Chapter

Antimicrobial Usage and Resistance in Dairy Cattle Production

Enli Loo, Kok Song Lai and Rozaihan Mansor

Abstract

Antimicrobial resistance (AMR) has been a public health threat globally, with millions of lives lost due to AMR infections each year. The cases of AMR continue to escalate and cause devastating effect to both humans and animals. AMR contributes to high morbidity and mortality of the livestock, which results in staggering economic losses to the livestock producers. The main factor for AMR to arise in this industry is mainly due to the eagerness of livestock producers to meet high demand by using antimicrobials to promote animal growth and disease prevention. From a public health perspective, AMR in dairy cattle can also jeopardize human population due to the potential dissemination of AMR pathogens to humans via consumption of infected dairy products or direct contact with infected dairy cattle. At the current rate of unrestricted antimicrobial usage, AMR will be expedited and soon we will run out of effective treatment for even the simplest infection. World Health Organization (WHO) has issued a set of guidelines for the use of medically important antimicrobials on animals to mitigate the adverse consequences of AMR on human. Thus, this chapter will explain antimicrobial usage in dairy cattle production and the recent approaches and challenges on AMR.

Keywords: antimicrobial resistance, antimicrobial usage, dairy cattle, antimicrobial, one health

1. Introduction

AMR is undoubtedly one of the greatest health threats perceives by mankind. It causes increased morbidity, mortality and social and economic burdens [1–4]. For decades, antimicrobials were used not only in treating humans but also in veterinary medicine, agriculture and aquaculture, which had been linked to the global rise of AMR. By 2050, it is estimated that AMR will result in 10 million deaths per year and contribute to a shocking economic cost of 100 trillion USD, if we do not take action to tackle this devastating crisis [4]. In animals, the use of antimicrobials includes treatment and control of clinical bacterial infections as well as disease prevention and growth promotion. Although the evidence and mechanism of such benefits have not been clearly demonstrated, the apparent growth promotion benefits of antimicrobials when using antimicrobials in animals have resulted in higher usage of antimicrobials in animals, even in the absence of disease. The danger of using antimicrobials in animals to humans was uncertain until 1997 when experts concluded that the usage of antimicrobials in food-producing animals causes AMR selection, in a consultation on "medical impact of the use of antimicrobials in food animals" organized by WHO in Berlin, Germany [5]. Since then, various studies have further supported the theory in which AMR selection and dissemination from animals can be attributed to uncontrolled antimicrobial usage in animals [6–10]. An example in dairy cattle production shows dairies from the conventional production have a higher prevalence of AMR enteric bacteria than dairies from the organic production as more antimicrobials are usually being used in the conventional practice [9].

In general, AMR is the capability of a microorganism to resist the inhibitory activity of an antimicrobial at a normal susceptibility level. AMR occurs in previously susceptible strain due to a prolonged adaptation of the microorganism on the antimicrobial, which results in the evolution of the particular stain to survive in such condition. This can be acquired via mutation of the gene or horizontal gene transfer from another microorganism, which includes conjugation, transformation and transduction. The subsequent AMR selection in bacteria in animals can then be disseminated to humans because of the food chain relationships [10]. Moreover, this cross-species transmission can also occur via direct contact between humans and animals or shared environmental sources that are contaminated. In dairy cattle production, the dairy products can also be contaminated with AMR strains in several ways like directly from the environment such as soil, water and fecal material or cross-contamination during food processing [9]. This ultimately causes public health concern regarding the consequences of antimicrobial use in animals on food safety issue.

In 2005, WHO's committee had set up a few criteria to classify medically important antimicrobials in human medicine [11]. Among the classifications, the criteria for critically important antimicrobials were used to establish the WHO List of Critically Important Antimicrobials for Human Medicine, also known as the WHO CIA List. A guideline based on the WHO CIA List was formed to minimize the adverse consequences of unrestrictive usage of medically important antimicrobials in human medicine, and since then it has been updated regularly, with the latest fifth edition being published in 2017. To combat the increasingly significant health threat posed by AMR, the 68th World Health Assembly adopted a global action plan in May 2015 that proposed interventions to tackle AMR and also emphasized on the "One Health" approach in addressing AMR.

