Rev. Sci. Tech. Off. Int. Epiz., 2021, **40** (2), ... - ...

Antimicrobial resistance at the livestock-human interface: implications for Veterinary Services

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Summary

The emergence of antimicrobial resistance (AMR) is a major global public health issue but also jeopardises the efficiency of antimicrobials to cure animal infections that threatens their health, welfare and productivity. Several reports show that infections by antimicrobial resistant pathogens in humans may be linked to antimicrobial use (AMU) and AMR in food-producing animals; however, to what extent this happens is unknown. Use of antimicrobials drives the emergence of AMR, therefore, the extensive over and misuse in livestock is of concern.

Robust AMU and AMR data are important to monitor the progress of interventions aiming to reduce AMR in the livestock sector. Several countries have incomplete data on antibiotic sales or use and our current knowledge on the global AMU is primarily based on modelling estimates. Antimicrobial resistance prevalence data are scattered, particularly in low- and middle-income countries, but in some high-income regions fairly robust data are available. It should also be noted that monitoring guidelines and protocols are available to provide globally harmonised AMR data.

Disease prevention without antimicrobials and rational use of antimicrobials are key to reducing AMU. This involves: a) accessible and affordable veterinary services to farmers; b) antibiotics only sold by prescription; c) veterinarians earn no revenue linked to sale or prescription of antibiotics; d) veterinarians must have substantial skills in preventive medicine including good animal husbandry, efficient biosecurity and vaccinology; and e) the added values of these measures must appeal to farmers so they are willing to pay for that service.

Keywords

Animal husbandry – Antibiotics – Antimicrobial resistance – Antimicrobial use – Biosecurity – Farmers – Livestock – Vaccination – Veterinary service.

Introduction

Antimicrobial resistance (AMR) is major global public health issue that is getting increasing attention. Given that the use of antimicrobials drives the emergence of resistance, the extensive use in the livestock sector of antibiotics, the sub-set of antimicrobials effective against bacteria is under scrutiny (1, 2, 3). The widespread use in livestock is attributable to various kinds of prophylactic use and use as growth promoters, mostly as a feed additive. Similar practices are rare in human medicine. There are several reports on how resistant bacteria from animals have infected humans (4). To which extent this happens, or how much the livestock sector contributes to the overall AMR in humans, is at large unknown. Particularly, the livestock-human connection within AMR is of most concern with respect to resistance to antibiotics. This is because humans and livestock share pathogenic as well as commensal bacteria and because the same classes of antibiotics are used in human and veterinary medicine. Antibiotic resistance also jeopardises the efficiency of antibiotics in curing animals against bacterial infections that threaten their health, welfare and productivity (5). The extensive antibiotic use in the livestock sector for growth promotion and as a regular preventive mean, compensating for poor animal husbandry and biosecurity, should be stopped. This is challenging for Veterinary Services, but will, if wisely handled, contribute positively to human and animal health.

Here, we give an overview of antimicrobial use (AMU) as well as AMR in the world. Secondly, we give an assessment of the over-arching impact of antimicrobial resistance on animal health and discuss the link between resistance in livestock populations and in humans. Finally, we present approaches on how to apply a more prudent and medically rational use of antibiotics in livestock – an area where Veterinary Services play a key role.

Antimicrobial use and antimicrobial resistance in livestock

Antimicrobial use in the livestock sector

Antibiotics are essential veterinary medicines used in livestock to treat bacterial infections, to prevent disease in a herd and at sub-therapeutic concentrations for growth promotion, and are administered either orally via feed or in drinking water, or parenterally. Antibiotics are ranked in importance for human medicine (6) and veterinary medicine (7). In the few cases where the same antibiotic class is critically important to both sectors, e.g. fluroquinolones and third and fourth generation cephalosporins, recommendations for veterinary use is provided by the World Organisation for Animal Health (OIE), namely: a) should not be used for metaphylaxis (preventing specific disease outbreaks); b) not to be used as a first line treatment unless justified and should be guided by antimicrobial susceptibility testing; c) off label use should be limited and reserved for when no alternatives are available; and d) not to be used as growth promotors (8).

