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Manure anaerobic digestion effects and the role of pre- and post-treatments on veterinary antibiotics and antibiotic resistance genes removal efficiency

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35 1. Introduction

Manure based anaerobic digestion (AD) is practiced for energy production and environmental 36 risk reduction (Yazan et al., 2018) comprising about 72% of the total biogas production input 37 (Torrijos, 2016). The environmental benefits include removal of toxic substances such as 38 39 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 40 in manure affects biogas production (Beneragama et al., 2013; Huang et al., 2014; Stone et al., 41 2009) because it suppresses methanogenesis which in turn leads to less methane or biogas 42 43 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 44 challenging the world health sector, mainly because it supports microbes selection for antibiotic 45 46 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 47 applying knowledge, skill, and resources (Pruden et al., 2013). 48

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Other manure use scenarios are direct use for fertilizer or organic matter amendment 50 (Castellanos-Navarrete et al., 2015; Rufino et al., 2014; Sanginga, N. and Woomer, 2009) and 51 incorporating after composting (Lalander et al., 2015). The prevalence of veterinary antibiotics 52 in manure and their implication on the environment when directly used as fertilizer is widely 53 discussed in previous studies (J. Li et al., 2017; Massé et al., 2014; Spielmeyer, 2018; Udikovic-54 Kolic et al., 2014; F. H. Wang et al., 2015; J. Wang et al., 2015; Xie et al., 2018b). Composting 55 of manure under aerobic thermophilic condition effect on VA and ARG is also widely reported. 56 57 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 preand 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.

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The fact that VA is projected to increase by more than 100% in just the coming decade (Van 65 Boeckel et al., 2015) in the absence of an effective approach to avoiding emissions to the 66 environment is frightening. On top of this, in recent decades, antibiotics are getting resistance 67 more than ever. Dantas et al. (2008) found that from 18 antibiotics they evaluated against 68 hundreds of bacteria isolated from soils, about 70-90% showed resistance. Consequently, there is 69 much concern about the effect associated to the ARG which is being reflected in the economic 70 and health crisis. The World Bank recently calculated an annual World's expense of about 3.4 71 trillion \$ annually by 2030 for the loss in productive labor and development of alternative 72 treatments (World Bank, 2016). The latter is in response to the challenge when a disease-causing 73 bacterium is found to be subsisting on a given antibiotic and combined prescriptions or new 74 medicines are sought. This would increase the cost of the treatment, and even it could risk the 75 life. 76

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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).

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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.

96 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.

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Fig.1 displays the process through which a persisting VA can enter the food chain or re-enter the 111 AD process. With the effect of the presence of these VA, microbes in soils, animal or human gut 112 and AD can develop resistance, evolving with ARG that eventually can increase in quantity 113 (copies) when there is a more conducive environment. Like the VA, ARG could also enter the 114 food chain (Bengtsson-Palme, 2017) either through crop (F. H. Wang et al., 2015) or animal food 115 (Allen, 2014; Menkem et al., 2018; Sivagami et al., 2018). The interesting point here is that 116 117 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 118 will not undergo resistant gene selection (Risberg, 2015). Thus, the decrease in concentration of 119 120 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 121 VA for the different manure use scenarios. 122

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124 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 onpoultry manure was rarely reported.

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).

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One of the possible reasons associated to the positive effect on biogas production is the 138 disruptive role on the extra-cellular polymers in the substrate which could result in increased 139 production of acetic acid that leads to enhanced biogas production (Hu et al., 2018). For instance, 140 in a research report by Yin et al. (2016), biogas production was reduced only when OTC and 141 CTC concentrations exceeded 40 and 60 mg kg⁻¹ TS, respectively. Below these levels, a small 142 increment in biogas production was observed, implying that the existent of small proportion of 143 antibiotics might have positive impact on biogas production, but increased level might inhibit 144 microbial activities and, hence, reduce biogas production. However (as discussed in detail under 145 section 4), this might be dependent on the type of VA and the level of concentration present in 146 the substrate and, possibly, on the temperature regime under which the AD operates. 147

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).

