-12-817576-7.00008-0

Berneker, G.-Claude., & Ciucci, A. G. (1982). *Assessing causes of adverse drug reactions with special reference to standardized methods* (Jan. Venulet, Ed.). Academic Press.

Bertolaso, M. (2016). *Philosophy of Cancer: A Dynamic and Relational View* (Vol. 18). Springer Science+ Business Media Dordrecht. https://doi.org/10.1007/978-94-024-0865-2

Bertolaso, M., & Dupré, J. (2018). A Processual Perspective on Cancer. *Everything Flows*, 321–336. https://doi.org/10.1093/OSO/9780198779636.003.0016

Bierer, B. E. (2014). *ISCR-MRCT: Causality Assessment Workshop for Clinical Trial Investigators*. ISCR & MRCT. https://mrctcenter.org/wp-content/uploads/2015/11/2014-11-22_causality_assessment_workshop_for_clinical_trial_investigators.pdf

Bilkey, G. A., Burns, B. L., Coles, E. P., Mahede, T., Baynam, G., & Nowak, K. J. (2019). Optimizing precision medicine for public health. *Frontiers in Public Health*, *7*(MAR), 42. https://doi.org/10.3389/FPUBH.2019.00042/BIBTEX

Blough, D. (2021, January 28). *Vaccines help lay the foundation of public health*. The Ohio State University: College of Public Health. https://cph.osu.edu/news/2021/01/vaccines-public-health

Blumenthal, K. G., Peter, J. G., Trubiano, J. A., & Phillips, E. J. (2019). Antibiotic allergy. *Lancet (London, England)*, *393*(10167), 183–198. https://doi.org/10.1016/S0140-6736(18)32218-9

Blumenthal, K. G., Phadke, N. A., & Bates, D. W. (2021). Safety Surveillance of COVID-19 mRNA Vaccines Through the Vaccine Safety Datalink. *JAMA*, *326*(14), 1375–1377. https://doi.org/10.1001/JAMA.2021.14808

Boes, M. (2000). Role of natural and immune IgM antibodies in immune responses. *Molecular Immunology*, *37*(18), 1141–1149. https://doi.org/10.1016/S0161-5890(01)00025-6

Bonilla, F. A., & Oettgen, H. C. (2010). Adaptive immunity. *The Journal of Allergy and Clinical Immunology*, *125*(2 Suppl 2). https://doi.org/10.1016/J.JACI.2009.09.017

Bonnefont-Rousselot, D., Chantalat-Auger, C., Teixeira, A., Jaudon, M. C., Pelletier, S., & Cherin, P. (2004). Blood oxidative stress status in patients with macrophagic myofasciitis. *Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie*, *58*(9), 516–519. https://doi.org/10.1016/J.BIOPHA.2004.04.012

Bowcott, O. (2009). *Girl who died after cervical cancer injection had tumour in her chest*. The Guardian. https://www.theguardian.com/society/2009/oct/01/cervical-cancer-vaccination-tumour-natalie-morton

Bragazzi, N. L., Bridgewood, C., Sharif, K., Kamal, M., Amital, H., Watad, A., & Shoenfeld, Y. (2019). HPV vaccines and lupus: current approaches towards preventing adverse immune cross-reactivity. *Expert Review of Vaccines*, *18*(1), 31–42. https://doi.org/10.1080/14760584.2019.1557519

Bragazzi, N. L., Watad, A., Sharif, K., Adawi, M., Aljadeff, G., Amital, H., & Shoenfeld, Y. (2017). Advances in our understanding of immunization and vaccines for patients with systemic lupus erythematosus. *Expert Review of Clinical Immunology*, *13*(10), 939–949. https://doi.org/10.1080/1744666X.2017.1361321

Brambilla, L., Martorana, F., & Rossi, D. (2013). Astrocyte signaling and neurodegeneration: new insights into CNS disorders. *Prion*, *7*(1), 28–36. https://doi.org/10.4161/PRI.22512

Brickman, P., Ryan, K., & Wortman, C. B. (1975). Causal chains: Attribution of responsibility as a function of immediate and prior causes. *Journal of Personality and Social Psychology*, *32*(6), 1060–1067. https://doi.org/10.1037/0022-3514.32.6.1060

Brocardi. (2022, April 29). *Art. 40 Codice Penale - Rapporto di causalità - Brocardi.it*. Brocardi.It. https://www.brocardi.it/codice-penale/libro-primo/titolo-iii/capo-i/art40.html?utm_source=internal&utm_medium=link&utm_campaign=articolo&utm_content=nav_art_prec_top

Broom, B. (2020). The Practice of Whole Person-Centred Healthcare. In R. L. Anjum, S. Copeland, & E. Rocca (Eds.), *Rethinking causality, complexity and evidence for the unique patient A causehealth resource for healthcare professionals and the clinical encounter* (pp. 215–227). Springer. https://doi.org/10.1007/978-3-030-41239-5

Brown, G. C. (2019). The endotoxin hypothesis of neurodegeneration. *Journal of Neuroinflammation*, *16*(1), 180. https://doi.org/10.1186/S12974-019-1564-7

Brown, T. M., Cueto, M., & Fee, E. (2006). The World Health Organization and the transition from international to global public health. *American Journal of Public Health*, *96*(1), 62–72. https://doi.org/10.2105/AJPH.2004.050831

Budhiraja, S., & Akinapelli, R. (2010). Pharmacovigilance in vaccines. *Indian Journal of Pharmacology*, *42*(2), 115–118. https://doi.org/10.4103/0253-7613.64488

Bull, J. (2007). US activities in risk management of pharmaceutical products. In R. D. Mann & E. B. Andrews (Eds.), *Pharmacovigilance* (2nd ed., p. 543). John Wiley & Sons Ltd.

Buonavoglia, A., Leone, P., Dammacco, R., di Lernia, G., Petruzzi, M., Bonamonte, D., Vacca, A., Racanelli, V., & Dammacco, F. (2019). Pemphigus and mucous membrane pemphigoid: An update from diagnosis to therapy. *Autoimmunity Reviews*, *18*(4), 349–358. https://doi.org/10.1016/J.AUTREV.2019.02.005

Calain, P. (2007). Exploring the international arena of global public health surveillance. *Health Policy and Planning*, *22*(1), 2–12. https://doi.org/10.1093/HEAPOL/CZL034

Calvo, B., & Zuñiga, L. (2011). Risk Management Plan and Pharmacovigilance System. Biopharmaceuticals: Biosimilars. In G. Nota (Ed.), *Risk Management Trends* (p. Ch. 13). IntechOpen. https://doi.org/10.5772/16246

Camara-Lemarroy, C. R., Metz, L. M., & Yong, V. W. (2018). Focus on the gut-brain axis: Multiple sclerosis, the intestinal barrier and the microbiome. *World Journal of Gastroenterology*, *24*(37), 4217–4223. https://doi.org/10.3748/WJG.V24.I37.4217

Campaner, R. (2006). Mechanisms and Counterfactuals: a Different Glimpse of the (Secret) Connexion. In F. Longworth (Ed.), *Causation, Pluralism and Responsibility* (Vol. 77, pp. 15–44). PHILOSOPHICA. https://www.academia.edu/441705/Causation_Pluralism_and_Responsibility

Campaner, R. (2009). *La causalità nell'epistemologia contemporanea*. http://www.causal.altervista.org/seminars/Bologna%2017%20dicembre%2009.pdf

Campaner, R. (2011). Understanding mechanisms in the health sciences. *Theor Med Bioeth*, *32*, 5–17. https://doi.org/10.1007/s11017-010-9166-5

Campaner, R., & Galavotti, M. C. (2007). Plurality in Causality. In P. Machamer & G. Wolters (Eds.), *Thinking about Causes* (eds., pp. 178–199). University of Pittsburgh Press.

Campbell-Tofte, J., Vrahatis, A., Josefsen, K., Mehlsen, J., & Winther, K. (2019). Investigating the aetiology of adverse events following HPV vaccination with systems vaccinology. *Cellular and Molecular Life Sciences : CMLS*, *76*(1), 67–87. https://doi.org/10.1007/S00018-018-2925-6

Carroll, J. W. (1991). Property-level causation? *Philosophical Studies*, *63*(3), 245–270. https://doi.org/10.1007/BF00354193

Carruth, A. D. (2020). Emergence, Reduction and the Identity and Individuation of Powers. *Topoi*, *39*(5), 1021–1030. https://doi.org/10.1007/s11245-018-9621-x

Cartwright, N. (1979). Causal Laws and Effective Strategies. *Noûs*, *13*(4), 437. https://doi.org/10.2307/2215337

Cartwright, N. (1989). *Nature's Capacities and their Measurement*. Oxford University Press. https://books.google.com/books?hl=it&lr=&id=4wdREAAAQBAJ&oi=fnd&pg=PR9&ots=03c9T9usMf&sig=4AwjuGgyYRYcQk7ZFoEy2JJo6ho

Cartwright, N. (1994). Capacities. *Nature's Capacities and Their Measurement*, 141–182. https://doi.org/10.1093/0198235070.003.0005

Cartwright, N. (1999). The Dappled World: A Study of the Boundaries of Science. In *The Dappled World*. Cambridge University Press. https://doi.org/10.1017/CBO9781139167093

Cartwright, N. (2004). Causation: One word, many things. *Philosophy of Science*, *71*(5), 803–819. https://doi.org/10.1086/426771

Cartwright, N. (2007a). Hunting Causes and Using Them: Approaches in Philosophy and Economics. In *Journal of Economic Literature* (Issue January). Cambridge University Press.

Cartwright, N. (2007b). Are RCTs the Gold Standard? *BioSocieties*, *2*(1), 11–20. https://doi.org/10.1017/S1745855207005029

Cartwright, N. (2017). Single Case Causes: What Is Evidence and Why. In H.-K. Chao & J. Reiss (Eds.), *Philosophy of Science in Practice: Nancy Cartwright and the Nature of Scientific Reasoning* (pp. 11–24). Springer International Publishing. https://doi.org/10.1007/978-3-319-45532-7_2

Cartwright, N., & Hardie, J. (2012). *Evidence-based policy: A practical guide to doing it better*. https://books.google.it/books?hl=it&lr=&id=BN1oAgAAQBAJ&oi=fnd&pg=PP1&dq=Cartwright+and+Hardie+2012&ots=F2dIhenJvY&sig=0w_QUWXpjllm4-CPZgYgJSjkaJc

Casali, M. (2010). *L'accertamento del nesso di causalità*. https://www.responsabilitasanitaria.it/eventi_passati/2010-11-03/pdf/CASALI-L'accertamento_del_nesso_di_causalita.pdf

Cass. Civ. Sez. Lav. n. 8078. (2016). Malattia a patogenesi multifattoriale. In *Supreme Court*. Supreme Court. https://olympus.uniurb.it/index.php?option=com_content&view=article&id=14999:cassazione-civile-sez-lav-21-aprile-2016-n-8078-malattia-a-patogenesi-multifattoriale&catid=16&Itemid=138

Cass. Pen. Sez. Unite n.30328. (2002, September 11). *Responsabilità del medico: nesso di causalità tra omissione ed evento dannoso (cd. sentenza Franzese)*. Cassazione Penale, Sezioni Unite. https://olympus.uniurb.it/index.php?option=com_content&view=article&id=8383:cassazione-penale-sezioni-unite-11-settembre-2002-n-30328-responsabilita-del-medico-nesso-di-causalita-tra-omissione-ed-evento-dannoso&catid=17&Itemid=138

Castro, C., & Gourley, M. (2010). Diagnostic testing and interpretation of tests for autoimmunity. *The Journal of Allergy and Clinical Immunology*, *125*(2 Suppl 2). https://doi.org/10.1016/J.JACI.2009.09.041

CDC. (2010). Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) vaccine from the Advisory Committee on Immunization Practices. *MMWR. Morbidity and Mortality Weekly Report*, *60*(1), 13–15.

CDC. (2011, April 22). *Rotavirus Vaccine (RotaShield) and Intussusception*. Center for Disease Control and Prevention. https://www.cdc.gov/vaccines/vpd-vac/rotavirus/vac-rotashield-historical.htm

CDC. (2021, September 1). *Immunization: The Basics*. Centers Fro Disease Control and Prevention. https://www.cdc.gov/vaccines/vac-gen/imz-basics.htm

CDC. (2022, September 16). *Understanding Viral Vector COVID-19 Vaccines*. Understanding How COVID-19 Vaccines Work. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/how-they-work.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fvaccines%2Fdifferent-vaccines%2Fviralvector.html

Cerpa-Cruz, S., Paredes-Casillas, P., Landeros Navarro, E., Bernard-Medina, A. G., Martínez-Bonilla, G., & Gutiérrez-Ureña, S. (2013). Adverse events following immunization with vaccines

containing adjuvants. *Immunologic Research*, *56*(2–3), 299–303. https://doi.org/10.1007/S12026-013-8400-4

Chandler, R. E. (2019). Modernising vaccine surveillance systems to improve detection of rare or poorly defined adverse events. *BMJ*, *365*. https://doi.org/10.1136/BMJ.L2268

Charles A Janeway, J., Travers, P., Walport, M., & Shlomchik, M. J. (2001). Self-tolerance and its loss. In *Immunobiology: The immune system in health and disease* (5th eds). Garland Science.

Chatterjee, P. (2011). *Introduction to Immunization Safety and AEFI Surveillance*. State Health Resource Centre Chattisgarh. https://www.slideshare.net/prabirkc/01-introduction-to-aefi

Cheeti, A., Chakraborty, R. K., & Ramphul, K. (2022). Reactive Arthritis. *StatPearls*. https://www.ncbi.nlm.nih.gov/books/NBK499831/

Chen, R., Davis, R., & Rhides, P. (2005). Special methodological issues in pharmacoepidemiology studies of vaccine safety. In B. Strom (Ed.), *Pharmacoepidemiology*. 4th John Wiley & Sons.

Chen, R. T., Rastogi, S. C., Mullen, J. R., Hayes, S. W., Cochi, S. L., Donlon, J. A., & Wassilak, S. G. (1994). The vaccine adverse event reporting system (VAERS). *Vaccine*, *12*(6), 542–550. https://doi.org/10.1016/0264-410X(94)90315-8

Cheng, E. (2009). A Practical Solution to the Reference Class Problem. *Columbia Law Review*, *109*. https://scholarship.law.vanderbilt.edu/faculty-publications/154

Chinen, J., & Shearer, W. T. (2010). Secondary immunodeficiencies, including HIV infection. *The Journal of Allergy and Clinical Immunology*, *125*(2 Suppl 2). https://doi.org/10.1016/J.JACI.2009.08.040

Chinn, I. K., & Shearer, W. T. (2015). Severe Combined Immunodeficiency Disorders. *Immunology and Allergy Clinics of North America*, *35*(4), 671–694. https://doi.org/10.1016/J.IAC.2015.07.002

Chungath, M., & Shorvon, S. (2008). The mortality and morbidity of febrile seizures. *Nature Clinical Practice. Neurology*, *4*(11), 610–621. https://doi.org/10.1038/NCPNEURO0922

Cines, D. B., Liebman, H., & Stasi, R. (2009). Pathobiology of secondary immune thrombocytopenia. *Seminars in Hematology*, *46*(1 Suppl 2). https://doi.org/10.1053/J.SEMINHEMATOL.2008.12.005

CIOMS. (2010). *Practical Aspects of Signal Detection in Pharmacovigilan*. https://cioms.ch/wp-content/uploads/2018/03/WG8-Signal-Detection.pdf

CIOMS. (2012). *Definition and Application of Terms for Vaccine Pharmacovigilance* . www.who.int/bookorders

CIOMS, & WHO. (2012). *Definition and Application of Terms for Vaccine Pharmacovigilance*.

Clarke, B., Gillies, D., Illari, P., Russo, F., & Williamson, J. (2014). Mechanisms and the Evidence Hierarchy. *Topoi*, *33*(2), 339–360. https://doi.org/10.1007/S11245-013-9220-9/TABLES/7

Classen, J. B., & Classen, D. C. (1999). Public should be told that vaccines may have long term adverse effects. *BMJ : British Medical Journal*, *318*(7177), 193. https://doi.org/10.1136/BMJ.318.7177.193

Cobert, B. (2013a). *Causality Assessment*. https://www.health.gov.il/UnitsOffice/HD/MTI/Drugs/risk/Conferences/Documents/First-Causality-Israel-2013.pdf

Cobert, B. (2013b, October 30). *Signals, Risk & Reporting Safety Issues* . HCL. https://lifesciencescare.hcltech.com/blog/terminology-signals-potential-signals-risks-identified-risks-and-potential-risks/

Cobert, B., Gregory, W. W., & Thomas, J.-L. (2019). Cobert's Manual of Drug Safety and Pharmacovigilance. *Cobert's Manual of Drug Safety and Pharmacovigilance*. https://doi.org/10.1142/11228

Cobey, S., & Hensley, S. E. (2017). Immune history and influenza virus susceptibility. *Current Opinion in Virology*, *22*, 105–111. https://doi.org/10.1016/J.COVIRO.2016.12.004

Cod. Pen. Art. 41. (1930). Concorso di cause. In *Codice penale. Libro Primo dei Reati in generale: Titolo III, Capo I del Reato Consumato e Tentato* (No. 41). https://www.altalex.com/documents/news/2014/12/09/del-reato#art41

Coffman, R. L., Sher, A., & Seder, R. A. (2010). Vaccine adjuvants: putting innate immunity to work. *Immunity*, *33*(4), 492–503. https://doi.org/10.1016/J.IMMUNI.2010.10.002

Colafrancesco, S., Agmon-Levin, N., Perricone, C., & Shoenfeld, Y. (2013). Unraveling the soul of autoimmune diseases: pathogenesis, diagnosis and treatment adding dowels to the puzzle. *Immunologic Research*, *56*(2–3), 200–205. https://doi.org/10.1007/S12026-013-8429-4

Colafrancesco, S., Perricone, C., Priori, R., Valesini, G., & Shoenfeld, Y. (2014). Sjögren's syndrome: another facet of the autoimmune/inflammatory syndrome induced by adjuvants (ASIA). *Journal of Autoimmunity*, *51*, 10–16. https://doi.org/10.1016/J.JAUT.2014.03.003

Collins, F. S., & Varmus, H. (2015). A new initiative on precision medicine. *The New England Journal of Medicine*, *372*(9), 793–795. https://doi.org/10.1056/NEJMP1500523

Concas, A. (2017). Il nesso di causalità, definizione e caratteri. In *Diritto penale*. Diritto.it. file:///Users/marialaura/Downloads/il-nesso-di-causalita-definizione-e-caratteri.pdf

Corraini, P., Olsen, M., Pedersen, L., Dekkers, O. M., & Vandenbroucke, J. P. (2017). Effect modification, interaction and mediation: an overview of theoretical insights for clinical investigators. *Clinical Epidemiology*, *9*, 331. https://doi.org/10.2147/CLEP.S129728

Cosentino, M., & Marino, F. (2022). The spike hypothesis in vaccine-induced adverse effects: questions and answers. *Trends in Molecular Medicine*, *28*(10), 797–799. https://doi.org/10.1016/J.MOLMED.2022.07.009