In order to address this important health risks at the animal-human-ecosystem interfaces, a complementary partnership between the Food and Agriculture Organization (FAO), the World Organization for Animal Health (OIE) and WHO was made to prevent, detect, control, eliminate and manage disease risks to human transferred directly or indirectly from domestic and wild animals [12]. Part of the OIE strategy on AMR and to support prudent use of antimicrobials includes four main objectives, namely, improving awareness and understanding, strengthening knowledge through surveillance and research, supporting good governance and capacity building and encouraging implementation of international standards [13]. Realizing the importance and its impact of this global issue in human and animal population, Malaysia is extremely committed with the cross-sectoral action plan and thus has drafted the Malaysian Action Plan on AMR (MyAP-AMR) to support the global action plan in 2017 under collaboration between Ministry of Health and Ministry of Agriculture and Agro-Based Industry, Malaysia [14].

2. Usage of antimicrobials in dairy cattle production

Antimicrobials are one of the modern interventions utilize by veterinarians and farmers to improve animal health and also the quality of animal products. The usage of antimicrobials has significantly ameliorated the well-being of animals, which results in better health and higher productivity of the animals [15]. In dairy cattle production, the usage of antimicrobials is highly indicated, mostly in treating diseases affecting the dairy cattle, such as mastitis. Besides disease treatment, antimicrobials have also been used to prevent diseases and promote growth in the dairy cattle production [16, 17].

2.1 Treatment and disease prevention in dairy cattle

Bovine mastitis, usually caused by *Staphylococcus aureus*, is the most commonly treated diseases in dairy cattle. In fact, it has become the biggest consumers of antimicrobials in dairy cattle production due to its massive economic impact to the industry [18]. In UK dairy cattle production, an annual loss of €9.03 billion or an average of €279 per case was reported due to summer mastitis, a type of mastitis that occurs during the warmer months [19]. Meanwhile, the total economic cost is much higher in US dairy, which is $444 for an average mastitis case [20]. There are a few costs that contribute to the economic impacts due to mastitis such as milk production losses, drug treatments and diagnoses, discarded milk, culling and also labour costs, but production losses are the major constituent of the economic impact of mastitis [21, 22]. Clinical mastitis and subclinical mastitis can result in significant milk production losses, but subclinical mastitis has a higher prevalence and it is difficult to estimate its economic impacts due to the variability in case definition and screening intensity [20, 23]. Clinical mastitis can be identified based on the clinical examination on dairy cattle for local or systemic signs of mastitis such as swelling and redness of the udders or abnormal milk secretions. It is harder to characterize subclinical mastitis as milk secretions are not visually abnormal, thus it is usually diagnosed based on the inflammatory markers and somatic cell counts in the milk. Antimicrobial treatment of mastitis in dairy cattle depends on the etiology of the disease. Appropriate antimicrobials such as β-lactams like penicillin and third-generation cephalosporin, aminoglycosides like amikacin and gentamicin, and fluoroquinolones are used in treating mastitis. Dairy cattle mastitis has been more susceptible to a wide range of antimicrobials and less prone for the selection pressure of AMR than the same isolates in humans. This is due to the use of intra-mammary infusion treatment compared to the conventional parenteral treatment with the former has a limited bacterial exposure and the later has a huge risk of exposing the infected udder to other bacteria from a different environment [18]. Besides, the blood-milk barrier in bovine udder also limits the distribution of specific antimicrobials away from the infected sites [18], thus preventing bacterial selective pressure to occur in other sites. Besides mastitis, endometritis is another disease that affects dairy cow which requires antimicrobial treatment occasionally. Bovine endometritis is a post-partum uterine disease that affects the uterine endometrium. It can also be classified into clinical and subclinical cases by evaluating the vaginal mucus using an intravaginal device followed by a scoring system for clinical endometritis [24], and the proportion of polymorphonuclear leucocyte in the endometrial cytological slide, with >5% of cells will be characterized as subclinical endometritis [25], respectively. It has a detrimental effect to the economics due to the reduced reproductive performance in diseased cattle [25]. Generally, a broad spectrum antibiotic therapy will be chosen to fight against the main pathogens that cause bovine endometritis, such as *Actinobacillus pyogenes* and some Gram-negative anaerobes. Intrauterine cefapirin and oxytetracyclines can be used in endometritis for its good penetration to the endometrium.

