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Manure anaerobic digestion effects and the role of pre-and post-treatments on VA and ARG removal efficiency. A review

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1. Introduction

Manure based anaerobic digestion (AD) is practiced for energy production and environmental risk reduction (Yazan et al., 2018) comprising about 72% of the total biogas production input (Torrijos, 2016). The environmental benefits include removal of toxic substances such as veterinary antibiotic (VA) and antibiotic resistance genes (ARG) although AD can sometimes be a sink for VA (Spielmeyer et al., 2015). On the other hand, the presence of VA or their residues in manure affects biogas production (Beneragama et al., 2013; Huang et al., 2014; Stone et al., 2009) because it suppresses methanogenesis which in turn leads to less methane or biogas production. In addition, the presence of VA in manure supports anaerobes in AD system for selection of ARG which later enters agricultural field with digestate application. This has been challenging the world health sector, mainly because it supports microbes selection for antibiotic resistant genes (ARG) (Udikovic-kolic et al., 2014; Wolters et al., 2014; Xie et al., 2018a), and the management efforts so far are not effective mainly due to the lack of an integrated way of applying knowledge, skill, and resources (Pruden et al., 2013).

Other manure use scenarios are direct use for fertilizer or organic matter amendment (Castellanos-Navarrete et al., 2015; Rufino et al., 2014; Sanginga, N. and Woomer, 2009) and incorporating after composting (Lalander et al., 2015). The prevalence of veterinary antibiotics in manure and their implication on the environment when directly used as fertilizer is widely discussed in previous studies (J. Li et al., 2017; Massé et al., 2014; Spielmeyer, 2018; Udikovic-Kolic et al., 2014; F. H. Wang et al., 2015; J. Wang et al., 2015; Xie et al., 2018b). Composting of manure under aerobic thermophilic condition effect on VA and ARG is also widely reported. The removal efficiency for VA varies depending on the type of manure, the level of concentration of VA in manure and the type of VA. Previous studies on the effect of digestate composting on toxic substances (Bustamante et al., 2012) and the role of aerating digestate on VA (Li et al., 2018) suggest the need for post-AD treatment. Thus, a more comprehensive approach to reduce emission of VA and ARG includes not only the AD system but also the pre- and post-AD treatments. This starts from reducing VA use in animal husbandry, pre-treating manure before AD and treating the digestate before applying to soils.

The fact that VA is projected to increase by more than 100% in just the coming decade (Van Boeckel et al., 2015) in the absence of an effective approach to avoiding emissions to the environment is frightening. On top of this, in recent decades, antibiotics are getting resistance more than ever. Dantas et al. (2008) found that from 18 antibiotics they evaluated against hundreds of bacteria isolated from soils, about 70-90% showed resistance. Consequently, there is much concern about the effect associated to the ARG which is being reflected in the economic and health crisis. The World Bank recently calculated an annual World's expense of about 3.4 trillion $ annually by 2030 for the loss in productive labor and development of alternative treatments (World Bank, 2016). The latter is in response to the challenge when a disease-causing bacterium is found to be subsisting on a given antibiotic and combined prescriptions or new medicines are sought. This would increase the cost of the treatment, and even it could risk the life.

Although AD has been widely evaluated against antibiotics, and found to be effective for complete removal or potential degradation of some of antibiotics (Feng et al., 2017; Liu et al., 2018), but this is not always possible (Álvarez et al., 2010; Widyasari-Mehta et al., 2016a), and there are possibilities that significant quantities of antibiotics and ARG can be found in the digestate. This sheds a bad light on the direct application of digestate to soils as a fertilizer (Sui et al., 2018). Not only VA but also ARG can be detected in digestate or soil even in the absence or non-quantifiable amount of antibiotics (Wallace et al., 2018; Xie et al., 2018b). In other words, the low rate of degradation of VA in AD process could maintain microbes under a minimum inhibitory concentration (MIC) supporting the selection for ARG by microbes (Yang et al., 2016).

The importance of AD in removing VA was previously reviewed (Massé et al., 2014). However, AD in its current technological status is not efficient to guarantee 100 percent removal for all kinds of antibiotics in manure. Some are even highly persistent (Feng et al., 2017). In this review, research findings on removal of VA and ARG during the AD process are summarized, and the emerging modified technologies of AD particularly for removal of VA and ARG are critically evaluated. Pre-AD treatments and post-digestate managements are also focused to propose a more efficient removal approach.

2. Pathways of VA and ARG to the environment and the risk to human health

VA provided to animals could enter the human food chain through animal foods (Menkem et al., 2018; Phillips et al., 2018; Sivagami et al., 2018; Tasho and Cho, 2016), food crops grown on soils receiving manure or manure based digestate (Chung et al., 2017; Tasho and Cho, 2016). In one or most of the manure use scenarios, VA enters the soil although the concertation varies. When the amount in soils is above MIC, it means it can be harmful to organisms and negatively affect the microbial community (Grenni et al., 2018). However, when it is below the MIC, it could support microbes for ARG selection (Bengtsson-Palme and Larsson, 2016). In this situation, the amount of antibiotics that enters the human digestion system could be below the MIC, and this supports microbes for ARG selection in the gut. With the mobile genetic elements these genes could later transfer to pathogenic bacteria (Allen, 2014). Then, the pathogenic bacteria could get resistance to the existing antibiotics. This review will give emphasis to the possible flow of antibiotics into the environment through the biogas production system and the possible management opportunities mainly before it is applied to soils.

