

Risk factors for antimicrobial use in food-producing animals: disease prevention and socio-economic factors as the main drivers?

Risicofactoren voor antibioticumgebruik bij voedselproducerende dieren: ziektepreventie en socio-economische factoren als drijfveer?

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ABSTRACT

The European Union requests an urgent decrease in antimicrobial use (AMU) in food producing-animals to reduce antimicrobial resistance in animals and humans and safeguard the efficacy of antimicrobials for future generations. The identification of risk factors (RFs) for AMU is essential to obtain a rapid reduction. The aim of this review was to summarize the current knowledge of RFs for AMU in veal calves, pigs and poultry. Thirty-three observational studies were included. Well-identified RFs for an increased AMU are frequent purchase of animals, herd size (large or small depending on the animal species), and a lack of selected biosecurity measures. Also in beef breed calves, more antimicrobials are used than in Holstein calves. AMU is influenced by the farmer, the veterinarian and by the integration. In general, socio-economic RFs are largely unexplored. The causal factors for AMU are multiple and complex, with possible confounding factors and unidentified interactions. Additional knowledge of socio-economic drivers appears particularly urgent to create tailor-made guidelines and awareness campaigns for each sector.

SAMENVATTING

De Europese Unie vraagt om een dringende reductie van het antimicrobieel gebruik bij voedselproducerende dieren. Het uiteindelijke doel is een daling van het antimicrobiële resistentieniveau bij mens en dier en de doeltreffendheid van antimicrobiële middelen te behouden voor toekomstige generaties. De identificatie van risicofactoren voor antimicrobieel gebruik is essentieel om deze reductie te behalen. Dit overzichtsartikel heeft als doel de huidige kennis omtrent risicofactoren voor antimicrobieel gebruik bij vleeskalveren, varkens en pluimvee samen te vatten. Drieëndertig observationele studies voldeden aan de selectiecriteria. Bekende risicofactoren van antimicrobieel gebruik zijn de frequente aankoop van dieren, de grootte van de kudde (groot of klein, afhankelijk van de diersoort) en de afwezigheid van bepaalde bioveiligheidsmaatregelen. Bij witvleeskalveren worden er bij de vleesrassen meer antimicrobiële middelen gebruikt dan bij holsteinkalveren. Het antimicrobiële gebruik wordt beïnvloed door zowel de veehouder, de dierenarts als de integratie. In het algemeen worden socio-economische risicofactoren onvoldoende onderzocht. De uitlokkende factoren van antimicrobiële gebruik zijn multipel en complex, met mogelijke “confounders” en (nog) niet-geïdentificeerde interacties. Bijkomende kennis van de socio-economische factoren is cruciaal voor het ontwerpen van sectorspecifieke richtlijnen en sensibiliseringscampagnes.

INTRODUCTION

Antimicrobial resistance (AMR) is a worldwide health problem in humans and animals (EU, 2016; EFSA, 2017). It causes therapy failure with prolonged hospitalization, increased antimicrobial use (AMU) and mortality risk (Watts and Sweeney, 2010; Economou and Gousia, 2015). If no measures are taken, by 2050, ten million people per year might possibly die of AMR (O'Neill, 2016). Resistant bacteria and their genes can transfer between animal and human hosts directly or indirectly by food intake or through the environment (Box et al., 2005; Bosman et al., 2014). This is the most important reason why the Council of the European Union is determined to approach this health issue from a 'One Health' perspective, demanding collaboration and mutual efforts from both the human health sector as the agricultural and veterinary sectors (EU, 2016).

Food-producing animals, especially those reared under intensive conditions, like veal calves (Graveland et al., 2011; Haenni et al., 2014), pigs (Smith et al., 2009; Mutters et al., 2016) and poultry (Mulders et al., 2010; Persoons et al., 2011; Kluytmans et al., 2013), are important reservoirs for AMR genes (Callens et al., 2017). These industries have in common the use of both group and oral antimicrobial treatments (Casal et al., 2007; Callens et al., 2012; Pardon et al., 2012a; Persoons et al., 2012; Arnold et al., 2016), which are highly associated with AMR (Dunlop et al., 1998; Varga et al., 2009). However, every use of antimicrobials selects for AMR (Barbosa and Levy, 2000), which is seen in pathogens but also in commensal bacteria and zoonotic agents. In addition, the transfer of multidrug resistant bacteria between animals and humans is worrisome, for example methicillin-resistant *Staphylococcus aureus* (MRSA) in pigs and veal calves (Smith et al., 2009; Graveland et al., 2010), the emergence of extended spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBL) in veal calves and poultry (Hordijk et al., 2013; Kluytmans et al., 2013) and the recent discovery of transferable colistin resistance in *Escherichia coli* from veal calves (Malhotra-Kumar et al., 2016), pigs (Brauer et al., 2016; Liu et al., 2016), poultry (MARAN, 2016) and humans (McGann et al., 2016). AMR in animals is monitored in different countries in foodborne pathogens *Salmonella enterica* and *Campylobacter* spp. and in commensal indicator bacteria, such as *Escherichia coli* for Gram-negative bacteria and *Enterococcus faecium* and *Enterococcus faecalis* for Gram-positive bacteria (EFSA, 2017). Of all food-producing animals, veal calves, pigs and poultry have high (multi)resistance levels, in contrast to dairy and beef cattle (Kaesbohrer et al., 2012; Chantziaris et al., 2014; Hanon et al., 2015; CODA, 2016; Dorado-García et al., 2016).

