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Human, animal and environmental contributors to antibiotic resistance in low-resource settings: integrating behavioural, epidemiological and One Health approaches

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Antibiotic resistance (ABR) is recognized as a One Health challenge because of the rapid emergence and dissemination of resistant bacteria and genes among humans, animals and the environment on a global scale. However, there is a paucity of research assessing ABR contemporaneously in humans, animals and the environment in low-resource settings. This critical review seeks to identify the extent of One Health research on ABR in low- and middle-income countries (LMICs). Existing research has highlighted hotspots for environmental contamination; food-animal production systems that are likely to harbour reservoirs or promote transmission of ABR as well as high and increasing human rates of colonization with ABR commensal bacteria such as *Escherichia coli*. However, very few studies have integrated all three components of the One Health spectrum to understand the dynamics of transmission and the prevalence of community-acquired resistance in humans and animals. Microbiological, epidemiological and social science research is needed at community and population levels across the One Health spectrum in order to fill the large gaps in knowledge of ABR in low-resource settings.

1. Introduction

The One Health approach aims to attain optimal health for people, animals and the environment [1]. Antibiotic resistance (ABR) is recognized as a One Health challenge because of the rapid emergence and dissemination of resistant bacteria and genes among humans, animals and the environment at a global scale [2]. Global and National Action Plans (NAPs) to tackle antimicrobial resistance (AMR) have been instigated and coordinated through the tripartite alliance of the World Health Organization (WHO), the Food and Agricultural Organization (FAO) and the World Organization for Animal Health (OIE). All countries are now tasked with implementing NAPs on AMR through multisectoral working to ensure comprehensive surveillance, monitoring and policy implementation across human, animal and environmental domains [3]. However, research on ABR adopting a truly One Health approach is relatively sparse in low- and middle-income countries (LMICs). A recent WHO review concluded that high-quality data relating to prevalence and abundance of resistant bacteria and genes in humans, animals and food are missing, especially for community-acquired infections in low-income countries [4]. These gaps in evidence will limit the ability to assess progress towards meeting the goals of NAPs in many countries.

This critical review examines the extent of One Health research on ABR in low- and middle-income settings. Specifically, the review seeks to identify research that directly assesses ABR across one or more domain of the human, animal

and environmental system. A further aim is to evaluate evidence of shared resistance profiles in human and animal hosts acquired by direct or indirect (via the environment) transmission pathways.

2. The human health risk of antibiotic resistance in low- and middle-income countries

Clinical human studies on hospitalized patients constitute the majority of current knowledge of ABR in LMICs. A number of syntheses have highlighted the most common resistant organisms, susceptibility profiles and resistant mechanisms in clinical settings by LMIC region or countries [5–8]. A recent review found 90% of studies of neonatal bacterial resistance in LMICs are hospital-based with insufficient data from community settings to draw conclusions [9]. While valuable for monitoring and promoting stewardship in healthcare settings, these studies shed little light on the determinants and risk factors for ABR in the wider population.

The health threat of ABR is of particular concern in LMICs because of the greater likelihood of community-acquired resistant infections, the high infectious disease load in the general population, poor coverage of safe water and sanitation; poor access to health services and weak regulation and enforcement of antibiotic use in food production and healthcare [10–12]. Further health risks stem from some of the transmissible ABR mechanisms that have emerged from low-resource settings with subsequent global dissemination. Examples include extended-spectrum beta lactamases (ESBLs) conferring resistance to third generation cephalosporins (3GC); carbapenem resistance conferred by enzymes such as New Delhi metallo-beta-lactamases (NDM-1) [13], and colistin resistance via the gene *mcr-1* [14]. These resistance mechanisms are carried on mobile genetic elements hosted by different bacterial species in humans, animals, food and the environment providing multiple routes of transmission.

