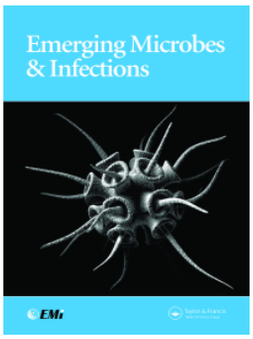

Emerging Microbes & Infections

ISSN: 2222-1751 (Online) Journal homepage: www.tandfonline.com/journals/temi20

Dengue and aging: challenges and opportunities in prevention and care. A narrative review

Alessia Beccacece, Laura Ponzetta, Maria Princiotto, Maria Elsa Gambuzza, Alessandra D'Abramo, Luca Soraci, Fabiola Olivieri, Fabrizia Lattanzio, Enrico Girardi, Leonardo Biscetti & Emanuele Nicastri

To cite this article: Alessia Beccacece, Laura Ponzetta, Maria Princiotto, Maria Elsa Gambuzza, Alessandra D'Abramo, Luca Soraci, Fabiola Olivieri, Fabrizia Lattanzio, Enrico Girardi, Leonardo Biscetti & Emanuele Nicastri (2026) Dengue and aging: challenges and opportunities in prevention and care. A narrative review, Emerging Microbes & Infections, 15:1, 2622217, DOI: 10.1080/22221751.2026.2622217

To link to this article: https://doi.org/10.1080/22221751.2026.2622217

Published online: 05 Feb 2026.

Emerging Microbes & Infections
2026, VOL. 15, 2622217 (11 pages)
https://doi.org/10.1080/22221751.2026.2622217

REVIEW ARTICLE

OPEN ACCESS Check for updates

Dengue and aging: challenges and opportunities in prevention and care. A narrative review

Alessia Beccacece[a]*, Laura Ponzetta[b]*, Maria Princiotto[a], Maria Elsa Gambuzza[c], Alessandra D'Abramo[d], Luca Soraci[a], Fabiola Olivieri[e,f], Fabrizia Lattanzio[g], Enrico Girardi[h], Leonardo Biscetti[i]† and Emanuele Nicastri[d]†

[a]Centre for Biostatistics and Applied Geriatric Clinical Epidemiology, Italian National Research Center on Aging (IRCCS INRCA), Ancona and Cosenza, Italy; [b]Unit of Infectious Diseases, Department of Medical Sciences, University of Turin at the Amedeo di Savoia Hospital, ASL Città di Torino, Turin, Italy; [c]Territorial Office of Messina, Ministry of Health, Messina, Italy; [d]Clinical and Research Infectious Diseases Department, National Institute for Infectious Diseases, Lazzaro Spallanzani IRCCS, Rome, Italy; [e]Department of Clinical and Molecular Sciences, Università Politecnica delle Marche, Ancona, Italy; [f]Advanced Technology Center for Aging Research and Geriatric Mouse Clinic, IRCCS INRCA, Ancona, Italy; [g]Scientific Direction, Italian National Research Center on Aging (IRCCS INRCA), Ancona, Italy; [h]Scientific Direction, National Institute for Infectious Diseases, Lazzaro Spallanzani IRCCS, Rome, Italy; [i]Section of Neurology, Italian National Research Center on Aging (IRCCS INRCA), Ancona, Italy

ABSTRACT

Dengue infection is a global health issue with significantly increased incidence and overall burden, especially since 2024. Specifically, epidemiological trends show a rising median age of affected individuals over 65 years/old. Older individuals face increased risks of severe disease, extended hospital stays, healthcare-associated infections, and higher mortality rates, mainly due to a decline in immune function, and multimorbidity. Antibody-dependent enhancement, cytokine dysregulation, and endothelial dysfunction exacerbate disease severity. Moreover, in older patients, dengue diagnosis can be difficult, due to atypical symptoms. To date, there are no specific prognostic markers and no specific antiviral drugs. Management requires age-specific considerations. Evidence on immunomodulatory and antiviral therapies is emerging, and vaccine efficacy and safety data in older adults remain limited, despite growing interest. With an aging global population, dengue represents an urgent clinical challenge: there is an unmet and increasing need for comprehensive, practical guidelines to help clinicians in the diagnosis, treatment, prevention, and control of dengue infection in older patients.

ARTICLE HISTORY Received 4 September 2025; Revised 19 December 2025; Accepted 22 January 2026

KEYWORDS Dengue infection; Dengue management; Older people; Immunosenescence; Inflammaging

1. Introduction

Dengue infection is considered the most rapid spreading mosquito-borne viral disease globally, exceeding 390 million Dengue virus (DENV) infections yearly [1]. DENV is a single-stranded RNA virus belonging to the family *Flaviviridae*, genus *Orthoflavivirus*, species *O. denguei*, with four antigenically distinct serotypes (DENV-1, DENV-2, DENV-3, DENV-4), transmitted by *Aedes spp*. mosquitoes, mainly *Aedes aegypti* [2].

Dengue infection epidemiology has rapidly evolved over the last decades, with a significant increase in both incidence and geographical spread [3,4]. Recent studies have reported lack of real-life data about the burden of the disease in older people probably because dengue infection has been historically considered a pediatric illness [5,6]. A rising median age of patients with dengue infections linked to demographic shifts in low-to-middle-income regions was observed [7]. Moreover, the age-related immune system declines as well as multimorbidity are causes of major frailty in older people, thus favouring a higher risk of severe diseases and unfavorable outcome. To date, no antiviral therapies are available, and vaccination effectiveness in older people is still under evaluation. This narrative review aims to identify the major features of dengue infection in older individuals, highlighting how age-related immunological dysfunctions may influence the clinical outcome. Furthermore, we will discuss the challenges in dengue management in older population.

2. Search strategy and selection criteria

A literature search was carried out to identify publications relevant to the review topic and published up

CONTACT Alessandra D'Abramo alessandra.dabramo@inmi.it National Institute of Infectious Diseases, IRCCS, Lazzaro Spallanzani, Via Portuense 292, Rome 00149, Italy
*Contributed equally to this work and share first authorship.
†Contributed equally to this work and share last authorship.

to May 31, 2025. The databases PubMed, Scopus, and Embase were queried to identify potential publications for review, with the following search string:

(dengue[Title/Abstract]) AND (old people OR old person* OR old population* OR old patient* OR aged population* OR aged people OR aged person* OR aged patient* OR elderly OR older adult* OR geriatric* OR senior* OR senescence OR immunosenescence OR aging OR ageing).

Observational and interventional studies were included if they examined immunological, epidemiological, or clinical aspects of severe dengue in individuals aged 65 and older. Exclusion criteria included case reports, publications without full-text availability, those predating 2000, or studies not reporting severe dengue outcomes (mortality, hospitalization, Intensive Care Unit admission, healthcare-associated infections, Dengue Hemorrhagic Fever, and Dengue Shock Syndrome) in the older population.

