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REVIEW ARTICLE

Antimicrobial resistance in Indonesia: A comprehensive One Health analysis and strategic roadmap for mitigation

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ABSTRACT

Antimicrobial resistance (AMR) has emerged as one of the most critical global health challenges and poses significant threats to human, animal, and environmental health. Indonesia, like many other developing nations, is facing widespread AMR because of the overuse and misuse of antibiotics in humans, livestock, aquaculture, and agriculture. The interconnected nature of AMR requires a holistic approach to understand its prevalence, pathways, and impact. A One Health perspective, which integrates human, animal, and environmental health, is vital for comprehensively and effectively addressing AMR. This study is significant because it provides a detailed analysis of AMR in Indonesia and identifies critical resistance patterns across various bacterial species and antibiotics. This study highlights reservoirs of resistance, such as wastewater and food-producing animals, which serve as major pathways for the spread of resistant genes. Furthermore, this study examines the policy landscape in Indonesia, emphasizing the need for data-driven interventions and multi-sectoral collaboration. This study offers insights into AMR's economic, health, and social implications and aligns with global and national AMR mitigation frameworks. The primary aim of this study was to evaluate the current state of AMR in Indonesia, focusing on the environmental, animal, and human health sectors. The One Health approach identifies key resistance patterns, transmission pathways, and contributing factors. In addition, the study proposes a research roadmap to guide future initiatives, emphasizing the development of rapid diagnostics, therapeutic innovations, and improved surveillance systems to combat the growing threat of AMR in Indonesia.

Keywords: antibiotic resistance, antimicrobial resistance animals, antimicrobial resistance environment, antimicrobial resistance humans, antimicrobial resistance policy.

INTRODUCTION

The World Health Organization (WHO) has identified antibiotic-resistant infections (antimicrobial resistance [AMR]) as one of the top ten global health threats, prompting the launch of the Worldwide Action Plan on AMR in 2015 [1, 2]. AMR, a growing concern in human, animal, and zoonotic pathogens, poses a significant health risk globally, with the emergence and spread of resistant microorganisms affecting various sectors under the "One Health" concept, which integrates veterinary medicine, the environment, and public health [1]. In Indonesia, the control of AMR is mandated by the 2009 Health Law, leading to the development of the Indonesian National Action Plan (RAN) for AMR in 2021, aimed at ensuring safe and responsible antimicrobial use [3]. AMR-related diseases increase healthcare costs and extend hospital stays, thereby contributing to treatment failure. In 2019, 12.7 million deaths worldwide were directly attributable to AMR. In Indonesia, misuse of antibiotics in humans, animals, and aquaculture, coupled with rising demand for animal protein, intensifies the problem [4, 5]. Despite legal restrictions, antibiotics are often sold without prescriptions, contributing to the spread of resistant bacteria, including extended-spectrum beta-lactamase (ESBL)-producing strains such as *Escherichia coli* and *Klebsiella pneumoniae*, which have resistance rates ranging from 26% to 56% [6].

The primary objective of this study was to assess the current status of AMR in Indonesia, with an emphasis on the environmental, animal, and human health domains. Using a One Health framework, this study

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identifies significant resistance patterns, transmission routes, and underlying contributing factors using a One Health framework. Furthermore, the study outlines a strategic research agenda designed to inform future efforts, with a focus on advancing rapid diagnostic methods, therapeutic innovations, and enhancing surveillance systems to address the escalating challenge of AMR in Indonesia.

The study findings demonstrate that the population, as well as healthcare facilities, such as hospitals and primary care centers, also engage in inappropriate AM use. The majority of inappropriate AM usage in the livestock and fisheries sectors occurs in livestock, which is comparable to the problem in many other developing nations, including India, the Philippines, and Vietnam [7, 8]. In addition, there is a growing lack of control over the use of antibiotics in the coronavirus disease 2019 pandemic. The public began using digitalization and telemedicine, two health services that emerged out of nowhere. However, private providers take advantage of this to increase their profits. Telemedicine in Indonesia has been popular with many applications and has made it easier for patients to have access to therapies and medicines, including antibiotics such as azithromycin. Antibiotic purchases can now occur without the oversight of government agencies or certified healthcare professionals because the government has not yet created legislation on application-based telemedicine [9]. Unsuitable antibiotic usage in healthcare facilities results from several policy variables and antibiotic use recommendations that have not been well communicated [10]. Therefore, assessing the AMR situation in Indonesia is important, as it includes several aspects of One Health. To minimize the impact of AMR on the environment, animal health, and human health in Indonesia, this review presents information about the state of AMR in Indonesia that can be used as a basic reference when implementing the use of antibiotics as an appropriate and effective therapy.

RESEARCH TRENDS IN AMR FROM INDONESIA TO WORLDWIDE

This study conducted a bibliometric analysis to examine research trends in Indonesia and globally. The Scopus database was utilized for the analysis (accessed on January 5th, 2025), covering the years 2000–2024, with the following keyword query: TITLE-ABS-KEY (antimicrobial AND resistance) AND PUBYEAR > 2000 AND PUBYEAR < 2024 AND (LIMIT-TO (DOCTYPE, “ar”)) AND (LIMIT-TO (PUBSTAGE, “final”)) AND (LIMIT-TO (LANGUAGE, “English”)) AND (LIMIT-TO (SRCTYPE, “j”)). A total of 97,630 documents were retrieved for further analysis. Data from Indonesia (596 documents) related to AMR were compared with data from countries with the highest number of AMR-related publications: The USA (19,307 documents), China (11,469 documents), the United Kingdom (7,932 documents), and India (7,767 documents), as shown in Figure 1. Based on the results obtained, the United States, China, the United Kingdom, and India will be included in the subsequent analysis. The analysis of publication counts by country revealed that Indonesia accounted for only 0.6% of the total, compared to the USA, China, UK, and India, which accounted for 19.7%, 11.7%, 8.12%, and 7.95%, respectively. Based on the document growth chart over the years, it was found that the publication trends in each country generally increased annually (Figure 2).

Co-occurrence network analysis was conducted on Indonesia and countries with the highest number of publications related to AMR (Figure 3). The analysis of the co-occurrence network showed that in Indonesia, the development of AMR studies from 2000 to 2024 was divided into two main clusters. The first cluster (blue) consists of terms related to antibacterial agents, including tetracycline (TE) and ciprofloxacin, as well as clinical trials in both children and adults by gender. The second cluster (red) includes studies on inhibition testing and detection of various bacteria, such as *E. coli* and *Staphylococcus aureus*.

In the United States, co-occurrence network analysis revealed three main clusters. The first cluster (red) contains terms related to antibiotic resistance, antibacterial agents, and anti-infective agents. The second cluster (green) generally consists of terms

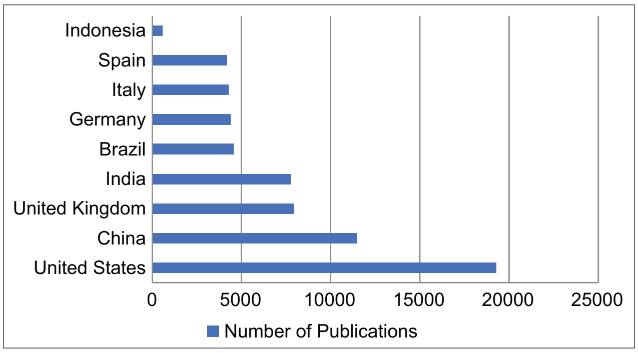

Figure 1: Number of publications per country from 2000 to 2024.

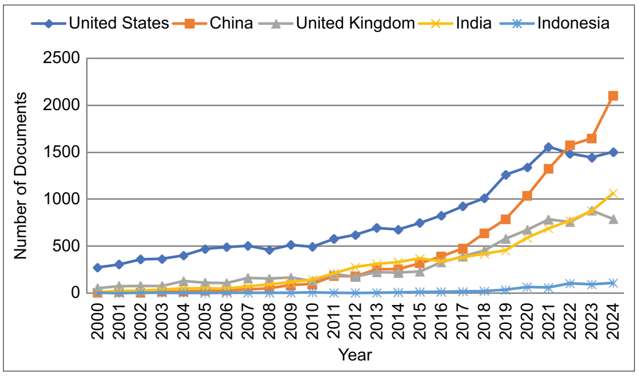

Figure 2: The number of documents per year from the four countries with the highest publication counts compared to Indonesia.

