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

PROCEEDINGS OF
THE ROYAL SOCIETY B
BIOLOGICAL SCIENCES

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

Journal:	*Proceedings B*
Manuscript ID	RSPB-2018-0332.R1
Article Type:	Review
Date Submitted by the Author:	n/a
Complete List of Authors:	Rousham, Emily; Loughborough University, School of Sport, Exercise and Health Sciences Unicomb, Leanne; International Center for Diarrheal Disease Research, Bangladesh Islam, Mohammad; International Center for Diarrheal Disease Research, Bangladesh
Subject:	Health and Disease and Epidemiology < BIOLOGY, Microbiology < BIOLOGY, Environmental Science < BIOLOGY
Keywords:	low and middle income countries, one-health, antibiotics
Proceedings B category:	Ecology

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

Dr Emily K Rousham[1], Dr Leanne Unicomb[2], Dr Mohammad Aminul Islam[3]

[1] Centre for Global Health and Human Development, School of Sport, Exercise and Health Sciences, Loughborough University, Loughborough, LE11 3TU, UK.

[2] Environmental Intervention Unit, Infectious Disease Division, International Centre for Diarrheal Disease Research, Dhaka, Bangladesh.

[3] Laboratory Sciences and Services Division, International Centre for Diarrheal Diseases Research, Dhaka, Bangladesh.

Corresponding author: Emily Rousham

email: e.k.rousham@lboro.ac.uk

.

Abstract

Antibiotic resistance (ABR) is recognised 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 antibiotic resistance 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 colonisation 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 of AMR 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.

Introduction

The One Health approach aims to attain optimal health for people, animals and the environment (1). Antibiotic resistance (ABR) is recognised 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. 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.

The human health risk of ABR in LMICs

Clinical human studies on hospitalised 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). Whilst 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 (3CG); 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.

Bacteria of relevance to One Health approaches in LMICs

The highest priority bacteria for ABR prevention, categorised as critical by the WHO, include *Acinetobacter baumanii*; *Pseudomonas aeruginosa* and *Enterobacteriaceae* (4). Of the *Enterobacteriaceae, E. coli* has the greatest likelihood for animal-human transmission and is a major organism of community associated ABR, carrying resistance to carbapenems and third generation cephalosporins. Pathogenic strains of *E. coli* are the leading cause of human urinary tract infection, bacteraemia and gastroenteritis. As a commensal bacterium, *E. coli* colonises 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 third generation cephalosporins and fluoroquinolone. These are ranked by the WHO as high priority rather than critical (4).

Scope of review

The databases Medline, Scopus, Science Direct 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 English language from 2007 to 2017. Studies conducted on inpatients samples were excluded, as were studies reporting therapeutic regimes, vaccines or diagnostics. Studies focussing 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 (Supplementary Table 1) included those that examined antibiotic resistance in one or more domain of the environment, humans and food-producing animals.

The human reservoir of ABR in LMICs

The dissemination of Enterobacteriaceae (bacteria colonising human guts, with or without disease) carrying extended spectrum beta-lactamase (ESBL) genes is

increasing in humans and animals globally (17). From 2000-2008, reported colonisation 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 colonisation with ESBL-EC in healthy humans at 14% globally (20) with rates of 22% in Southeast Asia and Africa (20).

Risk factors for human colonisation with resistant bacteria

The increase in colonisation 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 colonisation 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 to 24% in human samples from Sweden (23). Most of these studies are characterised by cross-sectional designs with unspecified sampling strategies, hence representativeness is hard to assess.

Studies of children in LMICs, whilst few, have shown 5.6% colonisation with ESBL-producing enteric bacteria among under 5 year olds in Nicaragua (24) and 3% in children under 5 years in Madagascar (25). Multi-drug 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 colonisation 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 colonisation or infection are likely but poorly researched. In Madagascar, higher socio-economic status, assessed by occupation, was associated with lower colonisation 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 colonisation with resistant organisms from LMICs to other regions is illustrated by studies of travellers. International travellers were four times more likely to be colonised 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 colonisation was 30 days, suggesting that colonisation 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).