Fig.1 displays the process through which a persisting VA can enter the food chain or re-enter the AD process. With the effect of the presence of these VA, microbes in soils, animal or human gut and AD can develop resistance, evolving with ARG that eventually can increase in quantity (copies) when there is a more conducive environment. Like the VA, ARG could also enter the food chain (Bengtsson-Palme, 2017) either through crop (F. H. Wang et al., 2015) or animal food (Allen, 2014; Menkem et al., 2018; Sivagami et al., 2018). The interesting point here is that although avoiding use of VA can certainly reduce ARG in animals or humans (Scott et al., 2018a), there is no evidence about the lower limit of VA concentration below which microbials will not undergo resistant gene selection (Risberg, 2015). Thus, the decrease in concentration of VA by the different biological or physical processes may not be useful if they are not completely removed. It is thus essential to look for novel approaches that can support complete removal of VA for the different manure use scenarios.

3. VA effects on biogas production

Studies on AD of antibiotics containing manure were widely reported in terms of the effects on biogas production and VA degradation. As shown in Fig. 2, tetracyclines were the most widely studied followed by macrolides. While most of the studies were on swine manure, study on poultry manure was rarely reported.

>>>>>>>>>>>>>>>>>>>>>>>> Fig.2 >>

Reports on VA effects on biogas production are conflicting. Many of the case studies show that the presence of antibiotics in the substrate of AD reduces biogas production (Lallai et al., 2002; Mitchell et al., 2013; Sara et al., 2013). In contrast, a few studies revealed that antibiotics can have positive impacts on biogas production (Hu et al., 2018; Stone et al., 2009; Turcios et al., 2016; Yin et al., 2016), or at least may not have significant negative impact (Beneragama et al., 2013; Feng et al., 2017). Others argue that VA can be only detrimental to biogas production only after a certain concentration level (Spielmeyer et al., 2015).

One of the possible reasons associated to the positive effect on biogas production is the disruptive role on the extra-cellular polymers in the substrate which could result in increased production of acetic acid that leads to enhanced biogas production (Hu et al., 2018). For instance, in a research report by Yin et al. (2016), biogas production was reduced only when OTC and CTC concentrations exceeded 40 and 60 mg kg^{-1} TS, respectively. Below these levels, a small increment in biogas production was observed, implying that the existent of small proportion of antibiotics might have positive impact on biogas production, but increased level might inhibit microbial activities and, hence, reduce biogas production. However (as discussed in detail under section 4), this might be dependent on the type of VA and the level of concentration present in the substrate and, possibly, on the temperature regime under which the AD operates.

Microbial activity plays a decisive role in production of biogas in the AD system. However, this can be limited by the existence and prevalence of antibiotics in the system. In this scenario, bacterial resistance to antibiotics may be also considered as a positive spectacle because in such cases the negative effect on biogas production would be reduced (Xin et al., 2014). In other words, the more resistant functional group of bacteria in AD, the less effect of antibiotics on biogas production. However, this condition could leverage microbes for ARG selection because AD processes in most cases contain low concentration of VA (below MIC).

4. AD effects on VA and ARG

AD is one of the waste management pathways for energy production (Kalia and Joshi, 1995), improving nutrient availability (Möller and Möller, 2012) and removal of toxic substances such as VA (Wallace et al., 2018) and ARG (Jang et al., 2018; Sun et al., 2019). However, these days the emphasis given sounds more towards the energy production than improving environmental quality. Antibiotics are rarely effectively removed in the system, and one of the reasons is associated to the unique intrinsic structural formation of a VA that determines their properties in AD system. Therefore, most of the studies were focused on understanding the processes responsible for the degradation as well as seeking improved approaches to enhanced removal efficiency. The improved technologies tested include pre-AD thermal treatment (Ennouri et al., 2016), modifying the AD temperature, and using separate reactors for acidogenesis and methanogenesis phases. However, none of these modifications was found to be effective to completely remove antibiotics and ARG despite the removal rate might improve, implying the need for further investigation.

Composition of the substrate is another important factor. The adsorption capability of the different antibiotics in the AD system could vary. Tetracyclines and quinolones have been reported to have strong affinity to solid substances (N. Li et al., 2017; Li et al., 2018; Sui et al., 2018; Zhang and Li, 2018), and when the total solid content of a substrate is high antibiotics undergo lower hydrolysis or other forms of degradation (Sui et al., 2018). However, for such antibiotics having strong affinity to the solid, sorption is the main mechanism for removal. In a case study, the degradation rate of antibiotics decreased with increasing rate of total solids (TS) in the AD system resulting in 4.5, 48.0, 32.3, and 25.7% antibiotic concentration in a digestate having TS content of 4, 8, 11, and 14%, respectively (Sui et al., 2018). Moreover, antibiotics in a similar group having almost similar structure could even also have differing sorption (adsorption/desorption) characteristics and may not show similar degradation rate under a specific treatment. Therefore, specific mechanism must be sought not only based on the type of antibiotic but also the properties of the substrates used. This will also take us to the next chapter of investigation to further understand about complex properties in the substrate during the AD. The properties of substrates could favor or inhibit the degradation of VA and ARG.