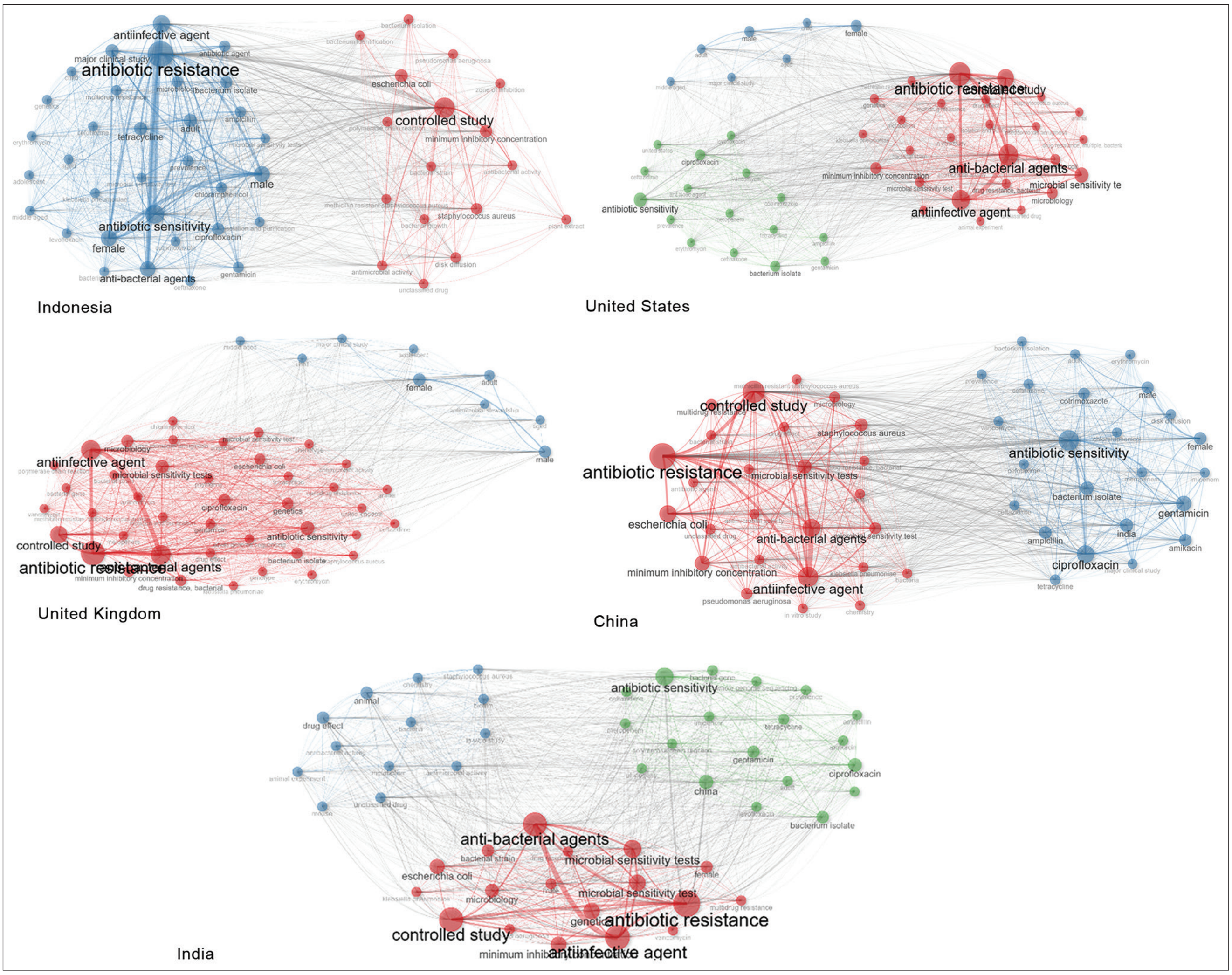

Figure 3: Co-occurrence analysis in Indonesia, United States, United Kingdom, China, and India from 2000 to 2024.

related to antibiotic sensitivity studies, including antibiotics such as ciprofloxacin, gentamicin, and TE. The third cluster (blue) of clinical trials is based on gender and age differences.

Analysis of various studies in the United Kingdom revealed two clusters. The larger cluster consists of terms related to antibiotic resistance associated with various microbial sensitivity tests, minimum inhibitory concentrations, and polymerase chain reactions in several bacterial species, primarily *E. coli*, *K. pneumoniae*, *S. aureus*, etc., against various antibiotics, especially ciprofloxacin, erythromycin, and gentamicin. The smaller cluster (blue) is related to various clinical trials based on gender and age differences.

Co-occurrence network analysis of studies in India revealed two major interconnected clusters. The first cluster primarily focused on antibiotic resistance, consisting mainly of control studies and testing for antibiotic resistance, particularly against *E. coli*, *S. aureus*, and *Pseudomonas aeruginosa.* The second cluster (blue) is associated with antibiotic sensitivity, particularly to ciprofloxacin, gentamicin, ampicillin, amikacin, TE, etc., and clinical trials based on gender differences.

Similar to the United States, which has more than 10,000 published documents, China has three main clusters. The first cluster (red) is dominated by terms related to antibiotic resistance, including microbial sensitivity tests, minimum inhibitory concentrations, and bacterial strains, especially *E. coli* and *K. pneumoniae*, and several clinical studies involving patients of different genders. The second cluster (green) mainly pertains to antibiotic sensitivity testing for various antibiotics, including ciprofloxacin, gentamicin, and TE. The third cluster (blue) consists of studies on antimicrobial activity in animal models. The results of the co-occurrence analysis indicate that, in fact, the countries included in the analysis predominantly conduct research containing similar terms or topics. The trend of topics by country over the years is depicted in Figure 4.

ENVIRONMENTAL ANTIBIOTIC RESISTANCE

A global threat to public health that may arise is AMR in the environment. It is projected that the number of deaths worldwide from illnesses caused by bacteria resistant to antibiotics will rise from 700,000 to 10 million years by 2050 [11]. Antibiotic-resistant bacteria can increase the risk of morbidity and mortality and make it more difficult to treat illnesses effectively [12]. Increasing antibiotic resistance, in particular, presents serious issues regarding social, economic, and health [13].

Environmental factors have also been repeatedly identified as infection-resistant gene reservoirs [14, 15]. One of the greatest challenges to treatment is the widespread emergence of antibiotic resistance in bacterial illnesses [16]. Horizontal gene transfer is frequently used in clinical infections to acquire resistance genes [17]. Novel antibiotic resistance genes present in clinical illnesses are derived from environmental bacteria [18]. The presence of AMR in environmental bacteria found in wastewater is concerning because these bacteria can spread resistance genes to other bacteria in aquatic environments. In aquatic ecosystems, hospital waste is considered the primary source of antibiotics. This is followed by wastewater from municipalities, aquaculture, and farms, including dairy farms, which have also been demonstrated to be a significant source of these compounds and resistant bacteria [19].

Marine pollutants, such as antimicrobial-resistant bacteria, antibiotics, metals, and contaminants of concern, mostly come from wastewater from processing plants, hospitals, and other health facilities (pharmacies), industry, and agriculture. In addition, these marine pollutants can affect human health and the environmental food chain by contaminating food originating from the sea [20]. The continuous use of antimicrobials in various disease therapy applications, animal food production, and horticulture results in high AMR in hospital, municipal, and industrial waste, as well as in wastewater treatment plants [21]. Water is a natural resource that living creatures need; therefore, it must be protected so that it remains beneficial for the lives of all living creatures. The lack of public awareness of the availability of clean water causes problems with water pollution that often occur [22]. *E. coli* is widely found in water and is a reservoir related to AMR [23].

Multiple drug resistance, a risk factor for cross-contamination between dairy cows and workers, is indicated by the presence of *E. coli* in the handwashing water used by workers [24]. However, since environmental contaminants, including wastewater, can pose a greater risk, the presence of these bacteria does not always imply zoonotic transfer between dairy cows and personnel [25]. Most of the time, *E. coli* thrives in the digestive tracts of people and other animals, but occasionally, it travels to different environments and spreads illness. Because it can cause diarrhea and some strains of *E. coli* are the primary cause of urinary tract infections (UTIs), *E. coli* impacts public health [26, 27]. *E. coli* has a high survival rate, making its presence an environmental indication. According to recent investigations, antibiotic resistance data from related populations correlate with the AMR profiles of *E. coli* isolates from sewage [28, 29]. Almost all *E. coli* are amoxicillin-resistant and erythromycin in Bogor, Indonesia [30]. Similarly, *E. coli* is resistant to penicillin in the aquatic environment in Palembang (Sumatra) [31].