However, sometimes the usage of antimicrobials in infected dairy cattle can be too late to treat the infected cattle back to health. Cases of subclinical mastitis will not be clinically obvious to detect, thus missing the right timing to administer antimicrobials to get rid of the pathogens. Besides, some dairy cattle that recovered completely from subclinical mastitis with antimicrobials can still have a low milk production and not increase for years [26]. Therefore, it is always better to prevent a disease from occurring in the herd rather than treating it. It is also rational to do so because it reduces the economic losses due to mastitis. Prevention use or prophylactic use of antimicrobials in dairy cattle refers to the administration of antimicrobials in healthy dairy cattle considered to be at risk, before the onset of any infectious diseases. The dairy cattle production in the USA has more than 90% of dairy farmers practised dry cow therapy at the end of lactation on the dairy cattle to prevent intra-mammary infections during the dry period [27]. The application of antimicrobials shows a significant reduction in the rate of intra-mammary infections during the dry period [27, 28]. Furthermore, antimicrobials can also be used for control treatment, also known as metaphylaxis, to prevent the spread of disease in the dairy cattle. It is usually given as a mass treatment to the healthy groups when part of the group is diagnosed with clinical disease, to prevent disease progression and spread in the herd. Conclusively, antimicrobials play an important role in the treatment, prevention and control of disease in dairy cattle production.

2.2 Growth promotion in dairy cattle

Growth promoters are any substances given to animals as supplements or nutrients to enhance their growth rate, without the specific intention of treating, preventing or controlling diseases. They were once used widely and uncontrollably in the food-producing animal industry like in dairy cattle production [29]. The growth-promoting effect of antimicrobials was discovered back in the 1940s when experimented chickens showed promising signs of growth after feeding with fermentation by-products of penicillin and streptomycin [30]. The practice of using antimicrobials then becomes widespread in the food-producing animal industry for the eagerness of farmers to obtain high profits in a shorter time by maximizing animal growth rates. In dairy cattle production, antimicrobials are used as feed additives in dairy cattle to enhance their digestive tract activity. Antimicrobials suppress competitive microorganism in the digestive tract that competes nutrients with the host or produces undesirable toxic substances to the host. This provides an optimum environment in the digestive tract of the dairy cattle that allows them to absorb all the food intake completely and effectively. The increase in nutrient utilization thus enhances the growth rate of dairy cattle. However, the public health concern about the usage of antimicrobials as growth promoters rises as prolonged use of antimicrobials increases the risk of AMR. To prevent AMR from jeopardizing the future of human medicine, many countries have taken action to reduce or ban the usage of antimicrobials as growth promoters in animals. Sweden became the first country to ban all usage of growth-promoting antimicrobials in food-producing animals in 1986 after the recommendations of the UK Swann Commission regarding the prohibition of antimicrobials as animal growth promoters in 1969. In 1997, the use of avoparcin was prohibited in the EU as evidence showed the use of avoparcin, a glycopeptide, closely related to vancomycin causes selection of the resistance gene (VanA). The EU further prohibited all use of antimicrobials for growth-promoting benefits in animals in 2006 in order to control the emergence of AMR.

The prohibition of antimicrobial usage for growth promotion in food-producing animals still remains a controversial debate [31–33]. It is still unconvinced about the potential issue of AMR from using antimicrobials as growth promoters in animals because the dose used is small than the therapeutic dose to select for resistance [33]. On the other hand, there are also some opinions about the prohibition on growth promoters that might actually increase the prophylactic usage of antimicrobials as some users might try to "play with the rules" [4].

3. Monitoring antimicrobial usage in dairy herds

With the emergence of AMR from antimicrobial usage in food-producing animals, many countries have formulated and implemented their surveillance and monitoring programmes to identify the extent of antimicrobial usage in their countries. It serves as the first step in reducing the unnecessary usage of antimicrobials in animals. These programmes differ between countries as several factors such as government policies and resource availability have to be considered to ensure flexibility in deciding how to reduce antimicrobial usage. A survey done by the OIE in 2012 had highlighted that only 27% of the participating countries were able to provide quantities of antimicrobials used in animals in their respective countries [34], which showed how poorly the development of the surveillance and monitoring system on veterinary antimicrobial usage in some of the countries.