156 4. AD effects on VA and ARG

AD is one of the waste management pathways for energy production (Kalia and Joshi, 1995), 157 improving nutrient availability (Möller and Möller, 2012) and removal of toxic substances such 158 as VA (Wallace et al., 2018) and ARG (Jang et al., 2018; Sun et al., 2019). However, these days 159 the emphasis given sounds more towards the energy production than improving environmental 160 quality. Antibiotics are rarely effectively removed in the system, and one of the reasons is 161 associated to the unique intrinsic structural formation of a VA that determines their properties in 162 AD system. Therefore, most of the studies were focused on understanding the processes 163 responsible for the degradation as well as seeking improved approaches to enhanced removal 164 165 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 166 methanogenesis phases. However, none of these modifications was found to be effective to 167 completely remove antibiotics and ARG despite the removal rate might improve, implying the 168 need for further investigation. 169

Composition of the substrate is another important factor. The adsorption capability of the 171 different antibiotics in the AD system could vary. Tetracyclines and quinolones have been 172 reported to have strong affinity to solid substances (N. Li et al., 2017; Li et al., 2018; Sui et al., 173 2018; Zhang and Li, 2018), and when the total solid content of a substrate is high antibiotics 174 undergo lower hydrolysis or other forms of degradation (Sui et al., 2018). However, for such 175 176 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) 177 in the AD system resulting in 4.5, 48.0, 32.3, and 25.7% antibiotic concentration in a digestate 178 having TS content of 4, 8, 11, and 14%, respectively (Sui et al., 2018). Moreover, antibiotics in a 179 similar group having almost similar structure could even also have differing sorption 180 (adsorption/desorption) characteristics and may not show similar degradation rate under a 181 specific treatment. Therefore, specific mechanism must be sought not only based on the type of 182 antibiotic but also the properties of the substrates used. This will also take us to the next chapter 183 of investigation to further understand about complex properties in the substrate during the AD. 184 The properties of substrates could favor or inhibit the degradation of VA and ARG. 185

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187 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 ratewas less than 10% (Bousek et al., 2018).

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^oC (Shi et al., 200 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.

In the AD system, sorption is the main degradation route for tetracyclines because they are 204 usually adsorbed to the solid state of the substrate (Kim et al., 2005; Sui et al., 2018). The higher 205 the concentration of TC in a substrate, the lower the rate of removal, implying the strong 206 adsorption of TC to the solid digestate (Nurk et al., 2019). Unlike other groups of antibiotics, 207 relatively lower proportion of TC is found in liquid digestate than in solid digestate because of 208 209 the sorption characteristics of these antibiotics to solid (Nurk et al., 2019). Thus, substrates that 210 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 211 higher concentration of tetracyclines in digestate compared to a more efficient AD given all other 212 conditions are similar. 213

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).

222

223 4.2. Sulfonamides

A previous systematic review report showed that concentration of sulfonamides (SD) in manure 224 was lower than TC with 18 mg kg⁻¹ dry weight basis (Xie et al., 2018a). However, recovery rate 225 from manure can be high, even higher than TC, and it could be possible to recover more than 226 90% of SD from a spiked manure (Zhao et al., 2010). This group of antibiotics are the most 227 widely used VA in animal husbandry, but their elimination rate during the AD was not widely 228 reported like macrolides and tetracyclines (Fig. 3). Also, there was little or no effect of AD on 229 these antibiotics (Table 2). Moreover, the elimination rates are also variable (Fig. 3). In a study 230 of antibiotics removal from manure using AD in Germany, it was reported that only 60% of 231 sulfamethazine was removed from the initial concentration and about 76 mg kg⁻¹ remained in 232 the digestate (Spielmeyer, 2018). This is the maximum concentration of SD reported in digestate 233 recently. 234

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236 >>>>>>Table 2 <	:<<<<<<<<<>>>>>>>>>>>>>>>>>>>>>>>>>>>>>
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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.

242 4.3. Quinolones and Fluoroquinolones (FQ)

This class of antibiotics are not widely used in animal husbandry, but up to 1480 mg of 243 enrofloxacin concentration in a kg of chicken manure was reported from China (Riaz et al., 244 2018). FQ are relatively more persistent in the environment (Riaz et al., 2018) and less degraded 245 during the AD system. However, like the classes of VA discussed in the above two sections, 246 removal rate varies among the species of VA within the group. For example, in AD of sludge 247 study reported by Narumiya et al. (2015), the highest removal (more than 90%) was observed 248 for sulfamethoxazole and trimethoprim and other groups were so persistent with a removal rate 249 as low as 30%. While it was possible to remove 100% tetracyclines using a pilot scale AD of pig 250 manure, there was no effect against flumequine (Bousek et al., 2018). Like for TC, sorption 251 could be the best path to removal of FQ from aqueous solution (Riaz et al., 2018). It is thus 252 253 evident that AD in its current technological level is not useful against FQ.

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255 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).