Ten (32.26%) of the *E. coli* isolates studied fit the TE, streptomycin (ST), trimethoprim (W) antimicrobial drug resistance pattern (TE, ST, W). Furthermore, it was discovered that two multidrug-resistant (MDR) *E. coli* isolates, accounting for 6.54% of the total, exhibited resistance to four different antibiotics and exhibited a resistance pattern toward the antimicrobial drug TE-ST-W-chloramphenicol (C). Similarly, additional study on the patterns of MDR *E. coli* isolates from dairy cow milk samples identified eight isolates (38.10%) that were resistant to the antimicrobial agents (TE-ST-W). Additionally, one isolate (4.76%) exhibited resistance to TE, ST, W, and aztreonam (ATM). Moreover, the overall resistance levels to TE, ST, and W remained low [32].

In addition to *E. coli*, *S. aureus* is a common environmental bacterium that requires particular attention. *S. aureus* is common in dairy cows and can contaminate milk. Methicillin-resistant *S. aureus* (MRSA) is the name given to *S. aureus* that is resistant to beta-lactam antibiotics, particularly cefoxitin. Sanitation management is inextricably linked to the transmission of MRSA, which can originate from farmers' hands or milk taken from udders during the milking process [12].

Lactic acid bacteria (LAB) are widely found in nature, in food products, and in the digestive tract of humans and animals. The role of bacteria in food processing can be traced back thousands of years, providing humans with fermented vegetables, dairy products, and meat and fish products [33]. The *Lactobacillus genus* is generally considered safe in America due to its extensive involvement in food fermentation. In recent years, the use of LAB as a probiotic has increased, providing significant health benefits for humans and animals [34]. Conversely, the increasing use of LAB has raised public concerns about safety issues, such as the spread of antibiotic resistance [35]. The excessive and incorrect use of antibiotics in agriculture and animal husbandry has triggered the circulation of antibiotic-resistant bacteria, thereby threatening human and animal health [36]. In medicine, the significant increase in MDR infectious diseases causes thousands of deaths annually, activating a global threat to public health and a huge financial burden [37].

Furthermore, LAB can transmit antibiotic-resistance genes from the animal microbiota to human gastrointestinal bacteria [38]. *Lactobacillus* spp. are usually resistant to aminoglycoside antibiotics (e.g. ST, kanamycin, neomycin, and gentamicin) and are mostly susceptible to C, erythromycin, TE, and clindamycin [39]. Strains resistant to C, erythromycin, TE, and clindamycin have been identified in *Lactobacillus* spp. from food fermentation [38]. Based on the European Food Safety Authority recommendations, bacteria with transferable antibiotic resistance genes should not be

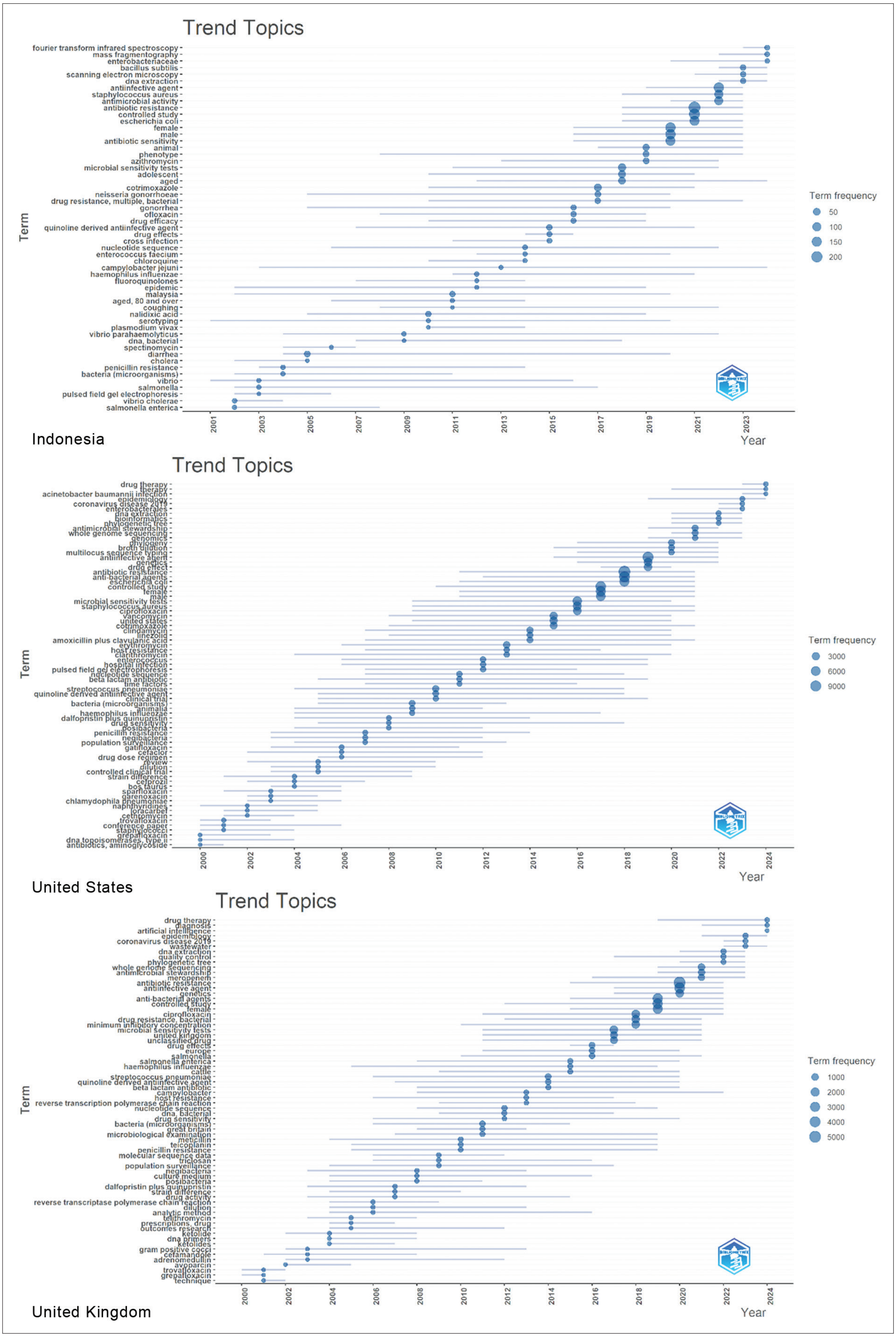

Figure 4: Similar terms and topics. Trends in topics in each country over time.