4.1. Tetracyclines

Chlortetracycline (CTC), oxytetracycline and tetracycline (TC) are the most widely reported antibiotics found in manure (Spielmeyer, 2018). This group was the most frequently studied for its response to AD process (Fig. 3), and the removal rate of this group is relatively higher than other groups. However, despite the similar structure they have, the response to a given AD differs among the antibiotics within the group (see Table 1). For instance, while the removal rate of doxycycline and oxytetracycline was reported to be more than 60%, tetracycline removal rate was less than 10% (Bousek et al., 2018).

<<<<<<<<<<<<<<<<<<<<<<<<<<<<Table >>>>>>>>>>>>>>>>> >>>>>>>>>>>>>>>>

As also shown in Fig. 3, the variability of removal rate by AD among tetracyclines is lower compared to other groups. This elaborates AD effect is more consistent for TC than other groups of VA. A study shows that complete removal was observed when pig manure containing 25 or 50 mg L^{-1} of tetracycline was subjected to AD for 20 days at a temperature of 25^0C (Shi et al., 2011). Nonetheless, as we emphasize under the different sections of this review, complete removal is not common, and disparities can also emanate from the variabilities of the composition of the substrates and the AD system itself.

>>>>>>>>>>>>>>>>>>>>>>>>>>>Fig.3 <<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<

In the AD system, sorption is the main degradation route for tetracyclines because they are usually adsorbed to the solid state of the substrate (Kim et al., 2005; Sui et al., 2018). The higher the concentration of TC in a substrate, the lower the rate of removal, implying the strong adsorption of TC to the solid digestate (Nurk et al., 2019). Unlike other groups of antibiotics, relatively lower proportion of TC is found in liquid digestate than in solid digestate because of the sorption characteristics of these antibiotics to solid (Nurk et al., 2019). Thus, substrates that have high total solid could help remove high amount of TC in AD, and vice versa. In other words, inefficient AD that can remove only some proportion of volatile solids, will result in higher concentration of tetracyclines in digestate compared to a more efficient AD given all other conditions are similar.

One of the reasons for low biodegradability of tetracyclines could be due to their high concentration in substrates that could suppress microbial activity in the AD. This can also be reflected in significant reduction of biogas production. For example, Álvarez et al. (2010) reported that concentration of 10-100 mg L^{-1} of CTC significantly reduced methane production by 45.2-64.1%, which corresponded to a reduction of methanogenetic activity by 56.2-62.3%. A higher concentration of CTC or OTC in a substrate can reduce the removal rate in AD system (Yin et al., 2016).

4.2. Sulfonamides

A previous systematic review report showed that concentration of sulfonamides (SD) in manure was lower than TC with 18 mg kg^{-1} dry weight basis (Xie et al., 2018a). However, recovery rate from manure can be high, even higher than TC, and it could be possible to recover more than 90% of SD from a spiked manure (Zhao et al., 2010). This group of antibiotics are the most widely used VA in animal husbandry, but their elimination rate during the AD was not widely reported like macrolides and tetracyclines (Fig. 3). Also, there was little or no effect of AD on these antibiotics (Table 2). Moreover, the elimination rates are also variable (Fig. 3). In a study of antibiotics removal from manure using AD in Germany, it was reported that only 60% of sulfamethazine was removed from the initial concentration and about 76 mg kg^{-1} remained in the digestate (Spielmeyer, 2018). This is the maximum concentration of SD reported in digestate recently.

>>>>>>>>>>>>>>>>>>>>>>>>Table 2 <<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<

In AD of pig manure with 40 days of retention period, sulfadiazine and sulfamethizole exhibited little or no degradation under both psychrophilic and thermophilic conditions (Feng et al., 2017). On the other hand, in the same study, almost complete removal was reported for sulfamethoxazole and trimethoprim (Table 2), heightening different antibiotics belonging even the same class may not show similar degradation rates in an AD system.

4.3. Quinolones and Fluoroquinolones (FQ)

This class of antibiotics are not widely used in animal husbandry, but up to 1480 mg of enrofloxacin concentration in a kg of chicken manure was reported from China (Riaz et al., 2018). FQ are relatively more persistent in the environment (Riaz et al., 2018) and less degraded during the AD system. However, like the classes of VA discussed in the above two sections, removal rate varies among the species of VA within the group. For example, in AD of sludge study reported by Narumiya et al. (2015), the highest removal (more than 90%) was observed for sulfamethoxazole and trimethoprim and other groups were so persistent with a removal rate as low as 30%. While it was possible to remove 100% tetracyclines using a pilot scale AD of pig manure, there was no effect against flumequine (Bousek et al., 2018). Like for TC, sorption could be the best path to removal of FQ from aqueous solution (Riaz et al., 2018). It is thus evident that AD in its current technological level is not useful against FQ.

4.4. Macrolides

Macrolides are the second most frequently reported VA on degradation rate study (Fig. 3) although the removal rate under the AD is so variable like other VA groups (Fig. 3). Tylosin, in the class of macrolides is the most widely used antibiotics for growth promotion (Moulin et al., 2016). While AD was reported to be effective against tylosin, monensin and clarithromycin are the two most recalcitrant macrolides in the AD (Table 3). Monensin was reported to cause environmental concern (Zidar et al., 2011) although its concentration in the environment was rarely reported in the recent reviews on VA in manure (Tasho and Cho, 2016), soils (Tasho and Cho, 2016), or aquatic systems (Kümmerer, 2009).