- 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° C) (Sui et al., 2018). Moreover, the removal rate of monensin was almost negligible with the AD at 35° C and improve to a maximum of 27% at a temperature of 55° C (Varel et al., 2012).

270 4.5. ARG and MGE

Antibiotic resistant genes (ARG) or mobile genetic elements (MGE) could degrade or potentially 271 increase in copies or counts. The conditions like thermophilic temperature that might help 272 remove VA in AD could have a reverse impact on ARG and MGE (Huang et al., 2019; Sun et 273 al., 2019). This might be related to the favoring conditions moderated by the temperature regime, 274 that may increase the abundance of antibiotic resistant thermophiles thereby increasing the ARG 275 276 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 277 ARG or MGE counts (Table 4). 278

- 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.

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The tet groups are the most widely observed and studied ARG for their behavior of gene 286 287 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 288 and reactor volume look unclear (Table 5). However, given the likelihood of the exponential 289 growth of ARG in a short period of time when there is conducive environment (Sun et al., 2019; 290 Wu et al., 2016; Zhang et al., 2017), a reduction of the count to a certain extent alone may not be 291 useful. So far studies reveal that none of the approaches resulted in complete elimination of 292 ARG, and conditions that favor production of methane and degradation of antibiotics could favor 293 ARG to exponential increase. This suggests technological modification of ordinary AD systems 294 to help removal of VA as well as ARG. Horizontal gene transfer supported by MGE might make 295 management of ARG in digestate more challenging (Han et al., 2018; Wolters et al., 2015). 296 Therefore, for AD processes, it can be suggested that more emphasis needs to be put on breaking 297 the chains of ARG selection routes than eliminating the ARG. 298

300 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).

312

While the use of VA is increasing, there needs to be breakthrough solutions to their impacts on 313 environment and health. The promising efforts in Europe could be sought to be up scaled in other 314 regions of the world. In Europe, with improved policies, the trend of VA use is declining (EMA 315 (European Medicines Agency, 2018) although the report was merely based on the amount of VA 316 sold. Refining the business as usual manure management approach should be the next step 317 forward. In Fig. 5, we illustrated the possible areas of focus to potentially remove VA or ARG 318 from manure under different manure use scenarios. One of the most important scenarios focused 319 by this review is the AD. The choice for this scenario stems primarily from the need for 320 bioenergy although this approach is also adapted for waste management. However, the AD could 321 underestimate the environmental concerns when the interest of farmers or energy producing 322 companies on manure is mostly derived by the economic gain, with less attention on 323 environmental sustainability (Logan and Visvanathan, 2019). 324

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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 328 sought in addition to the need for improved policies on banning the use of growth promoting 329 anti-microbials adapted by many European countries (Moulin et al., 2016) in all other countries 330 because the spread, indeed the impact, of ARG may not be limited by geographical boundaries 331 (Founou et al., 2016). Inappropriate use of VA, like using VA for healthy animals, must be 332 avoided, and policies need to be developed to apply prescription based so as to avoid excessive 333 use of VA (Tangcharoensathien et al., 2018). These approaches are more discussed in the next 334 sub-sections. The next steps complement the prior efforts, and they are focused to eliminate VA 335 or their residues from animal food and waste. The former is not included in this review, but the 336 latter will be discussed in detail. 337

338

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 340 341 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 342 growth promoting VA(Hughes and Heritage, 2004; Huyghebaert et al., 2011; Wegener, 2003). 343 This only complements the other efforts such as reducing or banning the excessive use of 344 therapeutic VA. Therefore, to achieve a meaningful reduction in environmental impacts of VA, 345 approaches to reducing use of antibiotics for both therapeutic and sub-therapeutic need to be 346 proposed (Pruden et al., 2013). According to these authors, one of these strategies can be 347 reducing drug prescription doses based on clinical efficacy and promoting the banning of growth 348 promoting drugs from animal husbandry. The ultimate objective in both cases is to reduce 349 negative impacts of antibiotic residues on human health and the challenges on healthcare that is 350

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).