Cosentino, M. ;, Marino, F., Cosentino, M., & Marino, F. (2022). Understanding the Pharmacology of COVID-19 mRNA Vaccines: Playing Dice with the Spike? *International Journal of Molecular Sciences 2022, Vol. 23, Page 10881*, *23*(18), 10881. https://doi.org/10.3390/IJMS231810881

Craig, J. (2008). Complex Diseases: Research and Applications . *Nature Education*, *1*(1), 184. https://www.nature.com/scitable/topicpage/complex-diseases-research-and-applications-748/

Crandall, L. G., Lee, J. H., Stainman, R., Friedman, D., & Devinsky, O. (2019). Potential Role of Febrile Seizures and Other Risk Factors Associated With Sudden Deaths in Children. *JAMA Network Open*, *2*(4), e192739. https://doi.org/10.1001/JAMANETWORKOPEN.2019.2739

Cruz-Tapias, P., Blank, M., Anaya, J. M., & Shoenfeld, Y. (2012). Infections and vaccines in the etiology of antiphospholipid syndrome. *Current Opinion in Rheumatology*, *24*(4), 389–393. https://doi.org/10.1097/BOR.0B013E32835448B8

Danan, G., & Benichou, C. (1993). Causality assessment of adverse reactions to drugs—I. A novel method based on the conclusions of international consensus meetings: Application to drug-induced liver injuries. *Journal of Clinical Epidemiology*, *46*(11), 1323–1330. https://doi.org/10.1016/0895-4356(93)90101-6

Daulatzai, M. A. (2014). Chronic functional bowel syndrome enhances gut-brain axis dysfunction, neuroinflammation, cognitive impairment, and vulnerability to dementia. *Neurochemical Research*, *39*(4), 624–644. https://doi.org/10.1007/S11064-014-1266-6

David, H., Mccague, W. P., & Yaniszewski, P. F. (2005). Proving Causation Where The But For Test Is Unworkable. *The Advocates Quarterly*, *30*, 216–238. https://mccagueborlack.com/uploads/articles/43/hd-pm-py_proving-causation.pdf?1299245845

de La Fuente, I. G., Wagner, N., Siegrist, C. A., & Posfay-Barbe, K. M. (2013). Tetanus immunity as a surrogate for past diphtheria-tetanus-pertussis immunization in migrant children. *The Pediatric Infectious Disease Journal*, *32*(3), 274–277. https://doi.org/10.1097/INF.0B013E3182748F0B

de Martino, M., Chiappini, E., & Galli, L. (2013). Vaccines and autoimmunity. *International Journal of Immunopathology and Pharmacology*, *26*(2), 283–290. https://doi.org/10.1177/039463201302600201

de Pretis, F., Landes, J., & Osimani, B. (2019). E-synthesis: A Bayesian framework for causal assessment in pharmacosurveillance. *Frontiers in Pharmacology*, *10*. https://doi.org/10.3389/FPHAR.2019.01317/FULL

de Vreese, L. (2006). Causal Pluralism And Scientific Knowledge: An Underexposed Problem. *Philosophica*, *77*(1), 125–150.

Dehner, C., Fine, R., & Kriegel, M. A. (2019). The microbiome in systemic autoimmune disease: mechanistic insights from recent studies. *Current Opinion in Rheumatology*, *31*(2), 201–207. https://doi.org/10.1097/BOR.0000000000000574

Demicheli, V., Rivetti, A., Debalini, M. G., & di Pietrantonj, C. (2012). Vaccines for measles, mumps and rubella in children. *The Cochrane Database of Systematic Reviews*, *2012*(2). https://doi.org/10.1002/14651858.CD004407.PUB3

Demir, S. A., Timur, Z. K., Ateş, N., Martínez, L. A., & Seyrantepe, V. (2020). GM2 ganglioside accumulation causes neuroinflammation and behavioral alterations in a mouse model of early onset Tay-Sachs disease. *Journal of Neuroinflammation*, *17*(1). https://doi.org/10.1186/s12974-020-01947-6

DeVrieze, B. W., & Hurley, J. A. (2022). Goodpasture Syndrome. *StatPearls*. https://www.ncbi.nlm.nih.gov/books/NBK459291/

Dlouhy, B. J., Ciliberto, M. A., Cifra, C. L., Kirby, P. A., Shrock, D. L., Nashelsky, M., & Richerson, G. B. (2017). Unexpected Death of a Child with Complex Febrile Seizures-Pathophysiology Similar to Sudden Unexpected Death in Epilepsy? *Frontiers in Neurology*, *8*(FEB). https://doi.org/10.3389/FNEUR.2017.00021

Donnan, M. (2018). Counterfactual Theories of Causation. In *OXFORD PHILOSOPHICAL SOCIETY -MEMBERS' WEEKEND, AUGUST 2018*. https://www.oxfordphilsoc.org/Weekend/2018/3_Counterfactual_theories_of_causation_Michael_Donnan/3_Notes.pdf

Dornell, J. (2022, October 7). *Humoral vs Cell-Mediated Immunity*. Immunology & Microbiology - Technology Networks. https://www.technologynetworks.com/immunology/articles/humoral-vs-cell-mediated-immunity-344829

Dou, J., Zeng, J., Wu, K., Tan, W., Gao, L., & Lu, J. (2019). Microbiosis in pathogenesis and intervention of atopic dermatitis. *International Immunopharmacology*, *69*, 263–269. https://doi.org/10.1016/J.INTIMP.2019.01.030

Dowe, P. (2000). *Physical Causation* (ed.). Cambridge University Press. https://doi.org/10.1017/CBO9780511570650

Dragulinescu, S. (2012). On Anti Humeanism and Medical Singular Causation. *Acta Analytica*, *27*(3), 265–292. https://doi.org/10.1007/S12136-011-0141-1/FIGURES/6

Duangchinda, T., Dejnirattisai, W., Vasanawathana, S., Limpitikul, W., Tangthawornchaikul, N., Malasit, P., Mongkolsapaya, J., & Screaton, G. (2010). Immunodominant T-cell responses to dengue virus NS3 are associated with DHF. *Proceedings of the National Academy of Sciences*, *107*(39), 16922–16927. https://doi.org/10.1073/pnas.1010867107

Ducasse, C. J. (1926). On the Nature and the Observability of the Causal Relation. *The Journal of Philosophy*, *23*(3), 57–68. https://doi.org/10.2307/2014377

Ducasse, C. J. (1965). Causation: Perceivable? Or only inferred? *Philosophy and Phenomenological Research*, *26*(2), 173. https://doi.org/10.2307/2106180

Ducasse, C. J. (1968). *Truth, Knowledge and Causation*. Routledge.

Dugan, H. L., Guthmiller, J. J., Arevalo, P., Huang, M., Chen, Y. Q., Neu, K. E., Henry, C., Zheng, N. Y., Lan, L. Y. L., Tepora, M. E., Stovicek, O., Bitar, D., Palm, A. K. E., Stamper, C. T., Changrob, S., Utset, H. A., Coughlan, L., Krammer, F., Cobey, S., & Wilson, P. C. (2020). Preexisting immunity shapes distinct antibody landscapes after influenza virus infection and vaccination in humans. *Science Translational Medicine*, *12*(573). https://doi.org/10.1126/SCITRANSLMED.ABD3601

Dyda, A., Stelzer-Braid, S., Adam, D., Chughtai, A. A., & Macintyre, C. R. (2018). The association between acute flaccid myelitis (AFM) and enterovirus D68 (EV-D68) – what is the evidence for causation? *Eurosurveillance*, *23*(3), 17–00310. https://doi.org/10.2807/1560-7917.ES.2018.23.3.17-00310/CITE/PLAINTEXT

Dyrkolbotn, S. K. (2017). On preemption and overdetermination in formal theories of causality. *ArXiv Preprint ArXiv:1710.03390*, 1–15. https://doi.org/10.4204/EPTCS.259.1

ECDC. (2018, February). *Training of Trainers in Epidemiology of Vaccine Preventable Diseases* . https://slideplayer.com/slide/14708374/

ECDC. (2022a). *What we do*. https://www.ecdc.europa.eu/en/about-us/what-we-do

ECDC. (2022b, April 26). *Questions and answers on COVID-19: Vaccines*. European Centre for Disease Prevention and Control. https://www.ecdc.europa.eu/en/covid-19/questions-answers/questions-and-answers-vaccines

Edwards, I. R. (2012). Considerations on causality in pharmacovigilance. *International Journal of Risk & Safety in Medicine*, *24*(1), 41–54. https://doi.org/10.3233/JRS-2012-0552

Edwards, I. R. (2018). Living with complexity and big data. *Uppsala Reports*, *78*, 28–29. https://scholar.google.com/scholar_lookup?&title=Living%20with%20complexity%20and%20big%20data&journal=Uppsala%20Rep&volume=78&pages=28-29&publication_year=2018&author=Edwards%2CR#d=gs_cit&t=1671206284473&u=%2Fscholar%3Fq%3Dinfo%3A8ELjcs7ooy8J%3Ascholar.google.com%2F%26output%3Dcite%26scirp%3D0%26hl%3Dit

Edwards, I. R., & Aronson, J. K. (2000). Adverse drug reactions: definitions, diagnosis, and management. *The Lancet*, *356*(9237), 1255–1259. https://doi.org/10.1016/S0140-6736(00)02799-9

Eells, E. (1991). Probabilistic Causality. In *Probabilistic Causality*. Cambridge University Press. https://doi.org/10.1017/CBO9780511570667

Eisen, D. P., & McBryde, E. S. (2009). Avoiding Guillan-Barré Syndrome following swine origin pandemic H1N1 2009 influenza vaccination. *The Journal of Infectious Diseases*, *200*(10), 1627–1628. https://doi.org/10.1086/644782

Eldred, B. E., Dean, A. J., McGuire, T. M., & Nash, A. L. (2006). Vaccine components and constituents: responding to consumer concerns. *The Medical Journal of Australia*, *184*(4), 170–175. https://doi.org/10.5694/J.1326-5377.2006.TB00178.X

Elorza, A., Melchor, L., Lacunza, I., Aukes, E., Ordóñez-Matamoros, G., Kuhlmann, S., Ebrahimi, S. H., & Young, M. (2021). Who Are the Science Diplomacy Stakeholders? In *S4D4C European Science Diplomacy Online Course, Module 3*. S4D4C.

EMA. (2005). Committee for medicinal products for human use. Guideline on Adjuvants in Vaccines for Human Use. In *European Medicines Agency*. European Medicine Agency. http://www.ema.europa.eu/ docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003809.pdf

EMA. (2020a). Pharmacovigilance Plan of the EU Regulatory Network for COVID-19 Vaccines. *European Medicine Agency, EMA/333964/2020*. https://www.ema.europa.eu/en/documents/other/pharmacovigilance-plan-eu-regulatory-network-covid-19-vaccines_en.pdf.

EMA. (2020b, February 10). *What we do* . European Medicines Agency. https://www.ema.europa.eu/en/about-us/what-we-do

EMA. (2022a). *Authorisation of medicines*. European Medicines Agency. https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines

EMA. (2022b). *History of EMA* . European Medicines Agency. https://www.ema.europa.eu/en/about-us/history-ema

EMA. (2022c). *Risk management* . European Medicines Agency. https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/pharmacovigilance/risk-management

EMA. (2022d). *Who we are* . European Medicines Agency. https://www.ema.europa.eu/en/about-us/who-we-are

EMA & HMA. (2017). Guideline on good pharmacovigilance practices (GVP), Annex I, Definitions (Rev 4). *European Medicine Agency and Heads of Medicine Agencies*. www.ema.europa.eu

Eneström, S., & Hultman, P. (1995). Does amalgam affect the immune system? A controversial issue. *International Archives of Allergy and Immunology*, *106*(3), 180–191. https://doi.org/10.1159/000236843

Engebretsen, K. (2020). Reflection on the Clinician's Role in the Clinical Encounter. In L. Anjum, S. Copeland, & E. Rocca (Eds.), *Rethinking causality, complexity and evidence for the unique patient A causehealth resource for healthcare professionals and the clinical encounter*. Springer. https://doi.org/10.1007/978-3-030-41239-5

Enserink, M. (2004). A global fire brigade responds to disease outbreaks. *Science*, *303*, 1605–1606.
ET. (2020). *COVID-19 pandemic most challenging crisis since Second World War: UN chief*. The Economic Times. https://www.google.it/amp/s/m.economictimes
EUR-Lex. (2000). *Communication from the Commission on the precautionary principle /* COM/2000/0001 final */ 52000DC0001* . European Commission. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A52000DC0001
EUR-Lex. (2002a). 12002E174 - Treaty establishing the European Community (Nice consolidated version) - Part Three: Community policies - Title XIX: Environment - Article 174 - Article 130r - EC Treaty (Maastricht consolidated version) . *Official Journal C 325* , 107–108. https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:12002E174:EN:HTML
EUR-Lex. (2002b, December 24). *Document 12002E174 - Treaty establishing the European Community (Nice consolidated version), Part Three: Community policies, Title XIX: Environment, Article 174, Article 130r - EC Treaty (Maastricht consolidated version)*. OJ C 325. https://eur-lex.europa.eu/eli/treaty/tec_2002/art_174/oj
European Medicines Agency, & Heads of Medicine Agencies. (2017). Guideline on good pharmacovigilance practices (GVP). Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2). In *EMA/873138/2011 Rev 2* (pp. 6–9). www.ema.europa.eu
Evans, M. S., Culton, D. A., Diaz, L. A., Googe, P. B., & Morrell, D. S. (2019). Childhood pemphigus foliaceus presenting as a polycyclic eruption: Case report and review of the literature. *Pediatric Dermatology*, *36*(2), 236–241. https://doi.org/10.1111/PDE.13750
Evans, S. J. W., Waller, P. C., & Davis, S. (2001). Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepidemiology and Drug Safety*, *10*(6), 483–486. https://doi.org/10.1002/PDS.677
Exley, C., Swarbrick, L., Gherardi, R. K., & Authier, F. J. (2009). A role for the body burden of aluminium in vaccine-associated macrophagic myofasciitis and chronic fatigue syndrome. *Medical Hypotheses*, *72*(2), 135–139. https://doi.org/10.1016/J.MEHY.2008.09.040
Faich, G. A. (1986). Adverse-Drug-Reaction Monitoring. *New England Journal of Medicine*, *314*(24), 1589–1592. https://doi.org/10.1056/NEJM198606123142427
Fauquert, J. L. (2019). Diagnosing and managing allergic conjunctivitis in childhood: The allergist's perspective. *Pediatric Allergy and Immunology : Official Publication of the European Society of Pediatric Allergy and Immunology*, *30*(4), 405–414. https://doi.org/10.1111/PAI.13035
Fedak, K. M., Bernal, A., Capshaw, Z. A., & Gross, S. (2015). Applying the Bradford Hill criteria in the 21st century: how data integration has changed causal inference in molecular epidemiology. *Emerging Themes in Epidemiology*, *12*(1). https://doi.org/10.1186/S12982-015-0037-4
Federal Food Drug and Cosmetic Act. (2011). *21 USC §321*. https://www.govinfo.gov/content/pkg/USCODE-2011-title21/html/USCODE-2011-title21-chap9.htm
Flynn, T. (2010). The handling of the H1N1 pandemic: more transparency needed. *AS/Soc (2010)12: Council of Europe*.
Franceschetti, P. (2017). *Causalità (penale)*. AltalexPedia. https://www.altalex.com/documents/altalexpedia/2016/09/26/causalita-penale
Frenk, J., & Moon, S. (2013). Governance Challenges in Global Health. *N Engl J Med* , *368*(10), 936–942. https://doi.org/10.1056/NEJMRA1109339
Fujinami, R. S., von Herrath, M. G., Christen, U., & Whitton, J. L. (2006). Molecular mimicry, bystander activation, or viral persistence: infections and autoimmune disease. *Clinical Microbiology Reviews*, *19*(1), 80–94. https://doi.org/10.1128/CMR.19.1.80-94.2006
GACVS, & WHO. (2009). Global safety of vaccines: strengthening systems for monitoring, management and the role of GACVS. *Expert Review Vaccines*, *8*(6), 705–716.
Galavotti, M. C. (2008). Causal Pluralism and Context. In M. C. Galavotti, R. Scazzieri, & P. Suppes (Eds.), *Reasoning, Rationality and Probability* (eds., pp. 233–252). CSLI.
Galli, G., Hancock, K., Hoschler, K., DeVos, J., Praus, M., Bardelli, M., Malzone, C., Castellino, F., Gentile, C., McNally, T., del Giudice, G., Banzhoff, A., Brauer, V., Montomoli, E., Zambon, M.,

Katz, J., Nicholson, K., & Stephenson, I. (2009). Fast rise of broadly cross-reactive antibodies after boosting long-lived human memory B cells primed by an MF59 adjuvanted prepandemic vaccine. *Proceedings of the National Academy of Sciences*, *106*(19), 7962–7967. https://doi.org/10.1073/pnas.0903181106

Gell, P. G. H., & Coombs, R. R. A. (1963). Clinical aspects of immunology. *Clinical Aspects of Immunology*.