>>>>>>>>>>>>>>>>>>>>>>Table 3 <<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<

Degradation of macrolides in the AD systems (Table 3) can be improved by enhancing temperature to thermophilic condition (Feng et al., 2017). Clarithromycin showed little degradation in AD with 140 days of retention time under mesophilic temperature (37^0C) (Sui et al., 2018). Moreover, the removal rate of monensin was almost negligible with the AD at 35^0C and improve to a maximum of 27% at a temperature of 55^0C (Varel et al., 2012).

4.5. ARG and MGE

Antibiotic resistant genes (ARG) or mobile genetic elements (MGE) could degrade or potentially increase in copies or counts. The conditions like thermophilic temperature that might help remove VA in AD could have a reverse impact on ARG and MGE (Huang et al., 2019; Sun et al., 2019). This might be related to the favoring conditions moderated by the temperature regime, that may increase the abundance of antibiotic resistant thermophiles thereby increasing the ARG counts. On the other hand, AD with lower temperature regimes (mesophilic or psychrophilic) could suppress activities of resistant microbes which ultimately could be expressed with lower ARG or MGE counts (Table 4).

>>>>>>>>>>>> >>>>>>>>>>Fig.4 <<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<

ARG count increases with increasing microbial activity, implying thermophilic temperature of the AD may not be useful when ARG degradation is sought. In other words, cooling the digestate for weeks could inhibit multiplication of anaerobic microbes that are carriers of ARG or MGE, thereby reducing the gene counts.

>>>>>>>>>>>>>>>>>>>>>>>Table 4 <<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<

The *tet* groups are the most widely observed and studied ARG for their behavior of gene multiplication or degradation (Fig. 4). Despite there are clear evidences that AD temperature has strong correlation with gene counts, the effect of other AD conditions such as retention period and reactor volume look unclear (Table 5). However, given the likelihood of the exponential growth of ARG in a short period of time when there is conducive environment (Sun et al., 2019; Wu et al., 2016; Zhang et al., 2017), a reduction of the count to a certain extent alone may not be useful. So far studies reveal that none of the approaches resulted in complete elimination of ARG, and conditions that favor production of methane and degradation of antibiotics could favor ARG to exponential increase. This suggests technological modification of ordinary AD systems to help removal of VA as well as ARG. Horizontal gene transfer supported by MGE might make management of ARG in digestate more challenging (Han et al., 2018; Wolters et al., 2015). Therefore, for AD processes, it can be suggested that more emphasis needs to be put on breaking the chains of ARG selection routes than eliminating the ARG.

>>>>>>>>>>>>>>>>>>>>>>>>>>Table 5 <<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<

5. Reducing antibiotics in manure before it is used for biogas production

Global trend shows farms are nowadays under more intensive use of VA (Van Boeckel et al., 2015; Zhao et al., 2010). The two main reasons for this are to prevent or treat diseases and promote animal growth (Cheng et al., 2014). The former is a common practice in different farming systems globally with the goal of reducing economic loss due to diseases. The latter is aimed at enhancing the biological development of animals to gain more economic return in relatively shorter period of investment. In both approaches, it is possible to find antibiotics (its residues) in both animal food (Landers et al., 2012) and wastes (Van Epps and Blaney, 2016; Xie et al., 2018a). The distribution and concentration in animal waste across the world depend on the country, animal type, and management intensity. China dominates in terms of amount of VA consumption in annual bases, followed by USA, Brazil and Germany, and the amount could also double in the next two decades (Van Boeckel et al., 2015).

While the use of VA is increasing, there needs to be breakthrough solutions to their impacts on environment and health. The promising efforts in Europe could be sought to be up scaled in other regions of the world. In Europe, with improved policies, the trend of VA use is declining (EMA (European Medicines Agency, 2018) although the report was merely based on the amount of VA sold. Refining the business as usual manure management approach should be the next step forward. In Fig. 5, we illustrated the possible areas of focus to potentially remove VA or ARG from manure under different manure use scenarios. One of the most important scenarios focused by this review is the AD. The choice for this scenario stems primarily from the need for bioenergy although this approach is also adapted for waste management. However, the AD could underestimate the environmental concerns when the interest of farmers or energy producing companies on manure is mostly derived by the economic gain, with less attention on environmental sustainability (Logan and Visvanathan, 2019).

>>>>>>>>>>>>>>>>>>>>Fig.5 <<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<

As a result, poor quality of digestate might have less demand to the end users due to the costs of removal of ammonia (Errico et al., 2018), weed infestation (Westerman and Gerowitt, 2013) and cost of application (Logan and Visvanathan, 2019). Therefore, improved technologies need to be sought in addition to the need for improved policies on banning the use of growth promoting anti-microbials adapted by many European countries (Moulin et al., 2016) in all other countries because the spread, indeed the impact, of ARG may not be limited by geographical boundaries (Founou et al., 2016). Inappropriate use of VA, like using VA for healthy animals, must be avoided, and policies need to be developed to apply prescription based so as to avoid excessive use of VA (Tangcharoensathien et al., 2018). These approaches are more discussed in the next sub-sections. The next steps complement the prior efforts, and they are focused to eliminate VA or their residues from animal food and waste. The former is not included in this review, but the latter will be discussed in detail.