355

356 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. 357 (2016) also shows that out of 130 member states of the World Organization for Animal Health, 358 about 74% of them do not authorize the use of growth promoting antimicrobials. This, along 359 with the reduction in use of excessive VA, appears to have positively impacted the overall 360 decline in use of VA in Europe (European Medicines Agency, 2018). In the authorizing 361 countries, the widely used growth promoting antibiotics are tylosin and bacitracin. Since these 362 are usually provided to animals with a dose below the MIC, they are blamed as the major factors 363 responsible for the development of ARG. Denmark drastically reduced the use of growth 364 promoting drugs by about one third after it was recognized that enterococcal developed 365 resistance to vancomycin, which was associated to provision of avoparcin in chicken production 366 (Pruden et al., 2013). 367

368 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 374 types like it has been discussed for the other management pathways. However, when it is a 375 376 pretreatment, it can be considered as a pre-treatment for a more effective removal. Spielmever (2018) reported that manure heap storage could eliminate monensin (< 10%), lincomycin (15%), 377 sulfamethazine (82-92%), oxytetracycline (99%) and tylosin (> 99%). In contrast, other manure 378 379 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 380 instance, Li et al. (2018) reported that manure stored under mesophilic temperature showed more 381 degradation rate of VA compared to higher temperature regimes. Most of the studies on the 382 impact of manure storage on removal of VA were aimed to address the problem associated to the 383 direct application of manure for fertilizer. However, if an advanced storage is considered as a 384 pre-AD processes, where the stored manure is used for biogas production followed by improved 385 digestate storage, a better elimination of VA and ARG can be achieved. 386

387

388 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.

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 397 processes are accounted for the reactions that degrade toxic substances including antibiotics in 398 the AD reactors. Modifications to any or all these processes could be significant on the fate of 399 antibiotics, but not all improvements have positive impacts.

400

401 6.1. Hydrolysis, acidogenesis and pH

402 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, 403 spiramycin, and tylosin in acidic and basic buffers (below pH 4 and above pH 8) and under 404 temperature of 50-60 °C. Below this temperature, all the four antibiotics remained stable. Sy et 405 al. (2017) also reported that ampicillin, which is known to have strong hydrolysis potential, 406 underwent formation of 2-hydroxy-3-phenylpyrazine, which can remain bio-active. A study 407 conducted by Loftin et al. (2008) showed tylosin hydrolysis was effective only at extreme pH 408 levels (2 and 11), and the hydrolysis of tetracycline group (TC, OTC and CTC) showed an 409 410 increasing trend with increasing pH and temperature.

411

The fact that the level of pH and temperature that is more appropriate to efficiently degrade 412 antibiotics is not optimum for biogas production can justify inefficiency of AD for removal of 413 VA. In the AD system, a lab scale study conducted by N. Li et al. (2017) showed that the highest 414 degradation rate of fluoroquinolones was achieved at pH 3. The controversial two phase AD 415 system that was reported to be inefficient in terms of biogas production could have this attribute 416 and may be useful for degrading VA and other toxic substances (Schievano et al., 2012; Wu et 417 al., 2016). However, it is usually recommended to maintain natural level pH of AD system for 418 optimum methane production (Zhang et al., 2017). 419

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).

427

428 6.2. Temperature based AAD

Although different biogas plants could have different bacterial communities that are most active 429 under a specific range of temperature, thermophilic condition (commonly ranges 40-60^oC) is the 430 highest possible temperature range any biogas plant can adopt. This would likely support the 431 degradation of antibiotics in the substrates more efficiently than an AD with mesophilic 432 temperature or lower. This is, however, not always true as the degree of degradation varies 433 depending on several other factors. This thermophilic temperature range is also useful to degrade 434 ARG (Miller et al., 2016). In some scenarios, methodologies to estimate antibiotics concentration 435 underestimate the level of concentration of antibiotics in the raw substrates because of the 436 adsorption to the cell of micro-organisms. Thus, they could result in higher concentration in the 437 digestate than in the feedstock as microbial cells are degraded by the AD or AAD (Zhang and Li, 438 2018). 439

440

Fig. 6 illustrates that the temperature of AD of manure considered under most of the studies
ranged from 35 to 50 °C. However, fermentation (retention) period varied among the different

studies reviewed. This is because most studies were laboratory level (shorter period) and only afew were at pilot or farm scale (longer period).