Gentili, G., Wirz, M., Collotti, C., Pasquini, P., Stroffolini, T., D'Amelio, R., Matricardi, P. M., & Nisini, R. (1993). Prevalence of hyperimmunization against tetanus in Italians born after the introduction of mandatory vaccination of children with tetanus toxoid in 1968. *Infection*, *21*(2), 80–82. https://doi.org/10.1007/BF01710736

Gershwin, L. J. (2018). Adverse Reactions to Vaccination: From Anaphylaxis to Autoimmunity. *The Veterinary Clinics of North America. Small Animal Practice*, *48*(2), 279–290. https://doi.org/10.1016/J.CVSM.2017.10.005

Ghazavi, M. K., & Johnston, G. A. (2011). Insulin allergy. *Clinics in Dermatology*, *29*(3), 300–305. https://doi.org/10.1016/J.CLINDERMATOL.2010.11.009

Gherardi, R. K., Coquet, M., Cherin, P., Belec, L., Moretto, P., Dreyfus, P. A., Pellissier, J. F., Chariot, P., & Authier, F. J. (2001). Macrophagic myofasciitis lesions assess long-term persistence of vaccine-derived aluminium hydroxide in muscle. *Brain : A Journal of Neurology*, *124*(Pt 9), 1821–1831. https://doi.org/10.1093/BRAIN/124.9.1821

Gholizadeh, P., Mahallei, M., Pormohammad, A., Varshochi, M., Ganbarov, K., Zeinalzadeh, E., Yousefi, B., Bastami, M., Tanomand, A., Mahmood, S. S., Yousefi, M., Asgharzadeh, M., & Kafil, H. S. (2019). Microbial balance in the intestinal microbiota and its association with diabetes, obesity and allergic disease. *Microbial Pathogenesis*, *127*, 48–55. https://doi.org/10.1016/J.MICPATH.2018.11.031

Giglio, V. G., & Radi, R. (2022, June 24). *La Cassazione e il principio dell'oltre ogni ragionevole dubbio* . Filodiritto. https://www.filodiritto.com/la-cassazione-e-il-principio-delloltre-ogni-ragionevole-dubbio

Gijsbers, V. (2021). Perceiving causation and causal singularism. *Synthese*, *199*(5–6), 14881–14895. https://doi.org/10.1007/S11229-021-03447-3

Gil-Cruz, C., Perez-Shibayama, C., de Martin, A., Ronchi, F., van der Borght, K., Niederer, R., Onder, L., Lütge, M., Novkovic, M., Nindl, V., Ramos, G., Arnoldini, M., Slack, E. M. C., Boivin-Jahns, V., Jahns, R., Wyss, M., Mooser, C., Lambrecht, B. N., Maeder, M. T., … Ludewig, B. (2019). Microbiota-derived peptide mimics drive lethal inflammatory cardiomyopathy. *Science (New York, N.Y.)*, *366*(6467), 881–886. https://doi.org/10.1126/SCIENCE.AAV3487

Gillies, D. (2018). CAUSALITY, PROBABILITY, AND MEDICINE. *Causality, Probability, and Medicine*, 1–300. https://doi.org/10.4324/9781315735542/CAUSALITY-PROBABILITY-MEDICINE-DONALD-GILLIES

Ginglen, J., & Doyle, M. (2022). Immunization. In *StatPearls* (Vol. 49, Issue 10). StatPearls Publishing LLC. https://doi.org/10.1016/j.mpmed.2021.07.004

Glennan, S. (2011). 37 Singular and general causal relations: A mechanist perspective. *Causality in the Sciences*. https://doi.org/10.1093/ACPROF:OSO/9780199574131.003.0037

Glennan, S. S. (1996). Mechanisms and the nature of causation. *Erkenntnis 1996 44:1*, *44*(1), 49–71. https://doi.org/10.1007/BF00172853

Godfrey-Smith, P. (2009). Causal pluralism. In H. Beebee, P. Menzies, & C. Hitchcock (Eds.), *The Oxford Handbook of Causation* (eds., pp. 326–337). Oxford University Press. https://philpapers.org/rec/GODCP

Godlee, F. (2010). Conflicts of interest and pandemic flu. *BMJ*, *340*, c2947. https://doi.org/10.1136/bmj.c2947

Gokuladhas, S., Schierding, W., Golovina, E., Fadason, T., & O'Sullivan, J. (2021). Unravelling the Shared Genetic Mechanisms Underlying 18 Autoimmune Diseases Using a Systems Approach. *Frontiers in Immunology*, *12*. https://www.frontiersin.org/articles/10.3389/fimmu.2021.693142

Golder, S., Loke, Y. K., & Bland, M. (2011). Meta-analyses of Adverse Effects Data Derived from Randomised Controlled Trials as Compared to Observational Studies: Methodological Overview. *PLoS Medicine*, *8*(5). https://doi.org/10.1371/JOURNAL.PMED.1001026

Goncalvez, A. P., Engle, R. E., st. Claire, M., Purcell, R. H., & Lai, C.-J. (2007). Monoclonal antibody-mediated enhancement of dengue virus infection in vitro and in vivo and strategies for prevention. *Proceedings of the National Academy of Sciences*, *104*(22), 9422–9427. https://doi.org/10.1073/pnas.0703498104

Gopalakrishnan, V., Helmink, B. A., Spencer, C. N., Reuben, A., & Wargo, J. A. (2018). The Influence of the Gut Microbiome on Cancer, Immunity, and Cancer Immunotherapy. *Cancer Cell*, *33*(4), 570–580. https://doi.org/10.1016/J.CCELL.2018.03.015

Gots, R. E. (2005). The Distinct Roles of Differential Diagnosis and Causation Assessment. *International Center for Toxicology and Medicine, Rockville, MD*.

Griem, P., & Gleichmann, E. (1995). Metal ion induced autoimmunity. *Current Opinion in Immunology*, *7*(6), 831–838. https://doi.org/10.1016/0952-7915(95)80056-5

Grimaldi-Bensouda, L., Rossignol, M., Koné-Paut, I., Krivitzky, A., Lebrun-Frenay, C., Clet, J., Brassat, D., Papeix, C., Nicolino, M., Benhamou, P. Y., Fain, O., Costedoat-Chalumeau, N., Courcoux, M. F., Viallard, J. F., Godeau, B., Papo, T., Vermersch, P., Bourgault-Villada, I., Breart, G., … Zenone, T. (2017). Risk of autoimmune diseases and human papilloma virus (HPV) vaccines: Six years of case-referent surveillance. *Journal of Autoimmunity*, *79*, 84–90. https://doi.org/10.1016/J.JAUT.2017.01.005

Grinfeld, G., Lagnado, D., Gerstenberg, T., Woodward, J. F., & Usher, M. (2020). Causal Responsibility and Robust Causation. *Frontiers in Psychology*, *11*. https://doi.org/10.3389/FPSYG.2020.01069/FULL

Grippe, A. (2021). La France n'a pas terminé de payer sa campagne de vaccination. *Le Monde.Fr*.

Gruber, M. F., & Marshall, V. B. (2018). Regulation and Testing of Vaccines. *Plotkin's Vaccines*, 1547. https://doi.org/10.1016/B978-0-323-35761-6.00079-1

Gruis, K. L., Teener, J., & Blaivas, M. (2006). Pediatric macrophagic myofasciitis associated with motor delay . *Clinical Neuropathology*, *25*(4), 171–179.

Gruver, A. L., Hudson, L. L., & Sempowski, G. D. (2007). Immunosenescence of ageing. *The Journal of Pathology*, *211*(2), 144–156. https://doi.org/10.1002/PATH.2104

Guimarães, L. E., Baker, B., Perricone, C., & Shoenfeld, Y. (2015). Vaccines, adjuvants and autoimmunity. *Pharmacological Research*, *100*, 190–209. https://doi.org/10.1016/J.PHRS.2015.08.003

Gül, A. (2018). Dynamics of Inflammatory Response in Autoinflammatory Disorders: Autonomous and Hyperinflammatory States. *Frontiers in Immunology*, *9*(OCT). https://doi.org/10.3389/FIMMU.2018.02422

Gvozdenovic, E., Vetter, V., Willame, C., & Rosillon, D. (2018). Impact of history of febrile convulsions on the risk difference of febrile convulsions with the tetravalent measles-mumps-rubella-varicella vaccine: Post-hoc exploratory analysis of results from a matched-cohort study. *Vaccine*, *36*(39), 5803–5806. https://doi.org/10.1016/J.VACCINE.2018.08.018

Haase, H., Hebel, S., Engelhardt, G., & Rink, L. (2016). Ethylmercury and Hg2+ induce the formation of neutrophil extracellular traps (NETs) by human neutrophil granulocytes. *Archives of Toxicology*, *90*(3), 543–550. https://doi.org/10.1007/S00204-015-1484-Y

Hacquard, S., Garrido-Oter, R., González, A., Spaepen, S., Ackermann, G., Lebeis, S., McHardy, A. C., Dangl, J. L., Knight, R., Ley, R., & Schulze-Lefert, P. (2015). Microbiota and Host Nutrition across Plant and Animal Kingdoms. *Cell Host & Microbe*, *17*(5), 603–616. https://doi.org/10.1016/J.CHOM.2015.04.009

Hagan, T., & Pulendran, B. (2018). Will Systems Biology Deliver Its Promise and Contribute to the Development of New or Improved Vaccines? From Data to Understanding through Systems Biology. *Cold Spring Harbor Perspectives in Biology*, *10*(8). https://doi.org/10.1101/CSHPERSPECT.A028894

Hájek, A. (2007). The reference class problem is your problem too. *Synthese 2007 156:3*, *156*(3), 563–585. https://doi.org/10.1007/S11229-006-9138-5

Hall, N. (2004). Two concepts of causation. In J. Collins, N. Hall, & L. Paul (Eds.), *Causation and Counterfactuals* (eds., pp. 225–276). MIT Press.

Halpern, J., & Kleiman-Weiner, M. (2018). Towards formal definitions of blameworthiness, intention, and moral responsibility. In *Proceedings of the AAAI Conference: Vol. Vol. 32, No.1*.

Hansson, S. O., & Rudén, C. (2008). A risk-neutral default for chemical risk management. *American Journal of Industrial Medicine*, *51*(12), 964–967. https://doi.org/10.1002/AJIM.20636

Haralambieva, I. H., Kennedy, R. B., Ovsyannikova, I. G., Schaid, D. J., & Poland, G. A. (2019). Current perspectives in assessing humoral immunity after measles vaccination. *Expert Review of Vaccines*, *18*(1), 75–87. https://doi.org/10.1080/14760584.2019.1559063

Haralambieva, I. H., Ovsyannikova, I. G., Kennedy, R. B., Larrabee, B. R., Zimmermann, M. T., Grill, D. E., Schaid, D. J., & Poland, G. A. (2017). Genome-wide associations of CD46 and IFI44L genetic variants with neutralizing antibody response to measles vaccine. *Human Genetics*, *136*(4), 421–435. https://doi.org/10.1007/S00439-017-1768-9

Harrison, M. (2006). Disease, diplomacy and international commerce: the origins of international sanitary regulation in the nineteenth century. *Journal of Global History*, *49*(2), 453–476.

Hart, & Honoré. (1985). *Causation in the law* (OUP Oxford, Ed.; 2nd eds.). Oxford University Press.

Hassan, W., & Oldham, R. (1994). Reiter's syndrome and reactive arthritis in health care workers after vaccination. *BMJ (Clinical Research Ed.)*, *309*(6947), 94. https://doi.org/10.1136/BMJ.309.6947.94

Hauben, M., & Aronson, J. K. (2007). Gold standards in pharmacovigilance: The use of definitive anecdotal reports of adverse drug reactions as pure gold and high-grade ore. *Drug Safety*, *30*(8), 645–655. https://doi.org/10.2165/00002018-200730080-00001

He, Y. (2016). Ontology-based Vaccine and Drug Adverse Event Representation and Theory-guided Systematic Causal Network Analysis toward Integrative Pharmacovigilance Research. *Current Pharmacology Reports*, *2*(3), 113–128. https://doi.org/10.1007/S40495-016-0055-0

Hefti, M. M., Kinney, H. C., Cryan, J. B., Haas, E. A., Chadwick, A. E., Crandall, L. A., Trachtenberg, F. L., Armstrong, D. D., Grafe, M., & Krous, H. F. (2016). Sudden unexpected death in early childhood: general observations in a series of 151 cases: Part 1 of the investigations of the San Diego SUDC Research Project. *Forensic Science, Medicine, and Pathology*, *12*(1), 4–13. https://doi.org/10.1007/S12024-015-9724-2

Hempel, C. G., & Oppenheim, P. (1948). Studies in the Logic of Explanation. *Philosophy of Science*, *15*(2), 135–175. http://links.jstor.org/sici?sici=0031-8248%28194804%2915%3A2%3C135%3ASITLOE%3E2.0.CO%3B2-E

Henry, C. J., Huang, Y., Wynne, A., Hanke, M., Himler, J., Bailey, M. T., Sheridan, J. F., & Godbout, J. P. (2008). Minocycline attenuates lipopolysaccharide (LPS)-induced neuroinflammation, sickness behavior, and anhedonia. *Journal of Neuroinflammation*, *5*. https://doi.org/10.1186/1742-2094-5-15

Herdeiro, M. T., Silva, T. M., Ribeiro-Vaz, I., Gomes, E. R., Figueiras, A., & Roque, F. (2021). Introductory Chapter: Pharmacovigilance and Public Health Safety. *New Insights into the Future of Pharmacoepidemiology and Drug Safety*. https://doi.org/10.5772/INTECHOPEN.95293

Hernandez-Trujillo, V. P., Scalchunes, C., Cunningham-Rundles, C., Ochs, H. D., Bonilla, F. A., Paris, K., Yel, L., & Sullivan, K. E. (2014). Autoimmunity and inflammation in X-linked agammaglobulinemia. *Journal of Clinical Immunology*, *34*(6), 627–632. https://doi.org/10.1007/S10875-014-0056-X

Heymann, D. L. (2008). NPHIs as focal points for leadership in prevention and control of infectious diseases. *Journal of Public Health Policy*, *29*(3), 374–376. https://doi.org/10.1057/JPHP.2008.19

Higgins, J. P. T., Soares-Weiser, K., López-López, J. A., Kakourou, A., Chaplin, K., Christensen, H., Martin, N. K., Sterne, J. A. C., & Reingold, A. L. (2016). Association of BCG, DTP, and measles containing vaccines with childhood mortality: systematic review. *BMJ (Clinical Research Ed.)*, *355*. https://doi.org/10.1136/BMJ.I5170

Hill, B. A. (1965). The Environment and Disease: Association or Causation? *Proceedings of the Royal Society of Medicine*, *58*(5), 295-300. https://doi.org/10.1177/003591576505800503

Hilton, D., McClure, J., & Sutton, R. (2010). Selecting explanations from causal chains: Do statistical principles explain preferences for voluntary causes? *European Journal of Social Psychology*, *40*(3), 383–400. https://doi.org/10.1002/ejsp.623

Hitchcock, C. (2003). Of Humean Bondage . *The British Journal for the Philosophy of Science*, *54*(1), 1–25.

Hitchcock, C. (2007a). How to be a causal pluralist. In P. K. Machamer & Gereon. Wolters (Eds.), *Thinking about causes: from Greek philosophy to modern physics* (pp. 200–221). University of Pittsburgh Press.

Hitchcock, C. (2007b). Prevention, preemption, and the principle of sufficient reason. *Philosophical Review*, *116*(4), 495–532. https://doi.org/10.1215/00318108-2007-012

Hitchcock, C. (2013). What is the "Cause" in Causal Decision Theory? . *Erkenntnis (1975-)*, *78*, 129–146.

Hitchcock, C. R. (1995). The Mishap at Reichenbach Fall: Singular vs. General Causation. *Philosophical Studies 1995 78:3*, *78*(3), 257–291. https://doi.org/10.1007/BF00990114

Hotez, P. J. (2021). *Preventing the Next Pandemic: Vaccine Diplomacy in a Time of Anti-Science*. John Hopkins University Press.

Howick, J., Glasziou, P., & Aronson, J. K. (2009). The evolution of evidence hierarchies: what can Bradford Hill's "guidelines for causation" contribute? *Journal of the Royal Society of Medicine*, *102*(5), 186–194. https://doi.org/10.1258/JRSM.2009.090020

Howick, J. H. (2011). *The philosophy of evidence-based medicine*. John Wiley & Sons.

HRC. (2023). *Top 20 Current Global Issues We Must Address*. Human Rights Careers. https://www.humanrightscareers.com/issues/current-global-issues/

Hua, C., Morel, J., Ardouin, E., Ricard, E., Foret, J., Mathieu, S., Combe, B., & Lukas, C. (2015). Reasons for non-vaccination in French rheumatoid arthritis and spondyloarthritis patients. *Rheumatology*, *54*(4), 748–750. https://doi.org/10.1093/rheumatology/keu531

Hughes, R. A., Choudhary, P. P., Osborn, M., Rees, J. H., & Sanders, E. A. (1996). *Immunization and risk of relapse of Guillain-Barré syndrome or chronic inflammatory demyelinating polyradiculoneuropathy*. *19*(9), 1230–1231.

Hume, D. (1739). *A Treatise of Human Nature* (L. A. Selby & M. A. Bigge, Eds.). Oxford: Clarendon Press.

Hume, D. A. (1739). *Treatise of Human Nature* (L. Selby-Bigge & P. Nidditch, Eds.; ed.).

Humphreys, E. (1989). *The Chances of Explanation: CausaI Explanations in the Social Medical and Physical Sciences*. Princeton University Press.

Hunter, D. J. (2005). Gene-environment interactions in human diseases. *Nature Reviews Genetics*, *6*(4), 287–298. https://doi.org/10.1038/NRG1578

Hurwitz, E. S., Schonberger, L. B., Nelson, D. B., & Holman, R. C. (1981). Guillain-Barré Syndrome and the 1978–1979 Influenza Vaccine. *New England Journal of Medicine*, *304*(26), 1557–1561. https://doi.org/10.1056/nejm198106253042601

Hussain, Z., Mr.Sabareesh, Dr.Kumar, K. K., & Mr.Kumar, S. (2019). Introduction. In *A Magnificient Text Book Of Pharmacovigillance* (pp. 1–14). Orangebooks Publication. https://books.google.it/books?id=zCXHDwAAQBAJ&dq=Regulatory+reporting+causality%E2%80%9D+(No+grey+zone)+%E2%80%9CMedical+causality%E2%80%9D+(Looks+at+the+grey+zone)+%E2%80%9CLegal+causality%E2%80%9D&hl=it&source=gbs_navlinks_s

Hutchinson, T. A., & Lane, D. A. (1989). Assessing methods for causality assessment of suspected adverse drug reactions. *Journal of Clinical Epidemiology*, *42*(1), 5–16. https://doi.org/10.1016/0895-4356(89)90020-6

Inácio, P., Cavaco, A., & Airaksinen, M. (2017). The value of patient reporting to the pharmacovigilance system: a systematic review. *British Journal of Clinical Pharmacology*, *83*(2), 227–246. https://doi.org/https://doi.org/10.1111/bcp.13098

Institute of Medicine (US) Immunization Committee. (2001). *Thimerosal-Containing Vaccines and Neurodevelopmental Disorders* (K. Stratton, A. Gable, & M. C. McCormick, Eds.). National Academies Press (US).

IOM, & Vaccine Safety Committee. (1994). Causality and Evidence . In K. R. Stratton, C. J. Howe, & R. B. Jr. Johnston (Eds.), *Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality* (pp. 19–31). National Academies Press (US). https://www.ncbi.nlm.nih.gov/books/NBK236283/

Israeli, E., Agmon-Levin, N., Blank, M., Chapman, J., & Shoenfeld, Y. (2012). Guillain-Barré syndrome--a classical autoimmune disease triggered by infection or vaccination. *Clinical Reviews in Allergy & Immunology*, *42*(2), 121–130. https://doi.org/10.1007/S12016-010-8213-3

ISS. (2006). *Virus dell'influenza aviaria ad alta patogenicità A/H5N1: aggiornamento e bilancio del 2006*. EpiCentro.

ISS-SNLG. (2009). Prevenzione delle complicanze trombotiche associate all'uso di estro-progestinici in età riproduttiva. *CONFERENZA NAZIONALE DI CONSENSO. Roma, 18-19 Settembre 2008.* . http://www.sefap.it/servizi_lineeguida_200905/sado101.pdf

IVB-WHO. (2012). Global vaccine safety blueprint. *Immunization, Vaccines and Biologicals, World Health Organization*. www.who.int/vaccines-documents/

Janeway, C., Travers, P., Walport, M., & Shlomchik, M. J. (2001). The Humoral Immune Response. In *Immunobiology: The Immune System in Health and Disease* (5th eds.). Garland Science.