The most important risk factor (RF) for developing AMR is AMU (Barbosa and Levy, 2000; Bosman

et al., 2013; Holmes et al., 2016). Therefore, the reduction of AMU is a top priority in the global health policy (WHO, 2011). In several EU countries, like Belgium, a new legislation has been initiated requiring sampling and antimicrobial sensitivity testing before critically important antimicrobials (in casu fluoroquinolones and third- and fourth-generation cephalosporins) can be used (KB 21st of July, 2016). Also, benchmarking farmers and veterinarians is done in different EU countries (www.aacting.org). This system allows farmers to compare their usage at the farm and veterinarians to compare prescription behavior with each other. Independent or governmental organisations are then able to identify high users and may stimulate them towards a reduced use or less antimicrobial-based prescriptions (SDa, 2016). Between countries, whether their general use is high or low, there is a huge variation in antimicrobial usage between farms and sectors (Pardon et al., 2012a; Bos et al., 2013; Sjölund et al., 2016). To be able to rationally reduce antimicrobial consumption, knowledge of the drivers of AMU is essential. Therefore, the objective of the present review was to summarize currently identified RFs for AMU in food-producing animals (veal calves, pigs and poultry).

MATERIALS AND METHODS

A search was conducted in Pubmed, Web of Science and Google Scholar on the following terms and their combinations: calves, pigs, poultry, cattle, antimicrobial use, antibiotic use, risk factor and socio-economics. Primary inclusion criteria were an observational study design and the use of standard daily dose methodology to quantify on-farm AMU (Jensen et al., 2004).

RISK FACTORS FOR ANTIMICROBIAL USE

The literature search identified a total of twenty articles with the primary inclusion criteria. Six studies for veal calves, twelve studies for pigs, and two studies for poultry, which in total identified 27 different RFs for AMU. Nine articles were excluded because of inadequate compliance with the STROBE guidelines (Elm et al., 2014). An overview of the significant RFs in veal calves, pigs and poultry is provided in Table 1. Most studies used 'defined daily doses' for animals (DDDvet), three used 'used daily dose' (UDD) and only one 'prescribed daily dose' (PDD). In the next paragraphs, an overview of the identified RFs for AMU is provided. RFs can be divided in two large groups, namely those associated with disease and/or disease prevention and those associated with socio-economic drivers. The interaction between these RFs is complex and extensive schematic representations are available elsewhere (Lhermie et al., 2016). A sim-

plified version is presented in Figure 1. The figure contains the different groups of RFs identified. The level of evidence for these RF groups is only derived from observational studies, as no randomized clinical trials or experimental studies were available to establish causality. The reporting of non-evidenced (hypothetical) relationships of RF groups with AMU was limited to these groups, judged as essential to provide an overview of what is important, based on human studies, but currently unexplored in food-producing animals. In Figure 1, the farmer's decision to use antimicrobials is put centrally in the causal diagram. Presenting the decision to use antimicrobials as a joint decision between farmer and veterinarian would likely most correctly represent the current situation in the field. However, more studies are needed to support this theory.

Risk factors for antimicrobial use associated with disease and/or disease prevention

From a perspective of rational AMU, disease associated with bacterial infection should be the primary motivator for AMU (Figure 1). Unfortunately, the most recognized RF for AMU is disease prevention (Chauvin et al., 2005; Casal et al., 2007; Pardon et al., 2012a; Arnold et al., 2016; Jarrige et al., 2017). In veal calves in France for example, 'starting treatments', i.e. treatments received in the first 15 days of fattening, are responsible for 33.7% of the AMU (Jarrige et

al., 2017). In pigs, 58% (Casal et al., 2007) up to 93% (Arnold et al., 2016) of the antimicrobials are used as a prophylactic oral therapy. Only a small percentage (7%) of the antimicrobials in pigs are used after diagnosis with pneumonia, diarrhea and lameness (Arnold et al., 2016). In contrast, only a couple of studies do associate the presence of disease with AMU (Hughes et al., 2008; Sjölund et al., 2015; Lava et al., 2016b). Lava et al. (2016b) showed that a 10% increase in bovine respiratory disease (BRD) incidence is a RF for metaphylactic antimicrobial therapy in veal calf farms. BRD is the main indication for AMU in veal calves, accounting for 53% of group treatments and up to 79% of the total AMU (Sargeant et al., 1994; Pardon et al., 2012; Lava et al., 2016a; Fertner et al., 2016). The relationship between disease and AMU is further supported by the observation that specific pathogen free (SPF) Swedish farrow-to-finish pig herds use significantly less antimicrobials compared to non-SPF herds (Sjölund et al., 2015). In poultry, positive associations between necrotic enteritis, coccidiosis, feet disorders and respiratory diseases and AMU have been demonstrated (Hughes et al., 2008; Persoons et al., 2012). It is important to realize that in intensively reared, food-producing animals, disease frequency estimates have historically been often blurred by the preventive/metaphylactic antimicrobial treatments on arrival. For example, in veal calves, 13 to 34% of the total AMU accounts for treatment on arrival (Pardon et al., 2012a; Jarrige et al., 2017).