A key objective in many national action plans, including the OIE's strategy (3), the Food and Agriculture Organization of the United Nations (FAO) action plan (2), and the World Health Organization (WHO) Global action plan on AMR (1), is prudent antibiotic use, which is connected to monitoring of antibiotic consumption patterns and understanding drivers of use. High-income countries, typically those in Europe and North America, have national monitoring programmes that capture antibiotic prescriptions that ideally should be stratified by animal species, age and disease indication (9). This information is important to: a) identify areas for targeted interventions, and b) to evaluate the impact of AMU/AMR reducing interventions (10). However, only 6% of low- and middle-income countries (LMICs) monitor AMU in animals (11) as they have limited capacity and resources to establish and sustain a nationwide surveillance system and hence there is a general scarcity of data at the detailed level on how much antibiotics are used and for what purpose.

It has been estimated that 73% of the global AMU is in livestock, and a recent study comprising sales data from 41 countries from all regions in the world is projecting an increase by 11.5% from 2017 to 2030, primarily in Asia (12, 13). This increase is driven by intensification of livestock farming to meet the growing demand for animal protein, particularly in LMICs, where AMU is poorly regulated and used irrationally to compensate for poor animal husbandry practices (13, 14, 15, 16). In LMICs, additional challenges include access barriers to antimicrobials and concerns with drug quality. In an attempt to obtain robust and harmonised global AMU data in food animals, OIE member countries are requested to submit AMU data annually since October 2015; however, the data are aggregated at the regional levels only (17). Moreover, the OIE has developed standards on monitoring AMU and surveilling AMR in livestock (Chapters 6.9 and 6.8 in the *Terrestrial Animal Health Code*) (18).

Steps to regulate AMU includes the ban of sub-therapeutic antimicrobials used for growth promotion, which in the European Union came into effect in 2006. Subsequent measures, such as improved biosecurity, vaccinations, etc., led to a regional 20% reduction in antimicrobial consumption between 2011 and 2016 (19). Similarly, in the United States of America, in 2017, antibiotic sales fell by 33% when use of antimicrobial growth promoters was restricted and use of antibiotics was allowed only under supervision of a veterinarian (20). Studies have showed that the negative impact of these bans on animal productivity was temporary and could be mitigated with increased biosecurity and better herd management (21, 22, 23).

Similarly, in LMICs like Bangladesh, Indonesia, India, and Thailand there are clear regulations that ban antibiotic use as growth promoters (24), but the challenge is enforcement of the policies, and there are no economic impact analyses conducted specifically in the LMIC livestock production context that assess the effect of restricting antimicrobial growth promoters, or the cost benefits of alternatives to antibiotics such as improved animal husbandry (15, 16, 25).

Antimicrobial resistance in livestock

As part of the Global action plan on AMR led by the Tripartite (FAO, OIE and WHO), the individual organisation strategies and national action plans, a key pillar in addressing AMR is surveillance. In human medicine, the WHO's Global Antimicrobial Resistance Surveillance System collects AMR data in selected indicator bacteria to estimate the global burden of AMR (11). However, in animals, no such global system exists. In Europe, AMR data in zoonotic and indicator bacteria from food animals and their products are collected annually by countries in selected food animal species and age groups depending on the year. In the latest report for 2017–2018, some promising trends were noted in food animals: a) decreased prevalence of extended-spectrum beta-lactamase-/AmpC-producing *Escherichia coli;* b) significant increase in the proportion of fully susceptible *E. coli* (approximately 25% in some Member States); c) resistance to colistin was uncommon; and d) carbapenemase-producing *E. coli* were not detected in poultry (26). In North America, similar monitoring of AMR in animals has been implemented. However, in LMICs, only 10% of countries reported monitoring AMR in animals (27). In the absence of national or regional AMR data, Van Boekel *et al.* (28) reviewed point prevalence surveys to provide a snapshot of AMR levels in animals and animal food products in LMICs in four bacterial species: *E. coli, Campylobacter* spp., non-typhoidal *Salmonella* spp. and *Staphylococcus aureus* between 2000 and 2018. Some of the key observations from this study were: a) geographic variation in the number of studies performed (fewer studies conducted in Africa compared to Asia); b) overall increase in AMR levels over time in different livestock commodities; and c) geographic difference in AMR levels and patterns of resistance appear to be associated to regional antimicrobial consumption patterns.