Jastrzębska, A., Jastrzębski, M., Ryniewicz, B., & Kostera-Pruszczyk, A. (2019). Treatment outcome in juvenile-onset myasthenia gravis. *Muscle & Nerve*, *59*(5), 549–554. https://doi.org/10.1002/MUS.26445

JHU. (2023). *Defintion of Autoimmunity and Autoimmune Disease*. Johns Hopkins Medicine-Pathology. https://pathology.jhu.edu/autoimmune/definitions

Jia, L., Weng, S., Wu, J., Tian, X., Zhang, Y., Wang, X., Wang, J., Yan, D., Wang, W., Fang, F., Zhu, Z., Qiu, C., Zhang, W., Xu, Y., & Wan, Y. (2022). Preexisting antibodies targeting SARS-CoV-2 S2 cross-react with commensal gut bacteria and impact COVID-19 vaccine induced immunity. *Gut Microbes*, *14*(1). https://doi.org/10.1080/19490976.2022.2117503/SUPPL_FILE/KGMI_A_2117503_SM7005.ZIP

Joffe, M. (2011). The gap between evidence discovery and actual causal relationships. *Preventive Medicine*, *53*(4–5), 246–249. https://doi.org/10.1016/J.YPMED.2011.07.011

Jones, C. E., Munoz, F. M., Spiegel, H. M. L., Heininger, U., Zuber, P. L. F., Edwards, K. M., Lambach, P., Neels, P., Kohl, K. S., Gidudu, J., Hirschfeld, S., Oleske, J. M., Khuri-Bulos, N., Bauwens, J., Eckert, L. O., Kochhar, S., Bonhoeffer, J., & Heath, P. T. (2016). Guideline for collection, analysis and presentation of safety data in clinical trials of vaccines in pregnant women. *Vaccine*, *34*(49), 5998–6006. https://doi.org/10.1016/J.VACCINE.2016.07.032

Jonville-Béra, A. P., Autret, E., Galy-Eyraud, C., & Hessel, L. (1996). Thrombocytopenic purpura after measles, mumps and rubella vaccination: a retrospective survey by the French regional pharmacovigilance centres and pasteur-mérieux sérums et vaccins. *The Pediatric Infectious Disease Journal*, *15*(1), 44–48. https://doi.org/10.1097/00006454-199601000-00010

Juurlink, D. N., Stukel, T. A., Kwong, J., Kopp, A., McGeer, A., Upshur, R. E., Manuel, D. G., Moineddin, R., & Wilson, K. (2006). Guillain-Barré syndrome after influenza vaccination in adults: a population-based study. *Archives of Internal Medicine*, *166*(20), 2217–2221. https://doi.org/10.1001/ARCHINTE.166.20.2217

Kanduc, D., & Shoenfeld, Y. (2016). From HBV to HPV: Designing vaccines for extensive and intensive vaccination campaigns worldwide. *Autoimmunity Reviews*, *15*(11), 1054–1061. https://doi.org/10.1016/J.AUTREV.2016.07.030

Karch, F. E., & Lasagna, L. (1975). Adverse Drug Reactions: A Critical Review. *JAMA*, *234*(12), 1236–1241. https://doi.org/10.1001/JAMA.1975.03260250028021

Kirkengen, A. L. (2020). A Broken Child – A Diseased Woman . In R. L. Anjum, S. Copeland, & E. Rocca (Eds.), *Rethinking causality, complexity and evidence for the unique patient A causehealth resource for healthcare professionals and the clinical encounter*. Springer. https://doi.org/10.1007/978-3-030-41239-5

Kirschfink, M., & Mollnes, T. E. (2003). Modern complement analysis. *Clinical and Diagnostic Laboratory Immunology*, *10*(6), 982–989. https://doi.org/10.1128/CDLI.10.6.982-989.2003

Kleinbaum, D. G., Kupper, L. L., & Morgenstern, H. (1991). *Epidemiologic Research: Principles and Quantitative Methods*. John Wiley & Sons.

Kment, B. (2010). CAUSATION: DETERMINATION AND DIFFERENCE-MAKING. *Noûs*, *44*, 80–111.

Koeske, G. F. (1992). Moderator variables in social work research. *Journal of Social Service Research*, *16*(1–2), 159–178. https://doi.org/10.1300/J079V16N01_08

Kohl, K. S., Bonhoeffer, J., Braun, M. M., Chen, R. T., Duclos, P., Heijbel, H., Heininger, U., Loupi, E., Marcy, S. M., & Collaboration, T. B. (2005). The Brighton Collaboration: Creating a Global Standard for Case Definitions (and Guidelines) for Adverse Events Following Immunization. In K. Henriksen, J. Battles, E. Marks, & et al. (Eds.), *Advances in Patient Safety: From Research to Implementation (Volume 2: Concepts and Methodology)*. Agency for Healthcare Research and Quality (US).

Koike, Y., Sato, S., Yanagida, N., Asaumi, T., Ogura, K., Ohtani, K., Imai, T., & Ebisawa, M. (2018). Predictors of Persistent Milk Allergy in Children: A Retrospective Cohort Study. *International Archives of Allergy and Immunology*, *175*(3), 177–180. https://doi.org/10.1159/000486311

Koplan, J. P., Bond, T. C., Merson, M. H., Reddy, K. S., Rodriguez, M. H., Sewankambo, N. K., & Wasserheit, J. N. (2009). Towards a common definition of global health. *The Lancet*, *373*(9679), 1993–1995. https://doi.org/10.1016/S0140-6736(09)60332-9

Kramer, M. S. (1986). Assessing Causality of Adverse Drug Reactions: Global Introspection and Its Limitations. *Drug Information Journal*, *20*(4), 433–437. https://doi.org/10.1177/009286158602000409

Kramer, M. S. (1988). *Clinical epidemiology and biostatistics : a primer for clinical investigators and decision-makers*. Springer-Verlag.

Kramer, M. S., & Lane, D. A. (1992). Causal propositions in clinical research and practice. *Journal of Clinical Epidemiology*, *45*(6), 639–649. https://doi.org/10.1016/0895-4356(92)90136-B

Kramer, M. S., Leventhal, J. M., Hutchinson, T. A., & Feinstein, A. R. (1979). An Algorithm for the Operational Assessment of Adverse Drug Reactions: I. Background, Description, and Instructions for Use. *JAMA*, *242*(7), 623–632. https://doi.org/10.1001/JAMA.1979.03300070019017

Krieger, N., & Smith, G. D. (2016). The tale wagged by the DAG: broadening the scope of causal inference and explanation for epidemiology. *International Journal of Epidemiology*, *45*(6), 1787–1808. https://doi.org/10.1093/IJE/DYW114

Kuhn, A., & Landmann, A. (2022). Systemic Lupus Erythematosus. *European Handbook of Dermatological Treatments, Third Edition*, 547–560. https://doi.org/10.1007/978-3-662-45139-7_55

Kundu, R., Narean, J. S., Wang, L., Fenn, J., Pillay, T., Fernandez, N. D., Conibear, E., Koycheva, A., Davies, M., Tolosa-Wright, M., Hakki, S., Varro, R., McDermott, E., Hammett, S., Cutajar, J., Thwaites, R. S., Parker, E., Rosadas, C., McClure, M., … Lalvani, A. (2022). Cross-reactive memory T cells associate with protection against SARS-CoV-2 infection in COVID-19 contacts. *Nature Communications*, *13*(1), 80. https://doi.org/10.1038/s41467-021-27674-x

la Rocca, C., Carbone, F., Longobardi, S., & Matarese, G. (2014). The immunology of pregnancy: regulatory T cells control maternal immune tolerance toward the fetus. *Immunology Letters*, *162*(1 Pt A), 41–48. https://doi.org/10.1016/J.IMLET.2014.06.013

Lagiou, P., Adami, H., Epidemiology, D. T.-E. J. of, & 2005, undefined. (2005). Causality in cancer epidemiology. *Springer*, *20*(7), 565–574. https://doi.org/10.1007/s10654-005-7968-y

Lagnado, D. A., Gerstenberg, T., & Zultan, R. (2013). Causal Responsibility and Counterfactuals. *Cognitive Science*, *37*(6), 1036–1073. https://doi.org/https://doi.org/10.1111/cogs.12054

Lagnado, D., & Channon, S. (2008). Judgments of cause and blame: The effects of intentionality and foreseeability. *Cognition*, *108*(3), 754–770.

Lagnado, D., & Gerstenberg, T. (2017). Causation in legal and moral reasoning. In *cicl.stanford.edu*. Oxford handbook of causal reasoning. https://cicl.stanford.edu/papers/lagnado2017causation.pdf

Landes, J., Osimani, B., & Poellinger, R. (2018). Epistemology of causal inference in pharmacology: Towards a framework for the assessment of harms. *European Journal for Philosophy of Science*, *8*(1), 3–49. https://doi.org/10.1007/S13194-017-0169-1/FIGURES/4

Lane, D. A. (1984). A Probabilist's View of Causality Assessment. *Drug Information Journal*, *18*(3–4), 323–330. https://doi.org/10.1177/009286158401800322

Lane, D. A., Kramer, M. S., Hutchinson, T. A., Jones, J. K., & Naranjo, C. (1987). The causality assessment of adverse drug reactions using a bayesian approach. *Pharmaceutical Medicine*, *2*(3), 265–284. https://eurekamag.com/research/006/611/006611627.php

Langmuir, A. D. (1979). Guillain-Barré syndrome: the swine influenza virus vaccine incident in the United States of America, 1976-77: preliminary communication. *Journal of the Royal Society of Medicine*, *72*(9), 660–669. https://doi.org/10.1177/014107687907200908

Lasky, T., Terracciano, G. J., Magder, L., Koski, C. L., Ballesteros, M., Nash, D., Clark, S., Haber, P., Stolley, P. D., Schonberger, L. B., & Chen, R. T. (1998). The Guillain-Barré syndrome and the 1992-1993 and 1993-1994 influenza vaccines. *The New England Journal of Medicine*, *339*(25), 1797–1802. https://doi.org/10.1056/NEJM199812173392501

Leape, L. L. (2002). Reporting of Adverse Events. *The New England Journal of Medicine*, *347*(20), 1633–1638. https://doi.org/10.1056/NEJMNEJMHPR011493

Lebiu G. et al. (2017, August 18). *Il Nesso Di Causalita': Definizioni A Confronto*. Compartosanita.It. http://www.compartosanita.it/nesso-causalita-definizioni-confronto/

Lee, E., Kim, M., Jeon, K., Lee, J., Lee, J. S., Kim, H. S., Kang, H. J., & Lee, Y. K. (2019). Mean Platelet Volume, Platelet Distribution Width, and Platelet Count, in Connection with Immune Thrombocytopenic Purpura and Essential Thrombocytopenia. *Laboratory Medicine*, *50*(3), 279–285. https://doi.org/10.1093/LABMED/LMY082

Lee, H. G., Bae, H. B., il Choi, J., Pyeon, T., Kim, S., & Kim, J. (2019). Febrile convulsions during recovery after anesthesia in an infant with history of MMR vaccination: A case report. *Medicine*, *98*(35). https://doi.org/10.1097/MD.0000000000017047

Lee, H., Kang, H.-Y., Cho, S., Park, S., Kim, A.-Y., Jung, S.-Y., Seong, B. L., & Lee, Y.-M. (2020). *Causality Assessment Guidelines for Adverse Events Following Immunization with a Focus on Guillain-Barré Syndrome*. https://doi.org/10.3390/vaccines8010101

Lee, S. J., & Lee, S. (2002). Toll-like receptors and inflammation in the CNS. *Current Drug Targets. Inflammation and Allergy*, *1*(2), 181–191. https://doi.org/10.2174/1568010023344698

Lehmann, H. C., Hartung, H. P., Kieseier, B. C., & Hughes, R. A. C. (2010). Guillain-Barré syndrome after exposure to influenza virus. *The Lancet Infectious Diseases*, *10*(9), 643–651. https://doi.org/10.1016/S1473-3099(10)70140-7

Leng, S., Ma, H.-F., Kurths, J., Lai, Y.-C., Lin, W., Aihara, K., & Chen, L. (2020). Partial cross mapping eliminates indirect causal influences. *Nature Communications*, *11*, 2632. https://doi.org/10.1038/s41467-020-16238-0

Leonard, A., Hittson Boal, L., Pary, P., Mo, Y. D., Jacquot, C., Luban, N. L., Darbari, D. S., & Webb, J. (2019). Identification of red blood cell antibodies in maternal breast milk implicated in prolonged hemolytic disease of the fetus and newborn. *Transfusion*, *59*(4), 1183–1189. https://doi.org/10.1111/TRF.15154

Leslie, D. L., Kobre, R. A., Richmand, B. J., Guloksuz, S. A., & Leckman, J. F. (2017). Temporal Association of Certain Neuropsychiatric Disorders Following Vaccination of Children and Adolescents: A Pilot Case-Control Study. *Frontiers in Psychiatry*, *8*(JAN). https://doi.org/10.3389/FPSYT.2017.00003

Lewis, D. (1973a). *Counterfactuals*. Oxford: Blackwell.

Lewis, D. (1973b). Causation. *The Journal of Philosophy*, *70*(17), 556–567. https://doi.org/10.2307/2025310

Lewis, D. (1986a). Postscripts to `causation' . In *Philosophical Papers: Volume II* (Vol. 2, pp. 172–213). Oxford University Press.

Lewis, D. (1986b). Causation. In *Philosophical Papers: Volume II* (Vol. 2, pp. 159–213). Oxford University Press. https://doi.org/10.1093/0195036468.001.0001

Li, T. X., Sun, F. T., & Ji, B. J. (2019). [Correlation of IgG Subclass with Blood Cell Parameters in Patients with Autoimmune Hemolytic anemia]. *Zhongguo Shi Yan Xue Ye Xue Za Zhi*, *27*(1), 197–201. https://doi.org/10.7534/J.ISSN.1009-2137.2019.01.032

Liao, H. X., Chen, X., Munshaw, S., Zhang, R., Marshall, D. J., Vandergrift, N., Whitesides, J. F., Lu, X., Yu, J. S., Hwang, K. K., Gao, F., Markowitz, M., Heath, S. L., Bar, K. J., Goepfert, P. A., Montefiori, D. C., Shaw, G. C., Alam, S. M., Margolis, D. M., … Haynes, B. F. (2011). Initial antibodies binding to HIV-1 gp41 in acutely infected subjects are polyreactive and highly mutated. *The Journal of Experimental Medicine*, *208*(11), 2237–2249. https://doi.org/10.1084/JEM.20110363

Lin, Y., & He, Y. (2014). The ontology of genetic susceptibility factors (OGSF) and its application in modeling genetic susceptibility to vaccine adverse events. *Journal of Biomedical Semantics*, *5*(1). https://doi.org/10.1186/2041-1480-5-19

Lindsay, K. E., Bhosle, S. M., Zurla, C., Beyersdorf, J., Rogers, K. A., Vanover, D., Xiao, P., Araínga, M., Shirreff, L. M., Pitard, B., Baumhof, P., Villinger, F., & Santangelo, P. J. (2019). Visualization of early events in mRNA vaccine delivery in non-human primates via PET-CT and near-infrared imaging. *Nature Biomedical Engineering*, *3*(5), 371–380. https://doi.org/10.1038/S41551-019-0378-3

Little, D. (2023). Endogenous variable and Exogenous Variables. *Encyclopedia of Social Science Research Methods*. http://www-personal.umd.umich.edu/~delittle/Encyclopedia%20entries/Endogenous%20variable.htm

Lombardi, N., Crescioli, G., Bettiol, A., Tuccori, M., Rossi, M., Bonaiuti, R., Ravaldi, C., Levi, M., Mugelli, A., Ricci, S., Lippi, F., Azzari, C., Bonanni, P., & Vannacci, A. (2019). Vaccines Safety in Children and in General Population: A Pharmacovigilance Study on Adverse Events Following Anti-Infective Vaccination in Italy. *Frontiers in Pharmacology*, *10*(AUG). https://doi.org/10.3389/FPHAR.2019.00948

Loughlin, A. M., Marchant, C. D., Adams, W., Barnett, E., Baxter, R., Black, S., Casey, C., Dekker, C., Edwards, K. M., Klein, J., Klein, N. P., LaRussa, P., Sparks, R., & Jakob, K. (2012). Causality assessment of adverse events reported to the Vaccine Adverse Event Reporting System (VAERS). *Vaccine*, *30*(50), 7253–7259. https://doi.org/10.1016/J.VACCINE.2012.09.074

Loughlin, M., Mercuri, M., Parvan, A., & et al. (2018). Treating real people: science and humanity. *J Eval Clin Pract* , *24*, 919–929.

Low, J. G., Wijaya, L., Li, G. K. Y., Lim, E. Y. L., Shum, A. K. L., Cheung, Y.-B., & Ooi, E.-E. (2015). The role of pre-existing cross-reactive antibodies in determining the efficacy of vaccination in humans: study protocol for a randomized controlled trial. *Trials*, *16*(1), 147. https://doi.org/10.1186/s13063-015-0651-z

Loyal, L., Braun, J., Henze, L., Kruse, B., Dingeldey, M., Reimer, U., Kern, F., Schwarz, T., Mangold, M., Unger, C., Dörfler, F., Kadler, S., Rosowski, J., Gürcan, K., Uyar-Aydin, Z., Frentsch, M., Kurth, F., Schnatbaum, K., Eckey, M., … Giesecke-Thiel, C. (2023). Cross-reactive CD4+ T cells enhance SARS-CoV-2 immune responses upon infection and vaccination. *Science*, *374*(6564), eabh1823. https://doi.org/10.1126/science.abh1823

Lynch, J. B., & Hsiao, E. Y. (2019). Microbiomes as sources of emergent host phenotypes. *Science (New York, N.Y.)*, *365*(6460), 1405–1409. https://doi.org/10.1126/SCIENCE.AAY0240

Ma, S. J., Xiong, Y. Q., Jiang, L. N., & Chen, Q. (2015). Risk of febrile seizure after measles-mumps-rubella-varicella vaccine: A systematic review and meta-analysis. *Vaccine*, *33*(31), 3636–3649. https://doi.org/10.1016/J.VACCINE.2015.06.009

MacDonald, N., & Law, B. J. (2017). Le système d'innocuité vaccinale canadien en huit étapes: des notions pour les travailleurs de la santé. *Paediatrics & Child Health*, *22*(4), e17–e20.

Machamer, P. (2004). Activities and causation: The metaphysics and epistemology of mechanisms. *International Studies in the Philosophy of Science*, *18*(1), 27–39. https://doi.org/10.1080/02698590412331289242

Machamer, P., Darden, L., & Craver, C. F. (2000). Thinking about Mechanisms. *Philosophy of Science*, *67*(1), 1–25. http://www.jstor.org/journals/ucpress.html.

Mackie, J. L. (1965). I. CAUSES AND CONDITIONS. *American Philosophical Quarterly*, *2*(4).

Mackie, J. L. (1974). *The Cement of the Universe: A Study of Causation*. Clarendon Press.