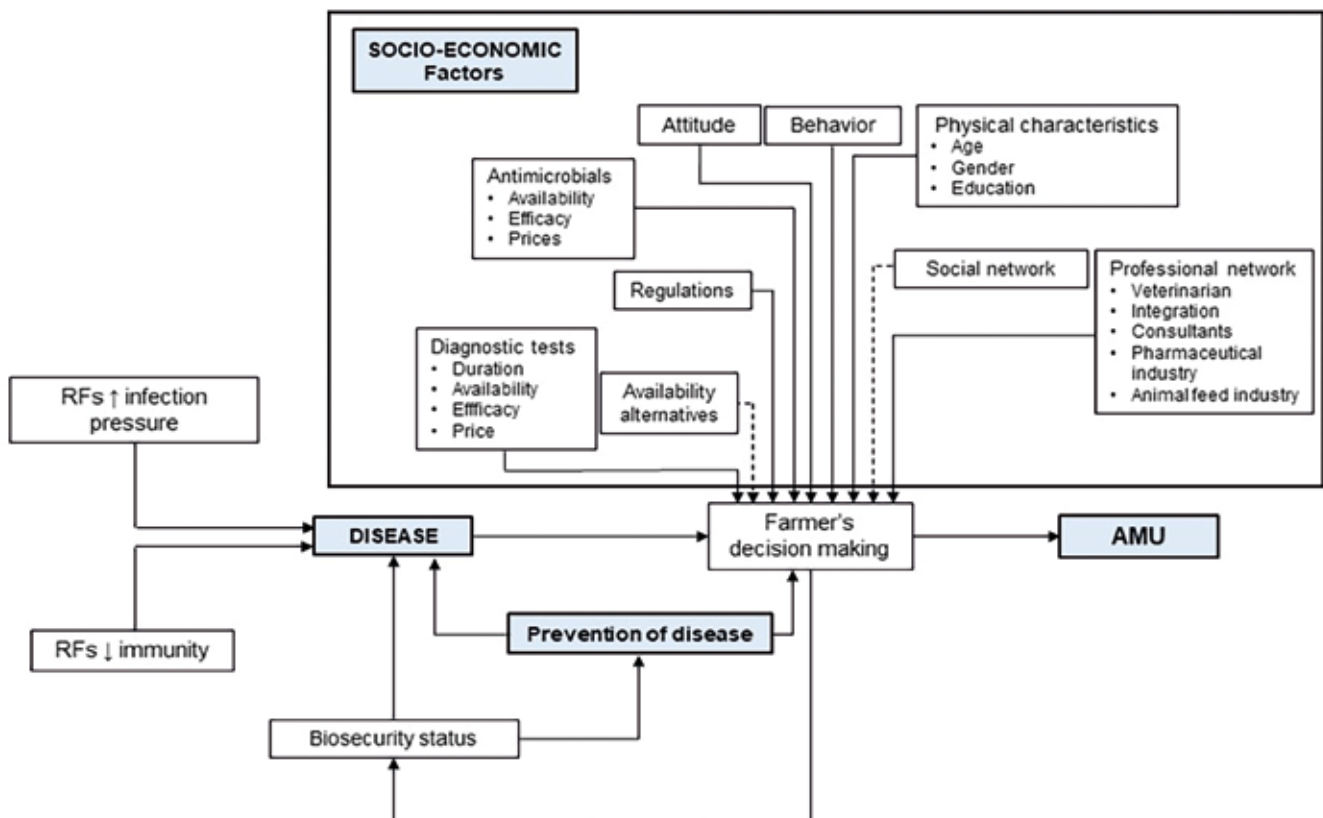


Figure 1. Causal diagram illustrating epidemiologically evidenced (full line) and hypothetical (dotted line) associations between groups of risk factors (RFs) and AMU in food animals (veal calves, pigs and poultry).

Next, identified RFs for AMU, which are associated with disease and disease prevention, are summarized. RFs that increase infection pressure or pathogen spread may be distinguished from RFs that compromise immunity.

