Front. Agr. Sci. Eng. 2018, **5**(3): 301–311
https://doi.org/10.15302/J-FASE-2018207
Available online at http://journal.hep.com.cn/fase

REVIEW

Antimicrobial use in food animal production: situation analysis and contributing factors

Ziping WU (✉)

Agri-Food & Biosciences Institute, Belfast BT9 5PX, Northern Ireland

Abstract By measuring the quantity and ways in which antimicrobials are used, and reviewing different technical and socioeconomic factors influencing antimicrobial use at farm level, this study discusses the main knowledge gaps in antimicrobial use in food animal production and provides recommendations for future research and policy development. The review reveals that antimicrobial use in food animals exhibit strong regional and species differences, and there are still large information gaps concerning the current state of antimicrobial use. Factors associated with animal health (including antimicrobial resistance), animal health improvement, economic costs and benefits relevant to animal diseases, and potential technological alternatives or alternative systems all have an impact on antimicrobial use on the farm. There is a clear need to resolve the data gap by monitoring antimicrobial use and developing an analytical framework to better understand farmer behaviors under different technical, economic and environmental circumstances.

Keywords antimicrobial use, drivers for antimicrobial use, food animal production

1 Introduction

Antimicrobial use has become an integrated part of modern intensive animal production systems for preventing and treating microbial pathogens (mostly bacteria) that cause animal diseases. It is estimated that in 2010, antimicrobial consumption by food animals was about 63151 t and it is projected that the amount will rise by 67% in 2030, while the human population is only expected to grow by 13% over the same period[1,2].

A key concern about antimicrobial use in food animal production is the development of resistance of bacterial pathogens to antimicrobials, known as antimicrobial resistance (AMR). AMR, an evolutionary mechanism for bacterial survival to the changing environment, develops in all sorts of physical environments. It is regarded as one of most important health threats in the 21st century[3]. Resistance can be accelerated by misuse of antimicrobials including both situations where antimicrobials are overused and where their use occurs at concentrations lower than the therapeutic need. Resistant organisms can be transmitted from animals to humans through product and environment contamination, and geographically through goods and human exchanges[4]. However, AMR is not simply the result of the antimicrobial use, particularly its misuse and overuse, because it also increases the usage of antimicrobials in animal production and accelerates the vicious cycle of high usage—high AMR incidents—further high usage[5].

Given that more than half of antimicrobials have been used for food animals and the AMR organisms are transmissible between animals and humans, reduction of antimicrobial use in food animals, either through direct reduction in misuse and overuse, or by use of alternatives, is a significant strategy in the international efforts to reduce the AMR risks to both animal and human health systems[6].

In food animal production, antimicrobials are mostly used at the farm level. AMR has a limited impact on farm production but potentially has a great impact on consumers and the environment (so called external effect), so a regulatory approach will be essential to effectively reduce the antimicrobial use on farms. This requires an understanding of the quantities of antibiotics used, the ways in which they are used at the farm level and the factors affecting their use[2,7].

This paper examines, through reviewing the literature, two main issues related to antimicrobial use, (1) how antimicrobials are used, and (2) what factors affect antimicrobial use in animal production. The paper is organized as follows. Firstly, the various aspects of antimicrobial use with possible AMR links are described and discussed. This is followed by an examination of factors influencing their use, with emphasize on those

Received June 28, 2017; accepted November 6, 2017

Correspondence: ziping.wu@afbini.gov.uk

operating at farm level in food animal production. Finally, the concept of antimicrobial misuse is examined.

2 State of antimicrobial use in food animal production

Development of AMR is a key concern of the antimicrobial use in food animal production. Although the links between AMR and antimicrobial use are still not clear, it is believed that the prevalence of AMR is not only related to the quantity of the antimicrobial used but also the way in which antimicrobials are administered[4,8].

2.1 Quantity of antimicrobials used

Although great efforts have been made in understanding the use of antimicrobials in food animal production, there are still substantial data gaps at global, regional, national and farm levels. At the global level, the only data available on antimicrobial use are those estimated by Van Boeckel et al.[2]. At the national level, antimicrobial use in animal production is only collected in less than one third of the 180 member countries of the World Organisation for Animal Health (OIE)[9]. Even where data are collected, such as in the EU and the USA, data are only available for the total sales[10]. Antimicrobial use for different species are only available in a few countries such as Denmark[11], Germany[12], Netherlands[13] and Sweden[14]. The data on antimicrobial use for representative farms are only available in the USA from the Agricultural and Resource Management Survey, and the National Animal Health Monitoring Survey[15]. The EU is working on collecting data at farm level and on different species[16]. Thus, time series data for antimicrobial sales at global level are not available, short-term series data are available in a few countries at the national level, but farm level time series data are rare. This data shortage has been a key obstacle in developing sensible antimicrobial reduction strategies and in the study of links between antimicrobial use and AMR.

Nevertheless, some interesting patterns emerge from the existing information on antimicrobial uses at different levels in animal production. Firstly, there is very high variability between countries and species. It is estimated that in 2010 the five countries with the largest share of global antimicrobial consumption in food animal production were China (23%), the United States (13%), Brazil (9%), India (3%), and Germany (3%), and these five countries accounted for more than half the global use of antimicrobials in animal production[2]. Secondly, among different species, antimicrobials are most intensively used in monogastric animals, such as pigs and poultry, followed by feedlot cattle systems and have limited use in dairy cows, sheep and companion animals. In the UK, for example, 87% of antibiotic products were sold for pigs and/or poultry production in 2015. Among those sold, 61% were sold for both pigs and poultry, 15% for pigs only, and 11% for poultry only, and only 13% were for other food animal production[17]. While in Denmark, the pig industry produced 43% of total live biomass but used 76% of total antimicrobials[11]. This indicates that the greatest potential for reduction in antimicrobial use lies with pig and poultry production.

Total antimicrobial use at a national level is relevant to the intensity of both animal population and antimicrobial use. In the past, for comparative purposes, use intensity was often measured in terms of the amount used per unit biomass or deadweight. In Europe, it is now measured in terms of total weight of active ingredient per population correction unit (PCU; i.e., the weight of active antimicrobial ingredient used to produce 1 kg of meat). In 2014, the intensity in the EU varies from the highest 418.8 $mg \cdot kg^{-1}$ in Spain to the lowest 3.1 $mg \cdot kg^{-1}$ in Norway[18]. By animal species, at the international level in 2010, the use intensities for cattle, chicken and pig were 45, 148 and 172 $mg \cdot PCU^{-1}$, respectively. The use of antimicrobials in different countries for selected food animals is shown in Table 1.