Maeda, Y., & Takeda, K. (2019). Host–microbiota interactions in rheumatoid arthritis. *Experimental & Molecular Medicine*, *51*(12). https://doi.org/10.1038/S12276-019-0283-6

Magen, E., Mukherjee, S., Bhattacharya, M., Detroja, R., Merzon, E., Blum, I., Livoff, A., Shlapobersky, M., Baum, G., Talisman, R., Cherniavsky, E., Dori, A., & Frenkel-Morgenstern, M. (2022). Clinical and Molecular Characterization of a Rare Case of BNT162b2 mRNA COVID-19 Vaccine-Associated Myositis. *Vaccines*, *10*(7). https://doi.org/10.3390/VACCINES10071135

Main, B. S., & Minter, M. R. (2017). Microbial Immuno-Communication in Neurodegenerative Diseases. *Frontiers in Neuroscience*, *11*(MAR). https://doi.org/10.3389/FNINS.2017.00151

Mannucci, P. M., & Franchini, M. (2015). Classic thrombophilic gene variants. *Thrombosis and Haemostasis*, *114*(5), 885–889. https://doi.org/10.1160/TH15-02-0141

Marani, S. (2014). *Colpa medica: giudizio di probabilità logica non definisce il nesso causale. Cassazione penale, sez. IV, sentenza 27/02/2014 n° 9695*. Altalex. https://www.altalex.com/documents/news/2014/03/25/colpa-medica-giudizio-di-probabilita-logica-non-definisce-il-nesso-causale

Marshall, J. S., Warrington, R., Watson, W., & Kim, H. L. (2018). An introduction to immunology and immunopathology. *Allergy, Asthma & Clinical Immunology*, *14*(2), 49. https://doi.org/10.1186/s13223-018-0278-1

Marson, A., Housley, W. J., & Hafler, D. A. (2015). Genetic basis of autoimmunity. *The Journal of Clinical Investigation*, *125*(6), 2234. https://doi.org/10.1172/JCI78086

Mateus, J., Dan, J. M., Zhang, Z., Rydyznski Moderbacher, C., Lammers, M., Goodwin, B., Sette, A., Crotty, S., & Weiskopf, D. (2023). Low-dose mRNA-1273 COVID-19 vaccine generates durable memory enhanced by cross-reactive T cells. *Science*, *374*(6566), eabj9853. https://doi.org/10.1126/science.abj9853

Mayo Clinic. (2022, August 25). *Different types of COVID-19 vaccines: How they work* . https://www.mayoclinic.org/diseases-conditions/coronavirus/in-depth/different-types-of-covid-19-vaccines/art-20506465

McCarthy, K. R., Watanabe, A., Kuraoka, M., Do, K. T., McGee, C. E., Sempowski, G. D., Kepler, T. B., Schmidt, A. G., Kelsoe, G., & Harrison, S. C. (2018). Memory B Cells that Cross-React with Group 1 and Group 2 Influenza A Viruses Are Abundant in Adult Human Repertoires. *Immunity*, *48*(1), 174-184.e9. https://doi.org/https://doi.org/10.1016/j.immuni.2017.12.009

McClenathan, B. M., & Edwards, K. M. (2019). Vaccine safety: An evolving evidence-based science. *British Journal of Clinical Pharmacology*, *85*(12), 2649. https://doi.org/10.1111/BCP.14080

McClure, J., Hilton, D., & Sutton, R. M. (2007). Judgments of voluntary and physical causes in causal chains: Probabilistic and social functionalist criteria for attributions. *European Journal of Social Psychology*, *37*(5), 879–901. https://doi.org/10.1002/ejsp.394

McGarvey, P. B., Suzek, B. E., Baraniuk, J. N., Rao, S., Conkright, B., Lababidi, S., Sutherland, A., Forshee, R., & Madhavan, S. (2014). In silico analysis of autoimmune diseases and genetic relationships to vaccination against infectious diseases. *BMC Immunology*, *15*(1). https://doi.org/10.1186/S12865-014-0061-0

McKinney, B. A., Reif, D. M., Rock, M. T., Edwards, K. M., Kingsmore, S. F., Moore, J. H., & Crowe, J. E. (2006). Cytokine expression patterns associated with systemic adverse events following smallpox immunization. *The Journal of Infectious Diseases*, *194*(4), 444–453. https://doi.org/10.1086/505503

McNaughton, A. L., Paton, R. S., Edmans, M., Youngs, J., Wellens, J., Phalora, P., Fyfe, A., Belij-Rammerstorfer, S., Bolton, J. S., Ball, J., Carnell, G. W., Dejnirattisai, W., Dold, C., Eyre, D. W., Hopkins, P., Howarth, A., Kooblall, K., Klim, H., Leaver, S., … Thompson, C. P. (2022). Fatal COVID-19 outcomes are associated with an antibody response targeting epitopes shared with endemic coronaviruses. *JCI Insight*, *7*(13), 34. https://doi.org/10.1172/JCI.INSIGHT.156372

Melchor, L., Josten, M., Paillette, C., Robinson, S., Elorza, A., Meyer, N., Lacunza, I., & Young, M. (2020). Hands On! Case Studies. In *S4D4C European Science Diplomacy Online Course, Module 7*. S4D4C.

Mentzer, D., Oberle, D. F., & Keller-Stanislawski, B. (2018). Adverse events following immunisation with a meningococcal serogroup B vaccine: report from post-marketing surveillance, Germany, 2013 to 2016. *Euro Surveillance : Bulletin Europeen Sur Les Maladies Transmissibles = European*

Communicable Disease Bulletin, *23*(17). https://doi.org/10.2807/1560-7917.ES.2018.23.17.17-00468

Merriam-Webster. (2022). *Vaccine* . Merriam-Webster.Com Dictionary. https://www.merriam-webster.com/dictionary/vaccine

Merriam-Webster Dictionary. (2022). *Prodrug*. Merriam-Webster.Com Dictionary. https://www.merriam-webster.com/dictionary/prodrug

Messina, N. L., Zimmermann, P., & Curtis, N. (2019). The impact of vaccines on heterologous adaptive immunity. *Clinical Microbiology and Infection*, *25*(12), 1484–1493. https://doi.org/https://doi.org/10.1016/j.cmi.2019.02.016

Meyer, A., Rotman-Pikielny, P., Natour, A., & Levy, Y. (2010). Antiphospholipid syndrome following a diphtheria-tetanus vaccination: coincidence vs. causality. *The Israel Medical Association Journal: IMAJ*, *12*(10), 638–639.

Middeldorp, S. (2011). Is thrombophilia testing useful? *Hematology. American Society of Hematology. Education Program*, *2011*, 150–155. https://doi.org/10.1182/ASHEDUCATION-2011.1.150

Mill, J. S. (1843). *A System of Logic, Ratiocinative and Inductive: Being a Connected View of the Principles of Evidence, and the Methods of Scientific Investigation: Vol. two volumes*. Longmans, Green, Reader, and Dyer. https://philpapers.org/rec/MILASO-7

Mill, J. S. (1862). *A System of Logic, Ratiocinative and Inductive* (5th eds.). Parker, Son and Bowin.

Mill, J. S. (1874). *On Nature* (Watts & Co., Ed.; ed. of 1904). Rationalist Press.

Mill, J. S. (1956). *A System of Logic, Ratiocinative and Inductive*. Longmans, Green.

Miller, E., Waight, P., Farrington, P., Andrews, N., Stowe, J., & Taylor, B. (2001). Idiopathic thrombocytopenic purpura and MMR vaccine. *Archives of Disease in Childhood*, *84*(3), 227-229. https://doi.org/10.1136/ADC.84.3.227

Ministers Of Foreign Affairs Of Brazil France Indonesia Norway Senegal South Africa And Thailand. (2007). Oslo Ministerial Declaration--global health: a pressing foreign policy issue of our time. *Lancet* , *369*(9570), 1373–1378. https://doi.org/10.1016/S0140-6736(07)60498-X

Missoni, E., Pacileo, G., & Tediosi, F. (2019). *Global health governance and policy : an introduction* (1st eds). Routledge.

Mitkus, R. J., Hess, M. A., & Schwartz, S. L. (2013). Pharmacokinetic modeling as an approach to assessing the safety of residual formaldehyde in infant vaccines. *Vaccine*, *31*(25), 2738–2743. https://doi.org/10.1016/J.VACCINE.2013.03.071

Molineros, J. E., Looger, L. L., Kim, K., Okada, Y., Terao, C., Sun, C., Zhou, X. jie, Raj, P., Kochi, Y., Suzuki, A., Akizuki, S., Nakabo, S., Bang, S. Y., Lee, H. S., Kang, Y. M., Suh, C. H., Chung, W. T., Park, Y. B., Choe, J. Y., … Nath, S. K. (2019). Amino acid signatures of HLA Class-I and II molecules are strongly associated with SLE susceptibility and autoantibody production in Eastern Asians. *PLoS Genetics*, *15*(4). https://doi.org/10.1371/JOURNAL.PGEN.1008092

Monateri, P. G., & Gianti, D. (2016). *Nesso causale [dir. civ.]*. Diritto on Line. https://www.treccani.it/enciclopedia/nesso-causale-dir-civ_(Diritto-on-line)/

Mongkolsapaya, J., Dejnirattisai, W., Xu, X., Vasanawathana, S., Tangthawornchaikul, N., Chairunsri, A., Sawasdivorn, S., Duangchinda, T., Dong, T., Rowland-Jones, S., Yenchitsomanus, P., McMichael, A., Malasit, P., & Screaton, G. (2003). Original antigenic sin and apoptosis in the pathogenesis of dengue hemorrhagic fever. *Nature Medicine*, *9*(7), 921–927. https://doi.org/10.1038/nm887

Mongkolsapaya, J., Duangchinda, T., Dejnirattisai, W., Vasanawathana, S., Avirutnan, P., Jairungsri, A., Khemnu, N., Tangthawornchaikul, N., Chotiyarnwong, P., Sae-Jang, K., Koch, M., Jones, Y., McMichael, A., Xu, X., Malasit, P., & Screaton, G. (2006). T Cell Responses in Dengue Hemorrhagic Fever: Are Cross-Reactive T Cells Suboptimal?1. *The Journal of Immunology*, *176*(6), 3821–3829. https://doi.org/10.4049/jimmunol.176.6.3821

Moore, M. (2003). *For What Must We Pay? Causation and Counterfactual Baselines*. *40*(1181), 1189–1191.

Moore, M. S. (2009). *Causation and Responsibility*. Oxford: Oxford University Press.

Morgenlander, W., Henson, S., Monaco, D. R., Chen, A., Littlefield, K., Bloch, E. M., Fujimura, E., Ruczinski, I., Crowley, A. R., Natarajan, H., Butler, S. E., Weiner, J. A., Li, M. Z., Bonny, T. S.,

Benner, S. E., Balagopal, A., Sullivan, D., Shoham, S., Quinn, T. C., … Larman, H. B. (2021). Antibody responses to endemic coronaviruses modulate COVID-19 convalescent plasma functionality. *The Journal of Clinical Investigation*, *131*(7). https://doi.org/10.1172/JCI146927

Morris, G., Puri, B. K., & Frye, R. E. (2017). The putative role of environmental aluminium in the development of chronic neuropathology in adults and children. How strong is the evidence and what could be the mechanisms involved? *Metabolic Brain Disease*, *32*(5), 1335–1355. https://doi.org/10.1007/S11011-017-0077-2

Moschese, V., Chini, L., Graziani, S., Sgrulletti, M., Gallo, V., di Matteo, G., Ferrari, S., di Cesare, S., Cirillo, E., Pession, A., Pignata, C., & Specchia, F. (2019). Follow-up and outcome of symptomatic partial or absolute IgA deficiency in children. *European Journal of Pediatrics*, *178*(1), 51–60. https://doi.org/10.1007/S00431-018-3248-1

Mota, D. M., & Kuchenbecker, R. de S. (2017). Causality in Pharmacoepidemiology and Pharmacovigilance: a theoretical excursion. *Revista Brasileira de Epidemiologia*, *20*(3), 475–486. https://doi.org/10.1590/1980-5497201700030010

MPH. (2015). *Causal Inference*. Boston University School of Public Health. https://sphweb.bumc.bu.edu/otlt/mph-modules/ep/ep713_causality/ep713_causality_print.html

Müller, A., Schmitz, S., Josten, M., Young, M., Rungius, C., & Aukes, E. (2020). Which thematic and regional approaches of science diplomacy exist? In *S4D4C European Science Diplomacy Online Course, Module 5*. S4D4C. https://www.s4d4c.eu/lessons/5-1-approaches-to-science-diplomacy-introduction-to-the-module/

Müller, H. D., van Landeghem, F. K. H., Schmidt, P. F., Sommer, C., & Goebel, H. H. (2009). Macrophagic myofasciitis plus (distinct types of muscular dystrophy). *Neuropediatrics*, *40*(4), 174–178. https://doi.org/10.1055/S-0029-1243172

Müller, J. M. (2021). Science for Multilateralism. *Science & Diplomacy*, *10*(2). www.ScienceDiplomacy.org

Mumford, S. (1998). *Dispositions* (Issue 2). Clarendon Press.

Mumford, S., & Anjum, R. L. (2010). A powerful theory of causation. In A. Marmodoro (Ed.), *The Metaphysics of Powers: Their Grounding and Their Manifestations*. Routledge.

Mumford, S., & Anjum, R. L. (2011). *Getting Causes From Powers*. Oxford University Press.

Murray, S. M., Ansari, A. M., Frater, J., Klenerman, P., Dunachie, S., Barnes, E., & Ogbe, A. (2022). The impact of pre-existing cross-reactive immunity on SARS-CoV-2 infection and vaccine responses. *Nature Reviews Immunology*. https://doi.org/10.1038/s41577-022-00809-x

Naidu, R. P. (2013). Causality assessment: A brief insight into practices in pharmaceutical industry. *Perspectives in Clinical Research*, *4*(4), 233. https://doi.org/10.4103/2229-3485.120173

Nakayama, J., & Arinami, T. (2006). Molecular genetics of febrile seizures. *Epilepsy Research*, *70 Suppl 1*(SUPPL.1), 190–198. https://doi.org/10.1016/J.EPLEPSYRES.2005.11.023

Nakayama, T. (2016). An inflammatory response is essential for the development of adaptive immunity-immunogenicity and immunotoxicity. *Vaccine*, *34*(47), 5815–5818. https://doi.org/10.1016/J.VACCINE.2016.08.051

Naranjo, C. A., Busto, U., Sellers, E. M., Sandor, P., Ruiz, I., Roberts, E. A., Janacek, E., Domecq, C., & Greenblatt, D. J. (1981). A method for estimating the probability of adverse drug reactions. *Clinical Pharmacology & Therapeutics*, *30*(2), 239–245. https://doi.org/10.1038/CLPT.1981.154

Nassar, G. N., & Wehbe, C. (2022). Erythroblastosis Fetalis. *PEDIAT.ANN.*, *3*(2), 7–34. https://doi.org/10.1542/peds.6.5.706

NCIRS. (2009, December). *Thiomersal*. NCIRS Fact Sheet. https://www.ncirs.org.au/sites/default/files/2018-12/thiomersal-fact-sheet.pdf

Nebeker, J. R., Barach, P., & Samore, M. H. (2004). Clarifying Adverse Drug Events: A Clinician's Guide to Terminology, Documentation, and Reporting. *Annals of Internal Medicine*, *140*(10), 795–801. https://doi.org/10.7326/0003-4819-140-10-200405180-00009

NHS. (2019). *SARS (Severe Acute Respiratory Syndrome)*. https://www.nhs.uk/conditions/sars/

Nieminen, U., Peltola, H., Syrjälä, M., Mäkipernaa, A., & Kekomäki, R. (1993). Acute thrombocytopenic purpura following measles, mumps and rubella vaccination. A report on 23

patients. *Acta Paediatrica (Oslo, Norway : 1992)*, *82*(3), 267–270. https://doi.org/10.1111/J.1651-2227.1993.TB12657.X

Noble, D. (2002). Modelling the heart: insights, failures and progress. *BioEssays*, *24*(12), 1155–1163. https://doi.org/10.1002/BIES.10186

Notarangelo, L. D. (2010). Primary immunodeficiencies. *The Journal of Allergy and Clinical Immunology*, *125*(2 Suppl 2). https://doi.org/10.1016/J.JACI.2009.07.053

Nur, B. G., Kahramaner, Z., Duman, O., Dundar, N. O., Sallakc, N., Yavuzer, U., & Haspolat, S. (2012). Interleukin-6 gene polymorphism in febrile seizures. *Pediatric Neurology*, *46*(1), 36–38. https://doi.org/10.1016/J.PEDIATRNEUROL.2011.10.008

Nusbaum, J. S., Mirza, I., Shum, J., Freilich, R. W., Cohen, R. E., Pillinger, M. H., Izmirly, P. M., & Buyon, J. P. (2020). Sex Differences in Systemic Lupus Erythematosus: Epidemiology, Clinical Considerations, and Disease Pathogenesis. *Mayo Clinic Proceedings*, *95*(2), 384–394. https://doi.org/10.1016/J.MAYOCP.2019.09.012

Offit, P. (2021, September 9). *Antibody-dependent Enhancement (ADE) and Vaccines* . Children's Hospital of Philadelphia. https://www.chop.edu/centers-programs/vaccine-education-center/vaccine-safety/antibody-dependent-enhancement-and-vaccines

Ogata, A. F., Cheng, C. A., Desjardins, M., Senussi, Y., Sherman, A. C., Powell, M., Novack, L., Von, S., Li, X., Baden, L. R., & Walt, D. R. (2022). Circulating Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Vaccine Antigen Detected in the Plasma of mRNA-1273 Vaccine Recipients. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America*, *74*(4), 715–718. https://doi.org/10.1093/CID/CIAB465

Olivieri, B., Betterle, C., & Zanoni, G. (2021). Vaccinations and Autoimmune Diseases. *Vaccines*, *9*(8). https://doi.org/10.3390/VACCINES9080815

O'Neill, K., Henne, P., Bello, P., Pearson, J., & de Brigard, F. (2022). Confidence and gradation in causal judgment. *Cognition*, *223*, 105036. https://doi.org/10.1016/J.COGNITION.2022.105036

Osimani, B. (2007). *Probabilistic information and decision making in the health context*. Università della Svizzera italiana. https://doc.rero.ch/record/28759

Osimani, B. (2010). Pharmaceutical risk communication: Sources of uncertainty and legal tools of uncertainty management. *Health, Risk & Society*, *12*(5), 453–469. https://doi.org/10.1080/13698575.2010.509493

Osimani, B. (2013). The precautionary principle in the pharmaceutical domain: A philosophical enquiry into probabilistic reasoning and risk aversion. *Health, Risk and Society*, *15*(2), 123–143. https://doi.org/10.1080/13698575.2013.771736

Osimani, B. (2014a). Philosophy of Pharmacology: Safety, Statistical standards and Evidence Amalgamation. In *ERC Starting Grant 2014 Research proposal [Part B1]*. https://www.mcmp.philosophie.uni-muenchen.de/research/research_projects/phil_pharma/osimaniercproposal.pdf

Osimani, B. (2014b). Philosophy of Pharmacology: Safety, Statistical Standards and Evidence amalgamation. In *ERC Starting Grant: Research Proposal [Part B2]*.