3. Bacteria of relevance to One Health approaches in low- and middle-income countries

The highest priority bacteria for ABR prevention, categorized as critical by the WHO, include *Acinetobacter baumanii*, *Pseudomonas aeruginosa* and Enterobacteriaceae [4]. Of the Enterobacteriaceae, *Escherichia coli* has the greatest likelihood for animal–human transmission and is a major organism of community-associated ABR, carrying resistance to carbapenems and 3GC. Pathogenic strains of *E. coli* are the leading cause of human urinary tract infection, bacteraemia and gastroenteritis. As a commensal bacterium, *E. coli* colonizes the gut of humans and animals, as well as being ubiquitous in soil, plants, vegetables and water [15]. For these reasons, *E. coli* is commonly chosen as a sentinel organism for One Health studies of ABR [16]. Other bacteria relevant to food-borne disease transmission are *Salmonella* spp. and *Campylobacter* spp. with potential for resistance to 3GC and fluoroquinolone. These are ranked by the WHO as high priority rather than critical [4].

4. Scope of review

The databases MEDLINE, Scopus, ScienceDirect and Clinical Trials were searched using the MeSH term 'drug resistant bacteria' with alternative terms 'antibiotic', 'antimicrobial resistance' or 'AMR'; and 'LMIC' or alternative terms (developing countries/global health/developing nations/low-income countries/middle-income countries). Searches were filtered for journal articles or reviews published in the English language from 2007 to 2017. Studies conducted on inpatient samples were excluded, as were studies reporting therapeutic regimes, vaccines or diagnostics. Studies focusing on resistant bacteria of relevance to the One Health paradigm were identified. Hand searches were carried out for referenced citations and new articles. Of all retrieved studies, those that directly assessed antibiotic-resistant bacteria or genes in community-based studies of humans, food-producing animals or the environment were included for general review. Of these, the final table of papers (electronic supplementary material, table S1) included those that examined ABR in one or more domain of the environment, humans and food-producing animals.

5. The human reservoir of antibiotic resistance in low- and middle-income countries

The dissemination of Enterobacteriaceae (bacteria colonizing human guts, with or without disease) carrying ESBL genes is increasing in humans and animals globally [17]. From 2000 to 2008, reported colonization rates with ESBL-producing *E. coli* (ESBL-EC) were generally less than 10%. After 2008, however, rates increased rapidly to as high as 60% in some LMICs [18] with India and China harbouring some of the largest reservoirs of ESBL genes [19]. A recent systematic review and meta-analysis estimated the prevalence of gut colonization with ESBL-EC in healthy humans at 14% globally [20] with rates of 22% in Southeast Asia and Africa [20].

6. Risk factors for human colonization with resistant bacteria

The increase in colonization with resistant ESBL-EC has been dramatic, but factors associated with the acquisition of resistant bacteria in humans are not well established. Some of the highest reported rates of colonization are from China, where 62.8% of *E. coli* isolates were ESBL-producing from outpatients in town hospitals across three regions of Shandong province [21]. These rates were considered to reflect contact with food-producing animals in rural areas [21]. In other areas of rural China, rates of infection with ESBL-EC from hospitals ranged from 57% in North China to 30.2% in East China [22]. For some resistance genes, extremely high prevalence rates have been reported. In India, 91% of faecal samples from human communities carried quinolone-resistance genes, compared with 24% in human samples from Sweden [23]. Most of these studies are characterized by cross-sectional designs with unspecified sampling strategies, hence representativeness is hard to assess.

Studies of children in LMICs, while few, have shown 5.6% colonization with ESBL-producing enteric bacteria among under 5-year-olds in Nicaragua [24] and 3% in children under 5 years in Madagascar [25]. Multidrug-resistant *E. coli* were isolated from 55% of healthy middle-class children aged

10–24 months ($n = 15$) in Bangladesh, some of which were ESBL-producing [26].

Occupational risk of resistance carriage has rarely been assessed. Korean fishery workers, who were exposed to antibiotics used in aquaculture, had a significantly higher proportion of *E. coli* isolates with resistance to cephalothin, tetracycline and trimethoprim–sulfamethoxazole compared with a 'control' group of restaurant workers. Rates of colonization with multidrug-resistant *E. coli*, however, were similar [27]. There was no assessment of antibiotic exposure or consumption and no control for potentially confounding effects.