The antimicrobial use intensity is believed to be positively related to production intensity in production of monogastric animals. Pork and poultry meat has been

Table 1 Annual antimicrobial use ($mg \cdot kg^{-1}$) in selected species of different countries

Country	Year	Pig	Broiler	Cattle	Multi-species average
Austria[19]	2010	26.1			62.9
Denmark[11]	2014	48.0	13.0	32.0	44.2
France[13]	2014	152.0	151.0	56.0	107.0
Netherlands[13]	2015	53.0	45.0	83.0	64.4
Sweden[14]	2014	12.3			11.5
UK[17]	2016	183.0	17.0	26.0	45.0
World[2]	2010	103.6	112.9	24.8	

Note: (1) Figures reported for individual country were calculated based on the cited sources, and those for the world are from Van Boeckel et al.[2]; (2) they are not totally comparable as the biomass adjustment used in two sources differs. Deadweight was originally used by Van Boeckel et al.[2] and for European countries a live weight measurement was used. For comparison purposes, the fixed conversion rates between live weight and deadweight for pig, broiler and cattle were 0.7, 0.75 and 0.55, respectively, and these were used to adjust the figures from Van Boeckel et al.[2]; (3) multi-specie average data are from the ESVAC[16] report except that for the UK which is from the UK-VARSS report[17].

produced over the last few decades more efficiently, more intensively and at larger scale in all but the poorest countries[20,21]. Antimicrobial use has been significant in ensuring animal health in these efficient and intensive production systems. However, there is no single agreed method to measure the antimicrobial use intensity. Using the weight of active ingredients is subject to some criticisms. Firstly, the effective weights of different medicines for the same disease control may be different. Using the weight as an indicator may lead a policy toward the low weight treatment plan which may not necessarily be the most effective one. Secondly, as the links between antimicrobial use and AMR are not fully quantified, but appear to be nonlinear and dependent on the use patterns and other circumstantial factors, a higher weight use does not necessarily cause AMR. Rather in some low weight cases (e.g., used as growth promoter; AGP), the subtherapeutic use causes AMR[22]. In many European countries, for example in the Netherlands, the intensity is also measured by the number of animal daily dose (ADD) per year to avoid the summation of different antimicrobial ingredient weights, and reflects animal health situation. ADD is defined as the average maintenance dose of a specified medicine per kg of a specified animal per day and ADD per year refers to days being treated with the standard dose in a year[23].

Historically, there are different total use tendencies for different countries. In America, domestic sales of antimicrobials in active ingredients for food animal use have steadily increased from 12587 t in 2009 to 15577 t in 2015, a 24% increase in the past 6 years[24]. While in Europe, the sales have steadily fallen in the period from 2005 for which data are available[18]. A report published in October 2015 by the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC)[18], indicates that sales of antibiotics for use in animals in Europe fell by about 8% between 2011 and 2014. The reduction was partly related to the the reduced level of animal production measured in the PCU (2%) over that period. It was also related to reduction in misuse and overuse of antimicrobials, and adoption of alternative measures[18]. This shows that there is potential to reduce the antimicrobial use in animal production.

2.2 Administration of antimicrobials

In food animal production, antimicrobials are mainly used on the farms for therapeutic use to treat sick animals, prophylactic or metaphylactic use to prevent a disease outbreak for an animal or a group animals, and for use in growth promotion of food animals, where they are called antibiotic growth promoters (AGP)[4]. Fundamentally, AGP use is for disease prevention and the main functions of antimicrobial use in animal production are either preventive or therapeutic[25].

Data on antimicrobial use for both preventive and therapeutic purposes are rarely available. Prophylaxis, or so called preventive antimicrobial use, involves the administration of an antimicrobial agent to apparently healthy individuals to prevent an infection due to a perceived risk. As AGP use is dominant internationally, it is therefore believed that most antimicrobials have been used for preventive purposes. In Denmark, the ban on AGP since 1992 has greatly reduced preventive use of antimicrobials while therapeutic use of antimicrobial has increased[26]. A UK broiler producer survey in 2002–2003 suggested that of farms surveyed, 42% used prescription antibiotics therapeutically, 54% for preventive purposes and 24% used them for dual purposes[27].

Different antimicrobials tend to be effective against different pathogens[28]. So the types of antimicrobials used in animal production appear to be different by country and species[10]. In Europe, the most frequently sold antimicrobials in food animal production in 2014 were tetracyclines (33%), penicillins (26%) and sulfonamides (11%)[18], while in the USA, the top three antimicrobial sales in 2015 were tetracyclines (44%), ionophores (30%) and penicillins (6%)[24]. The growing concern arising from the different types of antimicrobials used in different countries is that some countries might use those reserved for humans in food animal production, and antimicrobials banned in some countries might be used in other countries. A recent report suggested that the antimicrobial fluoroquinolones, which were banned in the USA 10 years ago for potential AMR, are widely used in the UK broiler industry. A recent Panorama program on BBC television also revealed that cephalosporin, a class of β-lactam antibiotic originally derived from the fungus and reserved for human use, is widely used in UK livestock industries. Misuse and overuse of the antimicrobials in different countries are hindering the effectiveness of global efforts to reduce AMR. These factors will continue to affect long-term antimicrobial use.

As a consequence of their importance to human health, some of antimicrobials are classified as critically important antimicrobials (CIA) by the World Health Organization[29], and macrolides, fluoroquinolones, and third and fourth generation cephalosporins are designated as high priority CIA (HP-CIA). In Europe, the sales of CIAs (including third and fourth generation cephalosporins, fluoroquinolones and macrolides) for food-producing animals accounted for about 10% (0.2%, 1.9% and 7.5%, respectively), of the total sales in the 29 countries participating in ESVAC in 2014[18]. In the UK, the total use of CIAs in animals has been reasonably stabled over the past 5 years and accounted for 1.1% of total antimicrobial use in 2015[17]. In the USA, the use of medically important antimicrobials has increased from 7687 t in 2009 to 9702 t in 2015, and the proportion in total domestic food animal use increased from 61% to 62%, but macrolide use increased by 12% during that period[24].

The timing of antimicrobial use for disease prevention seems to be quite similar in different countries. In the USA antimicrobials are mainly used in fallowing sows, in piglets leaving weaning, and in preventing respiratory diseases and diarrhea in pig production, while in broiler production they are injected into eggs and chicks to prevent infection in the breeding and hatching period and for disease treatment, disease prevention and growth promotion in the grow out period[15]. The pattern of use is similar in Europe[30].