5.1. Banning growth promoting and reducing overuse of therapeutic VA

Studies show that avoiding or limiting use of VA can reduce chances for evolution of antibiotic resistant microbes in both humans and animals although the magnitude of reduction cannot be estimated (Scott et al., 2018b). One of the strategies to achieve this goal is by banning use of growth promoting VA(Hughes and Heritage, 2004; Huyghebaert et al., 2011; Wegener, 2003). This only complements the other efforts such as reducing or banning the excessive use of therapeutic VA. Therefore, to achieve a meaningful reduction in environmental impacts of VA, approaches to reducing use of antibiotics for both therapeutic and sub-therapeutic need to be proposed (Pruden et al., 2013). According to these authors, one of these strategies can be reducing drug prescription doses based on clinical efficacy and promoting the banning of growth promoting drugs from animal husbandry. The ultimate objective in both cases is to reduce negative impacts of antibiotic residues on human health and the challenges on healthcare that is linked to ARG impacts (Landers et al., 2012). However, effectiveness would be more valid than efficacy as it is conducted taking the real conditions into account (Singal et al., 2014). Therefore, the effectiveness in this regard requires the involvement of different actors from the development of drugs, health sector, and environmental protection (Llor and Bjerrum, 2014).

The European Union banned growth promoting antibiotics in 1990 following the measures taken by Sweden and followed by Denmark (Pruden et al., 2013). A recent report by Moulin et al. (2016) also shows that out of 130 member states of the World Organization for Animal Health, about 74% of them do not authorize the use of growth promoting antimicrobials. This, along with the reduction in use of excessive VA, appears to have positively impacted the overall decline in use of VA in Europe (European Medicines Agency, 2018). In the authorizing countries, the widely used growth promoting antibiotics are tylosin and bacitracin. Since these are usually provided to animals with a dose below the MIC, they are blamed as the major factors responsible for the development of ARG. Denmark drastically reduced the use of growth promoting drugs by about one third after it was recognized that enterococcal developed resistance to vancomycin, which was associated to provision of avoparcin in chicken production (Pruden et al., 2013).

5.2. Improving manure storage as a prior condition for AD

In either direct application to soils or as input for anaerobic digestion (AD), storage is the principal management component where biomass must be placed for some time. This can be another potential management point where proportion of VA in manure can be removed (Berendsen et al., 2018; Joy et al., 2014; van Epps and Blaney, 2016) leading to a lower concentration in manure that will be later used for AD. However, storage effect on the removal efficiency of VA is considerably low (Lamshöft et al., 2010) and varies among the different VA types like it has been discussed for the other management pathways. However, when it is a pretreatment, it can be considered as a pre-treatment for a more effective removal. Spielmeyer (2018) reported that manure heap storage could eliminate monensin (< 10%), lincomycin (15%), sulfamethazine (82-92%), oxytetracycline (99%) and tylosin (> 99%). In contrast, other manure storage systems are not so satisfactory (Wallace et al., 2018; Widyasari-Mehta et al., 2016b). Manure storage effectiveness against VA may also be dependent on storage temperature. For instance, Li et al.(2018) reported that manure stored under mesophilic temperature showed more degradation rate of VA compared to higher temperature regimes. Most of the studies on the impact of manure storage on removal of VA were aimed to address the problem associated to the direct application of manure for fertilizer. However, if an advanced storage is considered as a pre-AD processes, where the stored manure is used for biogas production followed by improved digestate storage, a better elimination of VA and ARG can be achieved.

6. Improving conventional AD enhances degradation efficiency of antibiotics

The metadata presented in Fig. 6 show that the elimination rate of VA by AD ranges from 0 (no or non-significant effect) to 100% (or below detectable amount). The variability of the elimination rate depends on several factors. In the next subsections, the main factors that play significant role on the elimination of VA, particularly during AD of manure are discussed.

>>>>>>>>>>>>>> >>>>>>>Fig.6 <<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<

Methane production by AD of manure involves degradation of the feedstock by anaerobic bacteria and it passes through a chain of processes like hydrolysis, acidogenesis, acetogenesis, and methanogenesis reactions (Batsone and Jensen, 2011) These biological and physicochemical processes are accounted for the reactions that degrade toxic substances including antibiotics in the AD reactors. Modifications to any or all these processes could be significant on the fate of antibiotics, but not all improvements have positive impacts.

6.1. Hydrolysis, acidogenesis and pH

Several studies have revealed the effects of hydrolysis on the degradation rate of antibiotics in non-AD systems. Mitchell et al. (2014) found hydrolysis of chloramphenicol, florfenicol, spiramycin, and tylosin in acidic and basic buffers (below pH 4 and above pH 8) and under temperature of 50-60 ^{0}C. Below this temperature, all the four antibiotics remained stable. Sy et al. (2017) also reported that ampicillin, which is known to have strong hydrolysis potential, underwent formation of 2-hydroxy-3-phenylpyrazine, which can remain bio-active. A study conducted by Loftin et al. (2008) showed tylosin hydrolysis was effective only at extreme pH levels (2 and 11), and the hydrolysis of tetracycline group (TC, OTC and CTC) showed an increasing trend with increasing pH and temperature.

The fact that the level of pH and temperature that is more appropriate to efficiently degrade antibiotics is not optimum for biogas production can justify inefficiency of AD for removal of VA. In the AD system, a lab scale study conducted by N. Li et al. (2017) showed that the highest degradation rate of fluoroquinolones was achieved at pH 3. The controversial two phase AD system that was reported to be inefficient in terms of biogas production could have this attribute and may be useful for degrading VA and other toxic substances (Schievano et al., 2012; Wu et al., 2016). However, it is usually recommended to maintain natural level pH of AD system for optimum methane production (Zhang et al., 2017).