The prohibition of avoparcin as a growth promoter in food-producing animals in 1997 had resulted in more attention being focused to the usage of antimicrobials in animals and the potential link to the emergence of AMR. However, the lack of reliable data has still underestimated the magnitude of public health threat caused by antimicrobial usage in animals. In 1995 the Danish government became the first to establish a national surveillance programme called the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP) with the aims to monitor the trend of antimicrobial usage and the prevalence of AMR in food-producing animals, identify the potential link between antimicrobial usage and AMR in food-producing animals and understand the route of transmission for it to occur and areas for future research. The animal data obtained from DANMAP mainly focus on pigs and cattle as they are the two major food-producing animals in Denmark. DANMAP 2015 report showed an approximately 13 tonnes of antimicrobial consumption or 12% of total antimicrobial consumption in food-producing animals used in cattle. This amount was just second to the antimicrobial consumption in pigs, which was 75% of the total antimicrobial consumption [35]. As the majority of antimicrobial usage in cattle is used to treat mastitis which occurs in dairy cattle, the administration of antimicrobials in dairy cattle increases every year while the same usage in the production of beef and veal remains at the same level [35]. In Denmark, the use of fluoroquinolones in animals is restricted as a last resort after the implementation of strict regulation in 2002. Since then, the usage of fluoroquinolones in food-producing animals including dairy cattle dropped drastically to 18 kg in 2005, compared to 114 kg in 2001 [36]. Despite the reduced usage of quinolones in cattle, there was an increase in quinolone-resistant infection caused by *Campylobacter jejuni* from 2006 to 2014. Besides, the use of tetracycline in the cattle remained the same in 2015 as in 2014, but the prevalence of tetracycline-resistant *C. jejuni* increased from 2014 to 2015 [35]. These suggested that antimicrobial usage in animals might not be the only factor causing the emergence of AMR in animals.

In the EU, after the prohibition of all growth-promoting antimicrobial usage in animals in 2006, a more thorough and detailed surveillance on other antimicrobial usage was required in order to identify the potential risk of causing AMR and optimize antimicrobial usage. Therefore, the European Medicines Agency (EMA) had launched the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) programme in 2009 to collect and report data on antimicrobial usage from its member states. A report on antimicrobial sales and usage will be published yearly to inform antimicrobial policy and responsible antimicrobial usage to its member states. The seventh ESVAC report, with 30 participating European countries, showed a drop of 13.4% in the sales of antibiotics for animal usage between 2011 and 2015 [37]. As third and fourth generation of cephalosporins are listed in the WHO CIA List, the dairy cattle production in the Netherlands had taken the initiative to prohibit the usage of such antimicrobials completely in drying off dairy cattle. This prohibition also applied in the pig sector, which resulted in both sectors contributing a significant drop of 98% in the sales of third- and fourth-generation cephalosporins from 2011 to 2015 in the Netherlands [37]. Also, surveillance conducted in 90 dairy farms in the same country also showed half of the farms have a below average and decreasing trend in antimicrobials usage between 2010 and 2012. The decrease in the trend of antimicrobial usage was due to the early detection of increasing trend in antimicrobial usage among dairy farmers before 2010 via the surveillance programmes, which then allowed local veterinarians to take action by spreading the awareness of antimicrobial usage in animals to the farmers [38]. In the UK dairy cattle sector, the Cattle Health and Welfare Group had conducted a study in 2015 to collect antibiotics usage data from dairy farmers in order to develop a more robust surveillance and monitoring system in the dairy sector in the future. The UK Veterinary Antibiotic Resistance and Sales Surveillance (UK-VARSS) 2015 report found that the sales of antibiotics for dairy cattle reduced by 6% between 2014 and 2015 [39]. However, an increase in sales by 18% was shown between 2015 and 2016 in UK-VARSS 2016 [40]. A significant change in sales within the period of 1 year can suggest an increase in antibiotic usage in dairy farms, although the sales of antibiotics are generally an overestimate if to use in determining its usage in dairy farms. Thus, a new monitoring tool, known as the Nottingham University Dairy Antimicrobial Usage Calculator was developed in 2018 following a quantitative analysis on antimicrobial usage in the UK dairy herds [41] which allows dairy farmers to closely monitor the antibiotic usage in their herds.

Japan launched the Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM) in 1999 due to a lack of nationwide information on AMR in food-producing animals in Japan. The latest data from JVARM was published in the Nippon AMR One Health Report (NAOR) 2017, and it showed that antimicrobial-resistant strains of *Salmonella* spp. and *Escherichia coli* were quite prevalent in diseased cattle from 2011 to 2015 in Japan [42]. Overall, the usage of veterinary antimicrobials showed a decreasing trend from 2009 to 2013, with tetracyclines being the most consumed antimicrobials in animals. In Malaysia, the Department of Veterinary Services Malaysia (DVS) and Ministry of Health are responsible in monitoring the antimicrobial usage in animals. However, there is still a lack of a more reliable, nationwide surveillance and monitoring system developed by the DVS to monitor antimicrobial usage in food-producing farms, including dairy farms to ensure the safety of livestock products for human consumption.