Increased infection pressure

Purchase and size of the herd

Purchase is a major RF for AMU identified in veal calves and pigs (Casal et al., 2007; Hybschmann et al., 2011; Van der Fels-Klerx et al., 2011; Fertner et al., 2016; Lava et al., 2016b). Purchase is still most prominently present in the veal industry, but whether calves originate from a market or directly come from the farm of origin does not affect the total AMU (Fertner et al., 2016). Commingling piglets from different farms is a higher risk for oral AMU than the purchase from a single farm (Arnold et al., 2016). Hughes et al. (2008) reported that when broilers were purchased from different hatcheries, the therapeutic AMU reduced, but preventative AMU increased. No information about the total AMU was shown. In another study however, it was concluded that prophylactic use in turkeys is associated with a higher AMU (Chauvin et al., 2005). In contrast, in a study with veal calves, therapeutic antimicrobial treatment of BRD was higher in herds not receiving arrival treatment. However, the total AMU over the study period was the same in both groups (Rérat et al., 2012).

Purchase and commingling likely influence AMU through a higher disease incidence. When commingling, animals are exposed to an increased number of pathogens (Callan and Garry, 2002) and to stress caused by transport and creating new groups (Carroll and Forsberg, 2007), leading to increased morbidity rates and subsequent AMU. In a veal setting, an increased herd size is always linked with a higher degree of purchase and more herds of origin. In a study with Swiss veal calves, the likelihood to administer metaphylactic antimicrobial therapy increased significantly with a larger herd size, more farms of origin and a higher number of calves per pen (Lava et al., 2016b). In pigs, there is a contradiction of the effect of herd size on AMU. Several studies have shown an increased AMU with an increased number of sows on the farm (Van der Fels-Klerx et al., 2011; Backhans et al., 2016; Temtem et al., 2016). It is possible that disease was a confounding/intervening factor in these studies, as herd size is also an identified RF for developing different diseases in pigs (Tuovinen et al., 1992; Maes et al., 2001), because of the increased risk of introduction and pathogen spread in larger herds. In contrast, Hybschmann et al. (2011) found a negative association between herd size and AMU for gastrointestinal diseases. This is in line with Vieira et al. (2011), who studied fattening pigs and also concluded that smaller herds are a RF for AMU. In another study,

an influence of farm size on AMU was found, but only when accounting for the veterinarian (van Rennings et al., 2015). Postma et al. (2016) did not find a link between herd size and AMU in a study on 227 pig herds. A possible explanation is that some veterinarians deal with farms with different sizes and treatment protocols may be highly variable. Moreover, it might be that larger herds are managed in a more professional way, with a higher level of biosecurity, less pathogen spread and less disease (Gardner et al., 2002; Van der Wolf et al., 2011; Laanen et al., 2013). So far, in poultry, flock size as a RF for AMU has not been identified yet. However, a larger flock is positively associated with disease (Tablante et al., 2002) and mortality (Heier et al., 1999).

Altogether, purchase is a well-identified RF, whereas herd size is less clear, because of the additional differences, which are associated with herd size, i.e. purchase, herds of origin, infection pressure, management and biosecurity.

Internal and external biosecurity

Biosecurity can be separated in internal and external biosecurity. External biosecurity is about keeping pathogens from entering a herd (Laanen et al., 2013) and internal biosecurity deals with reducing infection pressure within a herd. Laanen et al. (2013) found a negative association between biosecurity scores and prophylactic AMU in breeder-finisher pig herds in Belgium, indicating that higher biosecurity scores are associated with lower AMU levels. They divided measurements in internal biosecurity, i.e. disease management, different units, cleaning and disinfection, and external, i.e. purchase, transport and environment, and combined these to an overall score. The overall score and the internal biosecurity were both negatively associated with AMU, whereas there was no relationship with external biosecurity. In contrast, a Swedish study on farrow-to-finish farms showed no association between biosecurity and AMU at all (Backhans et al., 2016). Possible explanations are the already very low AMU and the advanced internal biosecurity in Swedish farms (Postma et al., 2016a), and an overall better health status of the pigs (free of porcine reproductive and respiratory syndrome virus) or a lack of power in this study. The strongest associations reported by Laanen et al. (2013) were disease management and measurements during the birth and suckling period. In another study, treating ill animals before visiting the healthy piglets and the absence of an all-in-all-out production system were RFs for oral AMU (Arnold et al., 2016). Considering external biosecurity, the use of quarantine and performing a clinical examination upon arrival have been associated with a lower AMU in Swiss veal calves (Lava et al., 2016a). In pig farms, the availability of changing facilities has been associated with lower prophylactic AMU (Casal et al., 2007) and the absence of working clothing has

been a RF for oral AMU (Arnold et al., 2016). In turkey, changing clothes and shoes before entering the facility has also been associated with lower AMU (Chauvin et al., 2005). Farmers working in a single farm are also a RF for increased AMU, probably because there is less exchange of knowledge about biosecurity (Arnold et al., 2016). Farms with a higher external biosecurity status have been associated with a lower AMU (Postma et al., 2016a).

Hygiene is an internal biosecurity factor, which influences AMU. Poor hygiene of the water supply system has been associated with an increased oral AMU in recently weaned piglets (Hirsiger et al., 2015). Similarly, also at broiler farms not controlling water quality has been a RF for increased AMU (Persoons et al., 2010). In veal calves, the effect of hygiene has hardly been studied, but disinfection between batches (Jarrige et al., 2017) and cleaning frequency within or longer than thirty days have not been associated with AMU (Lava et al., 2016a). In broiler farms, wet litter is a RF for therapeutic AMU (Hughes et al., 2008). In this association, disease is probably a confounder, because wet litter is often a result of coccidiosis (Hermans et al., 2006) and may induce ulcerative lesions resulting in secondary infections (Martland, 1985).