Socio-demographic risk factors for ABR colonization or infection are likely but poorly researched. In Madagascar, higher socio-economic status, assessed by occupation, was associated with lower colonization rates with ESBL-producing Enterobacteriaceae in a community-based survey of adults [28]. Managers and employers had a significantly lower risk of ESBL-EC carriage than manual and non-manual occupation groups (4% versus 26.5% and 30%, respectively) [28]. These differences may be mediated by housing quality, differential occupational exposures or access to water, sanitation and hygiene facilities.

The transmission of human colonization with resistant organisms from LMICs to other regions is illustrated by studies of travellers. International travellers were four times more likely to be colonized by ESBL-EC than non-travellers in a systematic review [20]. Similarly, a prospective study of Dutch back-packers reported that 34% of travellers carried ESBL-EC after their return, with highest acquisition rates among those who had travelled to southern Asia [29]. The median duration of colonization was 30 days, suggesting that colonization is transient, but onward transmission to household members was detected, demonstrating human–human transmission [29]. The human carriers with more resistant forms (e.g. carbapenem resistance) also had greater persistence [29].

7. The role of food-producing animals in One Health approaches to antimicrobial resistance transmission in low- and middle-income countries

Food-producing animals, fish and seafood in LMICs provide large reservoirs for ABR because of the high use of antibiotics for prophylaxis, growth promotion and metaphylaxis. The BRIC economies are estimated to have the highest consumption of antimicrobials for livestock in LMICs, projected to increase by 99% in Brazil, Russia, India, China and South Africa from 2010 to 2030 [30]. The intensification of farming in LMICs corresponds with the increasing consumption of animal protein, particularly meat, fish, poultry and eggs [31]. Urbanization, population growth and rising incomes contribute further to this demand for animal-based foods [32].

Poultry production is considered a high risk for ABR emergence in low-income settings, particularly in smaller-scale unregulated operations. Commercial poultry farming is highly profitable and ideally suited to settings where land is scarce [33]. Poultry commonly receives higher quantities of antibiotics than other animal livestock [34,35], and resistance is more likely to develop in conditions of animal overcrowding and poor sanitation.

In Vietnam, a high prevalence of MDR *E. coli* (81.3%), but low prevalence of ESBL-EC (3.2%) was reported in a survey of 208 household and small-scale chicken farms in the Mekong Delta [36]. Antibiotic use was significantly associated with MDR resistance in poultry samples, with antimicrobials being a common addition to commercial feeds in Vietnam. The presence of an integrated fish pond on farms was associated with ESBL-EC in poultry, attributed to the chickens acquiring resistance from water contaminated with human sewage [36].

The type of poultry farming (broiler versus layer), and the size and scale of farming (contracted versus independent) is associated with rates of ABR colonization. Broiler production relies on rapid growth of chicks to increase profit. To this end, antibiotics are applied as additives to feed or water to promote growth. Among 16 poultry farms (broiler and layer) in India, 100% reported using antimicrobials for routine prophylaxis and 67% reported using antibiotics as growth promotors [37]. The prevalence of resistance to multiple antimicrobials was higher in farms (both broiler and layer) that used antimicrobials for growth promotion, suggesting an association between usage and resistance [37]. In urban Ghana (Kumasi and Accra), 56% of poultry farmers reported routine antibiotic use from 75 poultry farms with a range of flock size [38]. In a survey of 20 poultry farmers in Ecuador, 80% reported using antibiotic supplements but no differences were observed in ABR among birds with and without supplementation [39].