Also, different routes of antimicrobial administration are reported. In Europe in 2014, 92% of overall antimicrobial sales were for oral administrations, 7.6% of sales were injectable preparations and 0.5% were for intramammary delivery. Among the EU countries, Iceland, Norway and Sweden used more injections, Portugal, Spain and the UK used more premix, and many other countries used more oral powders and oral solutions[18]. Little information is available on the ways antimicrobials are used in food animal production in other countries, particularly developing countries.

The use of antimicrobials is believed to have created selective pressures for the emergence of resistant microbial strains[31]. So far, the general picture for antimicrobial use measured in terms of quantity and method of use is only partly clear. Although antimicrobials have been used intensively in monogastric animals in confined systems, the usage differs between countries and species, with different types of antimicrobials being used and administrated differently in various countries. Sales data are only available at national level, and short-term time series data are available for only a limited number of countries. Data shortage is still the main problem preventing full understanding of the link between antimicrobial use in farming and AMR[32,33], and the ambiguity of this link in turn limits effective monitoring of antimicrobial use. The current information, however, may be sufficient to conclude that limiting antimicrobial use is the safest option[33]. To reduce antimicrobial use, it is essential to understand the factors affecting their use.

3 Factors affecting antimicrobial use

The method and form of antimicrobial use are likely to be depended on how antimicrobial use in animal production is regulated, what animal diseases are present and how the antimicrobial supply chain is organized. Without properly implemented regulation, antimicrobial use will mostly be determined by farmer's decisions and availability of antimicrobials in the market. In regulated markets, such as in the EU and the USA, the relationship between veterinarians and farmers is also important for understanding farm antimicrobial use[34–36].Therefore, a proper regulation of antimicrobial use needs to cover 'what' and 'how' antimicrobials are supplied and used.

Antimicrobials have been traditionally managed as chemicals, as for other veterinary medicines, and usage is monitored via their maximum residue levels in animal products. The specific regulations on antimicrobial use in animal production have received more attention in recent years as AMR became widespread, usually as part of 'action plans' to combat AMR. The current focuses of the regulation internationally appear to be in two main areas: (1) whether to use antimicrobials as AGP or by prescription and (2) defining regional or country specific CIAs. Some progress in these two areas has been made. A survey of food animal products in 17 key US trading partners suggested that in six jurisdictions, AGP banning and use by prescription is required, five jurisdictions have restrictions in one category but not the other, another five jurisdictions have no restrictions on either category, and no information was available for one jurisdiction[37]. AGP use has been banned in Europe since 2006[38,39], and in the USA the use of medically important antimicrobials in animal feed is being phased out, commencing from the beginning of 2017[40]. As little scientific evidence of the preventive use of antimicrobials is available, scientists have asked for more scrutiny of clinical justifications of their preventive use[30]. Based on the importance in protecting human and animal health and availability of alternatives, CIA lists for humans and animals at global and some regional/country specific levels have also been developed[29,30,40,41].

3.1 Farm use

Broadly speaking, factors affecting antimicrobial use at the farm level can be divided into technical, economical and alternative categories. Of these, technical factors are the basis of antimicrobial use, and economic and alternative factors dictate the choice for their use.

Technically, antimicrobials are used to prevent and control diseases. Therefore, factors and environmental conditions that cause and affect animal diseases against which antimicrobials are used, and factors affecting antimicrobial impacts will directly or indirectly affect antimicrobial use.

Antimicrobials have been used to treat different diseases in different animal species. For example, in Europe, antimicrobials are mainly used to treat post-weaning diarrhea associated with multiple weaning stressors, and respiratory diseases associated with re-mixing, stress caused by transport, inadequate housing or insufficient biosecurity measures on pig farms. Similarly in broilers, the main use of antimicrobials has been for digestive disorders (coccidiosis and necrotic enteritis) and respiratory disease related to inappropriate hatchery hygiene and biosecurity, day-old chick management and environmental control[30]. In adult ruminants the use has been for udder infections and obstetric disorders[30]. A large survey of UK broiler producers in 2002–2003 examined reasons behind the use of antimicrobials for both therapeutic and preventive purposes[27]. It found that therapeutic antimicrobial use was positively and closely associated with enteric diseases (necrotic enteritis), respiration (coccidiosis and wet litter), infectious bursal disease vaccine use and whole wheat feed (in that order), but negatively related to numbers of hatcheries supplying the farms. Preventive use was mostly attributed to individual farm response, positively related to the numbers of hatcheries supplying farms and average slaughter weight, and negatively associated with AGP and alternative use. Therefore, no direct association was found between prophylactic use and disease. Although antimicrobial use is primarily for bacterial infections, it is also used to treat secondary bacterial infections following a primary viral infection[30]. The technical factors relevant to these animal health issues, and animal and farm conditions to combat the diseases need further consideration.

A specific technical reason for the antimicrobial use is AMR. This is mainly because the recommended dose of antimicrobials needed to reduce the risk of AMR has increased over time. It is reported that in the USA the recommended dosage of subtherapeutic antibiotics in AGP has increased from 10 to 20 $mg \cdot kg^{-1}$ in the early 1950s to 40–50 $mg \cdot kg^{-1}$ in the 1970s, to 30–110 $mg \cdot kg^{-1}$ today[42]. The extent of AMR impact on antimicrobial use at the farm level is still not clear due to data shortage problems.

At the individual animal level, the resilience capacity, or immune response, of an animal as it adapts to environmental changes is regarded as a key factor in disease resistance and this capacity can be improved through improved housing, appropriate nutrition, stress reduction, vaccination and genetic selection[30]. Therefore, animal housing, nutritional, stress, vaccination and genetics can also be the factors influencing antimicrobial use.

Technical effectiveness of antimicrobial use is often measured in terms of animal mortality, daily growth and feed conversion rates. Antimicrobial use has been reported to have increased in technical effectiveness at both animal and farm level, though the efficiency seems to have fallen with improvements in animal production conditions[15,43,44].

Current antimicrobial use is also affected by their substitution with alternatives and this provides choices for farmers to reduce antimicrobial use while maintains food security. There is no clear definition of antimicrobial alternatives. As they are mainly used to protect animal health, this definition is used here and all measures to improve animal health and to avoid increases in AMR are defined as alternatives to antimicrobials. Analyzing the key functions of these antimicrobials, we can divide them into either treatment or preventive measures. The preventive measures are used before disease prevalence by improving animal health from birth to slaughter in the production process, including measures in animal breeding, feeding, housing and management.