Unlike the traditional AD system that has only one phase, the two-phase AD systems having two separate reactors for acidogenesis and methanogenesis, could be more effective in removing toxic metabolites and ARG. This enhanced technology consists acidogenesis phase that plays the functional role (Wu et al., 2016) possibly due to the promotion of H_2 producing bacteria that are effective in degrading diverse metabolites and limiting activities of pathogenic strains (Duan et al., 2018; Schievano et al., 2012).

6.2. Temperature based AAD

Although different biogas plants could have different bacterial communities that are most active under a specific range of temperature, thermophilic condition (commonly ranges 40-60^{0}C) is the highest possible temperature range any biogas plant can adopt. This would likely support the degradation of antibiotics in the substrates more efficiently than an AD with mesophilic temperature or lower. This is, however, not always true as the degree of degradation varies depending on several other factors. This thermophilic temperature range is also useful to degrade ARG (Miller et al., 2016). In some scenarios, methodologies to estimate antibiotics concentration underestimate the level of concentration of antibiotics in the raw substrates because of the adsorption to the cell of micro-organisms. Thus, they could result in higher concentration in the digestate than in the feedstock as microbial cells are degraded by the AD or AAD (Zhang and Li, 2018).

Fig. 6 illustrates that the temperature of AD of manure considered under most of the studies ranged from 35 to 50 ^{0}C. However, fermentation (retention) period varied among the different studies reviewed. This is because most studies were laboratory level (shorter period) and only a few were at pilot or farm scale (longer period).

6.2.1. Pre-AD thermal treatment

Since the conventional AD systems could have low effect on degradation of antibiotics and ARG, advanced AD (AAD) technologies on improving removal efficiency of VA were investigated. Among these, thermal pre-treatment was the most widely studied (N. Li et al., 2017; Wallace et al., 2018; Zhang and Li, 2018). Wallace et al. (2018) evaluated the effect of pasteurization of manure at 67^0C and found that this treatment significantly reduced concentration of tetracyclines in manure effluents. Another thermal pre-anaerobic digestion treatment could be thermal hydrolysis as described in Li et al. (2016). In this study, sewage sludge was pre-treated at 160^0C for 60 minutes. However, the pre-treatment did not affect degradation of fluoroquinolones (FQ) in the AD system although the AD process without pre-treatment was effective for about 60% degradation of FQ. Zhang and Li (2018) also found that AD system alone supported about 40% removal of TC while the ADD had little impact and the role of pre-treatment was insignificant. These antibiotics may require higher temperature for longer time to be effectively degraded. However, since the main goal of AD is to maximize methane production, higher temperature for longer period compromises optimum biogas production because such pretreatments could be effective only to a certain extent of temperature, retention time and pressure.

On the other hand, an advanced thermal pre-treatment (ATH) that combines application of H_2O_2 and pre-thermal treatment could help improve methane production at reduced temperature, time and pressure. Abelleira-Pereira et al. (2015) reported that more yield of methane could be achieved pre-treating sewage sludge at 115^{0}C for 5 minutes at a pressure of 1 bar compared to the commonly applied 170^{0}C for 30 minutes at a pressure of 8 bar. AAD thermal treatment is helpful not only against antibiotics and other toxic substances removal, significant proportions of ARG can also be degraded (Wallace et al., 2018). As it can be observed in Table 5, so far ATH has been tested only against a few groups of antibiotics that are recalcitrant under conventional AD. The treatments appear to be unsatisfactory, and further well-planned pre-treatment studies are required.

6.2.2. Modified AD temperature

Different biogas production scales would employ different temperature ranges under which specific group of bacteria maintain potential metabolic activity. However, AD systems that operate under the temperature regime of psychrophilic (Stone et al., 2009) and mesophilic (Miller et al., 2016) conditions have lower effect on toxic substances removal and ARG compared to the thermophilic conditions. On the other hand, the thermophilic range has been widely reported to be effective against harmful chemicals (including antibiotics) and ARG. This range of temperature can be achieved at no extra cost by heating up the reactors with solar energy (El-mashad et al., 2004).

Temperature is regulated in the biogas digestion to facilitate a conducive environment for better microbial activity and thereby enhancing methane production (Lin et al., 2016) and reducing ARG or the carrier bacteria (Sun et al., 2016; Tian et al., 2016; Wu et al., 2016). This condition improves heat energy and enzyme activity of thermophilic microbes in the system, which could improve the breakdown of antibiotic molecules. However, significant proportion of antibiotics or their secondary metabolites formed during the degradation process could still be found in the digestate that could support the evolution of ARG. On top of this, in the AD systems with long retention time, high relative abundance of multidrug ARG can be found in the digestate. Moreover, some groups of ARG, for instance, *sul* and *tet* could respond to temperature modification at a lower rate compared to other groups (Tian et al., 2016; Wu et al., 2016), elaborating the complexity of the problem and the need for further studies.

On the other hand, increasing temperature may compromise biogas production as there is a threshold thermophilic condition because metabolic activity of some anaerobic bacteria groups is limited above the threshold level (Lin et al., 2016). The retention time of the AD could also complement the enhanced temperature condition for a better removal efficiency and biogas production. Hence, they can be interdependent, meaning that the higher the temperature of the AD, the shorter retention period required. Thus, thermophilic condition could have more advantage over the mesophilic or psychrophilic conditions in terms of biogas production and degradation of antibiotics while mesophilic condition could be a preferable AD for removal of ARGs.