In India, broiler poultry was more likely than layers to carry ESBL-EC (87% versus 42%, respectively) [37] correspondingly with higher reported antibiotic use in broiler farms. In Ecuador, significantly higher rates of resistant *E. coli* were reported among commercially produced birds (layers and broilers) compared with 'backyard' (household) poultry. Resistance to tetracycline was detected in 78% of production birds compared with 34% of household birds; resistance to sulfisoxazole and trimethoprim–sulfamethoxazole were 69% and 63%, respectively, in production birds compared with 20% and 17% in household birds ($p < 0.001$) [39]. High and uncontrolled usage of antimicrobials (most commonly sulfonamides, tetracyclines and fluoroquinolones) was noted in 98 small-scale chicken farms in Yaoundé, Cameroon. Almost half of farms did not observe a withdrawal period before the poultry went to market [40].

Qualitative research among poultry workers and those involved in the food chain can shed important light on the potential drivers of antibiotic use [41]. In-depth interviews with commercial food-animal farms, retailers and veterinarians in Cambodia identified four main drivers: the belief that antibiotics were necessary for animal raising; limited knowledge; unrestricted antibiotic access and weak monitoring and control systems [41]. There were also reports of switching from an animal-use antibiotic to a human-use antibiotic if treatment was perceived to be ineffective [41].

In domestic settings and subsistence farming, there is less evidence of inappropriate antibiotic use in livestock. Antibiotics are used primarily for treatment rather than as growth promotors or prophylaxis and evidence suggests the prevalence of ABR in these farming systems is low. Free-range pigs in Tibet raised without antibiotic administration had low levels of antibiotic-resistant *E. coli* relative to more intensive farm systems [42]. Backyard poultry in India was found to have no cases of ESBL-EC in 360 sampled birds [43]. In a contemporaneous comparison of poultry, the prevalence of ESBL-EC in poultry meat was 46% from broiler production compared with 15% in free-range production [44]. In a rural survey of households owning cattle or poultry in Bangladesh

53.4% (of 521) reported using at least one animal treatment in the previous six months. However, 'medicine' (likely including antibiotics) and feed additives were generally only used in cases of diarrhoea or fever in livestock [45].

Antibiotic use in aquaculture is important as a potential driver of ABR in aquatic systems in LMICs [46]. Of 94 fish and shrimp freshwater farms surveyed in Vietnam, 72.3% used at least one antibiotic [47]. Higher antibiotic use was associated with farms that had a higher density of fish or shrimp and higher total annual production. The same study assessed fish products in local markets, but with no direct supply connection to farms. Of retail shrimp and fish samples from local markets, 26.9% (28/104) were positive for fluoroquinolone and tetracycline antibiotic residues, indicating a lack of adequate withdrawal times on farms. Quinolone and ESBL resistance genes have been identified in retail fish farmed across Guangdong province in southern China [48]. Resistance rates were particularly high to the antimicrobial agents commonly used in fish cultivation: tetracyclines, florfenicol and co-trimoxazole, strongly indicating links between antimicrobial use in fish farming and resistance [48].

8. Evidence of animal to human transmission of antibiotic resistance

Studies linking animal and human profiles of resistance have been based predominantly on indirect associations. In China, the ESBL-producing enzyme CTX-M-55 is increasing both in colonized healthy humans and community-acquired *E. coli* infections [22]. Prior to this, the enzyme was predominantly present in organisms from food-producing animals (globally since 2002 and in China since 2005) [49,50], suggesting possible transmission from animals to humans [49]. Whole genome sequencing (WGS) of resistant bacterial isolates allows more direct associations to be made between animal and human isolates. WGS analysis from broiler poultry in India confirmed two globally emergent human pathogenic lineages of *E. coli* identified among the poultry *E. coli* isolates [44], indicating that commercial poultry meat is a potential carrier of human *E. coli* pathotypes [44].

Abdissa *et al*. [51] examined the prevalence of *E. coli* O157 : H7 in beef cattle at slaughter: beef carcasses at retail shops and humans with diarrhoea attending health centres in Ethiopia. *E. coli* O157 : H7 was found at a low prevalence in slaughtered cattle (2%) but there were no positive samples for *E. coli* O157 : H7 from human diarrhoea cases. The findings were limited by small sample size ($n = 70$) and no direct or putative pathways of transmission [51].