New generation of antimicrobials and other medical practices are used as treatment measures to replace failing antimicrobial treatments. An OIE symposium in 2012 identified five categories of potential new medical alternatives to antimicrobials in current use. These included (1) gene-encoded natural antibiotics including host-derived antimicrobial peptides, such as defensins and cathelicidins, (2) prebiotics and probiotics, (3) bacteriophages, (4) recombinant synthesized enzymes, such as phytases and carbohydrases, and (5) natural phytogenic feed additives. Development of the new antimicrobials, however, is subject to different economic, ethical and regulatory constraints, consequently only a limited number of new commercial antimicrobials are currently available. It is imperative to create economic incentives for R&D on new antimicrobials and reduce bureaucracy in the approval of new antimicrobials internationally[45]. Concerns about using alternative antimicrobials are usually related to their high cost, long development cycle and risk of resistance development.

It is likely that more alternatives will be for disease prevention rather than treatment. Other alternatives include vaccination, animal welfare and biosecurity measures, animal nutrition, and animal genetic measures. Vaccines have proven to be good alternatives to the antimicrobials. DANMAP reported that the use of vaccine and zinc oxide as alternatives to antimicrobials for both bacterial and viral infections in Danish pig production during the period 2005 to 2014 has led to reduced antimicrobial consumption in Denmark[11].

Changing animal nutrition may also be an important way to reduce antimicrobial use[46]. It has been reported that a mannose-rich fraction, the second generation product of mannan oligosaccharides, has proven to be an effective addition to antibiotic-free diets, providing support for immunity and digestion[47]. It is suggested that using enzymes, particularly phytase and non-starch polysaccharide enzyme segments, would potentially help break down antinutritional factors that are present in many feed ingredients and supplement immature digestive system in young animals, therefore being an indirect substitute for antimicrobials[48]. Danish experience has indicated that combination of vaccines and zinc oxide with control of protein intake of weaning piglets can be an effective nutritional measure to help reduce antimicrobial use[11]. The efficacy of the nutritional measures as an alternative, however, is very much dependent on the targeted microbial strain. They can also have potentially negative side-effects on environment and AMR. For example, use of zinc oxide is reported to have caused heavy metal accumulation on soils through slurry spreading and potentially increased selection pressure toward AMR, and more controlled trials are still needed[30]. Use of zinc oxide as a feed additive has been planned to be phased out in the EU in 5 years from 2017.

Using different animal welfare measures, such as improving animal housing, dietary and hygienic conditions, and maintaining appropriate stocking levels and consistent management practices, may also improve animal health and reduce antimicrobial use in animal production. The substitution of animal welfare measures for antimicrobial use has been approved in many organic farming systems[49,50]. A case study in 61 Flemish pig farms indicated that with different animal and biosecurity measures, including optimization of herd management, biosecurity status, vaccination strategy, anthelmintic therapy and advice on prudent antimicrobial use, antimicrobial use in pigs from birth to slaughter and for breeding animals has been reduced by 52% and 32%, respectively, with concurrent improvements in technical effectiveness of pig production[51]. At the individual animal level, antimicrobial use is negatively and significantly related to the animal internal biosecurity score[52]. Another study using the biosecurity concept also recommended that in order to reduce rapid infectious disease transmissions and mixing of zoonosis viruses, the biosecurity regulations should be promulgated to restrict the colocation of concentrated swine and poultry feeding operations on the same site, and to set appropriate separation distances[53].

More systematic appraisals of potential and existing technology for antimicrobial reduction have become available recently. In a review commissioned by the European Innovation partnership for Agricultural Productivity and Sustainability on how to reduce the use of antibiotics in pig farming, the focus group identified three specific alternatives: vaccination, feeding approaches and breeding, along with general enhancement of animal health and welfare, changing attitudes, habits and behavior of farmers, agricultural advisors and veterinarians, and improving the dissemination of information[54]. More recently, EMA and EFSA reviewed[30] all available measures and successes in reducing the need for antimicrobial use in animal production. It classified available measures into (1) animal management and husbandry procedures that prevent introduction, spread and transmissions of animal diseases between farms, within a farm and by individual animals, (2) diagnostic tools to enable early detection and targeted treatment in a precise way, and (3) alternative measures which include medical substitutes and feed additives. The authors state that antimicrobial use reduction should be based on the concept of prevention being better than cure and the need to work in an integrated way, as multiple parameters in the farming system are highly interdependent. This review called for multidisciplinary research to combine animal production science, animal welfare, veterinary and social sciences[30].

Most of the above discussions are at individual technology level. When combining different technologies into a production system, they may enhance or offset each other due to their possible competitive, complementary or neutral relationships. In the application of technology, there are also adaptability issues — different technologies suit different farming conditions. Therefore, alternative production systems instead of simple technologies should be considered, and a clearer understanding of the interdependency and adaptability of different technologies is required.

One way to define alternative systems is to differentiate technologies and farming environments. At the farm level, animal production is conducted in a production system and technologies are organized seamlessly. Therefore, it is likely that farm level data can be used to identify different alternative systems. For example, a study that examined AGP impact on poultry farms in the USA identified four key measures (i.e., using pathogen testing, expanded sanitary protocols, altered feeding regimens, and hazard analysis and critical control point plans) as the key alternatives to AGP use[55].

Substitution of antimicrobials requires the alternatives to have similar technical functions and cost effectiveness as the antimicrobials they replace. However, substitution by non-medical alternatives often has other effects.

Although farm decision making is fundamentally important in the reduction of antimicrobial use in agriculture, limited studies in quantification of antimicrobial uses at the farm level are available and little is known about factors affecting antimicrobial uses on farms. A statistical examination of over 300 fattening pig and sow farms from 2004 to 2007 in the Netherlands found that the main factors associated with the use of antibiotics include farm system, number of pigs and population density in the region of the farm (the latter only significant for sow farms), while the majority of economic and technical factors such as net farm profit, concentrate price, piglet price and mortality were not significant[56]. Another study examining changes in producer's behavior with regard to input adjustments following a ban on the AGP use in the Danish broiler sector suggested that farmers should improve breeding stocks and increase their expenditure on sundry inputs to improve hygiene, sanitation and prevent bacterial infection in broiler production[57]. By three criteria, (1) perceived effectiveness to reduce disease incidence and/or antimicrobial consumption, (2) believed practical feasibility at farm level, and (3) the expected return on investment (ROI) for the farmer, a study evaluated potential technologies with high technical readiness to be used as alternatives to antimicrobials in food animal production[58]. It was found that the top five measures chosen differ by criteria and expert group. For example, by perceived effectiveness, they were ordered as (1) internal biosecurity, (2) external biosecurity, (3) climate/environmental conditions, (4) high health/specific pathogen free/disease eradication, and (5) vaccination. The top five measures in terms of perceived ROI, however, were ordered as (1) internal biosecurity, (2) zinc/metals, (3) diagnostics/action plan, (4) feed quality/optimization, and (5) climate/environmental improvements. Veterinary practitioners ranked internal biosecurity, vaccination, use of zinc/metals, feed quality optimization and climate/environmental as the top five, while researchers focused more on increased use of diagnostics and action plans. Financial incentives/penalties ranked low in all countries and biosecurity is often cited as one of key measures for improving animal health. Different rankings by different criteria and by different professional groups suggest that the adoption of a potential technology can be a complex process, the impact of the technology may be different and more empirical evidence will be needed.