Osimani, B. (2014c). Hunting Side Effects and Explaining Them: Should We Reverse Evidence Hierarchies Upside Down? *European Physical Journal: Special Topics*, *224*(1), 295–312. https://doi.org/10.1007/S11245-013-9194-7/FIGURES/1

Osimani, B. (2020). Epistemic Gains and Epistemic Games: Reliability and Higher Order Evidence in Medicine and Pharmacology. In A. LaCaze & B. Osimani (Eds.), *Uncertainty in Pharmacology: Epistemology, Methods, and Decisions* (eds., pp. 345–374). Boston Studies in the Philosophy and History of Science.

Osimani B., & Ilardo, M. L. (2022). «Nessuna correlazione»: gli strumenti per la valutazione del nesso causale tra vaccinazione ed evento avverso. In E. Lello & N. Bertuzzi (Eds.), *Dissenso informato. Pandemia: Il Dibattito Mancato E Le Alternative Possibili* (pp. 167–185). Castelvecchi, Lit Edizioni s.a.s.

Osimani, B., & Mignini, F. (2015). Causal assessment of pharmaceutical treatments: why standards of evidence should not be the same for benefits and harms? *Drug Safety*, *38*(1), 1–11. https://doi.org/10.1007/S40264-014-0249-5

Owczarczyk-Saczonek, A., Wygonowska, E., Budkiewicz, M., & Placek, W. (2019). Serum sickness disease in a patient with alopecia areata and Meniere' disease after PRP procedure. *Dermatologic Therapy*, *32*(2). https://doi.org/10.1111/DTH.12798

PAHO. (2021). *Risk Management Plans and Periodic Safety Reports for COVID-19 Vaccines Recommendations for Their Request, Preparation, Management, and Assessment*. https://iris.paho.org/bitstream/handle/10665.2/53631/PAHOHSSMTCOVID-19210003_eng.pdf?sequence=1&isAllowed=y

Palinkas, L. A. (2014). Causality and Causal Inference in Social Work: Quantitative and Qualitative Perspectives. *Research on Social Work Practice*, *24*(5), 540. https://doi.org/10.1177/1049731514536056

Panda, A., Qian, F., Mohanty, S., van Duin, D., Newman, F. K., Zhang, L., Chen, S., Towle, V., Belshe, R. B., Fikrig, E., Allore, H. G., Montgomery, R. R., & Shaw, A. C. (2010). Age-associated decrease in TLR function in primary human dendritic cells predicts influenza vaccine response. *Journal of Immunology (Baltimore, Md. : 1950)*, *184*(5), 2518–2527. https://doi.org/10.4049/JIMMUNOL.0901022

Pande, S. (2018). Causality or Relatedness Assessment in Adverse Drug Reaction and Its Relevance in Dermatology. *Indian Journal of Dermatology*, *63*(1), 18. https://doi.org/10.4103/IJD.IJD_579_17

Pani, L. (2015). Sicurezza dei farmaci e farmacovigilanza. In *LANCIO EUPATI NATIONAL PLATFORM. Istituto Superiore di Sanità* . Agenzia Italiana del Farmaco. AIFA . https://www.aifa.gov.it/sites/default/files/2015-04-10_EUPATI_FV_PANI_rev_graf_SV.pdf

Papanikolaou, P., Christidi, G., Cmaj, J. I.-, & 2006, undefined. (2006). Comparison of evidence on harms of medical interventions in randomized and nonrandomized studies. *Can Med Assoc*. https://doi.org/10.1503/cmaj.050873

Parascandola, M. (1998). WHAT IS WRONG WITH THE PROBABILITY OF CAUSATION? *Jurimetrics*, *39*(1), 29–44. http://www.jstor.org/stable/29762583

Parascandola, M., & Weed, D. L. (2001). Causation in epidemiology. *Journal of Epidemiology and Community Health*, *55*(12), 905–912. https://doi.org/10.1136/JECH.55.12.905

Parida, S. (2013). Clinical causality assessment for adverse drug reactions. *Indian Journal of Anaesthesia*, *57*(3), 325–326. https://doi.org/10.4103/0019-5049.115608

Passeri, E., Villa, C., Couette, M., Itti, E., Brugieres, P., Cesaro, P., Gherardi, R. K., Bachoud-Levi, A. C., & Authier, F. J. (2011). Long-term follow-up of cognitive dysfunction in patients with aluminum hydroxide-induced macrophagic myofasciitis (MMF). *Journal of Inorganic Biochemistry*, *105*(11), 1457–1463. https://doi.org/10.1016/J.JINORGBIO.2011.08.006

Patterson, B. K., Francisco, E. B., Yogendra, R., Long, E., Bream, J., Kreimer, M., Heide, R. vander, Guevara-Coto, J., Mora, R. R., & Mora, J. (2022). SARS-CoV-2 S1 Protein Persistence in SARS-CoV-2 Negative Post-Vaccination Individuals with Long COVID/ PASC-Like Symptoms. *Research Square*. https://doi.org/10.21203/RS.3.RS-1844677/V1

Pearl, J. (2000). Models, reasoning and inference. In *library.mpib-berlin.mpg.de* (Vols. 19, 2). Cambridge, UK: Cambridge University Press. http://library.mpib-berlin.mpg.de/toc/z2008_2219.pdf

Pearl, J. (2009). Causality: Models, reasoning, and inference. In *Causality: Models, Reasoning, and Inference, Second Edition* (2nd ed.). Cambridge University Press. https://doi.org/10.1017/CBO9780511803161

Perman, G., & Vos, E. (2010). EU regulatory agencies and health protection. In *Health Systems Governance in Europe: The Role of European Union Law and Policy* (pp. 134–185). Cambridge University Press. https://doi.org/10.1017/CBO9780511750496.004

Perricone, C., Ceccarelli, F., Nesher, G., Borella, E., Odeh, Q., Conti, F., Shoenfeld, Y., & Valesini, G. (2014). Immune thrombocytopenic purpura (ITP) associated with vaccinations: a review of reported cases. *Immunologic Research*, *60*(2–3), 226–235. https://doi.org/10.1007/S12026-014-8597-X

Perricone, C., Colafrancesco, S., Mazor, R. D., Soriano, A., Agmon-Levin, N., & Shoenfeld, Y. (2013). Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) 2013: Unveiling the

pathogenic, clinical and diagnostic aspects. *Journal of Autoimmunity*, *47*, 1–16. https://doi.org/10.1016/J.JAUT.2013.10.004

Physiopedia. (2022). *Vaccines*. https://www.physio-pedia.com/Vaccines#cite_note-:1-2

Pierson, T. C., Xu, Q., Nelson, S., Oliphant, T., Nybakken, G. E., Fremont, D. H., & Diamond, M. S. (2007). The Stoichiometry of Antibody-Mediated Neutralization and Enhancement of West Nile Virus Infection. *Cell Host & Microbe*, *1*(2), 135–145. https://doi.org/https://doi.org/10.1016/j.chom.2007.03.002

Poland, G. A., Kennedy, R. B., McKinney, B. A., Ovsyannikova, I. G., Lambert, N. D., Jacobson, R. M., & Oberg, A. L. (2013). Vaccinomics, adversomics, and the immune response network theory: individualized vaccinology in the 21st century. *Seminars in Immunology*, *25*(2), 89–103. https://doi.org/10.1016/J.SMIM.2013.04.007

Pollard, A. J., & Bijker, E. M. (2021). A guide to vaccinology: from basic principles to new developments. *Nature Reviews Immunology*, *21*(2), 83–100. https://doi.org/10.1038/s41577-020-00479-7

Pollard, K., & Hultman, P. (1997). Effects of mercury on the immune system. *Metal Ions in Biological Systems*, *34*, 421–440.

Pollard, K. M., Cauvi, D. M., Toomey, C. B., Hultman, P., & Kono, D. H. (2019). Mercury-induced inflammation and autoimmunity. *Biochimica et Biophysica Acta - General Subjects*, *1863*(12). https://doi.org/10.1016/j.bbagen.2019.02.001

Pomara, C., Sessa, F., Ciaccio, M., Dieli, F., Esposito, M., Giammanco, G. M., Garozzo, S. F., Giarratano, A., Prati, D., Rappa, F., Salerno, M., Tripodo, C., Mannucci, P. M., & Zamboni, P. (2021). *diagnostics COVID-19 Vaccine and Death: Causality Algorithm According to the WHO Eligibility Diagnosis*. *11*, 955. https://doi.org/10.3390/diagnostics11060955

Psillos, S. (2006). *Causal Pluralism*.

PSU. (2022). *Interaction Revisited*. STAT 507: Epidemiological Research Methods. Penn State University: Eberly College of Science . https://online.stat.psu.edu/stat507/lesson/12/12.4

Pujar, S. S., Martinos, M. M., Cortina-Borja, M., Chong, W. K. K., de Haan, M., Gillberg, C., Neville, B. G., Scott, R. C., & Chin, R. F. (2018). Long-term prognosis after childhood convulsive status epilepticus: a prospective cohort study. *The Lancet. Child & Adolescent Health*, *2*(2), 103. https://doi.org/10.1016/S2352-4642(17)30174-8

Puliyel, J., Naik, P., Jefferson, T., Health, B., & -Bissau, G. (2018). *World Health Organization (WHO)'s causality assessment of adverse events following immunization-a critique [version 2; referees: 2 approved] Referee Status: Invited Referees version 2*. https://doi.org/10.12688/f1000research.13694.1

Qiu, C. C., Caricchio, R., & Gallucci, S. (2019). Triggers of Autoimmunity: The Role of Bacterial Infections in the Extracellular Exposure of Lupus Nuclear Autoantigens. *Frontiers in Immunology*, *10*. https://doi.org/10.3389/FIMMU.2019.02608

Ragunathan-Thangarajah, N., le Beller, C., Boutouyrie, P., Bassez, G., Gherardi, R. K., Laurent, S., & Authier, F. J. (2013). Distinctive clinical features in arthro-myalgic patients with and without aluminum hydroxyde-induced macrophagic myofasciitis: an exploratory study. *Journal of Inorganic Biochemistry*, *128*, 262–266. https://doi.org/10.1016/J.JINORGBIO.2013.07.020

Rajan, T. v. (2003). The Gell-Coombs classification of hypersensitivity reactions: A re-interpretation. *Trends in Immunology*, *24*(7), 376–379. https://doi.org/10.1016/S1471-4906(03)00142-X

Ralph Edwards, I. (2017). Causality Assessment in Pharmacovigilance: Still a Challenge. *Drug Safety*, *40*(5), 365–372. https://doi.org/10.1007/S40264-017-0509-2

Ramani, P. K., & Sankaran, B. P. (2022). *Tay-Sachs Disease*. StatPearls Publishing.

Rehan, H. S., & Chopra, D. (2009). Guide to reporting adverse drug reactions. *International Journal of Risk and Safety in Medicine*, *21*(4), 229–234. https://doi.org/10.3233/JRS-2009-482

Reiss, J. (2009). Causation in the Social Sciences: Evidence, Inference, and Purpose. *Philosophy of the Social Sciences*, *39*(1), 20–40. https://doi.org/10.1177/0048393108328150

Reiss, J. (2012). Causation in the sciences: an inferentialist account. *Studies in History and Philosophy of Biological and Biomedical Sciences*, *43*(4), 769–777. https://doi.org/10.1016/J.SHPSC.2012.05.005

Reiss, J. (2015). *Causation, Evidence, and Inference*. Routledge. https://www.routledge.com/Causation-Evidence-and-Inference/Reiss/p/book/9780815371984

Reiss, J. (2016a). Causality and Causal Inference in Medicine. In M. Solomon, J. R. Simon, & H. Kincaid (Eds.), *Routledge Companion to Philosophy of Medicine* (1st ed., Issue 10922, pp. 72–84). Routledge. https://doi.org/10.4324/9781315720739-12

Reiss, J. (2016b). Are There Social Scientific Laws? In *The Routledge Companion to Philosophy of Social Science* (1st eds., pp. 315–329). Routledge. https://doi.org/10.4324/9781315410098-36

Reiss, M., & Czypionka, T. (2022, February 15). *What roles were played by public health agencies in Europe during the COVID-19 pandemic?* European Observatory on Health Systems and Policies. https://eurohealthobservatory.who.int/monitors/hsrm/analyses/hsrm/the-roles-played-by-public-health-agencies-in-europe-during-the-covid-19-pandemic

Relman, D. A. (2020). Thinking about the microbiome as a causal factor in human health and disease: philosophical and experimental considerations. *Current Opinion in Microbiology*, *54*, 119–126. https://doi.org/10.1016/J.MIB.2020.01.018

Ribeiro-Vaz, I., Silva, A. M., Costa Santos, C., & Cruz-Correia, R. (2016). How to promote adverse drug reaction reports using information systems - a systematic review and meta-analysis. *BMC Medical Informatics and Decision Making*, *16*(1). https://doi.org/10.1186/S12911-016-0265-8

Rigolet, M., Aouizerate, J., Couette, M., Ragunathan-Thangarajah, N., Aoun-Sebaiti, M., Gherardi, R. K., Cadusseau, J., & Authier, F. J. (2014). Clinical features in patients with long-lasting macrophagic myofasciitis. *Frontiers in Neurology*, *5*. https://doi.org/10.3389/FNEUR.2014.00230

Rinaldi, M., Perricone, C., Ortega-Hernandez, O. D., Perricone, R., & Shoenfeld, Y. (2014). Immune thrombocytopaenic purpura: an autoimmune cross-link between infections and vaccines. *Lupus*, *23*(6), 554–567. https://doi.org/10.1177/0961203313499959

Rizzi, D. A. (1994). Causal reasoning and the diagnostic process. *Theoretical Medicine 1994 15:3*, *15*(3), 315–333. https://doi.org/10.1007/BF01313345

Rizzi, D. A., & Pedersen, S. A. (1992). Causality in medicine: Towards a theory and terminology. *Theoretical Medicine*, *13*(3), 233–254. https://doi.org/10.1007/BF00489201

Roberts, J. T. (2004). There are no laws of the Social Sciences. In Hitchcock. C. (Ed.), *Contemporary Debates in Philosophy of Science* (ed., pp. 151–167). Backwell.

Rocca, E. (2020). *CauseHealth Risk and Safety: Philosophy of Science Meets Patient Safety*. Uppsala Reports: Covering the World of Pharmacovigilance . https://www.uppsalareports.org/articles/causehealth-risk-and-safety-philosophy-of-science-meets-patient-safety/

Rocca, E., & Anjum, R. L. (2020a). Complexity, reductionism and the biomedical model. In R. L. , Anjum, S. , Copeland, & E. Rocca (Eds.), *Rethinking Causality, Complexity and Evidence for the Unique Patient: A CauseHealth Resource for Healthcare Professionals and the Clinical Encounter* (pp. 75–94). Springer International Publishing. https://doi.org/10.1007/978-3-030-41239-5_5/COVER

Rocca, E., & Anjum, R. L. (2020b). Causal Evidence and Dispositions in Medicine and Public Health. *International Journal of Environmental Research and Public Health 2020, Vol. 17, Page 1813*, *17*(6), 1813. https://doi.org/10.3390/IJERPH17061813

Rocca, E., Anjum, R. L., & Mumford, S. (2020). Causal Insights from Failure: Post-marketing Risk Assessment of Drugs as a Way to Uncover Causal Mechanisms. In A. LaCaze & B. Osimani (Eds.), *Uncertainty in Pharmacology: Epistemology, Methods, and Decisions* (pp. 39–57). Springer International Publishing. https://doi.org/10.1007/978-3-030-29179-2_2

Rocca, E., Copeland, S., & Ralph Edwards, I. (2019). Pharmacovigilance as Scientific Discovery: An Argument for Trans-Disciplinarity. *Drug Safety*, *42*(10), 1115–1124. https://doi.org/10.1007/S40264-019-00826-1

Rock, M. T., Yoder, S. M., Talbot, T. R., Edwards, K. M., & Crowe, J. E. (2004). Adverse events after smallpox immunizations are associated with alterations in systemic cytokine levels. *The Journal of Infectious Diseases*, *189*(8), 1401–1410. https://doi.org/10.1086/382510

Röltgen, K., Nielsen, S. C. A., Silva, O., Younes, S. F., Zaslavsky, M., Costales, C., Yang, F., Wirz, O. F., Solis, D., Hoh, R. A., Wang, A., Arunachalam, P. S., Colburg, D., Zhao, S., Haraguchi, E., Lee,

A. S., Shah, M. M., Manohar, M., Chang, I., … Boyd, S. D. (2022). Immune imprinting, breadth of variant recognition, and germinal center response in human SARS-CoV-2 infection and vaccination. *Cell*, *185*(6), 1025-1040.e14. https://doi.org/10.1016/J.CELL.2022.01.018

Rose, N. R. (2017). Negative selection, epitope mimicry and autoimmunity. *Current Opinion in Immunology*, *49*, 51–55. https://doi.org/10.1016/J.COI.2017.08.014

Rosenthal, S., & Chen, R. (1995). The reporting sensitivities of two passive surveillance systems for vaccine adverse events. *American Journal of Public Health*, *85*(12), 1706–1709. https://doi.org/10.2105/AJPH.85.12.1706

Rossi, B. (2000). Analisi del concetto di casualità nel diritto penale: le tesi. In *Redazione*. https://www.diritto.it/concetto-casualita-dottrina-giurisprudenza/

Rothman, K. J. (1976). Causes. *American Journal of Epidemiology*, *104*(6), 587–592. https://doi.org/10.1093/OXFORDJOURNALS.AJE.A112335

Rothman, K. J. (1981). INDUCTION AND LATENT PERIODS. *American Journal of Epidemiology*, *114*(2), 253–259. https://doi.org/10.1093/OXFORDJOURNALS.AJE.A113189

Rothman, K. J. (2012a). Epidemiology: An introduction. In *Epidemiology: an introduction* (2nd ed.). Oxford University Press, Incorporated.

Rothman, K. J. (2012b). What Is Causation? In *Epidemiology: An Introduction* (pp. 23–37). Oxford University Press. https://global.oup.com/us/companion.websites/9780199754557/pdf/2e-Chap3.pdf

Rothman, K. J., & Greenland, S. (2005). Causation and causal inference in epidemiology. *American Journal of Public Health*, *95 Suppl 1*(SUPPL. 1). https://doi.org/10.2105/AJPH.2004.059204

Rothman, K. J., Greenland, S., Poole, C., & Lash, T. L. (2008). Causation and Causal Inference. In S. Seigafuse & L. Bierig (Eds.), *Modern Epidemiology* (3rd ed., pp. 5–6). Lippincott Williams & Wilkins.

Rowhani-Rahbar, A., Fireman, B., Lewis, E., Nordin, J., Naleway, A., Jacobsen, S. J., Jackson, L. A., Tse, A., Belongia, E. A., Hambidge, S. J., Weintraub, E., Baxter, R., & Klein, N. P. (2013). Effect of age on the risk of Fever and seizures following immunization with measles-containing vaccines in children. *JAMA Pediatrics*, *167*(12), 1111–1117. https://doi.org/10.1001/JAMAPEDIATRICS.2013.2745

Ruhrman-Shahar, N., Torres-Ruiz, J., Rotman-Pikielny, P., & Levy, Y. (2017). Autoimmune reaction after anti-tetanus vaccination-description of four cases and review of the literature. *Immunologic Research*, *65*(1), 157–163. https://doi.org/10.1007/S12026-016-8822-X

Russo, F., & Williamson, J. (2007). *Causality and Probability in the Sciences* (ed.). College Publications .