6.2.3. Double temperature phased AD

Use of a double temperature phase (thermophilic and mesophilic) AD (DTP) has been evaluated against a single phase on volatile solid removal and biogas production efficiency on food waste (Wu et al., 2015; Xiao et al., 2018b), sewage sludge (Montañés Alonso et al., 2016), and municipal solid waste (Fernández-Rodríguez et al., 2016), and the outcomes were not consistent.

The mesophilic single-phased AD of food waste, with 10 days hydrolytic retention period, was the best in methane production when compared to the thermophilic and the DTP. However, other studies with longer retention period show DTP yielded significantly higher biogas from food waste when compared to the single temperature AD (De Gioannis et al., 2017; Xiao et al., 2018a). For the municipal waste, the efficiency of methane production was improved up to 60% as compared to the single-phase process. The need for optimum retention time might be critical (Fernández-Rodríguez et al., 2016; Xiao et al., 2018b) to better understand the relative importance of the double-temperature phased AD process efficiency.

>>>>>>>>>>>>>>>>>>>>>>>>>>>> Fig.7. >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>

While a single thermophilic AD is better in degrading antibiotics, mesophilic AD is better in suppressing resistant bacteria. In some cases, thermophilic can also be a hub for reproduction of resistant bacteria (Ma et al., 2011). Thus, it would be vital to evaluate a two-temperature phased thermophilic-mesophilic AD (Montañés Alonso et al., 2016) against both VA and ARG.

7. Post-AD management

Most antibiotics do not degrade completely, implying some proportion would remain in digestate at only slightly or not significantly lower than the concentration in the respective substrates. Thus, significant amount of antibiotics and ARG can enter the soil with digestate if a subsequent management practice is not followed to further remove the toxicants. Consequently, application of digestate for long period would potentially increase the abundance of ARG in soils (Pu et al., 2018). Even though the absence of VA or their residues in soils is not a guarantee for the absence of ARG (Wallace et al., 2018), digestate could be the source for diverse ARG and MGE when used for fertilizer or soil amendment. The reason the link between the presence of VA and ARG diversity and counts sometimes be weak can partly be because microbes can be resistant to multi-drugs. For instance, in a sludge, *sul* ARG were detected while sulfonamide concentration was not (Wallace et al., 2018), but their concentration was reduced to non-significant level. Moreover, the quantity of ARG of *tet* groups was also not affected. Similarly, after AD of combined herbal residues and swine manure for 90 days, *qnrA* and *tetW* were so recalcitrant (Zhang et al., 2018).

Therefore, removal approaches need to address both VA and ARG in digestate, and even in the preceding stages. Moreover, it can also be suggested that further studies need to be focused more on detection and quantification of ARG than VA while the knowledge about the cause and effect relationship between VA and ARG is advancing.

7.1. Improving digestate storage

Digestate storage constitutes one of the major components of manure management along the AD process (Li et al., 2018; Plana and Noche, 2016; Tambone et al., 2015). It can also be one of the areas of focus to further reduce VA or ARG. In this review, a few studies on the effect of solid digestate management approaches on VA or ARG were summarized in Table 6. The different studies reveal that appropriate digestate storage could help further remove the remaining portion of VA or ARG during the AD.

>>>>>>>>>>>>>>>>>>>>>>>>Table 6 <<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<

After having stripped off the ammonia, digestate is applied for fertilizer in many countries for growing both field crops or vegetables despite the criticism that it may not be still free from antibiotics and ARG contaminants as AD systems are not efficient against all the varieties of antibiotics and ARG. A common treatment applied to digestate before it is applied to soils is stripping off ammonia and keeping it in open air for some period. This approach may also be useful to remove some amount of other toxic substances including antibiotics that remained in the digestate (Bousek et al., 2018). These researchers found that stripping off air and ammonia from the digestate following the AD system helped complete removal of tetracycline, but the removal rate for flumequine was less than 50%. If this approach had been preceded by thermal pre-treatment, a more removal rate of the VA might be obtained. Stripping ammonia could also be advanced with the use of technologies such as the drying approach evaluated by Pantelopoulos et al. (2016). The high temperature condition (70-160°C) evaluated in the study to dry the digestate can be useful to remove the persistent VA and ARG.

Li et al. (2018a) also studied the effect of different storage conditions of manure based digestate on antibiotics, and some level of reduction in concentration. However, complete removal was not reported for any of the 17 antibiotics detected in the digestate after storing under mesophilic (30^0C) and psychrophilic (15^0C) conditions treated as covered and uncovered. This is another good indicator that AD operating under low temperature regime (equal to or below mesophilic condition) has little effect on VA.

7.2. Composting digestate

Composting of raw manure or sludge at thermophilic condition has the capacity to remove antibiotics and ARG (Chen et al., 2018; Ezzariai et al., 2018; Ho et al., 2013; S M Mitchell et al., 2015; S. M. Mitchell et al., 2015; Zhang et al., 2019). Effect of manure composting on antibiotics ranges from no effect to 100% removal (van Epps and Blaney, 2016). Sulfonamides are the most widely studied for their degradation rate during manure composting, followed by macrolides and tetracyclines (Fig. 8).