In summary, the relationship between biosecurity measures and AMU in the different sectors is complex and likely severely influenced by behavioral factors/farmer characteristics (Backhans et al., 2016) and the presence of particular pathogens in a given farm. It is important to realize that so-called 'early adapters', might take efforts to reduce AMU and increase biosecurity at the same time to comply with current societal demands from the industry.

Housing and region

In only five studies, the relationship between housing factors and AMU has been explored. Lava et al. (2016a) concluded that a shared air space by different groups of white veal calves is positively associated with AMU. Additionally, housing pigs with age differences larger than one month in a shared air space is a RF for respiratory diseases (Jäger et al., 2012), which may indicate that disease is the direct driver for the higher AMU. Moreover, Jarrige et al. (2017) concluded that calves housed with six to ten animals in a pen are more treated with antimicrobials than pair-housed calves. Also, separated feed and lying area are positively associated with AMU (Lava et al., 2016a). Influence of ventilation system, floor type, number of calves per nipple and stall climate on AMU has not been reported (Lava et al., 2016a; Jarrige et al., 2017).

Additionally, regional farm density affects AMU. Oral AMU is higher when more sow-farms are present (Van der Fels-Klerx et al., 2011) or when the next pig farm is located within 500 metres (Arnold et al., 2016). Also Hybschmann et al. (2011) found an association between region and AMU in pigs with gastro-

intestinal problems, and Lava et al. (2016a) found a regional effect on AMU in veal calves. Other studies in veal calves (Jarrige et al., 2017) and pigs (van Rennings et al., 2015) could not identify any regional effects. Disease incidence and likely also the treating veterinarian and the socio-economic background of the region may act as confounders for these regional differences and housing effects. For example, swine density in an area is a known RF for seroprevalency of different pathogens (Maes et al., 2000).

Housing (shared airspace, pen density and separated feed and lying area) and regional farm density influence AMU; however, further research is needed because only a few factors associated with housing and region have been investigated.

Year and season

A significant annual variation in AMU has been documented in Belgian veal calves (Bokma, 2017). A possible reason may be the variable meteorological conditions, i.e. temperature, humidity and abrupt changes, which affect the infection pressure and exposure to cold stress. In the same study by Bokma (2017), independent of year, calves which arrived in the warmer months of the year, e.g. May, were administered significantly less antimicrobials than calves arriving in September to December. Also in Danish veal calves, the largest AMU has been seen in autumn and winter (Fertner et al., 2016). Other explanations for an annual variation in AMU might be influences of legislation and campaigns concerning antimicrobial reduction or other currently unidentified socio-economic drivers.

Mortality

Results from a study in white veal calves in France showed that more antimicrobials were used in farms with mortality risks over 5% (Jarrige et al., 2017). Casal et al. (2007) found a lower frequency of prophylactic AMU when the mortality rate was beneath 3% in pigs. In broilers, a higher mortality rate has been associated with increased therapeutic AMU (Hughes et al., 2008). Until today, the risk of an increased mortality when lowering AMU, as feared by all food-animal sectors, has actually not been substantiated by any study.

Compromised immunity

Apparently, 77% of Dutch veterinarians and 67% of Flemish veterinarians (n=611 veterinarians) believe a compromised immune system is an important reason for AMU (Postma et al., 2016b). However, hard evidence on the association of compromised immunity and the need for AMU is completely lacking. In calves, breed has been associated with an increased AMU on different occasions, with beef breeds, in which more

Table 1. Overview of identified risk factors (RFs)* for antimicrobial use (AMU) in food-animal studies.

Veal calves		Pigs		Poultry	
Reference	Identified RFs	Reference	Identified RFs	Reference	Identified RFs
Bokma (2017)	Belgium blue breed	Arnold et al. (2016)	No work sequence depending on healthy before sick pigs	Chauvin et al. (2005)	One full-time job at farm
	Integration		Working on other farms		No changing of clothes and shoes upon entering the facilities
	Month of arrival		Distance to the next pig farm < 500m		No competitive exclusion flora administration
	Year		Absence of visitor boots		Prophylactic antimicrobial treatment
Fertner et al. (2016)	Number of calves introduced		No analysis of production parameters	Persoons et al. (2010)	No control of water quality
	Season		No application of homeopathic agents		Bad hygienic condition of medicinal treatment reservoir
Jarrige et al. (2017)	Number of calves per pen		Mixing pigs of different suppliers within the same pen		
	Mortality rate		Backhans et al. (2016)		Number of sows
Lava et al. (2016a)	Beef breed		Gender farmer		
	No clinical examination upon arrival		Education farmer		
	No quarantine upon arrival		Age farmer		
	Same air space different groups		Callens et al. (2012)		Weaned piglets
Pardon et al. (2012a)	Smaller integration size	Hirsiger et al. (2015)	Poor hygiene of water supply		
			< 2 veterinary visits per year		
			No analysis of production parameters		
			Continuous occupation		
		Kruse et al. (2016)	Vaccination against PCV-2		
		Laanen et al. (2013)	Vaccination against <i>M. hyopneumoniae</i>		
			Disease management		
			Farrowing and suckling period		
			Inadequate biosecurity		
		Postma et al. (2016a)	Weaned piglets		
			Vaccination		
			Inadequate biosecurity		
		Sjölund et al. (2015)	No specific pathogen free herd		
Sjölund et al. (2016)	Weaned piglets				
Temtem et al. (2016)	Number of sows				
	Vaccination against PCV-2				
	Vaccination against <i>M. hyopneumoniae</i>				
Van der Fels-Klerx et al. (2011)	Farm system				
	Population density of region				
	Number of sows				
Van Rennings et al. (2015)	Farm size				
	Weaned piglets				