3. Dengue infection and older people: clinical evidence

In 2009, World Health Organization (WHO) revised dengue classification into dengue fever with or without warning signs (abdominal pain, vomiting, fluid accumulation, mucosal bleeding, lethargy, hepatomegaly, hemoconcentration, thrombocytopenia) and severe dengue (shock, respiratory distress, bleeding, or severe organ involvement) [8]. Older adults could have atypical features: fever, rash, and bone pain may be less common, while concurrent bacteremia, gastrointestinal bleeding, renal failure, and pleural effusion are more prevalent [9]. Consequently, WHO diagnostic criteria could be less sensitive in older people, thus leading to a delayed diagnosis [10]. Although a single study from Singapore did not find significant difference in disease outcomes including mortality between old and young patients [11], the scientific literature globally suggest that older people with dengue infection have higher risk of severe infection with a prolonged hospital stay, nosocomial infections, and increased fatality-rate [9,12,13]. Old age, diabetes, and hypertension have been identified as significant risk factors for severe dengue; moreover, a high risk of Intensive Care Unit admission with an in-hospital fatality-rate due to multi-organ failure and coagulopathy was observed in aged population [12–19]. Table 1 reports the epidemiological and clinical data of dengue in the older adults.

4. Immunological response and potential biomarkers for disease severity

Primary dengue infection induces serotype-specific immunity through the activation of naïve B cells, which differentiate into plasma cells producing neutralizing antibodies and memory B cells [20]. Upon secondary infection with a different serotype, cross-reactive non-neutralizing antibodies are generated (original antigenic sin, or Hoskins effect), and bind the virus promoting its entry and replication, finally leading to an antibody-dependent enhancement (ADE) [21]. ADE occurs via an extrinsic mechanism, which promotes viral replication and release, and an intrinsic one, which amplifies pro-inflammatory responses and complement deposition [22]. Figure 1 summarizes the mechanism of ADE. During secondary infection, ADE facilitates immune evasion by suppressing Toll-like receptors 3 (TLR-3) and TLR-7 expression and activating negative regulators like TANK (TRAF family member-associated NF-κB activator) and SARM (selective androgen receptor modulator) [23]. This process upregulates interleukin-10 (IL-10), shifting the immune response toward a Th2 profile, finally impairing viral clearance [24]. At the same time, $CD8^+$ T cells antiviral activity, mediated via interferon-γ (IFN-γ) and tumor-necrosis-factor-α (TNF-α), may be dysregulated as well. This favour the formation of a cytokine storm, characterized by elevated levels of pro-inflammatory markers (IL-1β, TNF-α, IL-6, IFN-γ, and IL-17), contributing to severe disease: TNF-α is, in fact, implicated in dengue-induced thrombocytopenia, while IL-17 in kidney injury [25].

In older adults, immunosenescence and inflammaging, marked by elevated IL-6, TNF-α, and IL-10 and by a reduced phagocytic activity, apoptotic cell clearance, and pattern-recognition-receptor-signaling compromise both innate and adaptive immunity [26–29]. In this context, T-cell immunity is typically deranged: this in turn causes on one hand, the expression of both senescent phenotypes of naïve $CD4^+$ and $CD8^+$ subsets and shortened telomeres, and, on the other hand, increased pro-inflammatory cytokine production [30]. However, the age-related decline of immune system manifests in very different degree among older people. To this regard, the novel concept of `immunobiography' linked to the global set of immune stimuli encountered during life aims to explain the different responses to infections and vaccines in old age [31]. Emerging evidence also challenges the idea that immunological memory is limited to adaptive immunity: innate immune cells seem to be able, in fact, of developing long-lasting, epigenetically programmed responses known as `trained immunity'. The dysregulation of trained immunity is also reported during aging [32]. Taken together, these phenomena may explain the typical age-related decline in immune responses, that nowadays falls under the umbrella concepts of immunosenescence and inflammaging [33]. More in detail, immunosenescence is associated to the lack of efficiency of immune response against infections typically observed during

Table 1. Dengue in old people: prevalence, severity and outcome.

Author, year	Country	Study design	Sample size (n)	Age	Symptoms	Disease severity in older adults	Outcomes
Lye [11]	Singapore	Retrospective	1,971	66 were aged ≥60 years.	Fever, leukopenia, hemoconcentration	DHF: 6% vs 2% compared with younger patients	High risk of secondary dengue infections for patients aged ≥60 years compared with younger patients (<60 years); no difference in LOS, ICU admission, mortality
Low [10]	Singapore	Prospective	250	38 were aged ≥56 years.	Myalgia, arthralgia, retro-orbital pain and mucosal bleeding	SD: 20 patients	Reduced sensitivity of the WHO classification schemes in older adults even though they showed increased risks of hospitalization and SD
Rowe [9]	Singapore	Retrospective	6,989	295 (4.4%) were elderly	Elderly were more likely to have hepatomegaly and malaise/lethargy	DHF: 29.2% SD: 20.3%	The elderly were less likely to fulfil WHO 1997, but not WHO 2009 probable dengue classification. Longer LOS, more pneumonia and urinary infection
Wang [14]	Taiwan	Retrospective	135	55 were aged ≥60	Skin rash, arthralgia, headache, myalgia, retro-orbital pain, hemorrhagic manifestations, and leukopenia	DF: 22.2% DHF: 77.8%	High mortality
Kuo [15]	Taiwan	Retrospective	669	146 (21.8%) were aged ≥65 years	Fever, myalgia, persistent vomiting, headache	DHF: 2.7% SD: 6.9%	Older adults had lower frequency of classical dengue symptoms, yet were at higher risk of development of SD
Hsieh [17]	Taiwan	Retrospective	75	mean age 72.3 ± 9.3 years	Severe GI bleeding, ALI, shock	DWWS:18.7% SD: 81.3%	CFR: 41.3%
Sangkaew [18]	Multicenters	Systematic review and meta-analysis	na	na	Vomiting, abdominal pain and tenderness, spontaneous or mucosal bleeding, and the presence of clinical fluid accumulation	na	Older age in adults, and female sex were demographical risk factors for progression to severe disease
Haider [19]	Worldwide (WHO's database)	Database analysis	14,127,435	na	na	na	Countries in the Southern hemisphere, aged population, and mean annual temperature were significantly associated with higher dengue-related mortality per million population

ALI: acute lung injury; CFR: case fatality-rate; CI: confidence interval; DHF: dengue hemorrhagic fever; DF: dengue fever; DWWS: dengue with warning signs; GI: gastrointestinal; ICU: Intensive Care Unit; IRR: incidence rate ratio; LOS: length of hospital stay; na: not available; SD: severe dengue; WHO: World Health Organization.