>>>>>>>>>>>>>>>>>>>>>>>>>>>>Fig.8 >>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>>

On the other hand, composting solid digestate is not a common practice because it is perceived that digestate is safe and can be used as fertilizer without undergoing further processes (Koszel and Lorencowicz, 2015; Logan and Visvanathan, 2019). Instead, digestate contains low nutrient and can be alkaline (Teglia et al., 2011; Torres-Climent et al., 2015) and, indeed, it could contain diverse pollutants. On top of this, many of the studies relied on the agronomic effect of digestate and the nutrient contents (Koszel and Lorencowicz, 2015), without looking at environmental problems such as VA and ARG diffusion, which are also missing in many of the standard guidelines that many countries have developed for digestate utilization.

On the other hand, many studies suggest composting as one of the best management approaches for further improving digestate quality for fertilizer before it is applied to soils (Bustamante et al., 2013, 2012; Logan and Visvanathan, 2019; Min Jang et al., 2019; Zeng et al., 2016). Vermicomposting for five months significantly improved compost quality indicators (Hanc and Vasak, 2015). With thermophilic aerobic digestion of sludge digestate, remarkable additional removal of bacterial pathogens was also reported (Min Jang et al., 2019). The fact that AD is not efficient in removing VA from manure, thermophilic aerobic composting of digestate could be one of the best follow up strategies for additional or complete removal. Future researches could consider the effect of composting digestate on further removal of antibiotics and ARG.

7.3. Mixing biochar with digestate or converting digestate to biochar

Biochar having high sorption characteristics has been widely reported to remove pollutants including antibiotics from aqueous solutions (Chen et al., 2011; Tan et al., 2015). However, sorption potential of antibiotics depends on physicochemical properties (Peiris et al., 2017) and the type of biomass from which it is produced (Ngigi, 2019). Wood based biochar is reported to be the best in adsorbing antibiotics and reducing their bioavailability when compared to a biochar made from sludge or digestate (Ngigi, 2019). However, modifying biochar derived from other biomass sources could also improve the effectiveness (Jiang et al., 2018) and reduce dependency on wood based biochar that can be more expensive. Even without further modification, a biochar derived from swine manure was effective in removing sulfadimidine and tylosin from digestate by 83.76% and 77.34%, respectively (Jiang et al., 2018). Modifying biochar derived from such biomass may improve the removal efficiency. Co-precipitation with iron (Chen et al., 2011), activation with steam (Rajapaksha et al., 2015), and acid and alkali modifications (Ahmed et al., 2016) are examples of biochar modifications that can help improve efficiency of VA or ARG removal. While the biochar sorption of the different antibiotics from manure could be increased, the sorption rate could vary among the different types of antibiotics (Ngigi et al., 2019). Zeng et al. (2018) evaluated the effect of rice straw biochar produced at different pyrolysis temperatures on removal of doxycycline and ciprofloxacin and found that biochar produced by pyrolysis at 700°C was more effective to adsorb the two antibiotics than biochar produced at 300-500°C.

Conversion of the solid digestate to a biochar (Zhou et al., 2019) would help improve the use of digestate as bio-fertilizer (Hung et al., 2017) or biofuel (Kratzeisen et al., 2010), and it would also help completely remove VA. Using biochar for removing antibiotics from waste could be not only more environmentally friendly but also cheaper than using activated carbon (Thompson et al., 2016). However, economic feasibility and life cycle assessment studies are required to strongly suggest for scale up.

8. Conclusion and areas of focus for further research

This review highlights the use of digestate without further treatment could be a means for channeling VA and ARG to the environment. Although some findings show the possibility of complete removal of some VA by a specific AD, evidence is still lacking on why most VA are still persistent and what conditions must be fulfilled to get complete removal. On the other hand, since the lower limit of VA concentration required to support selection for resistant microbes is unknown, future research needs to focus on realizing obtaining antibiotic free digestate or making it VA free before applying to soils. In this regard, the current state of technologies of AD cannot guarantee effective removal of VA and ARG, not only technological but also management approaches need further research and improvement.

The current review results show that a focus on improving AD process alone is not satisfactory when it comes to achieving effective VA and ARGs removal. Therefore, the approach needs to be more comprehensive by considering the different stages of manure management as opportunities for intervention. The first step should start from pre-AD manure handling. As this stage, stripping-off water and improving storage has a role against removal of VA and ARG both at onsite and off-site when it later enters AD. Second, before it enters the AD, it is recommended to be incubated at a high temperature for a certain time period. However, optimizing the temperature without compromising biogas production potential requires further study since evidences are lacking on the range of temperature required to potentially remove VA at lowest possible cost. The third stage is AD. The focus here needs to be optimizing the temperature for VA and ARG removal and biogas production. While thermophilic condition is widely reported to have positive impact on both, it has negative correlation with ARG. In contrast, mesophilic condition was reported to be more efficient for reduction of ARGs. The reason is not well understood, but it can be linked to the increase in activity of anaerobes following the rise of temperature and vice versa. Therefore, a multi-phase AD technology, with thermophilic followed by mesophilic temperature regime could help improve removal efficiency of both elements.

It is still possible to find some proportion VA and ARGs in digestate. Therefore, this is the last stage to put the maximum possible effort before it is applied to soils. Digestate can be either landfilled (in some countries such as the Netherlands) or used as fertilizer after aerated for some days (e.g. in Italy) or aerobic composted. These treatments are so crucial to help remove the previously persisting VAs. However, in the worst scenario, a few could still show some sort of persistence due to the nature of the VA. In this case, the most effective method could be converting the digestate (solid) to biochar. However, the economic feasibility of converting digestate to biochar and the agronomic effect needs further study.

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