Movement of food and animals has also led to the global dissemination of ABR. The plasmid-mediated resistance mechanism to the antibiotic colistin, *mcr-1*, was first identified in China among intensively farmed pigs [52]. Since this discovery in 2015, *mcr-1* has been detected in Enterobacteriaceae strains from five continents: in humans, food, farm and wild animals, and aquatic environments [53].

9. Antibiotic resistance dissemination from food-producing animals to the environment

ABR dissemination from food-producing animals to the surrounding environment takes place through either the excretion of antimicrobials through urine or faeces into surface waters and soils, or the application of animal manure as fertilizer to soil or ponds. Untreated animal waste is used for a variety of purposes in subsistence economies. Poultry waste is commonly used for feeding of fish and shellfish in aquaculture [54]. Intestines from poultry are also used as feed for aquaculture, leading to higher levels of resistance in *Enterococcus* spp. isolates in fish intestines [55].

In China, duck faecal and surface water samples were analysed from a large breeding farm where 1-day old ducklings were routinely injected with cetiofur [50]. The prevalence of cetiofur-resistant *E. coli* isolates and ESBL gene types in pond water samples were similar to those of duck faecal samples. Faecal contamination therefore had a measurable effect on the environmental prevalence of ABR bacteria and genes [50].

Other studies in China observed that soil treated with pig manure was positive for ESBL-EC, with $bla_{\text{CTX-M}}$ being the predominant ESBL gene, whereas no resistant isolates were detected in control soil samples [56]. Three isolates from soil had above 90% genetic similarity with strains from pig farm samples, pointing strongly to transmission of AMR organisms from pig manure to the environment [56].

10. Animal studies including assessment of farm workers

Very few studies have examined the resistance profiles of bacteria and genes in food-producing animals and directly-exposed humans in LMICs (electronic supplementary material, table S1). Donkor *et al*. [57] assessed MDR *E. coli* in cattle and their farmers in Ghana. Animal and human *E. coli* isolates showed high levels of MDR ABR (70.6% and 97.7%, respectively), although animal-derived isolates had high resistance to five antimicrobials (cefuroxime, co-trimoxazole, tetracycline, ampicillin and amikacin) and human-derived isolates had higher resistance to chloramphenicol and gentamycin. Thus, while resistance was high in both animals and humans, the susceptibility profiles were different.

A study of ABR in faeces and milk from healthy dairy cows and their associated dairy farmers from 23 farms in Ethiopia showed 10% of samples from cows and 13% of the human faecal samples were positive for *Salmonella* spp. 58% (14/24) of all *Salmonella* spp. isolates were resistant to three or more antibiotics [58]. There were no data on non-dairy workers, however, to assess whether dairy farmers had higher prevalence through direct exposure to cows. Such studies ideally require molecular methods to examine the phylogenetic associations between human and animal isolates which may then provide evidence of common lineages [59].

11. Anthropogenic influences on the environmental resistome in low- and middle-income countries

Environmental contamination with antibiotic residues and resistant organisms/genes due to human activity has been demonstrated from pharmaceutical plants, hospital effluents and untreated wastewater [7], and may be a leading driver of ABR in low-resource settings [60]. In central India, hospital effluent contained *E. coli* resistant to extended-spectrum

cephalosporin and fluoroquinolone antibiotics [61,62]. In Hyderabad, 95% of water samples taken near drug manufacturing facilities were positive for ESBL and carbapenemase-producing Enterobacteriaceae [63]. The latter study found fluconazol concentrations 20 times in excess of the recommended therapeutic dose [63]. In Bangladesh, 71% of wastewater samples next to hospitals (51/72) were positive for NDM-1-producing bacteria compared to 12% of wastewater samples in community areas in the same city of Dhaka [64]. In Nicaragua, ESBL-EC were detected in hospital sewage samples with all isolates encoding for the $bla_{\text{CTX-M}}$ gene [65]. Higher concentrations of ABR genes were detected downstream from pharmaceutical industries in western Havana [66].