The role of food-producing animals in One Health approaches to AMR transmission in LMICs

Food-producing animals, fish and seafood in LMICs provide large reservoirs for antibiotic resistance 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). Urbanisation, 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 receive 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 vs independent) is associated with rates of ABR colonisation. 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 were 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 to ‘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 antibiotic resistance 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 were 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

261 farms that had a higher density of fish or shrimp and higher total annual production.
262 The same study assessed fish products in local markets, but with no direct supply
263 connection to farms. Of retail shrimp and fish samples from local markets, 26.9%
264 (28/104) were positive for fluoroquinolone and tetracycline antibiotic residues,
265 indicating a lack of adequate withdrawal times on farms. Quinolone and ESBL
266 resistance genes have been identified in retail fish farmed across Guangdong
267 province in southern China (48). Resistance rates were particularly high to the
268 antimicrobial agents commonly used in fish cultivation: tetracyclines, florfenicol and
269 co-trimoxazole, strongly indicating links between antimicrobial use in fish farming
270 and resistance (48).
271
272 **Evidence of animal to human transmission of ABR**
273 Studies linking animal and human profiles of resistance have been based
274 predominantly on indirect associations. In China, the ESBL-producing enzyme CTX-
275 M-55 is increasing both in colonised healthy humans and community-acquired *E. coli*
276 infections (22). Prior to this, the enzyme was a leading form of resistance in food-
277 producing animals (globally since 2002, and in China since 2005) (49,50) suggesting
278 possible transmission from animals to humans (49). Whole genome sequencing
279 (WGS) of resistant bacterial isolates allows more direct associations to be made
280 between animal and human isolates. WGS analysis from broiler poultry in India
281 confirmed two globally emergent human pathogenic lineages of *E. coli* identified
282 among the poultry *E. coli* isolates (44), indicating that commercial poultry meat is a
283 potential carrier of human *E. coli* pathotypes (44).
284
285 Abdissa et al. (51) examined the prevalence of O157:H7 in beef cattle at slaughter;
286 beef carcasses at retail shops, and humans with diarrhoea attending health centres
287 in Ethiopia. *E. coli* O157:H7 was found at a low prevalence in slaughtered cattle (2%)
288 but there were no positive samples for *E. coli* O157:H7 from human diarrhoea cases.
289 The findings were limited by small sample size (n=70) and no direct or putative
290 pathways of transmission (51).
291
292 Movement of food and animals has also led to the global dissemination of antibiotic
293 resistance. The plasmid-mediated resistance mechanism to the antibiotic colistin,
294 *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).

ABR 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 in 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 one-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).

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 (supplementary Table 1). 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 antibiotic resistance (70.6% and 97.7%, respectively), although animal-derived isolates had high resistance to five antimicrobials (cefuroxime, cotrimoxazole, tetracycline, ampicillin and amikacin) and human-derived isolates had higher resistance to