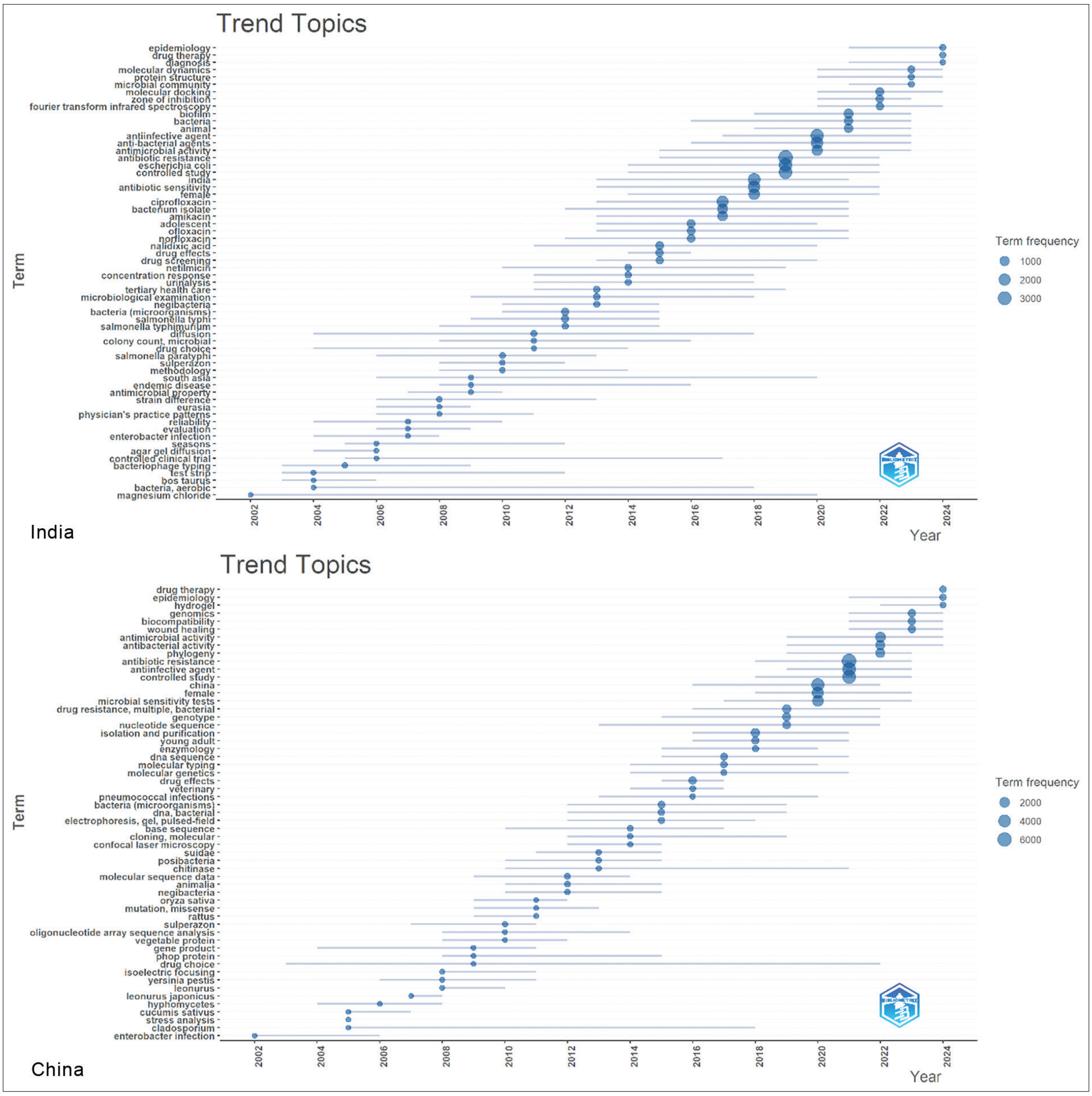

Figure 4: *(Continued).*

used in animal feed, fermented foods, and probiotics for human consumption [40]. Andriani *et al*. [41] found that all *Lactobacillus* spp. strains resisted aminoglycosides and ciprofloxacin but were sensitive to amoxicillin, clindamycin, and erythromycin.

Several studies on the antibiotic resistance of various bacterial species obtained from environmental aspects to various antibiotics have been conducted in Indonesia (Supplementary data). The number of occurrences of bacterial resistance to several antibiotics can be seen in the diagram (Figure 5). Information regarding the incidence of resistance to existing antibiotics such as obiter meropenem, ciprofloxacin, cefixime, ampicillin, amoxicillin-clavulanic acid, enrofloxacin, cefotaxime, sulfamethoxazole-trimethoprim, gentamicin, C, amoxicillin, cefazolin, ceftriaxone, aztreonam, ceftazidime, ampicillin-sulbactam, cefepime, TE, marbofloxacin, pradofloxacin, doxycycline, neomycin, oxacillin, oxytetracycline, cefoxitin, penicillin, clindamycin, erythromycin, ceftazidime, piperacillin-tazobactam, tobramycin, kanamycin, cotrimoxazole, and ST can be seen in antibiotic resistance data from the environment in Indonesia (Supplementary data).

ANTIBIOTIC RESISTANCE IN ANIMALS

In addition to being used in human medicine, many antimicrobials are also employed in animal health to treat sick animals, add growth-promoting ingredients to animal food, or prevent diseases on an industrial scale. Additional research indicated that the use of antibiotics is relatively high in Indonesian small-scale commercial broiler chicken farms because breeders can easily obtain antimicrobials at relatively low costs through local veterinary drug sales sources [42]. However, breeders also face challenges in obtaining veterinarian advice or taking appropriate action regarding the responsible use of antimicrobials [43].

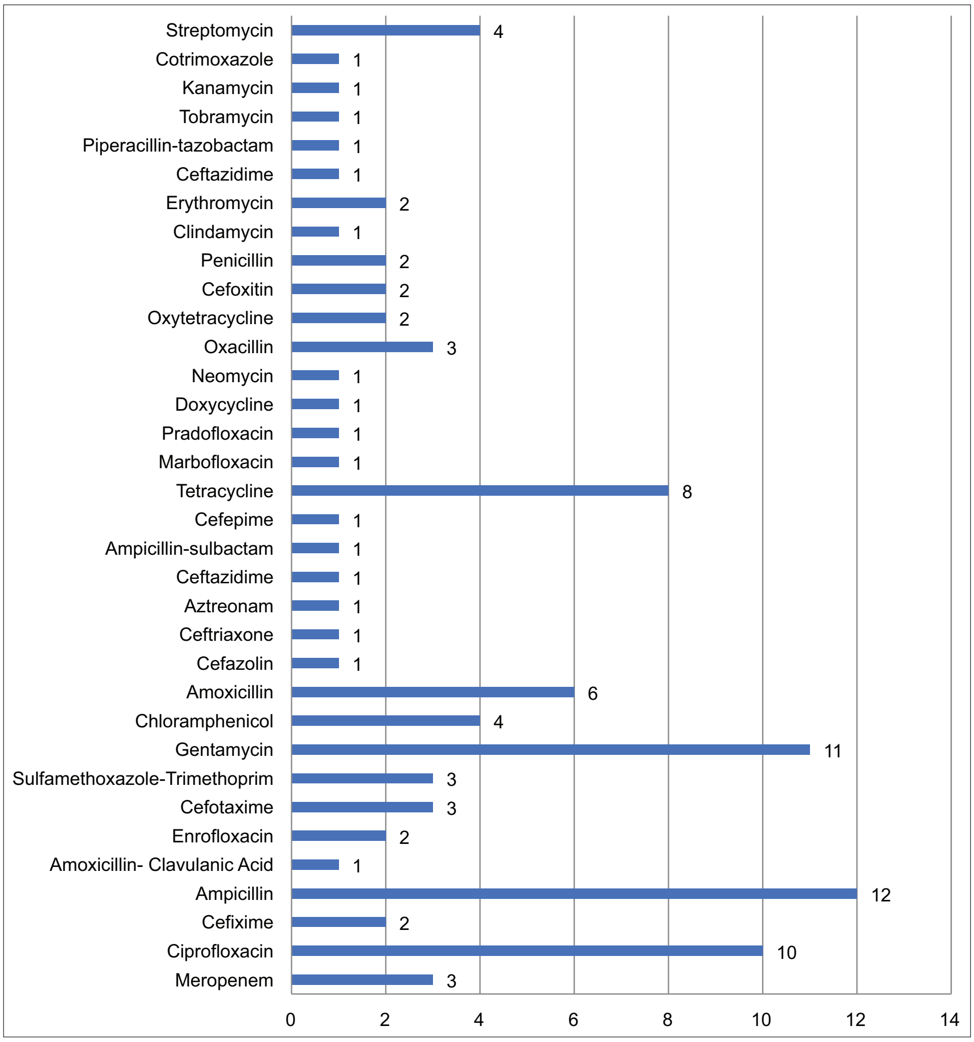

Figure 5: Incidence of antimicrobial resistance in the environment.

The use of antimicrobials in animal husbandry provides benefits for animals and farmers; however, they can pose a risk of AMR if they are not used according to the dose and time of use. Livestock animals are a source of AMR [44, 45]. The medical consumption of antibiotics in animals in this sector is around 80%, mostly to promote animal growth and health. The most common antibiotics used in animal husbandry are beta-lactam antibiotics [46]. Beta-lactam antibiotics are derived from penicillin and cephalosporins [44, 47]. Microorganisms that experience AMR make them more resistant to drugs; as a result, the infection continues and increases the risk of future spread by the host [46].