445

446 6.2.1. Pre-AD thermal treatment

Since the conventional AD systems could have low effect on degradation of antibiotics and 447 ARG, advanced AD (AAD) technologies on improving removal efficiency of VA were 448 investigated. Among these, thermal pre-treatment was the most widely studied (N. Li et al., 449 450 2017; Wallace et al., 2018; Zhang and Li, 2018). Wallace et al. (2018) evaluated the effect of pasteurization of manure at 67°C and found that this treatment significantly reduced 451 concentration of tetracyclines in manure effluents. Another thermal pre-anaerobic digestion 452 treatment could be thermal hydrolysis as described in Li et al. (2016). In this study, sewage 453 sludge was pre-treated at 160°C for 60 minutes. However, the pre-treatment did not affect 454 degradation of fluoroquinolones (FQ) in the AD system although the AD process without pre-455 treatment was effective for about 60% degradation of FQ. Zhang and Li (2018) also found that 456 AD system alone supported about 40% removal of TC while the ADD had little impact and the 457 role of pre-treatment was insignificant. These antibiotics may require higher temperature for 458 longer time to be effectively degraded. However, since the main goal of AD is to maximize 459 methane production, higher temperature for longer period compromises optimum biogas 460 production because such pretreatments could be effective only to a certain extent of temperature, 461 462 retention time and pressure.

463

464 On the other hand, an advanced thermal pre-treatment (ATH) that combines application of H_2O_2 465 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 466 achieved pre-treating sewage sludge at 115°C for 5 minutes at a pressure of 1 bar compared to 467 the commonly applied 170°C for 30 minutes at a pressure of 8 bar. AAD thermal treatment is 468 helpful not only against antibiotics and other toxic substances removal, significant proportions of 469 ARG can also be degraded (Wallace et al., 2018). As it can be observed in Table 5, so far ATH 470 471 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 472 are required. 473

474

475 6.2.2. Modified AD temperature

Different biogas production scales would employ different temperature ranges under which 476 specific group of bacteria maintain potential metabolic activity. However, AD systems that 477 operate under the temperature regime of psychrophilic (Stone et al., 2009) and mesophilic 478 (Miller et al., 2016) conditions have lower effect on toxic substances removal and ARG 479 compared to the thermophilic conditions. On the other hand, the thermophilic range has been 480 widely reported to be effective against harmful chemicals (including antibiotics) and ARG. This 481 range of temperature can be achieved at no extra cost by heating up the reactors with solar 482 energy (El-mashad et al., 2004). 483

484

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.

496

On the other hand, increasing temperature may compromise biogas production as there is a 497 threshold thermophilic condition because metabolic activity of some anaerobic bacteria groups is 498 limited above the threshold level (Lin et al., 2016). The retention time of the AD could also 499 complement the enhanced temperature condition for a better removal efficiency and biogas 500 production. Hence, they can be interdependent, meaning that the higher the temperature of the 501 AD, the shorter retention period required. Thus, thermophilic condition could have more 502 advantage over the mesophilic or psychrophilic conditions in terms of biogas production and 503 degradation of antibiotics while mesophilic condition could be a preferable AD for removal of 504 505 ARGs.

506

507 6.2.3. Double temperature phased AD

508 Use of a double temperature phase (thermophilic and mesophilic) AD (DTP) has been evaluated 509 against a single phase on volatile solid removal and biogas production efficiency on food waste 510 (Wu et al., 2015; Xiao et al., 2018b), sewage sludge (Montañés Alonso et al., 2016), and 511 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 512 the best in methane production when compared to the thermophilic and the DTP. However, other 513 studies with longer retention period show DTP yielded significantly higher biogas from food 514 waste when compared to the single temperature AD (De Gioannis et al., 2017; Xiao et al., 515 2018a). For the municipal waste, the efficiency of methane production was improved up to 60% 516 517 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 518 importance of the double-temperature phased AD process efficiency. 519

520

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.

526 7. Post-AD management

Most antibiotics do not degrade completely, implying some proportion would remain in digestate 527 at only slightly or not significantly lower than the concentration in the respective substrates. 528 529 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 530 of digestate for long period would potentially increase the abundance of ARG in soils (Pu et al., 531 2018). Even though the absence of VA or their residues in soils is not a guarantee for the absence 532 of ARG (Wallace et al., 2018), digestate could be the source for diverse ARG and MGE when 533 used for fertilizer or soil amendment. The reason the link between the presence of VA and ARG 534

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.

545

546 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.

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 558 useful to remove some amount of other toxic substances including antibiotics that remained in 559 560 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 561 removal rate for flumequine was less than 50%. If this approach had been preceded by thermal 562 563 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 564 Pantelopoulos et al. (2016). The high temperature condition (70-160°C) evaluated in the study to 565 dry the digestate can be useful to remove the persistent VA and ARG. 566

567

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^oC) and psychrophilic (15^oC) 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.

574

575 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 bymacrolides and tetracyclines (Fig. 8).