Impact of antimicrobial resistance on animal health and the interaction with human health

Impact of antimicrobial resistance on animal health

The impact of AMR on animal health has been given far less attention than that for human health. Similar to humans, AMR in animals will lead to suffering from infections that would not have otherwise occurred, increased frequency of treatment failures, and increased severity of infections (29). Furthermore, losing treatment options, either through the occurrence of resistance or through restrictions on their use, will have consequences for animal health and welfare (3). For owners of food and commodity producing animals, AMR may lead to financial losses directly through higher mortality and indirectly through reduced production and growth, decreased feed conversion, as well as early culling of breeding and production animals. Eventually this may lead to higher prices of commodities and food from animal production for the end consumer (29, 30).

Although beyond the scope of this review, in animals kept for social reasons, sports, or breeding such as dogs, cats, horses and exotic animals there are other challenges in managing an emerging AMR. These animals are likely to receive advanced veterinary care in animal clinics or hospitals that have a high animal density and frequent use of antibiotics which cater for nosocomial infections, similar to what is seen in human medicine (30, 31, 32).

Food animals and food of animal origin are traded worldwide. Thus, resistant bacteria selected by antimicrobial usage in one country may cause problems in several other countries, as exemplified by the spread of cephalosporin-resistant *E. coli* from broiler parents imported from England, through Sweden to Denmark where it was detected in the broiler meat (22, 33). Output and trade in livestock and livestock products are especially vulnerable to AMR impacts (34). In the 2017 World Bank report, it was estimated that by 2050, the global livestock production will fall by 3% to 8% each year due to AMR and on the economic and development consequences of AMR, the high AMR-impact scenario estimates 11% loss in the livestock production by 2050, with the highest decline expected in low-income countries (25). The AMR impact may, furthermore, be protruded in countries that experience a higher burden of infectious disease, thus, where higher antimicrobial use is required. In the small- and medium sized farming systems commonly found in LMICs, animals are in frequent and close contact with humans with limited biosecurity in place which allows AMR to spread between farms and from livestock to humans (35). Weaker systems for AMR surveillance and less regulation of antimicrobials which are more likely to be substandard, falsified or unregistered further enhance the negative impacts of AMR in these countries (24, 35).

Impact of antimicrobial resistance seen from a One Health perspective

Solid scientific evidence is available showing that infections with resistant pathogens may affect humans as a result of AMU in food producing and companion animals (4, 36). Depending on species and production systems, AMR is transferred to humans via contact with animals, animal products colonised by resistant organisms, or ingested food that is incompletely cooked (30, 36) (Fig. 1). Antimicrobial resistant organisms from animals can also spread from animal waste through the excretion of unmetabolised antibiotics and the spreading of manure and urine from livestock production as fertilisers (37, 38). Notably, data gaps remain to be filled on the extent of this zoonotic transmission.

Antimicrobial resistance is considered an increasingly serious threat to the gains made in global health and development and for the attainment of the Sustainable Development Goals (39) including a widening of the inequity gap within and between countries. In the European Union alone, AMR is estimated to causes 25,000 human deaths annually, and should AMR continue to increase, the economic cost will be substantial, as projected by several studies (25, 40, 41). It is estimated that by 2050, the economic costs of AMR may comprise as much as 1.1% to 3.8% of GDP and result in 10 million lives lost a year with a cumulative US$ 100 trillion of economic output at risk (25, 42, 43).

Medically rational use of antibiotics in livestock

A key pillar in curbing AMR in livestock is practices in how antibiotics are used (2, 3). Antibiotics should be used in a medically rational way, i.e. reducing the need for antibiotics, use them only when needed and use them as efficiently as possible without jeopardising animal health, welfare and productivity.

Reducing the need for antibiotics

The need for antibiotics in livestock can be reduced by improving the overall animal husbandry and applying disease preventive measures in a herd. This has been successfully shown in countries where antibiotics used as growth promoters or for prophylaxis were phased out several decades ago (5). The phasing out must, however, be done carefully and matched by appropriate measures to maintain animal health. Recommended measures have been summarised for the pig, poultry, beef and dairy sectors (44). These measures can be organised in three categories, often applied in a hierarchical order (Fig. 2). The first is good animal husbandry including sufficient access to water and nutritious feed, appropriate shelter and housing, proper hygiene, etc., all promoting robust and generally disease resistant animals. The second is efficient biosecurity, protecting the animals from any kind of infections. This includes preventing introduction of infections to the farm from animals or humans entering the farm (i.e. external biosecurity) and hindering the transmission of infections from one group of animals to another group within the farm by restrictions in how animals and personnel move inside the farm (i.e. internal biosecurity). The third is application of relevant vaccination schemes against specific, and for the farm hazardous, infectious diseases. A major share of these preventive measures depends on good management skills, whereas others also need financial and material resource investment. The Veterinary Services must be competent to provide correct and implementable advice on all these three categories of disease preventive measures, which can be a challenge in high- as well as low-income countries.