The contamination of antibiotic-resistant bacteria in food-producing animals is possibly caused by the use of antibiotics in livestock. Resistance to certain antibiotics in commensal *E. coli* isolates from pigs, poultry, and cattle is closely correlated with the level of use of these drugs [48]. The use of antibiotics in livestock is reported in East Asian countries [49] and worldwide [50]. Indonesia is estimated to be among the five countries with the highest estimated increase in antimicrobial consumption in 2030 [50].

Furthermore, Indonesia is ranked second among the 50 countries with the largest number of antibiotics used on livestock in 2010, including Myanmar (205%), Indonesia (202%), Nigeria (163%), Peru (160%), and Vietnam (157%) [50]. The large production of cattle to meet the high demand for beef in Indonesia [51] has resulted in the high use of antibiotics among livestock in this country. Livestock animals, including cattle, have the potential to be sources of microorganisms that are resistant to antibiotics [52]. Therefore, the emergence of antibiotic resistance among pathogens from food-producing animals represents a growing problem for veterinary medicine and public health [53].

The use of antibiotics in cattle has grown to be a significant food safety problem. Animal-based food ingredients can act as carriers of foodborne pathogens with resistant genetic material and have occasionally been linked to foodborne illnesses in humans [54]. Antibiotic-resistant commensal and pathogenic microorganisms, including *E. coli*, can arise. Foodborne diseases can be caused by *E. coli* bacteria when raw or undercooked meat is consumed [55]. One of the primary microbes that promotes antibiotic resistance is *E. coli* [56].

E. coli is present in food, the environment, animals, and the intestines of humans. Both commensal and pathogenic *E. coli* strains exist [57, 58]. *E. coli* is a rod-shaped, 2.0 μm–6.0 μm (length), and 1.1 μm–1.5 μm (width) Gram-negative bacterium that belongs to the Enterobacteriaceae family [59]. *E. coli* can cause systemic, enteric, and extraintestinal infections in humans and animals [60]. Hemolytic uremic syndrome is one of the worst illnesses that *E. coli* O157:H7, a pathogenic strain of the bacteria, can produce in humans [58].

According to another study, 88.2% of chickens developed *E. coli* resistant to different antibiotics. The veterinary and animal health communities are greatly concerned about this [61]. Chicken susceptibility to antibiotic-resistant *E. coli* can be directly or indirectly spread through food, other animals, or chickens. Normal flora can be colonized by resistant bacteria that can transfer their resistance features to them. Resistance genes can be passed horizontally or vertically between bacteria of different genera and families [62]. Because *E. coli* can spread resistance genes to other dangerous bacteria, even though it is a commensal bacterium, it poses a health risk.

Apart from *E. coli*, the presence of *Staphylococcus* spp. is also closely related to AMR characteristics. Complex interactions between bacterial species from diverse "environments" intensify AMR across humans, animals, and the environment, posing a threat to public health [63]. The anti-antibiotic defense strategies of *S. aureus* include altering binding and active sites, generating transmembrane proteins called efflux proteins, and creating plasmids containing genes for antibiotic resistance [64].

MRSA was first identified in 1961 when it was reported that the organism had become resistant to methicillin and other β-lactam antibiotics [65]. MRSA infections have been reported in dogs, cats, sheep, cattle, horses, rabbits, seals, cockroaches, and chinchillas [66–68]. Numerous variables, such as dense population, possibility of nosocomial transmission from humans, insufficient cleaning and disinfection practices, unknown carrier status of numerous animals, or the environment, can contribute to this exposure [69].

Although pets frequently harbor diverse strains of *Staphylococcus*, these bacteria can occasionally survive in these animals [70]. *S. aureus* can cause several illnesses when it enters the body, from minor skin infections to dangerous invasive infections that can be fatal [71, 72]. Pets and their owners frequently have close physical contact, which can expose people to harmful MRSA bacteria through petting and licking [73]. The risk of MRSA transmission increases with close relationships between humans and animals [74]. Molecular detection research has shown that the frequency of identical MRSA strains in cats and individuals residing in the same home is associated with the transfer of bacterial strains from pets to their owners [75].

Since there is no cure for MRSA, adopting healthy lifestyle practices is essential to control and stop the spread of the infection from one animal to another and from people to animals [67, 76]. Early detection through microbiological surveillance and prudent antibiotic use can also prevent MRSA in humans and animals [77]. While colonization in cats and other animals is often transient, it can be completely eradicated in some cases when the environment is regularly cleaned, disinfected, and measures are taken to prevent reinfection. [78]. Veterinarian clinics and hospitals must implement protocols to reduce MRSA cross-contamination [79]. Good hygiene habits, such as cleaning and disinfecting one's hands, are essential for prevention [80].

In addition, traditional markets in Indonesia sell various goods, such as fresh and dried meat, fish, fruit, and vegetables, as well as daily necessities. In urban areas, rodents such as mice are often found in traditional markets. The interesting fact is that house shrews (*Suncus murinus*) live near food sources such as markets, which have great potential as a source of bacteria with characteristics that are resistant to certain antibiotics, which can infect and endanger human health [81].

The aquatic sector provides a vital additional source of food for humans. Aquaculture products provide food for human consumption. Antibiotics have a significant impact on aquatic environments and can increase the susceptibility of microbiota to antibiotics [82]. The existence of resistance to bacteria in the environment is also significantly affected by human actions [83]. Aquaculture is currently developing AMR, a concern because AMR is a growing component of the food supply [84].

The rising fish yield keeps up with the world's food supply. Due to their high domestic and international demand, freshwater fish like tilapia are ideal for long-term sustainable farming [85]. After China, Indonesia is the world's second-largest producer of tilapia, with over 50,000 tons of this fruit produced in 2018. Indonesia is the country of origin for 1,222,700 tons or 20.27% of global production. Other major producers are the Philippines, Vietnam, Thailand, Ghana, Egypt, Bangladesh, Brazil, the Philippines, Colombia, Taiwan, Republic of China and Mexico [86]. Aquaculture production systems are becoming increasingly important as the demand for fish continues to increase globally [87]. The increasing demand has been followed by a more intensive movement in the aquaculture sector. The Asian continent plays a very important role as an international supplier of shrimp and contributes 85% of global aquaculture production [88].

The management of parasites and infectious diseases in fish is crucial for the sustainability of fish farming operations [89]. Freshwater fish, also known as milkfish (*Chanos chanos*), are highly valued commodities in Indonesia. The Gram-negative bacterium *Aeromonas hydrophila* has the capacity to spread widely when milkfish are cultivated. High stocking density, high temperatures, high quantities of organic waste, and even well-kept pond conditions can all lead to *A. hydrophila* infection. Fish living in harsh conditions are more likely to become stressed and infected [90]. Bacteria generally enhance their virulence traits and develop resistance to various drugs. Because drugs are misused, *A. hydrophila* has developed AMR, a global issue [91].

Several studies (Supplementary data) have been carried out regarding bacteria that originate from animals and have the characteristics of being resistant to several types of antibiotics in Indonesia, such as TE, oxytetracycline, ampicillin, gentamicin, nalidixic acid, enrofloxacin, ciprofloxacin, erythromycin, C, ST, sulfamethoxazole-trimethoprim, W, cephalothin, oxacillin, clindamycin, penicillin, amoxicillin, methicillin, cefoxitin, fosfomycin, rifampicin, cefotaxime, kanamycin, and aztreonam can be seen in the antibiotic resistance data in animals in Indonesia. The number of occurrences of bacterial resistance to several antibiotics can be seen in the diagram (Figure 6).

ANTIBIOTIC RESISTANCE IN HUMANS

There is still much to learn about the threat of AMR to human health in Indonesia. AMR is high and poses a growing threat to public health [92]. According to the findings of a study on AMR surveillance conducted in 12 Asia-Pacific nations, ESBL-positive *E. coli* (71%), as well as *Klebsiella* spp. (64%), were most common in Indonesia [93]. According to preliminary data, livestock exhibit significant antibiotic usage and AMR [49, 50, 92]. Indonesia is one of the five nations most likely to experience a global increase in antimicrobial use, with a projected rise of 202% from 2010 levels by 2030 [50]. This estimate is based on models that were applied to empirical data, considering changes in the human population, the demand for protein, the origin of animals, and the type of farming system [42].