*all mentioned risk factors are positively associated with AMU (increased usage)

Table 2. Overview of studies on socio-economic drivers for antimicrobial use (AMU) included in the present review.

Reference	Year	Title
Cattaneo et al.	2009	Bovine veterinarians' knowledge, beliefs, and practices regarding antibiotic resistance on Ohio dairy farms
De Briyne et al.	2016	Factors influencing antibiotic prescribing habits and use of sensitivity testing amongst veterinarians in Europe
Ge et al.	2014	A Bayesian Belief Network to infer incentive mechanisms to reduce antibiotic use in livestock production
Gibbons et al.	2013	Influences on antimicrobial prescribing behaviour of veterinary practitioners in cattle practice in Ireland
Jones et al.	2015	Factors affecting dairy farmers' attitudes towards antimicrobial medicine usage in cattle in England and Wales
McDougall et al.	2016	Factors influencing antimicrobial prescribing by veterinarians and usage by dairy farmers in New Zealand
Postma et al.	2016b	Opinions of veterinarians on antimicrobial use in farm animals in Flanders and the Netherlands
Speksnijder et al.	2014	Determinants associated with veterinary antimicrobial prescribing in farm animals in the Netherlands: a qualitative study
Speksnijder et al.	2015	Attitudes and perceptions of Dutch veterinarians on their role in the reduction of antimicrobial use in farm animals
Stevens et al.	2007	Characteristics of commercial pig farms in Great Britain and their use of antimicrobials
Visschers et al.	2014	Swiss pig farmers' perception and usage of antibiotics during the fattening period
Visschers et al.	2015	Perceptions of antimicrobial usage, antimicrobial resistance and policy measures to reduce antimicrobial usage in convenient samples of Belgian, French, German, Swedish and Swiss pig farmers
Visschers et al.	2016	A comparison of pig Farmers' and veterinarians' perceptions and intentions to reduce antimicrobial usage in six European countries

antimicrobials are used than in dairy breeds (Lava et al., 2016a; Bokma, 2017). For the Belgian blue beef breed, this can possibly be explained by a difference in susceptibility of respiratory diseases, due to their anatomy (Bureau et al., 1999; Pardon et al., 2012b) or socio-economic drivers, like risk aversion (Bokma, 2017). Also young age is believed to increase disease susceptibility and subsequently AMU, but studies have shown different outcomes. In veal calves, Bähler et al. (2016) did not find an association between age at introduction at the farm and AMU. In pigs, weaned piglets have shown the highest AMU (Callens et al., 2012; Postma et al., 2016a; Van Rennings et al., 2015; Sjölund et al., 2016). In contrast, Stevens et al. (2007) did not find any age effect in pigs, which is possibly due to general herd health in this study.

To improve immunity, a lot is expected from vaccination as a tool to reduce AMU. Unfortunately, the amount of peer-reviewed studies on this matter is limited. In veal calves, both Fertner et al. (2016) and Jarige et al. (2017) did not find any effect of vaccination against BRD on AMU. Also in pigs, there has been no association between vaccination against *Lawsonia intracellularis* (Sjölund et al., 2015; Kruse et al., 2016; Temtem et al., 2016) or *Mycoplasma hyopneumoniae* (Sjölund et al., 2015) and AMU. Moreover, in Great Britain, vaccinating suckling piglets and weaners has been significantly associated with an increased AMU in feed (Stevens et al., 2007). Vaccinating weaners against porcine circovirus type 2 (PCV-2) and *M. hyopneumoniae* and vaccinating broilers against infectious bursal disease (IBD) has led to an increased AMU (Hughes et al., 2008; Kruse et al., 2016; Tem-

tem et al., 2016). In pigs, Postma et al. (2016a) found a positive association between the number of pathogens vaccinated against and AMU, suggesting that in farms where more vaccines are used, also more antimicrobials are used. A possible explanation might be that in herds and flocks facing a high disease incidence, it might be more likely to start vaccinating next to continuing AMU to counteract the problem until the infection pressure is reduced (Postma et al., 2016a). To date, there is no clear evidence that vaccination reduces AMU; however, it is questionable if cross-sectional studies are fit to explore this topic.