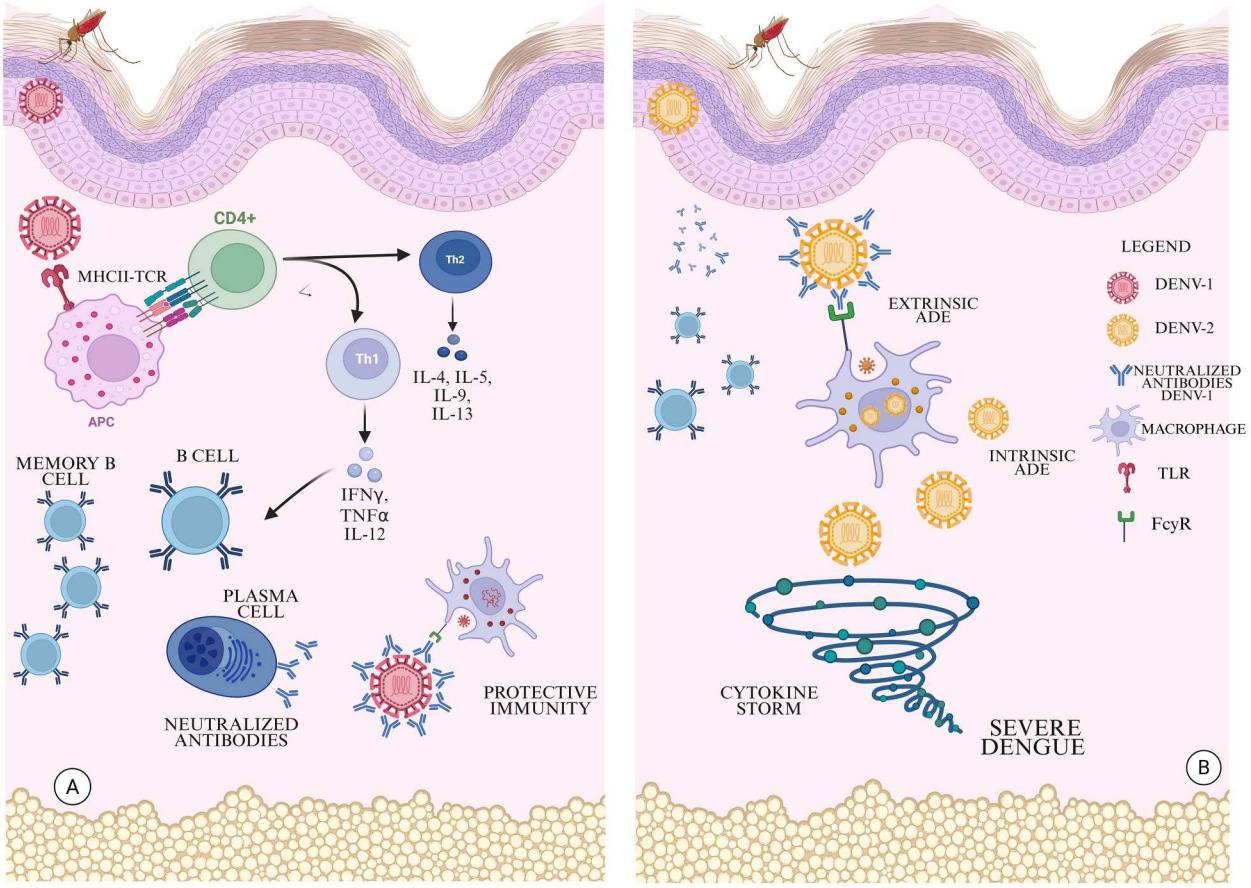

Figure 1. Mechanism of infection of primary dengue (A) and secondary dengue (B). In the primary infection (A), the virus antigen is recognized by antigen-presenting cells (APCs), through Toll-like receptors (TLRs). Helper T lymphocytes, after recognition of peptide fragments of antigen *bound* to major histocompatibility complex (*MHC*) *class II molecules* presented on the surface of APCs, differentiate into Th1 and Th2. The produced cytokines stimulate the activation and maturation of B cells, leading to the formation of plasma cells, secreting specific antibodies against DENV-1, and memory B cells, which persist in the bloodstream after infection. Anti-DENV-1 antibodies can be recognized and phagocytosed by macrophages to resolve the viral infection. During secondary infection with a different serotype (B), TLR expression is inhibited. Memory antibodies, directed against the first serotype, bind the DENV-2 via FcγR receptors (extrinsic ADE), without neutralizing it, a phenomenon known as the Hokins effect. Inside the cell, the virus replicates (intrinsic ADE), and its release leads to cytokine storm, evasion of the immune response and more severe illness.

aging, while inflammaging indicates an age-related low-grade sterile chronic inflammation which is now considered to be implicated in many chronic diseases. Both inflammaging and immunosenescence are probably implicated in producing short and long-term unfavorable outcomes in aged people affected by dengue. To this regard, some biomarkers of inflammaging such as CXCL5, CXCL9, CCL17, soluble ST2, and soluble CD163 are elevated in severe dengue, again underscoring a potential link between inflammaging and adverse outcomes in severe dengue older patients [34–36]. However, the available studies focused on the putative connection between age-related immunological changes and dengue infection outcomes in older people are still limited (see Table 2).

While, during dengue infection, the mechanism of inflammaging could enhance a very harmful cytokine storm, immunosenescence could exacerbate the expression of the viral receptor DC-SIGN (CD209), which is promoted by elevated levels of IL-10 [37]. IL-10, despite its anti-inflammatory role, could indeed enhance the viral entry and impair B-cell activation. In this context, age-related endothelial senescence, exacerbated by dengue-induced cytokines, contributes to plasma leakage in severe cases. Overall, the interplay between immunosenescence, ADE, and cytokine dysregulation is probably a concurrent cause of the known increased vulnerability and severity of dengue in older populations.

5. Clinical management of dengue in older patients: knowledge gaps, clinical challenges and future directions

5.1. Clinical management in the general population

The clinical management of dengue in the general population relies on careful evaluation of the warning signs, vital parameters and key laboratory values (e.g.

Table 2. The putative association between biomarkers of inflammaging and severe dengue.

Author, year	Study design	Sample size	Age group	Biomarker	Findings	Role of biomarkers in inflammaging
Mustafa [34]	Cohort study	1500	All ages	CXCL9	In secondary dengue infections, the serum levels of CXCL5, CXCL9, and CCL17 were significantly higher than in primary infections	CXCL9 is a mediator of chronic inflammation and cellular senescence
Hsieh [35]	Retrospective study	43	75.0 ± 12.2 years	Serum soluble ST2	Serum soluble ST2 levels increased in the elderly with DENV infection.	Serum soluble ST2 is related to chronic inflammation and oxidative stress
Sarayu Gopal [36]	Case-control study	82	31 ± 10	sCD163	sCD163 was found to be significantly higher in secondary cases compared to primary at both admission and defervescence.	Elevated sCD163 levels are associated with chronic inflammatory diseases

DENV: Dengue virus.

complete blood count, particularly hematocrit and platelet levels). Empirical intravenous fluid supplementation in patients without warning signs should generally be avoided to prevent fluid overload [8], while a careful fluid therapy is the cornerstone of supportive treatment in people with dengue complicated by hypotension. Moreover, in case of thrombocytopenia caused by dengue infection, in absence of major bleeding, prophylaxis platelet transfusion is not recommended [38]. WHO further advises against non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, due to their association with bleeding risk and immunosuppression, as well as with lack of mortality benefit. Similarly, use of invasive devices is not recommended unless clinically necessary [5].