Antibiotics for bacterial infections in children are potentially life-saving treatments. Based on the International Guidelines for the Integrated Management of Childhood Illnesses, antibiotics are recommended for the treatment of acute respiratory tract infections and dysentery [94]. However, antibiotics are frequently misused in underdeveloped nations, for example, when treating non-specific respiratory illnesses and non-bloody diarrhea [95, 96].

With 266 million people living there as of 2018, Indonesia was the fourth most populous country in the world, with 29% of its citizens under the age of 15. Antibiotics are the medications that doctors prescribe to children the most [97, 98]. The relatively high rates of antibiotic usage in communities, hospitals, and livestock in high-income nations contribute significantly to the emergence of resistance strains, forcing physicians to select more costly and broad-spectrum antibiotics [99].

The highest microbiology laboratory service standards have been implemented in numerous large hospitals in Indonesia in compliance with national (Ministry of Health) and international (latest Clinical and Laboratory Standards Institute) requirements. The development of hospital antibiograms and

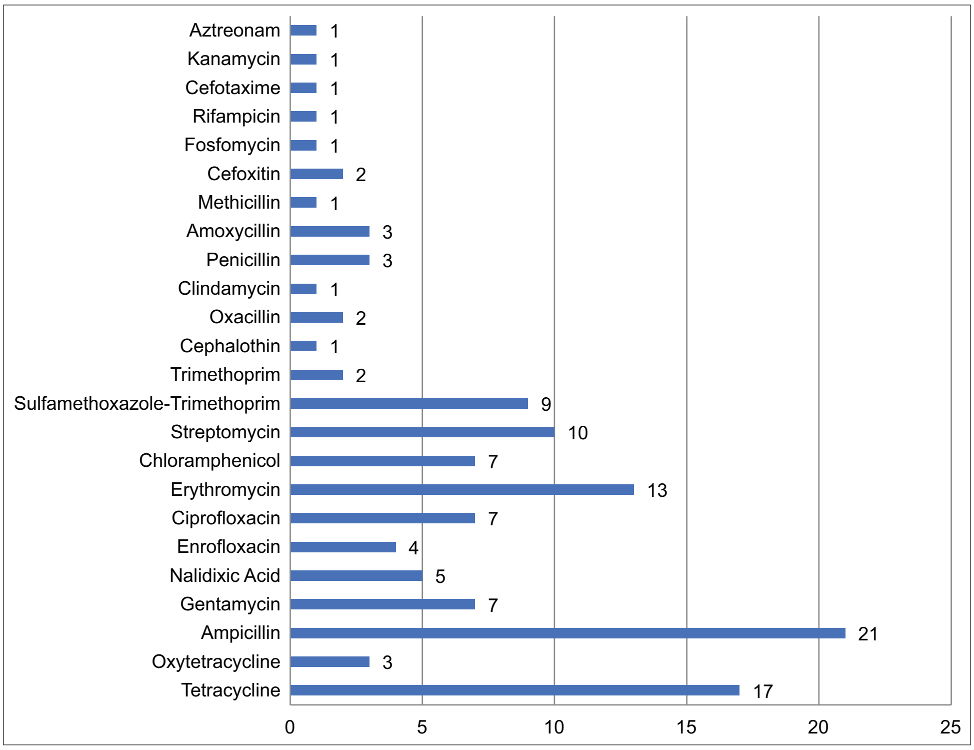

Figure 6: Incidence of antimicrobial resistance in animals.

microbiological patterns can be optimized in accordance with local requirements and the best guidelines. While this is going on, several other hospitals, such as type B and type C hospitals, spread throughout Indonesia's various regions and islands (more than 2000 hospitals), offer microbiology laboratory services using varying degrees of sophistication based on their limited resources, particularly in facilities. Several hospitals throughout Indonesia house physicians with extensive training in laboratory medicine, including microbiological laboratory services [100], and they keep track of local antibiograms and microbiological patterns based on particular resources. Local antibiogram limitations are typically caused by some examinations. There were extremely few and fewer representative isolates tested for antibiogram reporting in each period, and the analysis was rather straightforward [100].

Pneumonia ranks sixth worldwide in pediatric pneumonia cases and is a leading cause of death among children in Indonesia [101]. An estimated 6 million new cases are reported in Indonesia each year [102]. In 2018, it was anticipated that 505,331 Indonesian children under the age of five contracted pneumonia. The country had a case fatality rate (CFR) of 0.08% for children under the age of five in 2018, with Jambi, South Sumatra, Riau, DKI Jakarta (Special Capital Region), Central Kalimantan, Southeast Sulawesi, Maluku, Papua, and West Kalimantan having the lowest rates at 0%. It should be noted, therefore, that surveillance data availability differs significantly throughout provinces and is non-existent in some of them [101].

Pneumonia continues to be a serious global issue with significant morbidity and mortality rates. Treatment effectiveness is decreased by the growing number of pneumonia cases caused by germs, particularly MDR pathogens; the aging of patients with comorbidities; the growing population; and the use of the wrong antibiotics at first. In conclusion, this issue contributes to the high morbidity and mortality rates among hospitalized patients with pneumonia [103].

Pathogenic bacteria, such as *K. pneumoniae*, quickly develop MDR, representing a major risk to patients' health and increasing mortality rates because treatment choices are less effective. Hospital infections are mostly caused by *K. pneumoniae.* Due to the synthesis of enzymes such as carbapenems and ESBL, *K. pneumoniae* is more sensitive to antibiotic resistance than most other bacteria [64, 104]. The extensive and continuous use of antibiotics in hospitals is a primary contributor to the emergence and spread of highly resistant bacteria in illnesses [105]. In addition, *K. pneumoniae* is crucial for the clinically significant transfer of antibiotic resistance genes from one bacterium to another [106].

Another well-known characteristic of *K. pneumoniae* is its capacity to create biofilms, which are bacterial colonies encased in an extracellular matrix. Proteins, lipopeptides, exopolysaccharides, and DNA comprise this matrix [107]. Numerous virulence factors are present in *K. pneumoniae*, including lipopolysaccharide, capsule polysaccharide, type 1 and type 3 fimbriae, outer membrane proteins, and components that determine iron uptake and nitrogen utilization. By building biofilms, *K. pneumoniae* exploits these virulence characteristics to elude the immune system and survive throughout infection [108]. To prevent antibiotic penetration and lessen their effects, *K. pneumoniae* generates a thick coating of extracellular biofilm that facilitates bacterial adhesion to the surface of either living or dead cells [109].

According to another study, among human immunodeficiency virus (HIV)-negative children aged between 1 and 49 months, pneumococcal illness is considered responsible for 11% of all fatalities. Because vaccination programs can prevent high estimates of death rates, these estimates may be lower than the actual death rate. It is predicted that 8.9 million children worldwide suffered from pneumococcal pneumonia in 2015, accounting for over 95% of all cases of the disease. Depending on the region, pneumococcal pneumonia can have a CFR of 1%–6%. Southeast Asia has the highest rate of infection. Between 2000 and 2015, there were an estimated 83,900 occurrences of pneumococcal meningitis worldwide and 326,000 cases of invasive non-pneumonia and non-meningitis (i.e., sepsis and other invasive pneumococcal illnesses) [110]. In 2010, 21,578,876 children in Indonesia aged 0–4 years were projected to have pneumonia based on a systematic analysis using epidemiological models. Of these, 3,918,360 (18.2%) had pneumonia, with *S. pneumoniae* being the cause of 14.3% of cases [111]. Among Southeast Asian countries, this is the third highest number of cases of pneumonia. An estimated 6311 children died from pneumonia, accounting for 2.3% of the total population [110].

Diabetes, UTI, and a few other bacterial infection-related illnesses are also linked to antibiotic resistance. It has been demonstrated that diabetes has secondary effects on the urogenital system that increases the risk of UTIs. This type of illness is frequently accompanied by elevated blood sugar levels, insufficient white blood cell circulation, and bladder infections [112]. Urine stays in the bladder for an extended period because of autonomic neuropathy's poor emptying process of autonomic neuropathy, making the bladder a favorable environment for bacterial development [113]. Patients with hyperglycemia present with glycosuria or high-glucose urine, which is conducive to germ proliferation. Because glucose-6-phosphate dehydrogenase is inactivated in this hyperglycemic state, polymorphonuclear leukocyte movement through the endothelium is restricted, polymorphonuclear leukocyte death is increased, and antimicrobial function is inhibited [114].