Finally, the use of antimicrobials is also subject to their economic effectiveness. Like all other inputs in agricultural production, farmers will only use them when its benefit is greater or equal to the costs. In economics terms, the marginal costs should not be greater than marginal benefit. The main benefit of the antimicrobial use is the saving of losses associated with diseases. In the case of preventive antimicrobial use, it may also help to save potential production loss and reduce labor time needed for monitoring animal health, thereby reducing production costs.

As an externality, AMR costs are not usually shouldered by farmers. The net benefit of antimicrobial use at the farm level can be calculated as a change in value of outputs and inputs, which are associated with quantities and prices for both outputs and inputs. Because of AMR concerns, in some markets, antimicrobial-free products tend to command a price premium. It is estimated in the USA, for example, that production, cost of broilers without using antimicrobial is 10% to 15% higher, but supermarkets are selling the produce at about 4.4 $\$ \cdot kg^{-1}$ higher and sometimes even twice the price of meat produced with AGP[59].

Use of antimicrobials or alternatives may also be related to their relative prices. Although historic data on antimicrobial prices are rare, the price of antimicrobials and the total costs of antimicrobial use at the farm level are believed to have fallen in most of countries even with increased usage due to AMR. It is reported that in the USA between 1934 and 1988, the average price of agricultural products had risen while antimicrobial feed additive price had fallen[1]. The continuous decline in antimicrobial price is likely to make replacement of antimicrobial more difficult, at least initially.

Economically, there is no evidence that any alternative is more cost effective than using antimicrobials in animal disease prevention and treatment, other than vaccinations. However, vaccination, in some cases, may affect the animal export market[60]. This economic barrier, however, may only occur in the initial adoption stage of technology and the cost effectiveness of alternatives should improve when these alternatives get into a technical mature period with benefits of scale economies and advances in the technology, as described in the technology adoption life cycle model[61].

All alternatives discussed above are technical ones. The use of market mechanisms, with relative higher prices for antimicrobial-free food, although debatable for its feasibility, can be effective in reducing antimicrobial use in addition to the technical approach, and effective ways to develop such a market deserve more research[59,62,63]. A more recent development is to combine technical and socioeconomic measures as systematic alternatives. In the Netherlands and Denmark, there are reports of RESET model (Regulation, Education, Social pressure, Economics and Tools) and Yellow Card Scheme applications[64,65].

Understanding factors influencing antimicrobial use is a key step in developing effective strategies for reducing their use in animal production. Limited research in this area, as discussed above, is due partly to problems of data shortage, but could also be related to theoretical poverty in this area of study. A common problem for these studies is lack of a clear and logical structure to explain the factors influencing antimicrobial use in dealing with interdependency and causality issues between different variables. For example, in some empirical analysis, change in animal mortality rate, a result of antimicrobial use, is used as an explanatory variable for antimicrobial use[56]. Some others found that economic incentive is not important[58]. Antimicrobial use is mainly for prevention and treatment of animal diseases. The technical and economic factors influencing occurrence and spread of diseases should, therefore, be considered as the main variables in explaining antimicrobial use.

Factors affecting the quantity and methods of antimicrobial use are likely to be different, and the extent of the impact of various factors on antimicrobial use may also differ with the circumstances of use. So far there is no study that quantifies the contributions of these different factors and it is unclear what are the main drivers of antimicrobial use.

3.2 Misuse of antimicrobials in food animal production

Reduction in the use of antimicrobials in food animal production can also be achieved by reducing their misuse. Misuse in its broad sense refer to those of ineffective and inappropriate use of drug, time, dose and duration[9,36,66–68].

Examples include using antimicrobials for virus infections, or using them in overdose or low dose ways. A serious misuse of antimicrobials in the food animal production is using HP-CIAs, reserved for human use[30]. The misuse of antimicrobials in both animals and human has been regarded as one of the main reasons for increasing AMR[69]. The use of AGP in animals has also been regarded as a misuse of antimicrobials, although not all scientists agree[70].

The extent of and reasons for misuse of antimicrobials in human health have been well recorded[71,72] but the situation in animal production is less clear[73]. Instead of using the term ‘misuse’, many international organizations are now using a more positive term, ‘responsible and prudent use’. For example, the OIE has defined the responsible and prudent use of antimicrobials in animal use as “protecting the efficacy of antimicrobial agents, rationalising and supervising the use of antimicrobial agents, surveillance of the use of antimicrobial agents in animals and developing alternative treatments to antimicrobials”[9,41].

Reasons for misuse may relate to the knowledge farmers have and the advice they receive. Government-veterinarian-farmer links, particularly the veterinarian-farmer links, are key to reducing the misuse of antimicrobials in animal production[36,74]. In a prescription based system, a responsible and prudent use (by farmers) is not sufficient for the reduction of misuse of antimicrobials in food animal production, and concerted action by the farming community together with their consulting veterinarians is needed. A clear working plan to significantly increase the health of the food animal populations by optimizing the herd and flock health management is essential[36]. Government interventions is also needed to change the prescribing behaviors of farm animal veterinarians as well as to provide tools to deal with (perceived) pressure from farmers and advisors to have antimicrobials prescribed[35]. A UK government sponsored scientific review[68] also suggested that to reduce the unnecessary use and waste of antimicrobials in agriculture, the following are needed: (1) a global reduction target for food production use in quantity and in variety, along with restrictions on the use of antibiotics important for human health, (2) minimum standards to improve waste management in antimicrobial production, and (3) radical improvement of surveillance in agricultural use and manufacturing waste.

Risks and uncertainties farmers perceive in disease prevention cases can also be a reason for the overuse of antimicrobials in food animal production. There are many agricultural economics studies on the overuse of pesticides in crop production which suggested that the overuse is a typical and rational response of farmers to lack of certainty[75,76]. Governments should be able to help reduce the overuse of antimicrobial though reducing uncertainties in disease control in ways that provide better information and more confidence to farmers.