4. AMR issue

Antimicrobial-resistant infections that were only limited in the hospital or healthcare setting in the past have now become a primary public health threat that affects a wider community. The rapid and devastating spread of AMR to the community can be linked with the increasing usage of antimicrobials, as antimicrobials are no longer only being used in human medicine but also in veterinary medicine and agricultural sectors. In fact, agriculture could probably contribute to most of the antimicrobial consumption than medical usage due to the booming of agricultural industry in the past few years. The global antibiotic consumption in agriculture is estimated to be around 63,000 to 240,000 tonnes per year [43], but this is more likely to be an underestimate due to the poor monitoring and surveillance system on antimicrobial usage in many countries. A 67% increase in antimicrobial usage in agriculture from 2010 to 2030 is also estimated if the trends of antimicrobial usage continue [44].

Antimicrobial usage in animals, like in dairy cattle production, could lead to the potential resistant infections in humans. A report published in 2014 estimated a total of 700,000 people succumb to antimicrobial-resistant infections every year, and this will increase to 10 million by 2050 [45]. The main concern of antimicrobial usage in animals focuses on the possibility for the transfer of resistant bacterial strains from animals to humans to occur. Unrestricted and inappropriate usage of antimicrobials in animals can lead to selection pressure of antimicrobials in animals, as in the usage of antimicrobials in humans. Then, transfer of resistant strains from animals to humans allows resistant diseases to occur in humans. In dairy cattle production, this transfer can potentially occur via either direct contact on the infected sites or consumption of infected dairy products such as unpasteurized milk. Contamination of environmental reservoirs also allows the dissemination of resistant bacteria from dairy cattle to humans. Animal wastes that are excreted can contain resistant bacteria from the animal's gut and also unmetabolized antibiotics. Studies have suggested that 75–90% of the antibiotics used in animals might not be metabolized in the gut and then excreted out in the waste [46]. This will be an issue as the animal wastes containing resistant bacteria and antibiotics can enter to the sewage system or water sources, which aids the emergence of antimicrobial-resistant bacteria in the environment.

Antimicrobial usage in humans and animals often overlap as the infections are caused by the same or similar pathogens. Thirty-one of the 41 antimicrobials authorized for animal usage in the USA in 2012 were essential for human use [47]. Antibiotics that are being used extensively in the dairy farms to treat mastitis, such as penicillin, cephalosporin and tetracycline, are also important in treating the same pathogens in humans. Therefore, it is not surprising when AMR arises from the dairy herds causes increase morbidity and mortality in human population affected by the resistant pathogens due to the less effective antimicrobial treatment. Besides, the dual-use antimicrobials for humans and animals also show the lack of animal-specific antimicrobial for animal that will not threaten human health. In fact, it is not rational and practical to do so. Even if an antimicrobial for animals is successfully developed through animal research, there will always be a desire to make it for human usage due to the larger market for human antimicrobials. Even for human antimicrobials against infectious diseases, there has been a decline in investment and funding by the government and private sectors in the past few years. In the USA, less than 5% (1.8 billion USD) of research and development funds in pharmaceutical sectors was invested in antimicrobial research between 2003 and 2013. This is largely due to the change in perception in most of the developed countries that prioritize more in non-communicable diseases like obesity and heart diseases, which are also one of the greatest challenges to public health. With the higher global usage of antimicrobials and slower development of new antimicrobials, we will soon run out of treatment options against these superbugs, risking ourselves to return to the pre-antibiotic era. It is already clearly evident when doctors are using the last resort treatment like carbapenem and colistin to treat resistant infections. Colistin, which has been avoided for years due to its potential renal-damaging effect, is now used as the real last resort for carbapenem-resistant infection, but cases with colistin resistance have started to emerge in recent years [48].