Human and animal exposures to ABR in the environment occur through drinking water supplies that have not been disinfected. In Dhaka city, 36% of 223 *E. coli* isolates from water supply samples were multidrug resistant [67]; 26% of well-water samples in Nicaragua were positive for ESBL-EC [65]. Healthcare waste and solid waste management are further pollutants and potential drivers of ABR in low-income settings [68–70]. Refuse sites are attractive for human scavenging and recycling of medical waste products, adding further exposure risk [69]. These wastes often contain heavy metals and other pollutants that co-select for ABR causing further release of resistant genes [54].

Anthropogenic influences on the resistome have been inferred from 'natural' experiments as shown by the increased antibiotic resistance gene (ARG) contamination of rural river waters in India during the seasonal pilgrimage of urban residents to a religious site on the river [71]. Links have been demonstrated between human antibiotic use and environmental contamination. Diwan *et al.* [72] compared the quantities of the seven most commonly prescribed antibiotics in a hospital in India with the antibiotic concentrations and susceptibilities of *E. coli* in hospital-associated water. A significant correlation was observed with ciprofloxacin being the most common antibiotic prescribed and having the highest concentration in water [72]. However, the effect of these antibiotics on *E. coli* isolates in water was not clear. Rutgersson *et al.* [23] assessed the prevalence of fluoroquinolone antibiotics and quinolone-resistant genes (*qnr*) in river water, sediment, well water and irrigation farmland near a pharmaceutical manufacturing plant in India as well as the faecal concentration of *qnr* genes in healthy humans. Around 42% of well water; 7% of soil samples and 100% of Indian river sediment samples were positive for *qnr* genes. In sediment there was an association between fluoroquinolone and *qnr* gene concentrations, but no associations were present in well water or soil. The study failed to demonstrate direct linkage between environmental exposure to quinolone-resistance genes and the presence of *qnr* genes in humans, largely because the prevalence of the gene was so high in humans (91%) and human to human transmission was highly probable [23].

12. One Health studies across all three domains of humans, animals and the environment

Few studies in low-resource settings have examined the presence of resistant bacteria and genes in all three domains of humans, animals and the environment (see electronic supplementary material, table S1). Dhaka *et al.* [73] assessed ABR in diarrhoeagenic *E. coli* (DEC) in animals with diarrhoea ($n = 106$), food products ($n = 68$), environmental samples ($n = 59$) and infants with diarrhoea ($n = 103$) in India. Of the four DEC pathogens, enteroaggregative *E. coli* (EAEC) was the most common with a prevalence of 16.5% in infants, 17.9% in young animals, 16.2% in foods and 3.4% from environmental sources. Around 86% of isolates were resistant to three or more classes of antibiotics [73]. However, the study sampled hospitalized infants, and animal samples were collected from private farms and veterinary clinics. The only statistically significant similarities in ABR profiles of EAEC isolates were for ciprofloxacin (human versus environmental, and animal versus environmental). This was explained by the widespread use of fluoroquinolones for diarrhoea treatment which then leads to both human and animal ciprofloxacin-resistant EAEC isolates that contaminate the environment through faecal waste [73].

Goat carcasses, faeces, equipment and environmental samples were examined in a large abattoir in a pastoralist region of Ethiopia [74]. Antibiotic-resistant *E. coli* O157 was isolated from caecal contents, carcass swabs and water. Although the prevalence was low (2.5%; 3.2% and 7.1%), all isolates were resistant to two or more antimicrobials. The study identified *E. coli* resistant to drugs that are not used in goats and suggested that human infections may be the original source of resistance that is transferred to livestock in this ecosystem.