In poultry, in only a handful of studies, nutritional influences on AMU have been looked at. In broilers, diets predisposing for necrotic enteritis, like whole wheat diets, have been associated with an increased AMU (Hughes et al., 2008). In contrast, controlled feeding regimes decrease preventive AMU (Hughes et al., 2008), possibly due to less foot lesion problems and reduced mortality rate (Robinson et al., 1992).

AMU due to decreased immunity may be influenced by breed and nutrition. Also age and vaccination may be a RF, but further research is needed (Figure 1).

Socio-economic drivers for AMU

Socio-economics drivers are factors based on how economic activity and social processes influence each other. In few studies, socio-economic RFs for AMU have been identified, and in only a few of them, standard daily dose methodology was used. Therefore, also studies dealing with socio-economic RFs for AMU, but not applying standard daily dose methodo-

logy, were included in this article. In Table 2, an overview of these thirteen studies is given.

Integrations, farmers and veterinarians

Next to RFs associated with disease, socio-economic drivers for AMU in food animals can be identified and are also shown in Figure 1. These socio-economic drivers influence the behavior of farmers, veterinarians and integrations. Behavior is an important influencer of the management in a farm, which subsequently affects both disease incidence and antimicrobial drug administration. An integration is a company that has ownership of different branches in the industry like transport, farms and slaughterhouses. Integration is very common in intensive food animal production (veal calves, pigs and poultry). In veal calves, an integration directly affects the amount of antimicrobials used in a particular farm (Pardon et al., 2012a; Bokma, 2017). Smaller integrations in Belgium are likely to use more antimicrobials for group treatments than larger integrations (Pardon et al., 2012a). More recently, a significant effect of the integration on the total AMU and on the use of critically important antimicrobials has been found (Bokma, 2017). In that research however, only one veterinary practice was studied, which excluded the veterinarian as a confounder. In contrast, Jarrige et al. (2017) found a smaller intraclass correlation coefficient (0.06) between integrations in France, compared to farmers (0.14) and veterinarians (0.12), indicating a smaller influence of integration than the influence of farmers and veterinarians in France.

Logically, the prescription behavior of a veterinarian has an effect on quantitative and qualitative AMU on farms in his/her practice. Although studies on characteristics of the veterinarian associated with his/her prescription behavior in food animals are lacking, it has been observed that older veterinarians worry less about AMR than their younger colleagues (Cattaneo et al., 2009; Speksnijder et al., 2015; McDougall et al., 2016). A reason could be that older veterinarians have not gotten the most recent education to create awareness on this topic in combination with preventive veterinary medicine.

In farmers, a positive association between risk aversion and prophylactic AMU has been identified (Ge et al., 2014). This could be explained by fear for disease. At least in some cases, a part of the prophylactic AMU is replaced by other products, like pro- or prebiotics, homeopathy or herbs. Arnold et al. (2016) identified homeopathic substances as a factor reducing AMU in pigs. This is in contrast to what Lava et al. (2016a) concluded in veal calves, namely that homeopathic therapy is not associated with AMU. Chauvin et al. (2005) and Hughes et al. (2008) concluded that the use of competitive flora is negatively associated with AMU. Competitive flora interferes with certain pathogens in the gastrointestinal tract and prevent diseases. When antimicrobials are used, this effect

is probably nullified (Hakkinen and Schneitz, 1999). The previous findings can be explained by the risk-averse nature of farmers or veterinarians who might just desire that the animals receive at least something to protect them; so, any replacement of antimicrobials will do (Arnold et al., 2016).

Also other socio-economic and management related RFs for AMU were identified in weaned piglets, i.e. less than two mandatory visits by the veterinarian a year (Hirsiger et al., 2015) and the absence of an internal analysis of production parameters (Hirsiger et al., 2015; Arnold et al., 2016). Also Visschers et al. (2014) showed that only using antimicrobials after asking a veterinarian is associated with a lower animal treatment index. These factors might refer to a less developed relationship between farmer and veterinarian, which is positively associated with AMU in pig farms (Visschers et al., 2016), suggesting the influence of socio-economic drivers upon management decisions.

Awareness of antimicrobial use

Next to studies directly on AMU data, there are some studies available focusing on the opinion of vets and farmers on AMU and AMR. The main reasons for farmers to use antimicrobials appear to be personal experience and veterinary advice (McDougall et al., 2016). However, veterinarians do think that the farmer's state of mind is one of the important reasons why antimicrobial consumption is that high in food animals (Postma et al., 2016b). In a recent study among pig farmers, it has been shown that it is not biosecurity measures, nor the attitude towards the use of antimicrobials, which determine AMU, but rather farmer's characteristics, such as age (higher use of antimicrobials when older), gender (more in females) and level of education of the farmer (more antimicrobial use when university education) (Backhans et al., 2016). However, this is in contrast with findings of Visschers et al. (2014), who did not find any relation between characteristics (age, years of experience) of the farmer and AMU.