4 Discussion and conclusions

Considering AMR issues associated with antimicrobial use in food animal production, this review has examined research on the antimicrobial food animal use, the current situation and factors affecting antimicrobial use. It is assumed that the quantity and method of antimicrobial use in food animal production is likely to be contributing to emerging AMR issues, and reduction in antimicrobial use is probably the safest solution. Following this logic, it was found that the state of food animal antimicrobial use at different geographic levels and for different species is unclear due to the problem of data shortage. This shortage is likely to prevent our understanding of the links between the antimicrobial use and AMR, and this in turn will affect AMR monitoring. The existing data show that antimicrobial products, quantity and methods of use differ significantly between countries and animal species, but there are similar times of use. There are still disagreements about the best way to measure antimicrobial use. More effort is required in monitoring antimicrobial use at both national and farm levels to improve understanding of the factors contributing to antimicrobial use and to develop sensible action plans for reducing use.

As AMR is an externality of antimicrobial use in food animal production, a regulatory approach is essential. There are still large knowledge gaps that prevent the development of effective strategies and action plans to limited AMR in food animal production. Apart from efforts in phasing out AGP use, introducing prescription systems and defining CIAs, other government roles in combating AMRs such as monitoring of antimicrobial use and AMR, research and development of new antimicrobial agents need to be strengthened and clarified. Under the One Health concept which is a worldwide strategy for expanding interdisciplinary collaborations and communications in all aspects of health care for humans, animals and ecosystem, detailed action plans for food animal production need to be coherently jointed with those for human and ecosystems. It is also important to understand how a market mechanism which reflects consumer and societal concerns about AMR can be developed and used in reducing antimicrobial use in animal production, and how this can be combined with a regulatory approach in the strategies and action plans. Due to problems in market development, finance and food security, more attention needs to be given to developing countries to build their capacity to reduce antimicrobial use in animal production.

Overall reduction of antimicrobial use in food animal production will require the reduction of misuse, including overuse, of antimicrobials at the farm level, and understanding of the factors affecting farm antimicrobial use. Limited research evidence on misuse of antimicrobials at the farm level is available. Empirical studies in Europe have suggested that misuse needs to be controlled in the government–veterinarian–farmer triangle, through the training and education of both veterinarians and farmers, and reducing the incentives for sales. In reducing overuse on farms, a better understanding of farmer decision making processes is required. The literature suggests that the animal health situation, factors and environmental conditions causing animal health problems, farm economic considerations and different potential technological alternatives or alternative systems may be the main factors determining the quantity and method of antimicrobial use. However, due to the data shortage and theoretical poverty, very limited quantitative research in the area has been conducted, and the main drivers of antimicrobial use remain unclear as are the conditions needed to promote the adoption of possible alternative strategies or systems.

There are many potential antimicrobial alternatives and alternative systems with high technical readiness available. Different alternatives will have different technical, economic and environmental efficacies and applicability. However, the literature suggests that more evidence on the efficacies and applicability of alternatives is needed. To effectively adopt these alternatives, the interdependent relationships between various technologies at the farm level deserve specific attention. Strategically, to reduce antimicrobial use and AMR emergence, more preventive non-medical alternatives need to be adopted.

The pressure for reduction in antimicrobial use in food animal production is partly based on an assumption that high antimicrobial use is likely to present greater selection pressure leading to increased AMR. It is clear, however, that it is not the total quantity used, but the method of use that is a greater potential cause of AMR. Specifically, low dosage (i.e., a sub lethal dosage) may cause AMR. In the case of high dosage animal use, if the antimicrobial used is not sufficiently absorbed by the animal, it may lead to residues in animal products and the environment. This high dose may thus be effectively transformed into a low dose. Therefore, it is always best if antimicrobials are not used unless necessary.

Due to the constraint of data availability, research on appropriate use of antimicrobials in food animal production is still limited. We may, however, learn from the abundant research on control of pesticide use in crop production. The similarities of pesticides as special inputs in crop production with negative externalities, including development of resistance, should provide insights for researchers attempting to develop effective strategies to reduce the antimicrobial use in food animal production.

Compliance with ethics guidelines Ziping Wu declares that he has no conflict of interest or financial conflict to disclose.

This article is a review and does not contain any studies with human or animal subjects performed by the author.

References

1. Laxminarayan R, Van Boeckel T, Teillant A. The economic costs of withdrawing antimicrobial growth promoters from the livestock sector. In: OECD Food, Agriculture and Fisheries Papers. Cedex: *OECD Publishing*, 2015 (78): 1–42
2. Van Boeckel T P, Brower C, Gilbert M, Grenfell B T, Levin S A, Robinson T P, Teillant A, Laxminarayan R. Global trends in antimicrobial use in food animals. *Proceedings of the National Academy of Sciences of the United States of America*, 2015, **112**(18): 5649–5654
3. World Health Organization (WHO). Global action plan on antimicrobial resistance. *WHO*, 2015
4. Rushton J, Ferreira J P, Stärk K D. Antimicrobial Resistance. *OECD Food, Agriculture and Fisheries Working Papers*, 2014, (68): 1–44
5. Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet*, 2005, **365**(9459): 579–587
6. World Health Organization. The evolving threat of antimicrobial resistance: options for action. Geneva: *WHO Library Cataloguing-in-Publication Data*, 2012
7. Silbergeld E K, Graham J, Price L B. Industrial food animal production, antimicrobial resistance, and human health. *Annual Review of Public Health*, 2008, **29**(1): 151–169
8. Visschers V H, Backhans A, Collineau L, Iten D, Loesken S, Postma M, Belloc C, Dewulf J, Emanuelson U, Beilage E G, Siegrist M, Sjölund M, Stärk K D. 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. *Preventive Veterinary Medicine*, 2015, **119** (1–2): 10–20
9. OIE(World Organisation for Animal Health). Fact sheets: antimicrobial resistance. Geneva: *World Animal Health Organisation*, 2015
10. Pagel S W, Gautier P. Use of antimicrobial agents in livestock. *Revue Scientifique et Technique-OIE*, 2012, **31**(1): 145–188
11. Bager F, Birk T, Høg B B, Jensen L B, Jensen A N, de Knegt L, Korsgaard H, Dalby T, Hammerum A, Hoffmann S. DANMAP 2014: use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark. *DANMAP*, 2015
12. van Rennings L, von Münchhausen C, Ottilie H, Hartmann M, Merle R, Honscha W, Käsbohrer A, Kreienbrock L. Cross-sectional study on antibiotic usage in pigs in Germany. *PLoS One*, 2015, **10** (3): e0119114
13. Aliance to Save Our Antibiotics. Farm antibiotic use in the Netherlands. *Alliance to Save Our Antibiotics Publication No 1751*, 2016
14. Hellman J, Olsson-Liljequist B, Bengtsson B, Greko C. SWEDRES-SVARM 2014: use of antimicrobials and occurrence of antimicrobial resistance in Sweden. Solna/Uppsala: *Swedish Institute for Communicable Disease Control and National Veterinary Institute*, 2016
15. Sneeringer S, MacDonald J, Key N, McBride W, Mathews K. Economics of Antibiotic Use in US Livestock Production. *Economic Research Report*, 2015, (200): 1–100
16. ESVAC. ESVAC strategy 2016–2020. London: *Veterinary Medicines Division, European Medicines Agency*, 2016
17. UK-VARSS. UK Veterinary Antibiotic Resistance and Sales Surveillance 2016. UK: *Veterinary Medicines Directorate*, 2017
18. ESVAC. Sales of veterinary antimicrobial agents in 26 EU/EEA countries. *European Surveillance of Veterinary Antimicrobial Consumption (ESVAC)*, 2016 and 2017
19. Trauffler M, Griesbacher A, Fuchs K, Köfer J. Antimicrobial drug use in Austrian pig farms: plausibility check of electronic on-farm records and estimation of consumption. *Veterinary Record*, 2014, **175**(16): 402–410
20. Chavas J P. Structural change in agricultural production: Economics, technology and policy. In: Gardner B, Russer G, eds. North-Holland: *Handbook of Agricultural Economics*, 2001, 263–85