A comprehensive One Health study of ABR was carried out in a rural community in El Salvador and a peri-urban town in Lima, Peru, using high throughput and shot-gut metagenomics [75]. Samples were collected from humans, domesticated animals and the environment (soil, water, sewage or latrines). Human-associated and environmental resistomes were related along an ecological gradient corresponding with input from human faeces [75]. The study also identified key resistance genes that cross habitat boundaries and determined their association with mobile genetic elements. This is one of the most comprehensive studies across different ecological zones that encompasses the human, animal and environmental resistome.

13. Human–animal–environment interactions and socio-ecological behaviours

Aside from assessing ABR prevalence, there is an increasing need to understand behaviours, customs and practices that drive the evolution and transmission of resistance in low-resource settings. In rural areas, households commonly share living and sleeping areas with livestock [76] providing opportunities for transmission of resistant bacteria and genes through faecal shedding or contact with animal faeces. In rural Bangladesh, half of households reported that poultry slept in the bedroom [45]. Behaviours relating to the slaughter and processing of food-animals is a route of human exposure to resistant enteric bacteria. Family members often gather during the slaughter of poultry to say prayers. Handwashing with soap after slaughtering poultry was reported for only 14% of observations in domestic settings [33]. After butchering, animal waste is often discarded on open land then scavenged by dogs, wild birds and domestic poultry [33].

Biosecurity measures are often poor or absent in small-scale animal-food processing facilities. In Ethiopia, observations within an abattoir reported the absence of soap, running water and disinfectant during slaughter; the same buckets of water were used for cleaning knives, washing hands, washing

carcasses and washing the floor [74]. In Dhaka city, like many other urban areas in LMICs, poultry are slaughtered, processed and sold on site without regulation of the preparation, selling or disposal of solid waste [77]. Liquid waste from markets, including blood, faeces and wastewater is disposed into municipal drains through direct wash out [77]. Other potential sources of ABR transmission are shared surface waters used by humans for bathing, fishing or washing of clothes and household items. Animals use the same water for bathing and drinking while also grazing and defecating nearby [78].

Other behavioural risks may stem from food preparation and consumption. Raw or undercooked meat is one of the most common means of transmission of *E. coli* O157 to humans, but some communities, such as pastoralist groups in Ethiopia, have strong preferences for raw meat consumption [74].

Information about antibiotic use in agriculture is increasing, but there are likely to be many more undocumented practices around antibiotic use. Anthropological studies among Somali pastoralist tribes in Ethiopia observed that antibiotics are occasionally added to fresh unpasteurized milk before selling in unsterilized plastic containers [79]. This reflects the opportunistic use of inexpensive and readily available antimicrobials as well as an adaptation to modern food processing and storage in order to prolong the shelf life of milk produce.

14. One Health surveillance programmes

Large-scale programmes for surveillance of food-producing animals and non-hospitalized humans will provide much-needed data on the scale of ABR outside healthcare settings. While the global antimicrobial surveillance system initiative (GLASS) is focusing on human clinical surveillance, the WHO Advisory Group on Integrated Surveillance of AMR is supporting and promoting One Health programmes [16]. A framework for national/regional surveillance has been proposed to improve consistency and coverage of ABR reporting in LMICs [80]. Systems for monitoring and surveillance are also a high priority in NAPs among countries with the required infrastructure.

Integrated food surveillance systems are being developed for food production systems and food safety [16]. Colombia has successfully piloted an integrated surveillance system to monitor trends in ABR on poultry farms, abattoirs and retail markets [81]. In Mexico, surveillance of food-borne pathogens including *Salmonella* spp. and *Campylobacter* spp. is linked with human surveillance data for the same pathogens [82].

Other national surveys are underway to contribute to understanding the drivers of AMR. INDEPTH is a network currently comprising 37 Health and Demographic Surveillance System Sites in 20 LMICs [80]. This network aims to determine the true prevalence of ABR, to relate hospital-reported prevalence of ABR with community prevalence, to ascertain antibiotic use in low-resource communities, including perceptions and health-seeking behaviours and to assess the burden of disease attributable to ABR in LMICs [80].