Another issue with AMR is the economic impact in the healthcare and agricultural sectors. Increased morbidity and mortality of infectious diseases lead to more economic burden [1–4]. By 2050, AMR will have an enormous cost of 100 trillion USD to the world economy, not to mention the 10 million deaths per year due to AMR [4]. With the emergence of AMR, other medical interventions that are dependent on the availability of effective antimicrobials for lower risk of complications will also be affected. Antimicrobial prophylactic measures cannot be taken in chemotherapy treatment, major surgeries and organ transplants, which can compromise the immune system and increase the risk of infection. These problems combined with other consequences of AMR can cumulatively contribute a total of 210 trillion USD by 2050 [45]. This looming global crisis, possess with threats to the healthcare and economy, needs to be considered carefully for action plans to be implemented.

5. Solutions to AMR

The medical consequences of antimicrobial usage in food animals were first recognized by the WHO in 1997 [5]. Since then, the WHO Global Principles, with the participation of FAO and OIE, and the WHO CIA List were established to provide recommendations in antimicrobial usage reduction in food animals and minimize the usage of medically important medicine for humans in food animals, respectively. Recognizing the increasing health threat caused by AMR, the 68th World Health Assembly adopted a global action plan in May 2015 to combat AMR and ensure the availability of quality-assured medicine for effective treatment and infectious disease prevention for as long as possible [49]. The global action plan has a variety of interventions, which focus on antimicrobial global awareness and surveillance as well as reducing its usage in tackling this global health threat. In line with the global action plan, it is crucial for other countries to make these as the primary focus when developing their national action plans in order to achieve the goals.

The first strategic objective set out in the global action plan is to improve the awareness and understanding of AMR in the public. The booming of agricultural sectors in recent years causes the farmers to become more eager in enhancing their farms' productivity. As a result, growth-promoting antimicrobials are used widely in food-producing animals to enhance animal growth without the intention to treat any infectious diseases. Although the EU had prohibited all growth-promoting antimicrobials in food-producing animals in 2006, other countries that are not in the EU are still actively practising antimicrobial usage for growth promotion due to the lack of political will to adopt new policies. Data from OIE shows that the Americas, with a few agricultural giant countries like the USA and Brazil, are by far the largest region buyer for growth-promoting antimicrobials in livestock [34]. Besides, the convenience of purchasing antimicrobials over the counter also leads to some unnecessary usage of antimicrobials in the healthcare. Therefore, with the increase in antimicrobial demands, both in the healthcare and agricultural sector, it is essential for the users to understand the proper antimicrobial usage and the consequences of unnecessary antimicrobial usage. To achieve the objective, a nationwide AMR awareness campaign that is globally consistent with its core message has to be designed to disseminate message regarding the issue of AMR, in a way that is tailored locally based on the national AMR action plan in each country. It is also crucial for the campaign to be able to convince users for a behaviour change regarding the usage of antimicrobials. Besides, making AMR issue a core component in getting qualification or certification in the veterinary or agricultural practice is also important to ensure the professionals from the fields are knowledgeable with the issue of AMR.

Before making interventions or policies to tackle the emergence of AMR, a set of comprehensive and reliable data on the antimicrobial usage, AMR rate and biological mechanism of AMR in each country will be useful in determining its benefits and cost-effectiveness. Thus, the global action plan aims to strengthen the knowledge on AMR through surveillance and research. In line with it, OIE, with the support from FAO and WHO, will collect data on antimicrobial usage in animals. There are different levels in a surveillance system, with each level provides different information in improving patient health or delivering better health policies, thus serving as the basic foundation in disease management. Despite of its importance, many countries are still relying on poor surveillance system to monitor the antimicrobial usage in animals. Only 27% of the participating countries were able to provide quantitative data on antimicrobial usage in animals in a survey conducted by OIE in 2012 [34]. Besides, the surveillance system in most of the countries shows gaps in recoding and collecting information on AMR as there are no globally agreed standards for data collection and reporting. In line with the global action plan on AMR, the Global Antimicrobial Resistance Surveillance System (GLASS) was launched in 2015 to support this objective by providing a more standardized and harmonized approach in AMR data collection and recording as well as AMR data sharing at a global level. The rapid sharing of information on AMR globally on a regular basis will allow easier detection of AMR emergence and dissemination in other countries, thus minimizing the impact.