5.2. Clinical management in the older population

The application of these general rules is frequently challenging in older people affected by dengue due to immunosenescence, underlying comorbidities and long-term medications. Of course, the first strategy to mitigate the mortality of dengue infection in older people is limiting the spreading of the disease. To this regard, public health strategies and community-based settings, such as nursing homes, are crucial. Therefore, active surveillance protocols are needed to ensure early case identification and swift isolation and proper clinical management, mitigating the risk of clusters. In hospital setting, the management of older people with dengue forecasts the discontinuation of diuretics and antihypertensive drugs in cases of plasma leakage and/or hemodynamic instability to avoid hypotension and electrolyte disturbances; other drug-related complications can present as diuretic-induced hyponatremia and the risk of diabetic ketoacidosis and lactic acidosis in diabetic people on oral hypoglycemic agents [12,39].

5.2.1. Fluid management

Older patients are particularly susceptible to fluid overload, due to a reduced ability to maintain homeostatic control, amplified by impaired renal and myocardial function. Inappropriately aggressive fluid resuscitation may precipitate pulmonary edema or decompensated heart failure. Cardiogenic shocks may account for nearly 50% of shock episodes in dengue infection, suggesting that volume expansion must be undertaken with caution. In patients with cardiac dysfunction, early use of inotrope agents (e.g. dobutamine) may be preferable to excessive fluid administration and revised fluid management protocols are needed [5]. Therefore, guided and goal-directed meticulous fluid administration is crucial, guided by non-invasive ultrasound dynamic monitoring such as echocardiography or inferior vena cava ultrasound. Similarly, beta-blocker have to be administered carefully, since they can mask compensatory tachycardia and other early shock signs [5].

5.2.2. Antithrombotic therapy management

Dengue causes thrombocytopenia through bone marrow suppression and platelet destruction and leads to coagulopathy due to alterations in coagulation and fibrinolysis pathways [12]. Therefore, careful evaluation of thrombotic and bleeding risks is of fundamental importance, also considering that the dangerous effects of dengue-induced thrombocytopenia may be exacerbated by chronic treatment with antithrombotic drugs (acetylsalicylic acid, clopidogrel, enoxaparin, warfarin and the direct oral anticoagulant agents) which are often prescribed in older people [40].

Early discontinuation of antithrombotic drugs is crucial for patients with clinically significant bleeding events [41]. For dual antiplatelet therapy following coronary stenting, discontinuation is considered when thrombocytopenia decreases below 30–50 × 10^3/μL [42]. Real-world recommendations in case of recent percutaneous coronary intervention and acute dengue infection take into consideration: platelet count, bleeding and thrombotic risk, timing and type of coronary intervention together with severity of dengue infection. The platelet count cut-off for discontinuation of anti-coagulant therapy

was defined at $\geq 100 \times 10^3$/mmc in case of active bleeding, in contrast to 50×10^3/mmc and 70×10^3/mmc in patients at high and medium thrombotic risk without signs of active bleeding, respectively [42]. Similarly, four likely scenarios were identified [43]:

(1) General population: avoid aspirin for one-week post-dengue diagnosis to reduce the risk of Reye's syndrome and the worsening of thrombocytopenia.
(2) Patients with high thrombotic risk: continue antiplatelet therapy (aspirin and/or clopidogrel), monitoring the platelet counts, and switch temporarily from warfarin to heparin.
(3) Patients with low thrombotic risk: stop aspirin when platelet counts fall below $30–50 \times 10^3$/μL, and pause clopidogrel or warfarin for one-week, depending on platelet decline and bleeding risk.
(4) Severe dengue: immediately discontinue all antithrombotic medications.

However, current evidence is limited and conflicting. In a retrospective cohort study, discontinuation of antithrombotic drugs did not increase cardiac/cerebrovascular events or mortality, while their continuation in selected cases did not increase bleeding or transfusion risks, suggesting that therapeutic approaches should be guided by clinical judgment [44]. Figure 2 shows a suggested flow-chart for management of anti-coagulants in dengue.

6. New perspectives

6.1. Immunomodulators (with human trial data)

Immunomodulatory agents (e.g. dexamethasone/tocilizumab), successfully used during the COVID-19 pandemic or other viral outbreaks, represented an innovative therapeutic strategy in the clinical management of severe dengue [45]. The anti-inflammatory potential of targeting the interleukin-1 receptor (IL1R) with the IL-1-antagonist anakinra, as well as the inhibition of Janus-kinase (JAK) baricitinib has been considered [46], even though no evidence of use in dengue has been reported yet. To date, a single randomized double-blind placebo-controlled phase II clinical trial (AnaDen trial, NCT05611710) on the use of a 4-day course anakinra is currently ongoing in Vietnam [47].

In the absence of licensed direct-acting antiviral therapies for dengue, several repurposed and investigational compounds have attracted attention due to their mechanisms of action and encouraging preclinical `*in vitro*' and `*in vivo*' data [48]:

- Chloroquine, showed antiviral activity against DENV serotype-2.
- Lovastatin, showed an inhibitory activity on DENV. However, a randomized controlled trial in Vietnamese adults failed to demonstrate significant clinical benefits [49].
- Ivermectin, nitazoxanide, quinine, minocycline, trifluoperazine, N-acetyl cysteine, valproic acid, resveratrol, and paracetamol have shown variable degrees of antiviral or anti-inflammatory activity in laboratory studies, but clinical evidence remains limited.
- Further studies are needed to better explore the potential role of immunomodulatory drugs in dengue infection, especially in older population.

6.2. Antivirals (preclinical/clinical status)

Two novel antivirals targeting specific DENV proteins have been evaluated, JNJ-A07 and its analogue JNJ-64281802: they interfere with the virus's replication, inhibiting the interaction between non-structural proteins NS4B and NS3, critical for the formation of viral replication complexes [50]. Both JNJ-A07 and JNJ-64281802 were initially being evaluated in a Phase 2 study for the prevention of dengue in adults. However, despite no safety concerns have been reported, in October 2024 the trials were interrupted [51]. Similarly, the Double Prodrug of a Guanosine Nucleotide Analog AT-752, an oral candidate drug against DENV serotypes 2 and 3, showed promising results in preclinical and early clinical studies. A phase II study was initiated but terminated prematurely [52].

6.3. Monoclonal antibodies/nanobodies

Recently, the interest in the use of antibody-based immunotherapy as a treatment for dengue infection has increased: the human monoclonal antibodies 9C7 and VIS513 have demonstrated neutralizing activity against all DENV serotypes in preclinical models and early-phase human studies [53]. These antibodies are engineered to minimize the risk of ADE: early clinical data have shown acceptable safety profiles, and VIS513 has progressed to phase II clinical trials [54,55].