15. Mitigating strategies based on evidence from One Health studies

The paucity of One Health intervention studies in LMICs makes it difficult to identify successful mitigation strategies. However, multisectoral interventions at national scales will increase with the implementation of NAPs. Strategies for containment of ABR in animal health are likely to focus on reducing antimicrobial use. The ViParc study plans to target small-scale poultry farms and provide farmers with a locally adapted veterinary support service to help them reduce their reliance on antimicrobials [83]. Other studies have advocated for the withdrawal of non-therapeutic use of agricultural antimicrobials in countries such as India and Vietnam where antibiotic use in animal feeds is high [37,84]. Many countries have existing policies to restrict the addition of antibiotics to livestock feed but policy enforcement remains a challenge. Biosecurity in farming systems and improved waste management, along with water, sanitation and hygiene in human and animal systems, are important strategies for the prevention of ABR transmission [85–87].

16. Discussion

Data are sparse on the distribution and concentrations of ABR bacteria and ABR genes in humans, animals and the environment at a meaningful spatial and temporal scale in low-resource settings. The scarcity of integrated epidemiological data prevents a true assessment of the prevalence of ABR and transmission pathways, let alone assessment of transmission risk. Where detailed studies have been conducted, the evidence points to shared microbiomes and resistomes in humans, animals and the environment following gradients of exposure or contamination [75]. Future studies require sufficient statistical power and representative samples from interconnected livestock and humans, rather than convenience sampling of populations with no direct associations. Similarly, environmental assessments require an ecosystem-wide approach to mapping genes and bacteria [88]. As well as microbiological and epidemiological research, studies need to document 'informal food economies, changing household-level and community-level food preparation and storage techniques, and the structural impediments many people face accessing safe and regulated foods.' [79].

Molecular approaches such as WGS of bacteria and metagenomic analysis of whole DNA, coupled with analytical tools in bioinformatics, will increasingly replace conventional culture-dependent systems. Application of metagenomics allows the assessment of clonal diversity and similarity among human and animal bacterial isolates, providing greater insight into the shared resistance genes—but will not necessarily identify the source. While this technology is being rapidly adopted in many countries, some will lag behind because of a lack of technical skills, expertise and laboratory facilities [16]. Even with increasing affordability of WGS the costs are likely to be prohibitive for many programmes in low-resource settings.

The studies included in this critical appraisal do not represent a systematic review and, as such, may not be comprehensive. With the vast range of disciplines involved in research relating to ABR, it is challenging to collate studies from all fields. A wider adoption of One Health approaches in future will bring together disparate disciplines and data sources and provide much greater insights.

A One Health paradigm is particularly relevant in LMICs because of the risk of community-acquired ABR infections; the high prevalence of infectious diseases [89]; the high

rates of colonization with resistant commensal bacteria [20]; the close interactions between humans, animals and the outdoor environment and the high levels of environmental contamination with antibiotic residues; heavy metals and other co-selecting compounds [63].

The term 'eco-epidemiological' has been used to describe the complexity of the overlapping ecologies of ABR in humans, animals and the environment [39]. Quantitative microbiological and epidemiological studies are needed to understand risk, dose–response effects and strategies for intervention. In-depth qualitative studies are required to elucidate the drivers of antibiotic use, waste management and economic pressures, as well as the facilitators and barriers to change. In LMICs, where income generation is critical, economic drivers may be particularly powerful. This needs to be considered when developing mitigation strategies or interventions. Finally, systems-based modelling is needed to understand the key pathways of ABR transmission. As proposed by Wernli *et al*. [90], ABR research needs to focus on outcomes (epidemiology), processes (drivers and practices) as well as structures (regulations and current control policies). Single discipline studies will fail to identify the most effective methods to contain ABR. Multidisciplinary and holistic studies employing One Health approaches are required in low-resource settings.

Data accessibility. No original data have been used to produce this manuscript. All information in the review can be accessed from published articles.

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