21. Upton M. Scale and structures of the poultry sector and factors inducing change: intercountry differences and expected trends. In: Proceeding of Poultry in the 21st Century–Avian Influenza and Beyond Conference. Bangkok: *Food and Agricultural Organisation*, 2007
22. Wegener H C. Antibiotics in animal feed and their role in resistance development. *Current Opinion in Microbiology*, 2003, **6**(5): 439–445
23. Jensen V F, Jacobsen E, Bager F. Veterinary antimicrobial-usage statistics based on standardized measures of dosage. *Preventive Veterinary Medicine*, 2004, **64**(2-4): 201–215
24. Food and Drug Administration (FDA). Summary report on antimicrobials sold or distributed for use in food-producing animals. *US Food and Drug Administration, Department of Health and Human Services, USA, Various Years*
25. Wu Z. Balancing food security and AMR: a review of economic literature on antimicrobial use in food animal production. *China Agricultural Economic Review*, 2017, **9**(1): 14–31
26. Jensen H H, Hayes D J. Impact of Denmark's ban on antimicrobials for growth promotion. *Current Opinion in Microbiology*, 2014, **19**(1): 30–36
27. Hughes L, Hermans P, Morgan K. Risk factors for the use of prescription antibiotics on UK broiler farms. *Journal of Antimicrobial Chemotherapy*, 2008, **61**(4): 947–952
28. Aminov R. History of antimicrobial drug discovery: major classes and health impact. *Biochemical Pharmacology*, 2017, **133**: 4–19
29. World Health Organization (WHO). Critically important antimicrobials for human medicine, 3rd Revision. *World Health Organization*, 2012
30. Murphy D, Ricci A, Auce Z, Beechinor J G, Bergendahl H, Breathnach R, Bureš J, Da Silva D, Pedro J, Hederová J. EMA and EFSA Joint Scientific Opinion on measures to reduce the need to use antimicrobial agents in animal husbandry in the European Union, and the resulting impacts on food safety (RONAFA). *EFSA Journal*, 2017, **15**(1): efs24666
31. Tenover F C. Mechanisms of antimicrobial resistance in bacteria. *American Journal of Medicine*, 2006, **119**(6): S3
32. Chantziaras I, Boyen F, Callens B, Dewulf J. Correlation between veterinary antimicrobial use and antimicrobial resistance in food-producing animals: a report on seven countries. *Journal of Antimicrobial Chemotherapy*, 2014, **69**(3): 827–834
33. Aarestrup F M. Veterinary drug usage and antimicrobial resistance in bacteria of animal origin. *Basic & Clinical Pharmacology & Toxicology*, 2005, **96**(4): 271–281
34. Buller H, Hinchliffe S, Hockenhull J, Barrett D. Systematic review and social research to further understanding of current practice in the context of using antimicrobials in livestock farming and to inform appropriate interventions to reduce antimicrobial resistance within the livestock sector. Report O00558, UK: *Department for Environment, Food & Rural Affairs*, 2015
35. Speksnijder D C, Jaarsma A D, van der Gugten A C, Verheij T J, Wagenaar J A. Determinants associated with veterinary antimicrobial prescribing in farm animals in the Netherlands: a qualitative study. *Zoonoses and Public Health*, 2015, **62**(S1): 39–51
36. Blaha T. The use of antimicrobial substances in food animals: The big picture. In: The 44th International Conference on the Epidemiology and Control of Biological, Chemical and Physical Hazards in Pigs and Pork. 2011, 131–133
37. Maron D F, Smith T J, Nachman K E. Restrictions on antimicrobial use in food animal production: an international regulatory and economic survey. *Globalization and Health*, 2013, **9**(1): 48
38. Casewell M, Friis C, Marco E, McMullin P, Phillips I. The European ban on growth-promoting antibiotics and emerging consequences for human and animal health. *Journal of Antimicrobial Chemotherapy*, 2003, **52**(2): 159–161
39. Aarestrup F M, Jensen V F, Emborg H D, Jacobsen E, Wegener H C. Changes in the use of antimicrobials and the effects on productivity of swine farms in Denmark. *American Journal of Veterinary Research*, 2010, **71**(7): 726–733
40. Food and Drug Administration (FDA). Guidance for industry No 213. Center for Drug Evaluation and Research (CDER), USA: *FDA*, 2013
41. OIE (World Organisation for Animal Health). OIE list of antimicrobials of veterinary importance. *World Organisation for Animal Health*, 2007
42. Teillant A, Laxminarayan R. Economics of antibiotic use in US swine and poultry production. *Choices*, 2015, **30**(1): 1–11
43. Teillant A. Costs and benefits of antimicrobial use in livestock. *Amr Control*, 2015, 116–22
44. Cromwell G L. Why and how antibiotics are used in swine production. *Animal Biotechnology*, 2002, **13**(1): 7–27
45. Seal B S, Lillehoj H S, Donovan D M, Gay C G. Alternatives to antibiotics: a symposium on the challenges and solutions for animal production. *Animal Health Research Reviews*, 2013, **14**(1): 78–87
46. Rosen G D. Holo-analysis of the efficacy of Bio-Mos in broiler nutrition. *British Poultry Science*, 2007, **48**(1): 21–26
47. Spring P, Wenk C, Connolly A, Kiers A. A review of 733 published trials on Bio-Mos®, a mannan oligosaccharide, and Actigen®, a second generation mannose rich fraction, on farm and companion animals. *Journal of Applied Animal Nutrition*, 2015, **3**: e8
48. Rosen G. Holo-analysis of the efficacy of exogenous enzyme performance in farm animal nutrition. In: Bedford M R, Partridge G G, eds. Enzymes in farm animal nutrition. 2nd ed. London: *CAB International*, 2010
49. Hovi M, Sundrum A, Thamsborg S M. Animal health and welfare in organic livestock production in Europe: current state and future challenges. *Livestock Production Science*, 2003, **80**(1): 41–53
50. Von Borell E, Sørensen J T. Organic livestock production in Europe: aims, rules and trends with special emphasis on animal health and welfare. *Livestock Production Science*, 2004, **90**(1): 3–9
51. Postma M, Vanderhaeghen W, Sarrazin S, Maes D, Dewulf J. Reducing antimicrobial usage in pig production without Jeopardizing production parameters. *Zoonoses and Public Health*, 2017, **64**(1): 63–74
52. Laanen M, Ribbens S, Maes D, Dewulf J. The link between biosecurity and production and treatment characteristics in pig herds. In: The 47th International Conference on the Epidemiology and Control of Biological, Chemical and Physical Hazards in Pigs and Pork. 2011
53. Gilchrist M J, Greko C, Wallinga D B, Beran G W, Riley D G, Thorne P S. The potential role of concentrated animal feeding operations in infectious disease epidemics and antibiotic resistance.