Furthermore, nanobodies (Nbs) could represent a promising tool in dengue: consisting on the variable fragment of heavy-chain-only antibodies, they are the smallest functional antigen-binding fragments, able to bind specifically and with high affinity to target antigens. Their small size, high stability, feasibility to be produced in bacteria and yeast, and easy adaptability are other advantages. Nbs have shown potential in targeting conserved quaternary epitopes on the DENV capsid or envelope proteins, thereby providing cross-serotype protection and reducing ADE risk. Their compact structure allows them to access cryptic

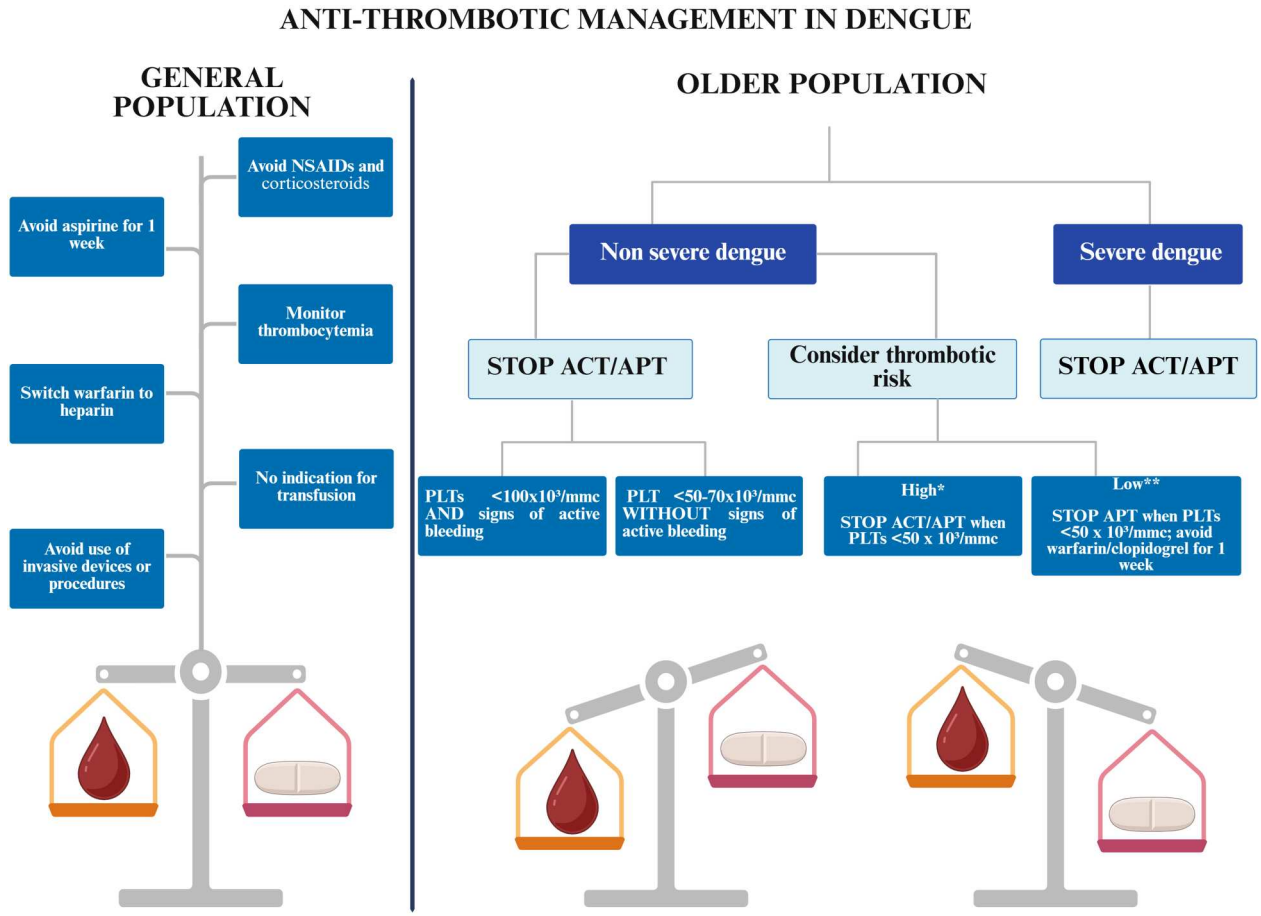

Figure 2. Suggested management of antiplatelet and anti-coagulant treatment in dengue infection. *High thrombotic risk: percutaneous coronary intervention occurred within the past 6 months; mechanical valvular prostheses; persistent atrial fibrillation associated with other multiple thrombotic risk factors (e.g. ventricular dysfunction, old age, intraventricular thrombus, diabetes, hypertension). **Low thrombotic risk: stable coronary artery disease; stent >6 months old; persistent atrial fibrillation without other thrombotic risk factors; bioprosthetic valves. NSAIDs = non-steroidal anti-inflammatory drugs. ACT = anti-coagulant therapy. APT = antiplatelets therapy. PLTs = platelets.

viral epitopes that are less accessible to conventional antibodies, which may enhance antiviral potency and provide an adaptable platform for future therapeutic development [56].

7. Dengue vaccines

To date, two recombinants, live attenuated, and tetravalent vaccines have been approved for dengue infection: Dengvaxia® (CYD-TDV) and Qdenga® (TAK003) [57,58].

Dengvaxia® has a modified yellow-fever 17D-vaccine backbone engineered to express DENV structural prM and E proteins of the four Dengue Virus serotypes. Recommendations are for individuals 6–45 years-old with laboratory-confirmed prior dengue infection [57].

Qdenga® employs an attenuated DENV-2 backbone into which protein M and E gene coding regions from DENV-1, DENV-3, and DENV-4 are inserted. Approval is for individuals ≥6 years-old, irrespectively of previous DENV exposure. Clinical trials have demonstrated broad protection though serotype-specific and age-stratified efficacy varies [58].

Notably significant evidence gaps remain regarding vaccine safety, immunogenicity, and efficacy in older adults, who have been underrepresented in clinical trials. Preliminary safety data on Qdenga® in older people were provided by a multicentric study in Germany: population between 60 and up to 84 years-old (15% of the cohort) exhibited a reduced occurrence of adverse events at first dose compared to other groups (40% vs. 59% at first dose, and 15% vs. 37% at second dose) [59]. However, its efficacy in individuals over 60 years of age has not yet been evaluated. A phase 3, randomized, double-blind, placebo-controlled (older adults, aged >60–79 years) and open-label (adults, aged 45–60 years), multicenter trial to investigate the safety and immunogenicity of the vaccine in old people has been registered to clinical trials [60]. Finally, there are two other new tetravalent and live attenuated vaccines in the future pipeline: TV003/Butantan-DV®, and TV005, both have shown promising results from Phase III studies as potential single-dose vaccines [61,62].