Quality of antibiotics

Access to good quality antimicrobials with proper labelling is a challenge in some parts of the world. The widespread use of substandard and falsified veterinary products cause harm, treatment failure and may lead to loss of confidence in animal health service providers. There are several reports of falsified or substandard pharmaceuticals, especially from LMICs, where health systems are weaker (45). Stronger regulations, standards, reporting systems and enforcement by competent authorities can limit the circulation and use of these drugs.

How to use antibiotics in a medically rational way

There are several international initiatives that advocate phasing out the excessive use of antibiotics for growth promotion and prophylaxis that is often in place to compensate for poor animal management (2, 3). Additionally, one should restrict the use of antibiotics to cure sick animals and strive to treat animals individually to reduce the total amount of antibiotics used (23, 46). Importantly, antibiotics should be used only after a proper diagnosis by a veterinarian at the prescribed dose and treatment intervals and length (18, 46). A professional clinical or post-mortem diagnosis may be the most feasible. Laboratory diagnosis, including susceptibility testing if the causative agent is a bacterium, is desired but may not always be possible due to urgency or lack of infrastructure. Obviously, it is important to use an antibiotic for which the diagnosed bacteria are susceptible and at the right timing, dose and duration. Notably, the use of antibiotics listed as critically important in human medicine by WHO (6) should be avoided. These antibiotics are banned for use in veterinary practice in some countries or approved only under certain circumstances.

How to change the use of antibiotics

To amend the use of antimicrobials in the livestock sector into a more medically rational use, as described above, hinges on that farmers trust that this kind of use is either more or equally good or cost-efficient, as the over and misuse. Also, the entire livestock and animal health sectors must take responsibility and be aware that the over and misuse in the long run will reduce the efficiency of antibiotics for curing disease both in humans and animals and ultimately may stigmatise the livestock sector. Effective veterinary service is at the core of this and must provide alternatives to the farmers without jeopardising incomes to the veterinarians or the Veterinary Service as an organisation. Even though more and more countries are banning the use of antibiotics as growth promotors (8), antibiotics are still available without prescription over the counter in many countries (Table I) and the advisory role commonly played by the veterinarians is increasingly taken over by the salespersons of companies, pharmacies and agricultural stores that sell their products directly to the farmers (38). Another obstacle, also where a veterinary prescription is required, is when a substantial part of the income for veterinarians comes from selling antimicrobial drugs (48). This may serve as a perverted incentive and drive the use of antibiotics. In some countries where a prescription is required, antimicrobials are allowed to be dispensed through pharmacies only (Fig. 3). Hence, veterinarians with substantial earnings from selling antibiotics may need to redefine their professional role and skill set (44). When the monetary cap on veterinarians' profits from antibiotic sales was introduced in the Scandinavian countries, the direct profit for veterinarians to prescribe antimicrobials was successfully removed, resulting in a viable livestock production and veterinary profession (48).

In summary, a reduction of AMU in the livestock sector by applying a medically rational use as described here will be a major contribution from the animal health sector to the global AMR fight. To launch medically rational use of antibiotics, several steps are necessary: a) veterinary services must be available and affordable to the farmers; b) antibiotics should be sold only by prescription; c) no revenue for veterinarians linked to sale or prescription of antibiotics; d) besides conventional diagnostic competence, the veterinarians must have well-grounded skills in preventive medicine including good animal husbandry, efficient biosecurity and vaccinology; and e) the skills in preventive medicine must be made attractive to the farmers so they are willing to pay for that service.