The risk of UTIs is increasing in individuals with diabetes mellitus (DM), according to current statistics. The increase in cases of type 2 diabetes also elevates the risk of infections caused by pathogens resistant to various antibiotics, such as ESBL Enterobacteriaceae, vancomycin-resistant enterococci, fluoroquinolone-resistant uropathogens, or carbapenem-resistant Enterobacteriaceae. Nevertheless, little is known about UTI microorganisms that are resistant to antibiotics, which has an impact on the prescription of appropriate medications for DM and UTI patients [112]. A common infectious condition in children is UTI, which is defined by a noticeable increase in the number of germs in the urine. Antibiotics are the mainstay of treatment for UTIs in children. However, improper and overuse of antibiotics has increased antibiotic resistance to UTIs globally. Significant regional differences exist in the distribution of bacteria that cause UTIs and patterns of antibiotic resistance [115].

According to estimates, 78 million new cases of gonorrhea (caused by *Neisseria gonorrhoeae*) occurred in 2012. Gonorrhea is the most prevalent bacterial infection in sexual relations [116]. In 2014, at 7.7 cases/100,000 males, Indonesian men had the second highest prevalence of gonorrhea in Southeast Asia in 2014, behind Thai men [117]. According to a 2015 article published in Integrated Biological and Behavioral Surveillance, female sex workers and transsexuals had an even greater prevalence of gonorrhea (34.2% and 11.2%, respectively). HIV infection is a sexually transmitted infection that can spread when gonorrhea is left untreated. It can also lead to serious problems [118].

Treatment efficacy is a problem because *N. gonorrhea* can become resistant to a few antibiotics. Extended-spectrum cephalosporin treatment failure has been recorded in at least 10 countries. The WHO has concluded that gonorrhea may have serious consequences for sexual and reproductive health and may become an incurable infection [119]. At present, the Indonesian guidelines for treating gonorrhea recommend the use of cefixime or ceftriaxone as monotherapy. Azithromycin should only be added to treat suspected chlamydial infections, not gonorrhea itself. In Indonesia, other medications such as spectinomycin and sulfonamide have never been employed as therapeutic alternatives [120].

Tuberculosis (TB) is one of the deadliest infectious diseases in many countries. Many innovations have been made in diagnostics, transmission, drug resistance, drug therapy programs, prevention, and control. Indonesia is one of eight countries that cover the majority of total TB cases worldwide, with a percentage of 8.5% [121]. Drug-resistant TB is a problem that requires extra attention when controlling TB. At present, TB control has become one of the national priority programs for health development in Indonesia; this disease is still one of the diseases in this country as the top four causes of death [122].

Since 2011, there have been many cases of diphtheria in Indonesia. The only province officially declared to have a diphtheria outbreak is East Java Province, which is also an endemic location for the disease. This province accounts for approximately 80% of all cases in Indonesia [123]. Despite several attempts, It is still impossible to stop the spread of diphtheria [124]. Every facet of treatment and prevention, including the causes of antibiotic resistance, was assessed. Anti-diphtheria serum (ADS) and antibiotics are the two primary treatments for diphtheria. ADS binds freely to circulating toxins. This advertisement does not neutralize toxins present in cells. Another crucial aspect of treating diphtheria therapeutically is the use of antibiotics [125].

In several nations, the emergence of antibiotic resistance to *Corynebacterium diphtheriae* has raised serious concerns [126]. It is also feasible that the inability to eradicate *C. diphtheriae* is due to decreased antibiotic susceptibility [127]. East Java had a spike in diphtheria cases at this time, but information about *C. diphtheriae's* pattern of antibiotic susceptibility was lacking. For a long time, first-line antibiotics such as penicillin and erythromycin have been advised as the best treatments for diphtheria; nevertheless, numerous investigations have found that these medications have decreased susceptibility [128].

Infections with MRSA are challenging for many patients in medical facilities across the globe [44]. Skin infections, bacteremia or sepsis, endocarditis, pneumonia, osteomyelitis, cellulitis, and impetigo are examples of MRSA infections that can range in severity in public health [129]. There are numerous reports of *S. aureus* hospital infections all over the world, but particularly in Asia [130]. In poor nations like Indonesia, where infectious diseases are common, antibiotic resistance is a major issue. *S. aureus* infection can prolong hospital stay and increase medical expenses. Antimicrobial chemotherapy has shown that *S. aureus* has developed resistance to most antibiotics; if this is the case, then control and eradication of the infection may prove challenging [131]. Data on the sensitivity and resistance of each antibiotic must be collected to prevent the spread of antibiotic resistance.

Several studies on antibiotic resistance of various bacterial species present in humans to various antibiotics have been conducted in Indonesia (Supplementary data). The number of cases of bacterial resistance to several antibiotics can be seen in the diagram (Figure 7). Information regarding the incidence of resistance to existing antibiotics in Indonesia can be found in the data on antibiotic resistance in humans in Indonesia

(Supplementary data).

ONE HEALTH APPROACH

It has been determined that the AMR crisis is a fundamental One Health concern [132]. The creation of an intergovernmental panel on AMR has been proposed [133]. A multi-government, multi-sectoral, and multi-species strategy is crucial for enhancing anticipation for AMR. New approaches to monitoring antimicrobial use and AMR must fill in the knowledge gaps regarding antimicrobial use in farmed animals and cultured aquatic animal species. In addition, the private sector must be involved in this innovation. A more comprehensive examination of the institutional, social, and economic contexts in which a policy will be developed is necessary to comprehend the usage of antimicrobials [134].

Food traders, farmers, veterinary professionals, and slaughterhouse workers can all be directly infected by resistant bacteria [135]. The indirect transmission route is intricate across the food chain. Humans can contract resistant bacteria by eating or coming into contact with contaminated foods. It has been determined that resistant bacteria are present in a range of food items from animal sources (poultry, cattle, pigs, goats, and sheep) and food processing stages [136, 137]. Numerous antibiotic resistances lead to decreased levels of hospitalized health services, increased patient morbidity and mortality, increased resource utilization, higher expenses, and poor treatment against harmful bacterial infections [138].

AMR CONTROL MITIGATION

The Coordinating Ministry for Human Development and Cultural Affairs Regulation No. 7 of 2021, Indonesia implemented an AMR control strategy. The strategy comprises six main points, as outlined in Article 6. These include (a) raising awareness and understanding of controlling AMR through communication, education, and training; (b) expanding scientific knowledge and evidence through surveillance and research; (c) lowering the incidence of infection through infection prevention and control measures, sanitation, and hygiene; (d) increasing funding to develop new treatment protocols, diagnostic techniques, and vaccines in an effort to slow the emergence of the AMR problem; (e) optimizing and monitoring as well as putting follow-up sanctions into place for distribution violations and the use of antimicrobials in humans, animals, fish,