329 chloramphenicol and gentamycin. Thus, while resistance was high in both animals
330 and humans, the susceptibility profiles were different.
331
332 A study of ABR in faeces and milk from healthy dairy cows and their associated dairy
333 farmers from 23 farms in Ethiopia showed 10% of samples from cows and 13% of
334 the human faecal samples were positive for *Salmonella* spp. 58% (14/24) of all
335 *Salmonella* spp. isolates were resistant to three or more antibiotics (58). There were
336 no data on non-dairy workers, however, to assess whether dairy farmers had higher
337 prevalence through direct exposure to cows. Such studies ideally require molecular
338 methods to examine the phylogenetic associations between human and animal
339 isolates which may then provide evidence of common lineages (59).
340
341 **Anthropogenic influences on the environmental resistome in LMICs**
342 Environmental contamination with antibiotic residues and resistant genes due to
343 human activity has been demonstrated from pharmaceutical plants, hospital effluents
344 and untreated wastewater (7) and may be a leading driver of ABR in low resource
345 settings (60). In central India, hospital effluent contained *E. coli* resistant to
346 extended-spectrum cephalosporin and fluoroquinolone antibiotics (61,62). In
347 Hyderabad, 95% of water samples taken near drug manufacturing facilities were
348 positive for ESBL and carbapenemase-producing Enterobacteriaceae (63). The latter
349 study found fluconazol concentrations 20 times in excess of the recommended
350 therapeutic dose (63). In Bangladesh, 71% of wastewater samples next to hospitals
351 (51/72) were positive for NDM-1-producing bacteria compared to 12% of wastewater
352 samples in community areas in the same city of Dhaka (64). In Nicaragua, ESBL-EC
353 were detected in hospital sewage samples with all isolates encoding for the $bla_{\text{CTX-M}}$
354 gene (65). Higher concentrations of antibiotic resistance genes were detected
355 downstream from pharmaceutical industries in western Havana (66).
356
357 Human and animal exposures to ABR in the environment occur through drinking
358 water supplies that have not been disinfected. In Dhaka city, 36% of 223 *E. coli*
359 isolates from water supply samples were multi-drug resistant (67). 26% of well-water
360 samples in Nicaragua were positive for ESBL-EC (65). Healthcare waste and solid
361 waste management are further pollutants and potential drivers of ABR in low income
362 settings (68–70). Refuse sites are attractive for human scavenging and recycling of

363 medical waste products, adding further exposure risk (69). These wastes often
364 contain heavy metals and other pollutants that co-select for ABR causing further
365 release of resistant genes (54).
366
367 Anthropogenic influences on the resistome have been inferred from 'natural'
368 experiments as shown by the increased ARG contamination of rural river waters in
369 India during the seasonal pilgrimage of urban residents to a religious site on the river
370 (71). Links have been demonstrated between human antibiotic use and
371 environmental contamination. Diwan et al. (72) compared the quantities of the seven
372 most commonly prescribed antibiotics in a hospital in India with the antibiotic
373 concentrations and susceptibilities of *E. coli* in hospital-associated water. A
374 significant correlation was observed with ciprofloxacin being the most common
375 antibiotic prescribed and having the highest concentration in water (72). However,
376 the effect of these antibiotics on *E. coli* isolates in water was not clear. Rutgersson et
377 al. (23) assessed the prevalence of fluoroquinolone antibiotics and quinolone-
378 resistant genes (*qnr*) in river water, sediment, well water and irrigation farmland near
379 a pharmaceutical manufacturing plant in India as well as the faecal concentration of
380 *qnr* genes in healthy humans. Around 42% of well-water; 7% of soil samples and 100%
381 of Indian river sediment samples were positive for *qnr* genes. In sediment there was
382 an association between fluroquinolone and *qnr* gene concentrations, but no
383 associations were present in well-water or soil. The study failed to demonstrate
384 direct linkage between environmental exposure to quinolone-resistance genes and
385 the presence of *qnr*-genes in humans, largely because the prevalence of the gene
386 was so high in humans (91%) and human to human transmission was highly
387 probable (23).
388
389 **One Health studies across all three domains of humans, animals and the**
390 **environment**
391 Few studies in low resource settings have examined the presence of resistant
392 bacteria and genes in all three domains of humans, animals and the environment
393 (see supplementary Table 1). Dhaka et al. (73) assessed ABR in diarrhoeagenic *E.*
394 *coli* (DEC) in animals with diarrhoea (n=106), food products (n=68), environmental
395 samples (n=59) and infants with diarrhoea (n=103) in India. Of the four DEC
396 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 hospitalised infants, and animal samples were collected from private farms and veterinary clinics. The only statistically significant similarities in antibiotic resistance 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 were 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* resistance 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 AMR 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.

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 unpasteurised 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.