Résumé français: titre

Résumé

Mots-clés

Resumen español: título

Resumen

Palabras clave

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Table I

Antimicrobial prescriptions required in animals, percentages by income group; data from 70 non-European Union countries (47)

World Bank income group	Yes, in all cases, %	Yes, some cases, %	No, %	No. of countries
High income	42	42	16	12
Upper middle income	48	26	26	11
Lower middle income	20	45	35	20
Low income	10	45	45	27

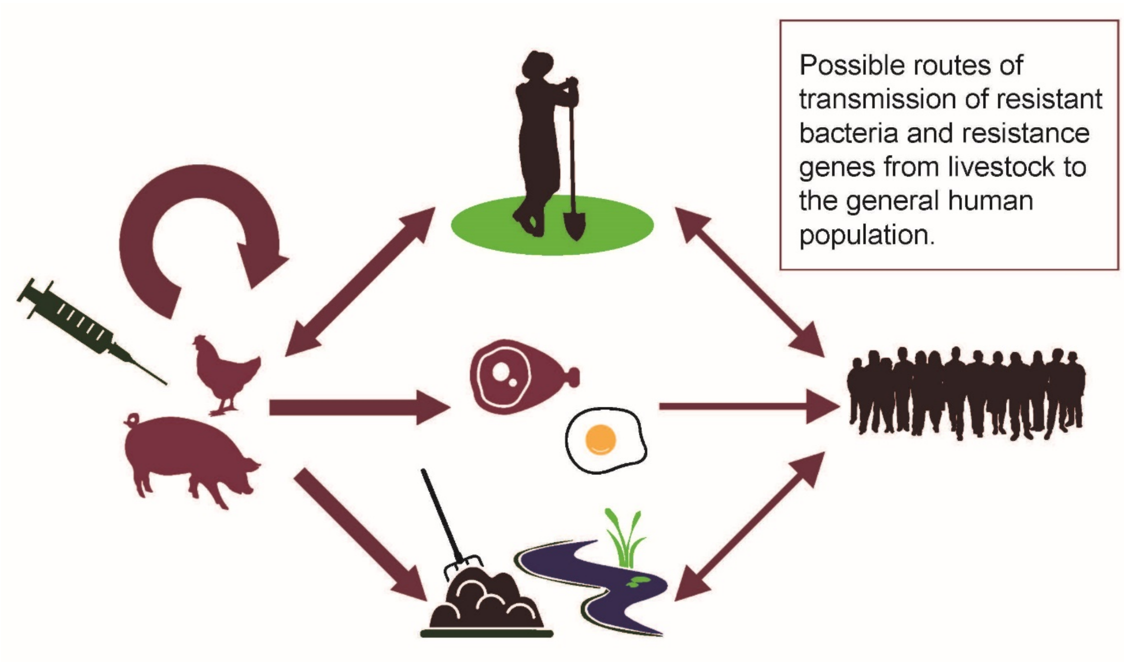


Fig. 1

Antimicrobial resistance may be transmitted from livestock to the general human population via farmers working with the animals, via the food chain or via manure and the environment. The relative importance of these various routes is at large unknown