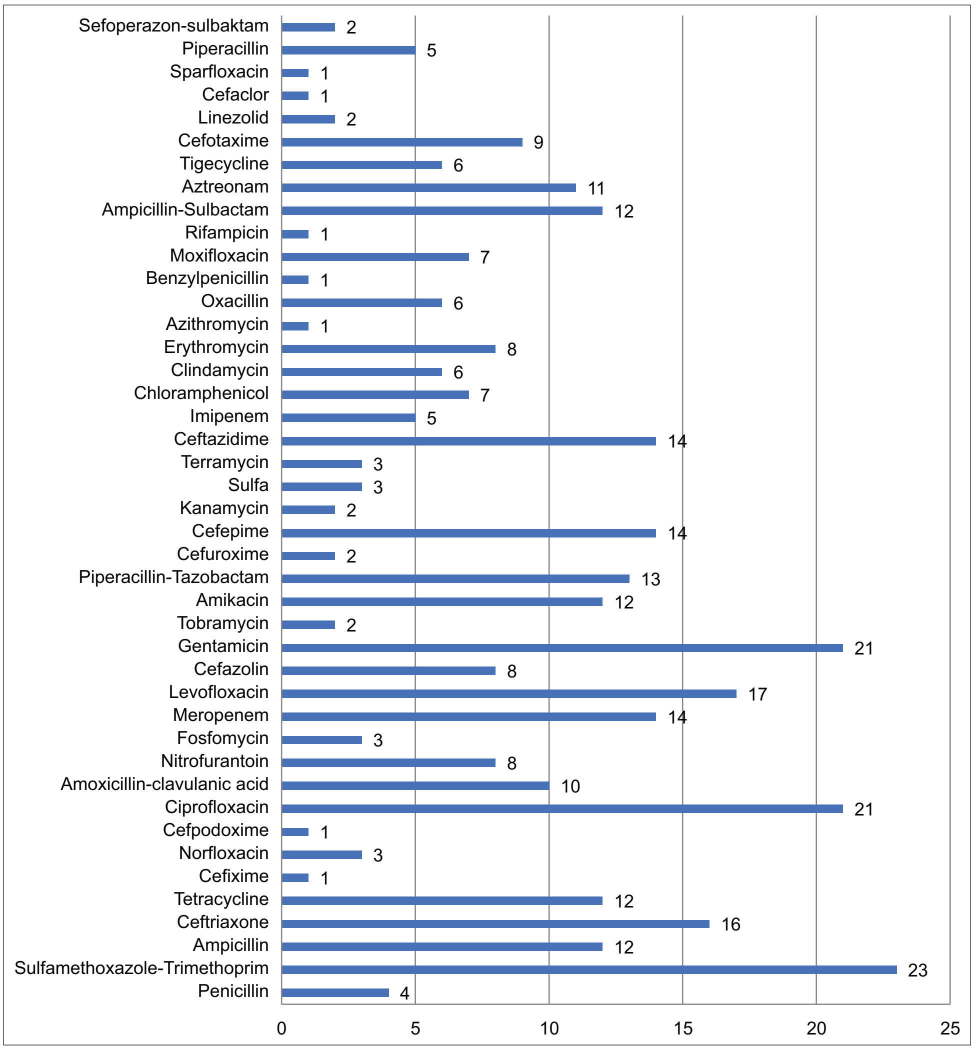

Figure 7: Incidence of antimicrobial resistance in humans.

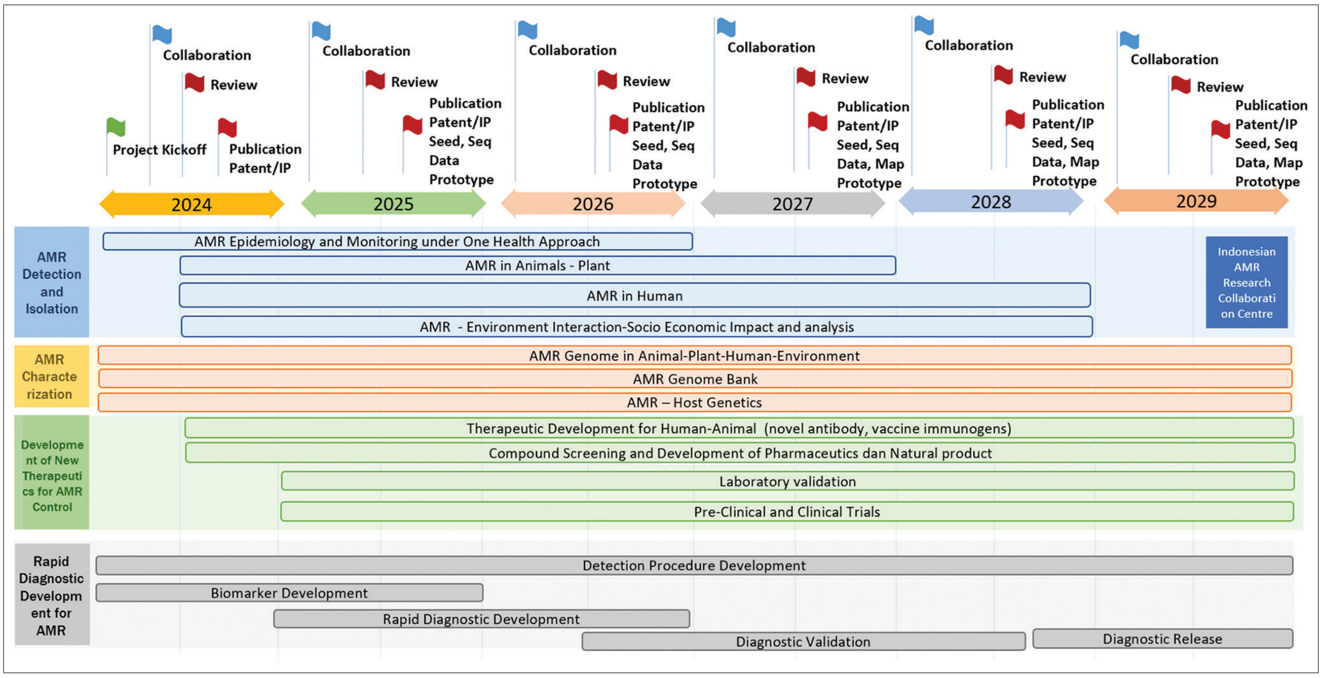

Figure 8: Roadmap for AMR Research in Indonesia.

and plants that do not comply with standards; and (f) establishing integrated governance and coordination in the context of controlling AMR.

The government's policies must be based on scientific evidence. In this case, research is an important supporter of AMR science-based policy. In this article, we propose an AMR research roadmap to support data related to AMR in Indonesia. Four main points of activity are carried out: AMR detection and isolation, AMR characterization, development of new therapeutics for AMR control, and rapid diagnostic development for AMR. Each main activity has a research activity theme that applies the One Health approach (Figure 8).

CONCLUSION

This study highlights the alarming prevalence of AMR in Indonesia, which significantly affects human, animal, and environmental health. It identified widespread resistance across 34 antibiotic types in environmental bacteria, 24 in animal pathogens, and 43 in human clinical isolates. Notably, Ampicillin, ciprofloxacin, and sulfamethoxazole-trimethoprim were among the most commonly used antibiotics. The findings underscore critical reservoirs and transmission pathways, such as wastewater, livestock, and food chains, demonstrating the interconnectedness of AMR from a One Health perspective.

The study's primary strength lies in its comprehensive scope, as it integrates data from multiple domains – environment, animals, and humans – into a cohesive One Health framework. This holistic view provides actionable insights for combating AMR. The proposed method uses robust data to highlight specific resistance patterns, particularly for significant pathogens such as *E. coli* and *K. pneumoniae*. In addition, alignment with global and national frameworks, such as the WHO's Global Action Plan and Indonesia's National Action Plan on AMR, enhances its relevance. The proposed research roadmap further emphasizes diagnostics, novel therapeutic approaches, and genome studies, providing a strategic guide for AMR mitigation.

However, the study has certain limitations. This study lacks longitudinal data that can provide insights into AMR trends over time and projections for future resistance scenarios. Although the AMR situation in Indonesia is detailed, comparisons with global or regional trends are lacking, limiting the contextual understanding of Indonesia's standing in the global AMR landscape. Furthermore, this study does not critically evaluate the effectiveness of existing policies and regulations, which is crucial for understanding enforcement challenges. The recommendations could also benefit from more practical, localized steps for addressing AMR, especially in underserved areas.

Future research should focus on longitudinal data collection to track AMR trends and the effectiveness of mitigation strategies. Comparative studies with other countries could identify best practices that are adaptable to the Indonesian context. Innovative technologies, such as AI, genomic sequencing, and bioinformatics, should be explored for their potential use in AMR surveillance and gene mapping. In addition, investigating the impact of community-based awareness programs and education campaigns on antibiotic use and stewardship could offer practical solutions. Evaluation of AMR-related policies, with a focus on regulatory enforcement and intersectoral coordination, can provide valuable insights. Economic analyses quantifying the burden of AMR on healthcare systems, agricultural productivity, and broader economic losses could further inform policymaking.

This study provides a strong foundation for addressing AMR in Indonesia, emphasizing the need for a coordinated One Health approach. Addressing its limitations and expanding its scope could significantly enhance its value for researchers, policymakers, and public health practitioners working toward mitigating this pressing global health challenge.

DATA AVAILABILITY

The supplementary data can be available from the corresponding author upon a reasonable request.

AUTHORS' CONTRIBUTIONS

NLPID, MKJK, and DN: Drafted and revised the manuscript and prepared the supplementary tables and images. NLPID, MKJK, HN, and DN: Reviewed the literature and revised the manuscript and drafted the manuscript. NLPID, MKJK, DN: Prepared the supplementary tables and images. NLPID, MKJK, HN, and DN: Drafted the manuscript. NLPID and DN: Software and data analysis. All authors have read and approved the final manuscript.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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