Table 3. Vaccines.

Vaccine name	CYD-TDV [57]	TAK-003 [58]	TV-003 [61]	TV-005 [62]
Type of Vaccine	Recombinant, live attenuated, tetravalent	Recombinant, live attenuated, tetravalent	Recombinant, live attenuated, tetravalent	Recombinant, live attenuated, tetravalent
Backbone	Yellow-fever Virus	DENV-2	DENV 1–4	DENV 1–4
Number of doses	3	2	1	1
Age of approval	6–45 years-old	WHO: from 6 years of age EMA: from 4 years of age ANVISA: 4–60 years of age	18–59 years-old	1–50 years-old
Serostatus of approval	Positive	Positive/negative	Positive/negative	Positive/negative
Commercial status	Discontinued	Currently available, WHO prequalified; manufacturer will start a phase 3 trial in adults >60 years-old	Awaiting for approval; phase 3 completed	Phase 2 trial
Year of 1st approval	2015	2018	–	–
Safety and efficacy data in older adults	Absent in regulatory trial	Absent in regulatory trial	Absent in regulatory trial	Absent in regulatory trial

ANVISA: Agência Nacional de Vigilância Sanitária; DENV: Dengue virus; EMA: European Medicines Agency; WHO: World Health Organization.

The main characteristics of the DENV vaccines are listed in Table 3.

8. Conclusions

The rising incidence of dengue infections in the older population is a significant concern, as it has been reported to be associated with a higher rate of severe disease and increased mortality. Furthermore, inflammaging and immunosenescence mechanisms may both exacerbate disease severity and potentially reduce the effectiveness of vaccine responses in the elderly. Although the precise relationship between inflammaging biomarkers and dengue severity remains unclear, preliminary data suggest that certain age-related inflammatory markers may prove valuable for the diagnosis and prognosis of dengue in older patients.

Relevant gaps of knowledge are still present also regarding the epidemiology of dengue infections in older people at global level.

The current clinical evidence concerning dengue in older adults is indeed largely derived from cohort studies in Southeast Asia. While these data highlight the increased severity and hospitalization risks, significant data gaps exist for other highly endemic regions such as Central and South America, limiting a comprehensive understanding of how varying dengue serotype distribution, local healthcare infrastructure, and specific regional co-morbidity profiles may influence clinical outcomes and mortality rates in the older population globally.

In this scenario, population aging places additional pressure on dengue control systems. Older adults often present atypical or muted symptoms, leading to delayed diagnosis and under-reporting reducing the effectiveness of surveillance systems. Therefore, dengue control systems must adapt by integrating geriatric risk-assessment tools, tailored early-warning indicators, and targeted prevention strategies. In this framework, vaccination may play an important role within an integrated strategy to reduce disease severity in frail individuals; however, robust clinical efficacy and safety data in older adults are still lacking.

As a narrative review, the present manuscript is inherently susceptible to selection bias, as the included studies were chosen primarily for their relevance to the topic rather than through a rigorous systematic methodology. A further major limitation is the scarcity of real-life data and clinical trials focusing on dengue infection in the older population. Specifically, evidence on the management of underlying conditions and medications use, particularly antithrombotic drugs, during acute dengue infection in the older people is limited and sometimes conflicting, requiring clinicians to rely heavily on individual clinical judgement. Likewise, evidence concerning the safety and immunogenicity of dengue vaccines in this age group remains insufficient. In conclusion, existing dengue guidelines do not provide age-specific recommendations for diagnosis, clinical monitoring, or treatment in older adults. Most frameworks focus on the general population and fail to address issues such as management of antithrombotic medications, handling of comorbidities, or geriatric-specific risk markers for severe disease. There is a clear need for evidence-based, geriatric-specific recommendations that integrate data on inflammation, immunosenescence, frailty, multimorbidity, and real-world care challenges. Additional research and future large multicentric clinical studies specifically focused on older people with dengue, also integrating the assessment of inflammaging, immunosenescence and endothelial dysfunction biomarkers, could fulfil the current gap of knowledge and address the specific challenges in this demographic setting.

Author contributions

Conceptualization: AB, LB, EN. Writing – Original Draft Preparation: AB, LP, MP. Writing – Review & Editing: ADA, AB, LB, MEG, EN, LP, LS. Visualization: LP, MP. Supervision: FL, EG, FO. All authors have read and approved the final manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by Italian Ministry of Health [grant number Line 1 project 3 of the Ricerca Corrente INMI].