It is clearly evident that increased usage of antimicrobials leads to higher risk of AMR emergence. With more antimicrobial-resistant infections affecting the people, more antimicrobials will be required to enhance the treatment, thus forming a vicious cycle which exacerbates the consequences. Therefore, it is vital to break the chain of transmission in infectious diseases if we want to reduce the usage of antimicrobials and limit the development of antimicrobial-resistant strains. The global action plan of AMR aims to reduce the incidence of infection by improving sanitation, hygiene and infection prevention measures. These measurements can be done by instilling the right attitude to the people, just like in the pre-antibiotic era when preventive measures were prioritized due to treatment limitation. In the healthcare setting, better sanitation and handwashing are as important as disease treatment or patient isolation to prevent the spread of infectious diseases from patients to patients. On the other hand, this strict practice should be followed in the agricultural sectors, especially those involve with food processing to ensure the safety of the animal products. Investing in sewerage and sanitation infrastructure in the farms prevents contamination of the water sources by animal wastes that contain dangerous pathogens and unmetabolized antimicrobial leftovers [46]. This ensures adequate access to safe water for the population, which can also directly affect the sustainability of the economic growth in a country and the life expectancy of its people [4]. Besides, vaccination should be used as a preventive measure to induce immunity within a herd, which will lower the risk of infection and the need of antimicrobial treatment.

Reducing the usage of antimicrobials is indeed the primary solution to tackle AMR. It is essential to reduce the usage of antimicrobials now with the projected increase in its usage with high market demands in the next few years. While all the countries in the EU has enforced strict regulation in the usage of antimicrobials in animals like complete prohibition on growth-promoting antimicrobial usage in animals, many countries in America and Asia still lack of similar regulation to control antimicrobial usage in animals. Enforcing a globally agreed regulation will be challenging due to different political will, therefore the FAO, OIE and WHO tripartite collaboration [12] should continue providing international action and consultation in these countries to establish regulations in antimicrobial distribution and prescription, which also tailored to their national action plans on AMR. Along with this, the WHO CIA List of medically important antimicrobials [11] should be taken into account in controlling such antimicrobial usage in agriculture and their marketing authorization. Financial incentives can be provided to assist farmers with optimized antimicrobial usage in their farms. Besides, antimicrobial stewardship programmes should be implemented in healthcare and agricultural sectors to ensure users are always up to date with the right choice of antimicrobials.

The global action plan foresees the needs of increased investment in new medicines and other medical interventions to fight against antimicrobial-resistant pathogens if the current trends of antimicrobial usage and AMR emergence persist. The plan aims to develop an economic case for this sustainable investment in the relevant fields. To achieve this, economic assessments are needed to compare the required cost for implementation and the consequential cost of no action, and this should be focused primarily in the least developed and developing countries with restrained financial resources. A good sanitation investment can easily improve life expectancy of a population by ensuring access to clean water, which is less costly than disease prevention and treatment [4]. The World Bank can play a role in the tripartite collaboration to access the economic impacts, in order to convince the countries to support the global action plan. The lack of investment for the development of new antimicrobials will cause hindrance in combating AMR if it spreads uncontrollably. The rapid development of AMR in pathogens causing restrictive antimicrobial usage has led to fears in the pharmaceutical industries to increase investment in antimicrobial development. Most of the major pharmaceutical companies rather shift their interests to drug development in chronic diseases and cancer treatment with promising returns. To encourage their participation in antimicrobial research and development, collaborative public-private partnerships can be established to ensure renewed investment with mutually agreed, fair and equitable benefits to both parties. The new antimicrobials will need to be governed based on the antimicrobial stewardship principles to ensure its effectiveness for as long as possible. Affordability and applicability of the antimicrobials should be considered carefully to ensure equitable access in all the countries without the risk of exploitation.

6. Conclusion

Antimicrobial usage in food-producing animals is one of the factors that causes the emergence of AMR and should be prioritized when tackling the AMR issue. There should not be any doubt in determining the severity of using growth promoters in food-producing animals if we practice the proper antimicrobial stewardship, which promotes the appropriate usage of antimicrobials. Besides, all countries need to be on the same side to tackle this global health threat, and in order to achieve this, efforts from each country have to be in line with the WHO's global action plan on AMR, which focuses on improving public awareness, strengthening knowledge on AMR through surveillance, reducing incidence of AMR infection, optimizing antimicrobial usage and developing sustainable investment for new AMR interventions. Ultimately, these strategies will not totally prevent the emergence of AMR but will prolong the effectiveness of quality-assured antimicrobials and delay the development of resistant strains in pathogens.

Conflict of interest

The authors declare that there is no conflict of interest in the text.

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