Russo, F., & Williamson, J. (2011). Generic versus Single-case Causality: The Case of Autopsy. *European Journal for Philosophy of Science*, *1*(1), 47–69. https://doi.org/10.1007/S13194-010-0012-4/FIGURES/2

Sackett, D., Rosenberg, W., Gray, J., Bmj, R. H.-, & 1996, undefined. (1996). Evidence based medicine: what it is and what it isn't. *Bmj*, *312*(7023), 71–72. https://www.bmj.com/content/312/7023/71?%25253Cbr

Salemi, S., immunology, R. D.-I. reviews of, & 2010, undefined. (2010). Could autoimmunity be induced by vaccination? *Taylor & Francis*, *29*(3), 247–269. https://doi.org/10.3109/08830181003746304

Salmon, W. C. (1998). Causality and Explanation. In *Oxford Academic* (ed.). Oxford University Press. https://doi.org/10.1093/0195108647.001.0001

Santiago, T., Rebelo, O., Negrão, L., & Matos, A. (2015). Macrophagic myofasciitis and vaccination: consequence or coincidence? *Rheumatology International*, *35*(1), 189–192. https://doi.org/10.1007/S00296-014-3065-4

Santoni de Sio, F. (2008). Causalità, colpa e responsabilità: l'eredità di Hart e Honoré. *Rivista Di Filosofia*, *XCIX*(2/2008), 263–290. https://doi.org/10.1413/27002

Santoro, A., Genov, G., Spooner, A., Raine, J., & Arlett, P. (2017). Promoting and Protecting Public Health: How the European Union Pharmacovigilance System Works. *Drug Safety*, *40*(10), 855–869. https://doi.org/10.1007/S40264-017-0572-8

Santoro, D., Vita, G., Vita, R., Mallamace, A., Savica, V., Bellinghieri, G., Benvenga, S., & Gangemi, S. (2010). HLA haplotype in a patient with systemic lupus erythematosus triggered by hepatitis B vaccine. *Clinical Nephrology*, *74*(2), 150–153. https://doi.org/10.5414/CNP74150

Sassolas, B., Haddad, C., Mockenhaupt, M., Dunant, A., Liss, Y., Bork, K., Haustein, U. F., Vieluf, D., Roujeau, J. C., & le Louet, H. (2010). ALDEN, an Algorithm for Assessment of Drug Causality in Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis: Comparison With Case–Control Analysis. *Clinical Pharmacology & Therapeutics*, *88*(1), 60–68. https://doi.org/10.1038/CLPT.2009.252

Saxena, K., Mittal, S., Banerji, D., Qadeer, I., Kurian, N., Priya, R., Shiva, M., Puliyel, J., & Dabade, G. (2009). *Delhi High Court. (2009) Writ Petition (Civil) No. 13698 of 2009. Public Interest Litigation.* . https://jacob.puliyel.com/paper.php?id=181

Schaffer, J. (2005). Contrastive Causation. *The Philosophical Review*, *114*(3), 327–358. https://doi.org/10.1215/00318108-114-3-327

Schaffner, K. F. (1993). *Discovery and Explanation in Biology and Medicine*. University Chicago Press.

Scheffer, I. E. (2012). Diagnosis and long-term course of Dravet syndrome. *European Journal of Paediatric Neurology : EJPN : Official Journal of the European Paediatric Neurology Society*, *16 Suppl 1*(SUPPL. 1), S5. https://doi.org/10.1016/J.EJPN.2012.04.007

Scheffler, U. (2003). On the logic of event causation. Part I. Fundamental reflections. *Logic and Logical Philosophy*, *0*(1), 129–155. https://doi.org/10.12775/LLP.1993.004

Schroeder, H. W., & Cavacini, L. (2010). Structure and function of immunoglobulins. *The Journal of Allergy and Clinical Immunology*, *125*(2 Suppl 2). https://doi.org/10.1016/J.JACI.2009.09.046

Schutte, N. M., Stassijns, J., Saso, M., van Oyen, H., & Bogaert, P. (2021). What role did National Public Health Institutes in Europe play in monitoring the COVID-19 pandemic? In *Epidemiology and Public Health*. European Observatory on Health Systems and Policies. https://eurohealthobservatory.who.int/monitors/hsrm/analyses/hsrm/what-role-did-national-public-health-institutes-in-europe-play-in-monitoring-the-covid-19-pandemic

Screaton, G., Mongkolsapaya, J., Yacoub, S., & Roberts, C. (2015). New insights into the immunopathology and control of dengue virus infection. *Nature Reviews Immunology*, *15*(12), 745–759. https://doi.org/10.1038/nri3916

Sebastian, J., Gurumurthy, P., Ravi, M. D., & Ramesh, M. (2019). Active surveillance of adverse events following immunization (AEFI): a prospective 3-year vaccine safety study. *Therapeutic Advances in Vaccines and Immunotherapy*, *7*. https://doi.org/10.1177/2515135519889000

Segal, Y., Calabrò, M., Kanduc, D., & Shoenfeld, Y. (2017). Human papilloma virus and lupus: the virus, the vaccine and the disease. *Current Opinion in Rheumatology*, *29*(4), 331–342. https://doi.org/10.1097/BOR.0000000000000398

SEP. (2001). Counterfactual Theories of Causation. *Stanford Encyclopedia of Philosophy*. https://plato.stanford.edu/entries/causation-counterfactual/

Shamji, M. H., Thomsen, I., Layhadi, J. A., Kappen, J., Holtappels, G., Sahiner, U., Switzer, A., Durham, S. R., Pabst, O., & Bachert, C. (2019). Broad IgG repertoire in patients with chronic rhinosinusitis with nasal polyps regulates proinflammatory IgE responses. *The Journal of Allergy and Clinical Immunology*, *143*(6), 2086-2094.e2. https://doi.org/10.1016/J.JACI.2019.02.001

Sharma, M., Krammer, F., García-Sastre, A., & Tripathi, S. (2019). Moving from Empirical to Rational Vaccine Design in the "Omics" Era. *Vaccines*, *7*(3). https://doi.org/10.3390/VACCINES7030089

Shimabukuro, T. T., Nguyen, M., Martin, D., & Destefano, F. (2015). Safety monitoring in the Vaccine Adverse Event Reporting System (VAERS) HHS Public Access. *Vaccine*, *33*(36), 4398–4405. https://doi.org/10.1016/j.vaccine.2015.07.035

Shoenfeld, Y., & Agmon-Levin, N. (2011). "ASIA" - autoimmune/inflammatory syndrome induced by adjuvants. *Journal of Autoimmunity*, *36*(1), 4–8. https://doi.org/10.1016/J.JAUT.2010.07.003

Shoenfeld, Y., Agmon-Levin, N., & Tomljenovic, L. (2015). *Vaccines and autoimmunity* (eds). John Wiley & Sons.

Singh, A. K., Wagner, A. L., Joshi, J., Carlson, B. F., Aneja, S., & Boulton, M. L. (2017). Application of the revised WHO causality assessment protocol for adverse events following immunization in India. *Vaccine*, *35*(33), 4197–4202. https://doi.org/https://doi.org/10.1016/j.vaccine.2017.06.027

Skyrms, B. (1980). *Causal Necessity: Pragmatic Investigation of the Necessity of Laws*. Yale University Press.

Šlosarčík, I., Meyer, N., & Chubb, J. (2020). Science diplomacy as a means to tackle infectious diseases. In M. Young, Flink T., & E. Dall (Eds.), *Science Diplomacy in the Making: Case-based insights from the S4D4C project* (eds.).

Smith, S. R. (2007). Causation and Its Relation to "Causal Laws." *The British Journal for the Philosophy of Science*, *58*(4), 659–688. http://www.jstor.org/stable/30115169

Smith, S. W., Hauben, M., & Aronson, J. K. (2012). Paradoxical and bidirectional drug effects. *Drug Safety*, *35*(3), 173–189. https://doi.org/10.2165/11597710-000000000-00000

Sobolev, O., Binda, E., O'Farrell, S., Lorenc, A., Pradines, J., Huang, Y., Duffner, J., Schulz, R., Cason, J., Zambon, M., Malim, M. H., Peakman, M., Cope, A., Capila, I., Kaundinya, G. v., & Hayday, A. C. (2016). Adjuvanted influenza-H1N1 vaccination reveals lymphoid signatures of age-dependent early responses and of clinical adverse events. *Nature Immunology*, *17*(2), 204–213. https://doi.org/10.1038/NI.3328

Son, J. H., Park, S. Y., Cho, Y. S., Chung, B. Y., Kim, H. O., & Park, C. W. (2018). Immediate Hypersensitivity Reactions Induced by Triamcinolone in a Patient with Atopic Dermatitis. *Journal of Korean Medical Science*, *33*(12). https://doi.org/10.3346/JKMS.2018.33.E87

Soriano, A., Nesher, G., & Shoenfeld, Y. (2015). Predicting post-vaccination autoimmunity: who might be at risk? *Pharmacological Research*, *92*, 18–22. https://doi.org/10.1016/J.PHRS.2014.08.002

Sosa, E., & Tooley, M. (1993). *Causation* (eds.). Oxford University Press.

Sottosanti, L. (2015). Il Risk Management System: le aspettative da parte delle Autorità. *AIFA*.

Spadaro, S., Park, M., Turrini, C., Tunstall, T., Thwaites, R., Mauri, T., Ragazzi, R., Ruggeri, P., Hansel, T. T., Caramori, G., & Volta, C. A. (2019). Biomarkers for Acute Respiratory Distress syndrome and prospects for personalised medicine. *Journal of Inflammation (London, England)*, *16*(1). https://doi.org/10.1186/S12950-018-0202-Y

Spellman, B. A. (1997). Crediting causality. *Journal of Experimental Psychology: General*, *126*(4), 323–348. https://doi.org/10.1037/0096-3445.126.4.323

Spohn, W. (1990). Direct and indirect causes. *Topoi* , *9*(2), 125–145. https://doi.org/10.1007/BF00135893

St John, A. L., & Rathore, A. P. S. (2019). Adaptive immune responses to primary and secondary dengue virus infections. *Nature Reviews. Immunology*, *19*(4), 218–230. https://doi.org/10.1038/S41577-019-0123-X

Stapleton, J. (2008). Choosing What We Mean by "Causation" in the Law. *Missouri Law Review*, *73*(2), 433–480. https://scholarship.law.missouri.edu/mlr/vol73/iss2/6

Stefanizzi, P., Stella, P., Ancona, D., Malcangi, K. N., Bianchi, F. P., de Nitto, S., Ferorelli, D., Germinario, C. A., & Tafuri, S. (2019). Adverse Events Following Measles-Mumps-Rubella-Varicella Vaccination and the Case of Seizures: A Post Marketing Active Surveillance in Puglia Italian Region, 2017-2018. *Vaccines*, *7*(4). https://doi.org/10.3390/VACCINES7040140

Stegenga, J. (2018). *Care and Cure: An Introduction to Philosophy of Medicine*. The University of Chicago Press.

Stephan, S., Mayrhofer, R., & Waldmann, M. R. (2020). Time and Singular Causation—A Computational Model. *Cognitive Science*, *44*(7). https://doi.org/10.1111/COGS.12871

Stevens, R. (2007). Causation. *Torts and Rights*, 129–151. https://doi.org/10.1093/ACPROF:OSO/9780199211609.003.0006

Stone, C. A., Hemler, J. A., Commins, S. P., Schuyler, A. J., Phillips, E. J., Peebles, R. S., & Fahrenholz, J. M. (2017). Anaphylaxis after zoster vaccine: Implicating alpha-gal allergy as a possible mechanism. *The Journal of Allergy and Clinical Immunology*, *139*(5), 1710-1713.e2. https://doi.org/10.1016/J.JACI.2016.10.037

Stone Jr, C. A., Rukasin, C. R. F., Beachkofsky, T. M., & Phillips, E. J. (2019). Immune-mediated adverse reactions to vaccines. *British Journal of Clinical Pharmacology*, *85*(12), 2694–2706. https://doi.org/https://doi.org/10.1111/bcp.14112

Strevens, M. (2003). *Mackie's Theory of Causation Revivified: New Oil in Old Jars*. https://www.webpages.uidaho.edu/inpc/6th-2003/papers/Strevens-long.pdf

Strianese, O., Rizzo, F., Ciccarelli, M., Galasso, G., D'agostino, Y., Salvati, A., del Giudice, C., Tesorio, P., & Rusciano, M. R. (2020). Precision and Personalized Medicine: How Genomic Approach Improves the Management of Cardiovascular and Neurodegenerative Disease. *Genes*, *11*(7), 1–24. https://doi.org/10.3390/GENES11070747

Summerer, K. (2013). Accertamento del nesso normativo: la formula della condicio sine qua non e il confronto tra evento reale ed evento ipotetico. In M. Clarich, A. Gentili, F. Giunta, M. Jori, & M. Taruffo (Eds.), *Causalità ed evitabilità: Formula della condicio sine qua non e rilevanza dei decorsi causali ipotetici nel diritto penale* (pp. 389–394). Edizioni ETS.

Suppes, P. (1970). *A Probabilistic Theory of Causality*. Acta Philosophica Fennica.

Susser, M. (1973). *Causal thinking in the health sciences: concepts and strategies of epidemiology*. Oxford University Press.

Suzumura, A., Takeuchi, H., Zhang, G., Kuno, R., & Mizuno, T. (2006). Roles of glia-derived cytokines on neuronal degeneration and regeneration. *Annals of the New York Academy of Sciences*, *1088*, 219–229. https://doi.org/10.1196/ANNALS.1366.012

Swadling, L., Diniz, M. O., Schmidt, N. M., Amin, O. E., Chandran, A., Shaw, E., Pade, C., Gibbons, J. M., le Bert, N., Tan, A. T., Jeffery-Smith, A., Tan, C. C. S., Tham, C. Y. L., Kucykowicz, S., Aidoo-Micah, G., Rosenheim, J., Davies, J., Johnson, M., Jensen, M. P., … Investigators, Covid. (2022). Pre-existing polymerase-specific T cells expand in abortive seronegative SARS-CoV-2. *Nature*, *601*(7891), 110–117. https://doi.org/10.1038/s41586-021-04186-8

Szarfman, A., Machado, S. G., & O'Neill, R. T. (2002). Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. *Drug Safety*, *25*(6), 381–392. https://doi.org/10.2165/00002018-200225060-00001

Szczech, J., Samotij, D., Werth, V. P., & Reich, A. (2017). Trigger factors of cutaneous lupus erythematosus: a review of current literature. *Lupus*, *26*(8), 791–807. https://doi.org/10.1177/0961203317691369

Szlezák, N. A., Bloom, B. R., Jamison, D. T., Keusch, G. T., Michaud, C. M., Moon, S., & Clark, W. C. (2010). The global health system: Actors, norms, and expectations in transition. *PLoS Medicine*, *7*(1). https://doi.org/10.1371/JOURNAL.PMED.1000183

Tadros, V. (2005). *Criminal Responsibility*. Oxford Oxford University Press.

Tavares Da Silva, F., di Pasquale, A., Yarzabal, J. P., & Garçon, N. (2015). Safety assessment of adjuvanted vaccines: Methodological considerations. *Human Vaccines & Immunotherapeutics*, *11*(7), 1814–1824. https://doi.org/10.1080/21645515.2015.1043501

TFEC Art. 191. (2007). Union policy on the environment . In *Treaty for the Functioning of the European Commission: Part three, Title XX, Art.191 (ex Article 174 TEC)*. https://lexparency.org/eu/TFEU/ART_191/#:~:text=Article%20191%20%E2%80%94%20(ex%20Article%20174%20TEC),-Union%20policy%20on&text=It%20shall%20be%20based%20on,that%20the%20polluter%20should%20pay.

The College of Physicians of Philadelphia. (2022). *How are vaccines made? Vaccine Development, Testing, and Regulation*. History of Vaccines. https://historyofvaccines.org/vaccines-101/how-are-vaccines-made/vaccine-development-testing-and-regulation

The Royal Society. (2022). *Do EU institutions have access to the latest scientific advice and evidence?* . https://royalsociety.org/topics-policy/projects/uk-research-and-european-union/role-of-EU-regulation-and-policy-in-governing-UK-research/do-EU-institutions-have-access-to-the-latest-scientific-advice-and-evidence/

Tooley, M. (2009). Causes, Laws, and Ontology. *The Oxford Handbook of Causation*. https://doi.org/10.1093/OXFORDHB/9780199279739.003.0019

Touborg, C. T. (2018). Hasteners and delayers: why rains don't cause fires. *Philosophical Studies*, *175*(7), 1557–1576. https://doi.org/10.1007/s11098-017-0923-4

Tourbah, A., Gout, O., Liblau, R., Lyon-Caen, O., Bougniot, C., Iba-Zizen, M. T., & Cabanis, E. A. (1999). Encephalitis after hepatitis B vaccination: recurrent disseminated encephalitis or MS? *Neurology*, *53*(2), 396–401. https://doi.org/10.1212/WNL.53.2.396

Toussirot, É., & Bereau, M. (2015). Vaccination and Induction of Autoimmune Diseases. *Inflammation & Allergy Drug Targets*, *14*(2), 94–98. https://doi.org/10.2174/1871528114666160105113046

Tozzi, A. E., Asturias, E. J., Ram Balakrishnan, M., Halsey, N. A., Law, B., & Zuber, P. L. (2013). Assessment of causality of individual adverse events following immunization (AEFI): A WHO tool for global use. *Vaccine*, *31*, 5041–5046. https://doi.org/10.1016/j.vaccine.2013.08.087

Trougakos, I. P., Terpos, E., Alexopoulos, H., Politou, M., Paraskevis, D., Scorilas, A., Kastritis, E., Andreakos, E., & Dimopoulos, M. A. (2022). Adverse effects of COVID-19 mRNA vaccines: the spike hypothesis. *Trends in Molecular Medicine*, *28*(7), 542–554. https://doi.org/10.1016/J.MOLMED.2022.04.007

Tubert, P., Bégaud, B., Péré, J. C., Haramburu, F., & Lellouch, J. (1992). Power and weakness of spontaneous reporting: a probabilistic approach. *Journal of Clinical Epidemiology*, *45*(3), 283–286. https://doi.org/10.1016/0895-4356(92)90088-5

UC Davis Health. (2023). *What is Precision Medicine*. Center for Precision Medicine and Data Sciences. https://health.ucdavis.edu/precision-medicine/what-is-precision-medicine.html

UMC. (2018, April 6). *The use of the WHO-UMC system for standardised case causality assessment*. The Uppsala Monitoring Centre. https://who-umc.org/media/164200/who-umc-causality-assessment_new-logo.pdf

UNESCO. (2020). *UNESCO mobilizes 122 countries to promote open science and reinforced cooperation in the face of COVID-19*. Availabhttps://en.unesco.org/news/unesco-mobilizes-122-countries-promote-open-science-and-reinforced-cooperation-face-covid-19

Unisi. (2015, February 2). *La nuova normativa di Farmacovigilanza*. Università Di Siena. Dipartimento Di Biotecnologie, Chimica E Farmacia . https://www.dbcf.unisi.it/sites/st13/files/allegati/02-02-2015/normativa_farmacovigilanza_2014.pdf

U.S. Federal Statute. (1944). *Public Health Service Act, July 1, 1944, ch. 373, Title III, 351, 58 Stat. 702, currently codified at 42 U.S.C. 262.* https://www.govinfo.gov/content/pkg/USCODE-2013-title42/html/USCODE-2013-title42-chap6A.htm

Usher, M. (2018). Agency, teleological control and robust causation. *Philosophy and Phenomenological Research*, *100*(2), 302–324. https://doi.org/10.1111/phpr.12537

Vaillant, A. A. J., & Qurie, A. (2022). Immunodeficiency. *StatPearls*. https://www.ncbi.nlm.nih.gov/books/NBK500027/

Vaillant, A. A. J., Vashisht, R., & Zito, P. M. (2022). Immediate Hypersensitivity Reactions. In *StatPearls*. StatPearls Publishing.