Environmental Health Perspectives, 2007, **115**(2): 313–316
54. Armstrong D, Bennedsgaard T W, Boyle L, Burch D, Debski B, Dewulf J, Fablet C, Manzanilla E G, Harlizius J, Henning-Pauka I. Reducing antibiotic use in pig farming: final report. *EIP-AGRI Focus Group, European Commission*, 2014
55. MacDonald J M, Wang S L. Foregoing sub-therapeutic antibiotics: the impact on broiler grow-out operations. *Applied Economic Perspectives and Policy*, 2011, **33**(1): 79–98
56. van der Fels-Klerx H J, Puister-Jansen L F, van Asselt E D, Burgers S L. Farm factors associated with the use of antibiotics in pig production. *Journal of Animal Science*, 2011, **89**(6): 1922–1929
57. Lawson L G, Jensen V F. The economics of use and non-use of antimicrobial growth promoters: the case of Danish broiler production. *Journal of International Farm Management*, 2008, **4**(2): 51–63
58. Postma M, Stärk K D, Sjölund M, Backhans A, Beilage E G, Lösken S, Belloc C, Collineau L, Iten D, Visschers V, Nielsen E O, Dewulf J. Alternatives to the use of antimicrobial agents in pig production: a multi-country expert-ranking of perceived effectiveness, feasibility and return on investment. *Preventive Veterinary Medicine*, 2015, **118**(4): 457–466
59. Kesmodel D, Bunge J. Mckay B. Meat companies go antibiotics-free as more consumers demand it. *The Wall Street Journal*, 2014
60. McLeod A, Rushton J. Economics of animal vaccination. *Revue Scientifique et Technique*, 2007, **26**(2): 313–326
61. Brown S A, Venkatesh V. Model of adoption of technology in households: a baseline model test and extension incorporating household life cycle. *Management Information Systems Quarterly*, 2005, **29**(3): 399–426
62. Key N, McBride W D. Sub-therapeutic antibiotics and the efficiency of US hog farms. *American Journal of Agricultural Economics*, 2014, **96**(3): 831–850
63. Bowman M, Marshall K K, Kuchler F, Lynch L. Raised without antibiotics: lessons from voluntary labelling of antibiotic use practices in the broiler industry. *American Journal of Agricultural Economics*, 2016, **98**(2): 622–642
64. Lam T J G M, Jansen J, Wessels R J. The RESET Mindset Model applied on decreasing antibiotic usage in dairy cattle in the Netherlands. *Irish Veterinary Journal*, 2017, **70**(1): 5
65. Danish Veterinary and Food Administration. Special provisions for the reduction of the consumption of antibiotics in pig holdings (the yellow card initiative). Denmark: *Ministry of Food, Agriculture and Fisheries*, 2017
66. Barton M D. Antibiotic use in animal feed and its impact on human healt. *Nutrition Research Reviews*, 2000, **13**(2): 279–299
67. Mathew A G, Cissell R, Liamthong S. Antibiotic resistance in bacteria associated with food animals: a United States perspective of livestock production. *Foodborne Pathogens and Disease*, 2007, **4**(2): 115–133
68. O'Neill J. Antimicrobials in agriculture and the environment: reducing unnecessary use and waste: the review on antimicrobial resistance. London: *Wellcome Trust and HM Government*, 2015
69. Blaser M J. Missing microbes: how the overuse of antibiotics is fuelling our modern plagues. London: *Macmillan*, 2014
70. Landers T F, Cohen B, Wittum T E, Larson E L. A review of antibiotic use in food animals: perspective, policy, and potential. *Public Health Reports*, 2012, **127**(1): 4–22
71. Pechère J C. Patients' interviews and misuse of antibiotics. *Clinical Infectious Diseases*, 2001, **33**(S3): S170–S173
72. Okeke I N, Lamikanra A, Edelman R. Socioeconomic and behavioral factors leading to acquired bacterial resistance to antibiotics in developing countries. *Emerging Infectious Diseases*, 1999, **5**(1): 18–27
73. Khachatourians G G. Agricultural use of antibiotics and the evolution and transfer of antibiotic-resistant bacteria. *Canadian Medical Association Journal*, 1998, **159**(9): 1129–1136
74. Mateus A, Brodbelt D, Stärk K. Evidence-based use of antimicrobials in veterinary practice. *In Practice*, 2011, **33**(5): 194–202
75. Sexton S E, Lei Z, Zilberman D. The economics of pesticides and pest control. *International Review of Environmental and Resource Economics*, 2007, **1**(3): 271–326
76. Dasgupta S, Meisner C, Huq M. A pinch or a pint? Evidence of pesticide overuse in Bangladesh. *Journal of Agricultural Economics*, 2007, **58**(1): 91–114