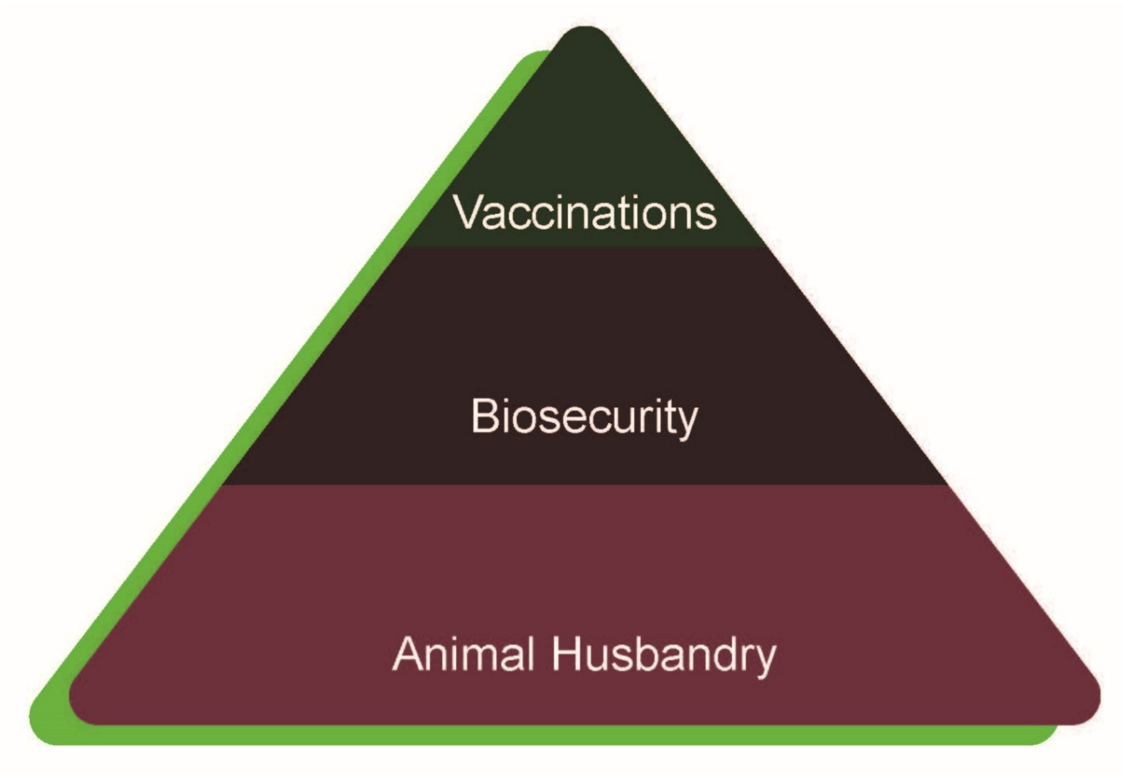
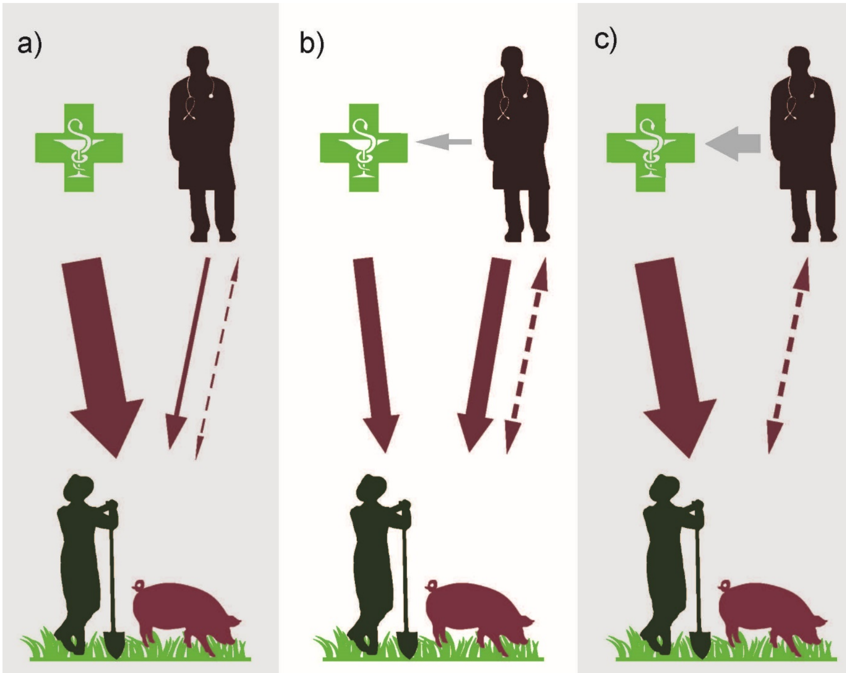


Fig. 2

The key means of disease prevention in a hierarchical order. Firstly, good animal husbandry contributing to robust animals forms the basis; secondly, effective biosecurity protects serves as a general barrier protecting the herd from introduction of infectious diseases; and thirdly, vaccinations protect the individual animal from specific pathogens



Legend:
Solid purple arrow: distribution of antibiotics
Dotted purple arrow: diagnostic/consultation with a veterinarian
Grey arrow: prescription of antibiotics

Fig. 3

Three different ways to distribute antibiotics to a livestock farmer: a) in a country with no requirement of prescription of antibiotics and weak Veterinary Services (mostly in low-income countries); b) in a country where there is requirement of veterinary prescription for antibiotics, but the veterinarian is allowed to sell antibiotics directly to the farmer (common in middle- and high-income countries); c) in a country where there is requirement of veterinary prescription for antibiotics and the veterinarian is not allowed to sell antibiotics directly to the farmer (some high-income countries)