Factors influencing the prescription of antimicrobials considered important by veterinarians are diagnosis, previous experience (Gibbons et al., 2013; McDougall et al., 2016; Postma et al., 2016b) and results from antibiograms (De Briyne et al., 2016; Postma et al., 2016b). Also non-clinical factors, such as withdrawal period (Speksnijder et al., 2014; McDougall et al., 2016), preferences and pressure from the farmer, price, temper of the animal, skills of the farmer (Gibbons et al., 2013), treatment interval and application route (Speksnijder et al., 2014) are important. In a study by Lava et al. (2016b), it was demonstrated that individual therapy reduces AMU in Swiss veal calves, but is sometimes difficult due to the temper of the animal and skills of the farmer. In contrast, Bokma (2017) found a positive association between a larger individual AMU and the total AMU, possibly because of frequently used long acting macrolides in that

study. In addition, risk management, such as fear to be blamed by the farmer afterwards and reducing animal suffering (Speksnijder et al., 2014), are important drivers for veterinarians to prescribe antimicrobials.

It still appears to be an important task to make farmers aware of the risk of AMR by excessive AMU (Visschers et al., 2014; Visschers et al., 2016). Of pig- and dairy farmers from New Zealand, England and Wales, respectively 26%, 30% and 32% are not aware of these risks (Stevens et al., 2007; Jones et al., 2015; McDougall et al., 2016). Moreover, there is a difference between countries. Especially French and Belgian farmers do not worry much about AMR in contrast to German, Swiss and Swedish farmers. Additionally, it is remarkable that Flemish pig farmers report to receive less information from their veterinarians about rational AMU, risks of AMU and alternatives for AMU than in other countries (Visschers et al., 2015).

Regulations and price-related objectives could help to reduce AMU (Ge et al., 2014; Visschers et al., 2014). By rising antibiotic costs, farmers with high AMU are more affected than those consuming less antimicrobial products. When farmers and veterinarians are asked about drivers, which will lead to reduce their AMU, farmers believe approval of their social network (Jones et al., 2015), cuts in meat price when pigs are treated with a lot of antimicrobials (Visschers et al., 2015), using vaccines and improving housing (Stevens et al., 2007) will reduce AMU. Motivational drivers for farmers to change their behavior are associated with animal welfare, economy (Visschers et al., 2015) and experience with therapeutic failure due to AMR (Visschers et al., 2016). Dutch veterinarians especially believe in the effect of benchmarking, improving feed quality (Speksnijder et al., 2015; Postma et al., 2016b) and housing (Speksnijder et al., 2015). In the Netherlands, benchmarking has already contributed to a noteworthy reduction in AMU, because veterinarians and farmers are able to compare themselves with colleagues (SDa, 2016). It confronts them with their own AMU, which leads to more awareness. More studies show that benchmarking will stimulate veterinarians and farmers to meet the regulations (Ge et al., 2014; Visschers et al., 2014; Visschers et al., 2016). Factors which keep farmers and veterinarians from reducing AMU, are in case of Dutch and Flemish farmers a financial matter (Visschers et al., 2015; Postma et al., 2016b). Reasons why they do not follow their veterinarians' advices is because of costs, too much time consuming measurements and contradictions in advices from different consultants at their farm (Speksnijder et al., 2014). It is important to mention the differences between countries in perception and behavior concerning AMU, which may demand different approaches to reduce AMU in different countries (Postma et al., 2016b; Visschers et al., 2016).

As mentioned earlier, studies directly evidencing the effect of behaviors on AMU are currently lack-

ing. To alter behavior and habits to reduce AMU, it is necessary to change the motivation of farmers, veterinarians and integrators to use antimicrobials. These changes may be initiated by collecting knowledge on the key drivers of AMU and by changing the current attitude towards AMU (Trepka et al., 2001). It is highly recommended that also studies on socio-economic and behavioral drivers use standard daily dose methodology to express AMU, so comparability between international studies can be strengthened.

CONCLUSION

Despite the high pressure to reduce AMU in food-producing animals, to date, only few RFs for AMU have been identified in a limited number of studies, mostly in veal calves and pigs. RFs for AMU are multiple and complex, with many suspected interactions. A general stimulation of the different intensive food-animal industries towards less purchase and/or a better control of the infectious status of purchased animals are recommended. Improving biosecurity is preferentially done in a tailor-made manner, adapted to a specific farm situation to minimize the cost/benefit ratio. More clarity is needed whether the observed breed differences in AMU in veal calves reflect an increased disease susceptibility in beef breeds or are due to farmer's or veterinarian's risk aversion in the more expensive beef veal calves. The exact influence of housing, region or season needs more clarification in each industry before recommendations can be made. Next to disease and its prevention, the farmer's and veterinarian's decision making process is a key driver of AMU. The socio-economic drivers of this decision are currently almost unexplored in food animals, although knowledge of these factors is crucial to achieve behavioral changes through sector-specific guidelines and awareness campaigns.

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