References

[1] Bhatt S, Gething PW, Brady OJ, et al. The global distribution and burden of dengue. Nature. 2013;496(7446):504–507. doi:10.1038/nature12060.
[2] Paz-Bailey G, Adams LE, Deen J, et al. Dengue. Lancet. 2024;403(10427):667–682. doi:10.1016/S0140-6736(23)02576-X.
[3] Xu Z, Bambrick H, Frentiu FD, et al. Projecting the future of dengue under climate change scenarios: progress, uncertainties and research needs. PLoS Negl Trop Dis. 2020;14(3):e0008118. doi:10.1371/journal.pntd.0008118.
[4] Dengue - global situation (World Health Organization). Available from: https://www.who.int/emergencies/disease-outbreak-news/item/2024-DON518.
[5] Lin RJ, Lee TH, Leo YS. Dengue in the elderly: a review. Expert Rev Anti Infect Ther. 2017;15(8):729–735. doi:10.1080/14787210.2017.1358610.
[6] Wichmann O, Yoon IK, Vong S, et al. Dengue in Thailand and Cambodia: an assessment of the degree of underrecognized disease burden based on reported cases. Guzman MG, editor. PLoS Negl Trop Dis. 2011;5(3):e996. doi:10.1371/journal.pntd.0000996.
[7] Cummings DAT, Iamsirithaworn S, Lessler JT, et al. The impact of the demographic transition on dengue in Thailand: insights from a statistical analysis and mathematical modeling. PLoS Med. 2009;6(9):e1000139. doi:10.1371/journal.pmed.1000139.
[8] World Health Organization. Dengue guidelines for diagnosis, treatment, prevention and control: new edition. 2009; Available from: https://iris.who.int/bitstream/handle/10665/44188/9789241547871_eng.pdf?sequence=1
[9] Rowe EK, Leo YS, Wong JGX, et al. Challenges in dengue fever in the elderly: atypical presentation and risk of severe dengue and hospital-acquired infection [corrected]. PLoS Negl Trop Dis. 2014;8(4):e2777. doi:10.1371/journal.pntd.0002777.
[10] Low JGH, Ong A, Tan LK, et al. The early clinical features of dengue in adults: challenges for early clinical diagnosis. Harris E, editor. PLoS Negl Trop Dis. 201131;5(5):e1191. doi:10.1371/journal.pntd.0001191.
[11] Lye DC, Lee VJ, Sun Y, et al. The benign nature of acute dengue infection in hospitalized older adults in Singapore. Int J Infect Dis IJID Off Publ Int Soc Infect Dis. 2010;14(5):e410–e413. doi:10.1016/j.ijid.2009.06.026.
[12] Tejo AM, Hamasaki DT, Menezes LM, et al. Severe dengue in the intensive care unit. J Intensive Med. 2023;4(1):16–33. doi:10.1016/j.jointm.2023.07.007.
[13] Toledo J, George L, Martinez E, et al. Relevance of non-communicable comorbidities for the development of the severe forms of dengue: a systematic literature review. PLoS Negl Trop Dis. 2016;10(1):e0004284. doi:10.1371/journal.pntd.0004284.
[14] Wang WH, Lin CY, Chang K, et al. A clinical and epidemiological survey of the largest dengue outbreak in Southern Taiwan in 2015. Int J Infect Dis. 2019;88:88–99. doi:10.1016/j.ijid.2019.09.007.
[15] Kuo HJ, Lee IK, Liu JW. Analyses of clinical and laboratory characteristics of dengue adults at their hospital presentations based on the World Health Organization clinical-phase framework: Emphasizing risk of severe dengue in the elderly. J Microbiol Immunol Infect. 2018;51(6):740–748. doi:10.1016/j.jmii.2016.08.024.
[16] Ting R, Dickens BL, Hanley R, et al. The epidemiologic and economic burden of dengue in Singapore: a systematic review. PLoS Negl Trop Dis. 2024;18(6):e0012240. doi:10.1371/journal.pntd.0012240.
[17] Hsieh CC, Cia CT, Lee JC, et al. A cohort study of adult patients with severe dengue in Taiwanese intensive care units: The elderly and APTT prolongation matter for prognosis. Gérardin P, editor. PLoS Negl Trop Dis. 2017;11(1):e0005270. doi:10.1371/journal.pntd.0005270.
[18] Sangkaew S, Ming D, Boonyasiri A, et al. Risk predictors of progression to severe disease during the febrile phase of dengue: a systematic review and meta-analysis. Lancet Infect Dis. 2021;21(7):1014–1026. doi:10.1016/S1473-3099(20)30601-0.
[19] Haider N, Hasan MN, Onyango J, et al. Global dengue epidemic worsens with record 14 million cases and 9000 deaths reported in 2024. Int J Infect Dis. 2025;158:107940. doi:10.1016/j.ijid.2025.107940. Epub 2025 May 29. PMID: 40449873.
[20] Martí MM, Castanha PMS, Barratt-Boyes SM. The dynamic relationship between dengue virus and the human cutaneous innate immune response. Viruses. 2024;16(5):727. doi:10.3390/v16050727.
[21] Zompi S, Harris E. Original antigenic sin in dengue revisited. Proc Natl Acad Sci. 2013;110(22):8761–8762. doi:10.1073/pnas.1306333110.
[22] Narayan R, Tripathi S. Intrinsic ADE: The dark side of antibody dependent enhancement during dengue infection. Front Cell Infect Microbiol. 2020;10:580096. doi:10.3389/fcimb.2020.580096.
[23] Fernandes-Santos C, Azeredo EL. Innate immune response to dengue virus: toll-like receptors and antiviral response. Viruses. 2022;14(5):992. doi:10.3390/v14050992.
[24] Tran L, Radwan I, Minh LHN, et al. Role of cytokines produced by T helper immune-modulators in dengue pathogenesis: a systematic review and meta-analysis. Acta Trop. 2021;216:105823. doi:10.1016/j.actatropica.2021.105823.
[25] Kuczera D, Assolini JP, Tomiotto-Pellissier F, et al. Highlights for dengue immunopathogenesis: antibody-dependent enhancement, cytokine storm, and beyond. J Interferon Cytokine Res. 2018;38(2):69–80. doi:10.1089/jir.2017.0037.
[26] Lee KA, Flores RR, Jang IH, et al. Immune senescence, immunosenescence and aging. Front Aging. 2022;3:900028. doi:10.3389/fragi.2022.900028.
[27] Cantaert T, Jouvenet N, Diehl SA. Editorial: Balanced and unbalanced immune response to dengue virus in disease protection and pathogenesis. Front Immunol; 2022;13:835731. doi:10.3389/fimmu.2022.835731
[28] Franceschi C, Bonafè M, Valensin S, et al. Inflamm-aging: an evolutionary perspective on

immunosenescence. Ann N Y Acad Sci. 2000;908(1):244–254. doi:10.1111/j.1749-6632.2000.tb06651.x.

[29] Theodorakis N, Feretzakis G, Hitas C, et al. Immunosenescence: how aging increases susceptibility to bacterial infections and virulence factors. Microorganisms. 2024;12(10):2052. doi:10.3390/microorganisms12102052.

[30] Rodriguez IJ, Lalinde Ruiz N, Llano León M, et al. Immunosenescence study of T cells: a systematic review. Front Immunol. 2021;11:604591. doi:10.3389/fimmu.2020.604591.

[31] Franceschi C, Salvioli S, Garagnani P, et al. Immunobiography and the heterogeneity of immune responses in the elderly: a focus on inflammaging and trained immunity. Front Immunol. 2017;8:982. doi:10.3389/fimmu.2017.00982.

[32] Grigorescu A, Riza AL, Streata I, et al. Metabolic dysregulation of trained immunity in immune aging and the impact of dietary patterns. Am J Physiol Cell Physiol. 2025;329(2):C456–C470. doi:10.1152/ajpcell.00153.2025. Epub 2025 Jun 16. PMID: 40699053.

[33] Tylutka A, Walas Ł, Zembron-Lacny A. Level of IL-6, TNF, and IL-1β and age-related diseases: a systematic review and meta-analysis. Front Immunol. 2024;15:1330386. doi:10.3389/fimmu.2024.1330386.

[34] Mustafa Z, Manzoor Khan H, Ghazanfar Ali S, et al. Distinct inflammatory markers in primary and secondary dengue infection: can cytokines CXCL5, CXCL9, and CCL17 act as surrogate markers? Pathog Glob Health. 2024;118(5):408–417. doi:10.1080/20477724.2024.2365581.

[35] Hsieh CC, Hong MY, Ho TS, et al. Dynamic changes of soluble ST2 levels predicted fatality and were involved in coagulopathy in dengue fever in the elderly. PLoS Negl Trop Dis. 2019;13(12):e0007974. doi:10.1371/journal.pntd.0007974.

[36] Sarayu Gopal SS, Pillai AB, Ramachandrappa VS, et al. Increased serum levels of macrophage activation marker sCD163 in Dengue patients. J Clin Virol. 2017;86:62–67. doi:10.1016/j.jcv.2016.10.009

[37] Almanan M, Raynor J, Ogunsulire I, et al. IL-10–producing Tfh cells accumulate with age and link inflammation with age-related immune suppression. Sci Adv. 2020;6(31):eabb0806, doi:10.1126/sciadv.abb0806.