582 On the other hand, composting solid digestate is not a common practice because it is perceived 583 that digestate is safe and can be used as fertilizer without undergoing further processes (Koszel 584 585 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 586 diverse pollutants. On top of this, many of the studies relied on the agronomic effect of digestate 587 and the nutrient contents (Koszel and Lorencowicz, 2015), without looking at environmental 588 problems such as VA and ARG diffusion, which are also missing in many of the standard 589 guidelines that many countries have developed for digestate utilization. 590

591

On the other hand, many studies suggest composting as one of the best management approaches 592 for further improving digestate quality for fertilizer before it is applied to soils (Bustamante et 593 al., 2013, 2012; Logan and Visvanathan, 2019; Min Jang et al., 2019; Zeng et al., 2016). 594 Vermicomposting for five months significantly improved compost quality indicators (Hanc and 595 Vasak, 2015). With thermophilic aerobic digestion of sludge digestate, remarkable additional 596 removal of bacterial pathogens was also reported (Min Jang et al., 2019). The fact that AD is not 597 efficient in removing VA from manure, thermophilic aerobic composting of digestate could be 598 one of the best follow up strategies for additional or complete removal. Future researches could 599 consider the effect of composting digestate on further removal of antibiotics and ARG. 600

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602 7.3. Mixing biochar with digestate or converting digestate to biochar

Biochar having high sorption characteristics has been widely reported to remove pollutants 603 604 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 605 the type of biomass from which it is produced (Ngigi, 2019). Wood based biochar is reported to 606 607 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 608 other biomass sources could also improve the effectiveness (Jiang et al., 2018) and reduce 609 610 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 611 tylosin from digestate by 83.76% and 77.34%, respectively (Jiang et al., 2018). Modifying 612 biochar derived from such biomass may improve the removal efficiency. Co-precipitation with 613 iron (Chen et al., 2011), activation with steam (Rajapaksha et al., 2015), and acid and alkali 614 615 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 616 manure could be increased, the sorption rate could vary among the different types of antibiotics 617 (Ngigi et al., 2019). Zeng et al. (2018) evaluated the effect of rice straw biochar produced at 618 different pyrolysis temperatures on removal of doxycycline and ciprofloxacin and found that 619 biochar produced by pyrolysis at 700°C was more effective to adsorb the two antibiotics than 620 biochar produced at 300-500°C. 621

622

623 Conversion of the solid digestate to a biochar (Zhou et al., 2019) would help improve the use of 624 digestate as bio-fertilizer (Hung et al., 2017) or biofuel (Kratzeisen et al., 2010), and it would 625 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.

629

630 8. Conclusion and areas of focus for further research

631 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 632 complete removal of some VA by a specific AD, evidence is still lacking on why most VA are 633 still persistent and what conditions must be fulfilled to get complete removal. On the other hand, 634 since the lower limit of VA concentration required to support selection for resistant microbes is 635 unknown, future research needs to focus on realizing obtaining antibiotic free digestate or 636 making it VA free before applying to soils. In this regard, the current state of technologies of AD 637 cannot guarantee effective removal of VA and ARG, not only technological but also 638 639 management approaches need further research and improvement.

640

The current review results show that a focus on improving AD process alone is not satisfactory 641 when it comes to achieving effective VA and ARGs removal. Therefore, the approach needs to 642 be more comprehensive by considering the different stages of manure management as 643 opportunities for intervention. The first step should start from pre-AD manure handling. As this 644 stage, stripping-off water and improving storage has a role against removal of VA and ARG both 645 at onsite and off-site when it later enters AD. Second, before it enters the AD, it is recommended 646 to be incubated at a high temperature for a certain time period. However, optimizing the 647 temperature without compromising biogas production potential requires further study since 648

evidences are lacking on the range of temperature required to potentially remove VA at lowest 649 possible cost. The third stage is AD. The focus here needs to be optimizing the temperature for 650 651 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 652 condition was reported to be more efficient for reduction of ARGs. The reason is not well 653 654 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 655 by mesophilic temperature regime could help improve removal efficiency of both elements. 656

657

It is still possible to find some proportion VA and ARGs in digestate. Therefore, this is the last 658 stage to put the maximum possible effort before it is applied to soils. Digestate can be either 659 landfilled (in some countries such as the Netherlands) or used as fertilizer after aerated for some 660 days (e.g. in Italy) or aerobic composted. These treatments are so crucial to help remove the 661 previously persisting VAs. However, in the worst scenario, a few could still show some sort of 662 persistence due to the nature of the VA. In this case, the most effective method could be 663 converting the digestate (solid) to biochar. However, the economic feasibility of converting 664 digestate to biochar and the agronomic effect needs further study. 665

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