Vaillant, A. A. J., & Zito, P. M. (2022). Neutropenia. *The Autoimmune Diseases*, 585–589. https://doi.org/10.1016/B978-012595961-2/50046-9

Valitutti, F., Cucchiara, S., & Fasano, A. (2019). Celiac Disease and the Microbiome. *Nutrients*, *11*(10). https://doi.org/10.3390/NU11102403

van der Gucht, A., Sebaiti, M. A., Itti, E., Aouizerate, J., Evangelista, E., Chalaye, J., Gherardi, R. K., Ragunathan-Thangarajah, N., Bachoud-Levi, A. C., & Authier, F. J. (2015). Neuropsychological Correlates of Brain Perfusion SPECT in Patients with Macrophagic Myofasciitis. *PloS One*, *10*(6). https://doi.org/10.1371/JOURNAL.PONE.0128353

Vandenbroucke, J. P. (2008). Observational research, randomised trials, and two views of medical science. *PLoS Medicine*, *5*(3), 0339–0343. https://doi.org/10.1371/JOURNAL.PMED.0050067

Vandervoort, R. (2018). Allergy and Asthma: Anaphylaxis. *FP Essentials*, *472*, 20–24.

Verbeek, N. E., Jansen, F. E., de Bondt, P. E. V., de Kovel, C. G., van Kempen, M. J. A., Lindhout, D., Knoers, N. V. A. M., van der Maas, N. A. T., & Brilstra, E. H. (2014). Etiologies for seizures around the time of vaccination. *Pediatrics*, *134*(4), 658–666. https://doi.org/10.1542/PEDS.2014-0690

Verbeek, N. E., van der Maas, N. A. T., Jansen, F. E., van Kempen, M. J. A., Lindhout, D., & Brilstra, E. H. (2013). Prevalence of SCN1A-related dravet syndrome among children reported with seizures following vaccination: a population-based ten-year cohort study. *PloS One*, *8*(6). https://doi.org/10.1371/JOURNAL.PONE.0065758

Verbeek, N. E., van der Maas, N. A. T., Sonsma, A. C. M., Ippel, E., Vermeer-De Bondt, P. E., Hagebeuk, E., Jansen, F. E., Geesink, H. H., Braun, K. P., de Louw, A., Augustijn, P. B.,

Neuteboom, R. F., Schieving, J. H., Stroink, H., Vermeulen, R. J., Nicolai, J., Brouwer, O. F., van Kempen, M., de Kovel, C. G. F., … Brilstra, E. H. (2015). Effect of vaccinations on seizure risk and disease course in Dravet syndrome. *Neurology*, *85*(7), 596–603. https://doi.org/10.1212/WNL.0000000000001855

Verlato, G. (2022). *RELAZIONE CAUSALE IN EPIDEMOLOGIA*. http://biometria.univr.it/sesm/files/lezione_6_0nf7t86m.pdf

Verstraeten, T., Baughman, A. L., Cadwell, B., Zanardi, L., Haber, P., & Chen, R. T. (2001). Enhancing vaccine safety surveillance: a capture-recapture analysis of intussusception after rotavirus vaccination. *American Journal of Epidemiology*, *154*(11), 1006–1012. https://doi.org/10.1093/AJE/154.11.1006

Vestergaard, M., Hviid, A., Madsen, K. M., Wohlfahrt, J., Thorsen, P., Schendel, D., Melbye, M., & Olsen, J. (2004). MMR vaccination and febrile seizures: evaluation of susceptible subgroups and long-term prognosis. *JAMA*, *292*(3), 351–357. https://doi.org/10.1001/JAMA.292.3.351

Vestergaard, M., Pedersen, M. G., Østergaard, J. R., Pedersen, C. B., Olsen, J., & Christensen, J. (2008). Death in children with febrile seizures: a population-based cohort study. *Lancet (London, England)*, *372*(9637), 457–463. https://doi.org/10.1016/S0140-6736(08)61198-8

Vyse, T. J., & Todd, J. A. (1996). Genetic analysis of autoimmune disease. *Cell*, *85*(3), 311–318. https://doi.org/10.1016/S0092-8674(00)81110-1

Wang, B., Shao, X., Wang, D., Xu, D., & Zhang, J. an. (2017). Vaccinations and risk of systemic lupus erythematosus and rheumatoid arthritis: A systematic review and meta-analysis. *Autoimmunity Reviews*, *16*(7), 756–765. https://doi.org/10.1016/J.AUTREV.2017.05.012

Wang, K. Y., Friedman, D. F., & DaVeiga, S. P. (2019). Immediate hypersensitivity reaction to human serum albumin in a child undergoing plasmapheresis. *Transfusion*, *59*(6), 1921–1923. https://doi.org/10.1111/TRF.15194

Warter, L., Appanna, R., & Fink, K. (2012). Human poly- and cross-reactive anti-viral antibodies and their impact on protection and pathology. *Immunologic Research*, *53*(1–3), 148–161. https://doi.org/10.1007/S12026-012-8268-8

Watad, A., Quaresma, M., Bragazzi, N. L., Cervera, R., Tervaert, J. W. C., Amital, H., & Shoenfeld, Y. (2018). The autoimmune/inflammatory syndrome induced by adjuvants (ASIA)/Shoenfeld's syndrome: descriptive analysis of 300 patients from the international ASIA syndrome registry. *Clinical Rheumatology*, *37*(2), 483–493. https://doi.org/10.1007/S10067-017-3748-9

Watad, A., Quaresma, M., Brown, S., Cohen Tervaert, J. W., Rodríguez-Pint, I., Cervera, R., Perricone, C., & Shoenfeld, Y. (2017). Autoimmune/inflammatory syndrome induced by adjuvants (Shoenfeld's syndrome) - An update. *Lupus*, *26*(7), 675–681. https://doi.org/10.1177/0961203316686406

Watanabe, T. (2017). Vasculitis Following Influenza Vaccination: A Review of the Literature. *Current Rheumatology Reviews*, *13*(3). https://doi.org/10.2174/1573397113666170517155443

Waters, C. K. (2007). Causes that Make a Difference . *The Journal of Philosophy*, *104*(11), 551–579.

Watson, R. (2010). WHO is accused of "crying wolf" over swine flu pandemic. *BMJ*, *340*, c1904. https://doi.org/10.1136/bmj.c1904

Weber, E. (2007). Conceptual tools for causal analysis in the social sciences. In F. Russo & J. Williamson (Eds.), *Causality and probability in the sciences* (pp. 197–213). King's College Publications.

Welsh, R. M., Che, J. W., Brehm, M. A., & Selin, L. K. (2010). Heterologous immunity between viruses. *Immunological Reviews*, *235*(1), 244–266. https://doi.org/https://doi.org/10.1111/j.0105-2896.2010.00897.x

Whitaker, J. A., Ovsyannikova, I. G., & Poland, G. A. (2015). Adversomics: a new paradigm for vaccine safety and design. *Expert Review of Vaccines*, *14*(7), 935–947. https://doi.org/10.1586/14760584.2015.1038249

WHO. (1968). The surveillance of communicable diseases. Final report of technical discussions of the 21st World Health Assembly. *WHO Chronicle*, *22*(10), 439–444.

WHO. (1995a). Revision and updating of the International Health Regulations, WHA48.7; Communicable diseases prevention and control: new, emerging, and re-emerging infectious

diseases, WHA 48.13. *Resolutions and Decisions of the 48th World Health Assembly Geneva World Health Organization*.
WHO. (1995b). *Press release WHO/75*.
WHO. (2001). Weekly epidemiological record: relevé épidémiologique hebdomadaire. *WER*, *76*(12), 85–98. https://vaccine-safety-training.org/tl_files/vs/pdf/GACVS_causality.pdf
WHO. (2002). *Adverse Events Following Immunization (AEFI): Causality Assessment*. AIDE MEMOIRE. https://apps.who.int/iris/bitstream/handle/10665/191391/a87773_eng.pdf?sequence=1&isAllowed=y
WHO. (2004). Adverse Event Following Immunization: Aide Memoire on AEFI Investigation World *Health Organization*. https://cdn.who.int/media/docs/default-source/pvg/global-vaccine-safety/new-aide-memoire-aefi.pdf?sfvrsn=66340a11_4
WHO. (2005a). *AIDE MEMOIRE: Adverse Events Following Immunization (AEFI): Causality Assessment*. World Health Organization. https://apps.who.int/iris/bitstream/handle/10665/191391/a87773_eng.pdf?sequence=1&isAllowed=y
WHO. (2005b). *International Health Regulations Third Edition. Resolution WHA58.3.* .
WHO. (2009). Global health risks: Mortality and burden of disease attributable to selected major risks. *World Health Organisation*. https://www.who.int/healthinfo/global_burden_disease/GlobalHealthRisks_report_full.pdf
WHO. (2013). *Vaccine Safety Basics: learning manual*. file:///Users/marialaura/Downloads/WHO-HIS-2013.06-eng.pdf
WHO. (2019). *Causality assessment of an adverse event following immunization (AEFI): User manual for the revised WHO classification* (second edition). https://apps.who.int/iris/bitstream/handle/10665/340802/9789241516990-eng.pdf?sequence=1&isAllowed=y
WHO. (2020, December 22). *Covid-19 vaccines: safety surveillance manual - Monitoring and responding to adverse events following immunization*. World Health Organization.
WHO. (2021, June 11). *Statement for healthcare professionals: How COVID-19 vaccines are regulated for safety and effectiveness*. https://www.who.int/news/item/11-06-2021-statement-for-healthcare-professionals-how-covid-19-vaccines-are-regulated-for-safety-and-effectiveness
WHO. (2022a). *MODULE 1 – Overview and outcomes*. Vaccine Safety Basics. https://vaccine-safety-training.org/overview-and-outcomes-1.html
WHO. (2022b). *National Regulatory Agencies*. https://www.who.int/southeastasia/activities/national-regulatory-agencies#:~:text=NRAs%20are%20national%20regulatory%20agencies,quality%20and%20safety%20and%20efficacy
WHO. (2022c). *Vaccines and immunization*. https://www.who.int/health-topics/vaccines-and-immunization#tab=tab_1
WHO Regional Committee for Europe. (2012). *European Action Plan for Strengthening Public Health Capacities and Services*. World Health Organization Regional Office for Europe. https://www.euro.who.int/__data/assets/pdf_file/0005/171770/RC62wd12rev1-Eng.pdf
WHO Regional Office for Europe. (2015). *Self-assessment tool for the evaluation of essential public health operations in the WHO European Region. 113.*
WHO Vaccine Safety Basics. (2022). *MODULE 4 – Vaccine pharmacovigilance*. WHO Vaccine Safety Basics. https://vaccine-safety-training.org/vaccine-pharmacovigilance.html
WHO-HIS-EMP. (2013). *Causality assessment of an adverse event following immunization (AEFI): User manual for the revised WHO classification* . 34–35. http://apps.who.int/iris/bitstream/handle/10665/80670/9789241505338_eng.pdf?sequence=1
Williams, W. B., Liao, H. X., Moody, M. A., Kepler, T. B., Alam, S. M., Gao, F., Wiehe, K., Trama, A. M., Jones, K., Zhang, R., Song, H., Marshall, D. J., Whitesides, J. F., Sawatzki, K., Hua, A., Liu, P., Tay, M. Z., Seaton, K. E., Shen, X., … Haynes, B. F. (2015). HIV-1 VACCINES. Diversion of

HIV-1 vaccine-induced immunity by gp41-microbiota cross-reactive antibodies. *Science (New York, N.Y.)*, *349*(6249). https://doi.org/10.1126/SCIENCE.AAB1253

Williamson, J. (2006). Causal Pluralism versus Epistemic Causality. *Philosophica*, *77*(1), 69–96. https://philpapers.org/rec/WILCPV

Williamson, J. (2013). *How Can Causal Explanations Explain? 78*, 257–275. https://doi.org/10.1007/s10670-013-9512-x

Williamson, J. (2019). Establishing Causal Claims in Medicine. *International Studies in the Philosophy of Science*, *32*(1), 33–61. https://doi.org/10.1080/02698595.2019.1630927

Wingspread Conference on the Precautionary Principle. (1998, January 26). *Wingspread Statement on the Precautionary Principle*. The Science and Environmental Health Network. https://www.gdrc.org/u-gov/precaution-3.html

Woodward, J. (2002). What Is a Mechanism? A Counterfactual Account. *Philosophy of Science*, *69*. https://doi.org/10.1086/341859

Woodward, J. (2004). Making Things Happen: A Theory of Causal Explanation. In *Making Things Happen: A Theory of Causal Explanation* (eds.). Oxford University Press. https://doi.org/10.1093/0195155270.001.0001/ACPROF-9780195155273-INDEXLIST-1

Wraith, D. C., Goldman, M., & Lambert, P. H. (2003). Vaccination and autoimmune disease: what is the evidence? *Lancet (London, England)*, *362*(9396), 1659–1666. https://doi.org/10.1016/S0140-6736(03)14802-7

Wright, R. W. (1985). Causation in Tort Law. *California Law Review*, *73*(6), 1735–1828. https://doi.org/10.2307/3480373

Wu, K. M., & Farrelly, J. G. (2007). Regulatory perspectives of Type II prodrug development and time-dependent toxicity management: nonclinical Pharm/Tox analysis and the role of comparative toxicology. *Toxicology*, *236*(1–2), 1–6. https://doi.org/10.1016/J.TOX.2007.04.005

Wu, O., Robertson, L., Langhorne, P., Twaddle, S., Lowe, G. D. O., Clark, P., Greaves, M., Walker, I. D., Brenkel, I., Regan, L., & Greer, I. A. (2005). Oral contraceptives, hormone replacement therapy, thrombophilias and risk of venous thromboembolism: a systematic review. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) Study. *Thrombosis and Haemostasis*, *94*(1), 17–25. https://doi.org/10.1160/TH04-11-0759

Wulff, H. R. (1981). *Rational Diagnosis and Treatment: Introduction to Clinical Decision-making* (2nd eds.). Wiley-Blackwell Scientific Publications. https://www.amazon.com/Rational-Diagnosis-Treatment-Introduction-Decision-making/dp/B01MZ56OTS

Wulff, H. R., Pedersen, S. A., & Rosenberg, R. (1986). *Philosophy of Medicine an Introduction*. Blackwell Scientific.

Xie, J., & He, Y. (2017). Ontology-Based Vaccine Adverse Event Representation and Analysis. *Advances in Experimental Medicine and Biology*, *1028*, 89–103. https://doi.org/10.1007/978-981-10-6041-0_6

Yamamoto, M., Kase, M., Sano, H., Kamijima, R., & Sano, S. (2022). Persistent varicella zoster virus infection following mRNA COVID-19 vaccination was associated with the presence of encoded spike protein in the lesion. *Journal of Cutaneous Immunology and Allergy*. https://doi.org/10.1002/CIA2.12278

Yazdani, R., Fekrvand, S., Shahkarami, S., Azizi, G., Moazzami, B., Abolhassani, H., & Aghamohammadi, A. (2019). The hyper IgM syndromes: Epidemiology, pathogenesis, clinical manifestations, diagnosis and management. *Clinical Immunology (Orlando, Fla.)*, *198*, 19–30. https://doi.org/10.1016/J.CLIM.2018.11.007

Yuan, J., Wang, S., Guo, X., & Hu, W. (2016). Acute Disseminated Encephalomyelitis following Vaccination against Hepatitis B in a Child: A Case Report and Literature Review. *Case Reports in Neurological Medicine*, *2016*, 1–3. https://doi.org/10.1155/2016/2401809

Zachos, I., & Sparos, L. (2004). Theories of "at least INUS condition" and "causal pie" in health sciences. *Archives of Hellenic Medicine*, *21*(5), 463–471. https://www.researchgate.net/publication/288473951_Theories_of_at_least_INUS_condition_and_causal_pie_in_health_sciences

Zafrir, Y., Agmon-Levin, N., Paz, Z., Shilton, T., & Shoenfeld, Y. (2012). Autoimmunity following hepatitis B vaccine as part of the spectrum of "Autoimmune (Auto-inflammatory) Syndrome induced by Adjuvants" (ASIA): analysis of 93 cases. *Lupus*, *21*(2), 146–152. https://doi.org/10.1177/0961203311429318

Zappaterra, F. (2018). *Il Rapporto di Causalità Materiale*. ASCI Trento Medicina Legale e Delle Assicurazioni. http://www.asci-trento-fzappaterra.it/ASCI/medicina%20legale/il%20rappcm.htm

Zhang, A., Stacey, H. D., Mullarkey, C. E., & Miller, M. S. (2019). Original Antigenic Sin: How First Exposure Shapes Lifelong Anti-Influenza Virus Immune Responses. *Journal of Immunology (Baltimore, Md.: 1950)*, *202*(2), 335–340. https://doi.org/10.4049/JIMMUNOL.1801149

Zhang, M., Sun, K., Wu, Y., Yang, Y., Tso, P., & Wu, Z. (2017). Interactions between Intestinal Microbiota and Host Immune Response in Inflammatory Bowel Disease. *Frontiers in Immunology*, *8*(AUG). https://doi.org/10.3389/FIMMU.2017.00942

Zheng, D., Liwinski, T., & Elinav, E. (2020). Interaction between microbiota and immunity in health and disease. *Cell Research*, *30*(6), 492–506. https://doi.org/10.1038/s41422-020-0332-7

Zhou, L., & Rupa, A. P. (2018). Categorization and association analysis of risk factors for adverse drug events. *European Journal of Clinical Pharmacology*, *74*(4), 389–404. https://doi.org/10.1007/S00228-017-2373-5

Zimmermann, P., & Curtis, N. (2019). Factors That Influence the Immune Response to Vaccination. *Clinical Microbiology Reviews*, *32*(2). https://doi.org/10.1128/CMR.00084-18

Zitvogel, L., Ayyoub, M., Routy, B., & Kroemer, G. (2016). Microbiome and Anticancer Immunosurveillance. *Cell*, *165*(2), 276–287. https://doi.org/10.1016/J.CELL.2016.03.001