[38] Metcalf RA, Nahirniak S, Guyatt G, et al. Platelet transfusion: 2025 AABB and ICTMG international clinical practice guidelines. JAMA. 2025;334(7):606–617. doi:10.1001/jama.2025.7529

[39] Carvalho LIMD, Azi LMTDA, Leal PDC, et al. Anesthesia and perioperative care management in patients with Dengue Fever: considerations and challenges. Braz J Anesthesiol Engl Ed. 2024;74(4):844511. doi:10.1016/j.bjane.2024.844511.

[40] Chandrasoma J, Song A, Szokol J, et al. New drug-eluting cardiac stents and dual antiplatelet therapy: how short is too short? APSF Newsletter. 2024;77;:79–80.

[41] Ehlepola NDB, Athurupana AASD, Bowatte PGCS, et al. Continuation of dual antiplatelet therapy in a patient with a coronary artery stent with dengue hemorrhagic fever: a clinical conundrum. Am J Trop Med Hyg. 2020;102(1):17–19. doi:10.4269/ajtmh.19-0512.

[42] Aditya W, Yap J, Chlebicki P, et al. Management of anti-thrombotic therapy in patients with recent percutaneous coronary intervention and acute dengue infection: a case series. Proc Singap Healthc. 2019;28(4):284–287. doi:10.1177/2010105819841395.

[43] Pesaro AE, D'Amico E, Aranha LF. Dengue: cardiac manifestations and implications in antithrombotic treatment. Arq Bras Cardiol. 2007;89(2):e12–e15. English, Portuguese. doi:10.1590/s0066-782×2007001400015

[44] Chia PY, Htun HL, Leo YS, et al. Safety of temporary interruption of antiplatelet therapy in dengue fever with thrombocytopenia. J Infect. 2021;82(2):270–275. doi:10.1016/j.jinf.2020.10.038.

[45] Screaton G, Mongkolsapaya J, Yacoub S, et al. New insights into the immunopathology and control of dengue virus infection. Nat Rev Immunol. 2015;15(12):745–759. doi:10.1038/nri3916.

[46] McBride A, Mehta P, Rivino L, et al. Targeting hyperinflammation in infection: can we harness the COVID-19 therapeutics momentum to end the dengue drugs drought? Lancet Microbe. 2021;2(7):e277–e278. doi:10.1016/S2666-5247(21)00087-2.

[47] Huyen TB, Trieu HT, Vuong NL, et al. Anakinra for dengue patients with hyperinflammation: protocol for a randomized double-blind placebo-controlled trial. Wellcome Open Res. 2024;9:689. doi:10.12688/wellcomeopenres.21017.1.

[48] Almulhim M, Ghasemian A, Memariani M, et al. Drug repositioning as a promising approach for the eradication of emerging and re-emerging viral agents. Mol Divers. 2025;29(6):5465–5485. doi:10.1007/s11030-025-11131-8

[49] Whitehorn J, Nguyen CVV, Khanh LP, et al. Lovastatin for the treatment of adult patients with dengue: a randomized, double-blind, placebo-controlled trial. Clin Infect Dis Off Publ Infect Dis Soc Am. 2016;62(4):468–476. doi:10.1093/cid/civ949.

[50] Kiemel D, Kroell ASH, Denolly S, et al. Pan-serotype dengue virus inhibitor JNJ-A07 targets NS4A-2K-NS4B interaction with NS2B/NS3 and blocks replication organelle formation. Nat Commun. 2024;15(1):6080. doi:10.1038/s41467-024-50437-3.

[51] Johnson & Johnson to discontinue phase 2 field study evaluating investigational antiviral for the Prevention of Dengue; 2024. [cited 2025 Jul 25]. Available from: https://www.jnj.com/media-center/press-releases/johnson-johnson-to-discontinue-phase-2-field-study-evaluating-investigational-antiviral-for-the-prevention-of-dengue

[52] Good SS, Shannon A, Lin K, et al. Evaluation of AT-752, a double prodrug of a guanosine nucleotide analog with *in vitro* and *in vivo* activity against dengue and other flaviviruses. Antimicrob Agents Chemother. 2021;65(11):e00988–21. doi:10.1128/AAC.00988-21.

[53] Vis513. Visterra; 2022. Available fromt: https://visterrainc.com/programs/vis513/

[54] Lu J, Chen L, Du P, et al. A human monoclonal antibody to neutralize all four serotypes of dengue virus derived from patients at the convalescent phase of infection. Virology. 2022;576:74–82. doi:10.1016/j.virol.2022.09.007.

[55] Ong EZ, Budigi Y, Tan HC, et al. Preclinical evaluation of VIS513, a therapeutic antibody against dengue virus, in non-human primates. Antiviral Res. 2017;144:44–47. doi:10.1016/j.antiviral.2017.05.007.

[56] Gavor E, Choong YK, Gada AH, et al. Challenges and design of nanobodies against arboviruses. Trends

Biotechnol. 2025;43(10):2395–2398. doi:10.1016/j.tibtech.2025.03.002

[57] Gailhardou S, Skipetrova A, Dayan GH, et al. Safety overview of a tecombinant live-attenuated tetravalent dengue vaccine: pooled analysis of data from 18 clinical trials. Morrison AC, editor. PLoS Negl Trop Dis. 2016;10(7):e0004821. doi:10.1371/journal.pntd.0004821.

[58] Tricou V, Yu D, Reynales H, et al. Long-term efficacy and safety of a tetravalent dengue vaccine (TAK-003): 4·5-year results from a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Glob Health. 2024;12(2):e257–e270. doi:10.1016/S2214-109X(23)00522-3.

[59] Köpke C, Rothe C, Zeder A, et al. First clinical experiences with the tetravalent live vaccine against dengue (Qdenga®) in travellers: a multicentric TravVacNet study in Germany. J Travel Med. 2025;32(2):taaf004. doi:10.1093/jtm/taaf004.

[60] A Phase 3, Randomized, double-blind, placebo-controlled (older adults, aged (60–79 years) and open-label (adults, aged 45–60 years), multicenter trial to investigate the safety and immunogenicity of a dengue tetravalent vaccine (TDV) administered subcutaneously to adults and older adults with or without comorbidities in endemic areas for dengue. clinicaltrials.gov; 2025 Apr. Report No.: NCT06579755. Available from: https://clinicaltrials.gov/study/NCT06579755

[61] Kallas EG, Precioso AR, Palacios R, et al. Safety and immunogenicity of the tetravalent, live-attenuated dengue vaccine Butantan-DV in adults in Brazil: a two-step, double-blind, randomised placebo-controlled phase 2 trial. Lancet Infect Dis. 2020;20(7):839–850. doi:10.1016/S1473-3099(20)30023-2.

[62] Walsh MR, Alam MS, Pierce KK, et al. Safety and durable immunogenicity of the TV005 tetravalent dengue vaccine, across serotypes and age groups, in dengue-endemic Bangladesh: a randomised, controlled trial. Lancet Infect Dis. 2024;24(2):150–160. doi:10.1016/S1473-3099(23)00520-0.