One Health surveillance programmes

Large scale programmes for surveillance of food-producing animals and non-hospitalised humans will provide much-needed data on the scale of ABR outside healthcare settings. While the global antimicrobial surveillance system initiative (GLASS) is focussing on human clinical surveillance, the WHO Alliance for Global Integrated Surveillance on Antimicrobial Resistance 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 antibiotic resistance on poultry farms, abattoirs and retail markets (81). In Mexico, surveillance of foodborne 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 Demographic Surveillance System Sites in 20 LMICs (80). This network aims to determine the true prevalence of antibiotic resistance; 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 antibiotic resistance in LMICs (80).

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).

Discussion

Data are sparse on the distribution and concentrations of ABR bacteria and antibiotic resistance 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 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 whole genome sequencing (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 colonisation 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 and colleagues (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 antibiotic resistance. Multidisciplinary and holistic studies employing One Health approaches are required in low resource settings.

References

1. King LJ et al. Executive summary of the AVMA One Health Initiative Task Force report, J Am Vet Med Assoc. 2008;233:259–261. doi:10.2460/javma.233.2.259.
2. Robinson TP, Bu DP, Carrique-Mas J, Fèvre EM, Gilbert M, Grace D, et al.

566 Antibiotic resistance is the quintessential One Health issue. Trans R Soc Trop
567 Med Hyg. 2016;377–80. doi:10.1093/trstmh/trw048
568 3. Jinks T, Lee N, Sharland M, Rex J, Gertler N, Diver M, et al. A time for action:
569 Antimicrobial resistance needs global response. Bull World Health Organ.
570 2016;94:558–558A. doi:10.1093/trstmh/trw048
571 4. World Health Organization. Global Priority List of Antibiotic Resistant Bacteria
572 to Guide Research, Discovery, and Development of New Antibiotics. Geneva;
573 WHO. 2017. Pp1-7. doi.org/10.1016/S1473-3099(09)70222-1
574 5. Mshana SE, Matee M, Rweyemamu M. Antimicrobial resistance in human and
575 animal pathogens in Zambia, Democratic Republic of Congo, Mozambique and
576 Tanzania: an urgent need of a sustainable surveillance system. Ann Clin
577 Microbiol Antimicrob. 2013;12:28. doi:10.1186/1476-0711-12-28
578 6. Kumar GS, Adithan C, Harish BN, Sujatha S, Roy G, Malini A. Antimicrobial
579 resistance in India: A review. J Nat Sci Biol Med. 2013;4:286–91.
580 doi:10.4103/0976-9668.116970
581 7. Gandra S, Joshi J, Trett A, & Sankhil Lamkang A. (2017). Scoping Report on
582 Antimicrobial Resistance in India. Washington, DC: Center for Disease
583 Dynamics, Economics & Policy. Retrieved from https://www.cddep.org/wp-
584 content/uploads/2017/11/AMR-India-scoping-report.pdf
585 8. Leopold SJ, van Leth F, Tarekegn H, Schultsz C. Antimicrobial drug resistance
586 among clinically relevant bacterial isolates in sub-Saharan Africa: A systematic
587 review. J Antimicrob Chemother. 2014;69:2337–53. doi: 10.1093/jac/dku176
588 9. Huynh BT, Padget M, Garin B, Delarocque-Astagneau E, Guillemot D.
589 Bacterial neonatal sepsis and antibiotic resistance in low-income countries.
590 Lancet 2016;6:387:533–4. doi:10.1186/s12879-015-0843-x
591 10. Okeke IN, Laxminarayan R, Bhutta ZA, Duse AG, Jenkins P, O'Brien TF, et al.
592 Antimicrobial resistance in developing countries. Part I: recent trends and
593 current status. Lancet Infect Dis. 2005;5:481–93. doi:10.1016/S1473-
594 3099(05)70189-4
595 11. Laxminarayan R, Duse A, Wattal C, Zaidi AKM, Wertheim HFL, Sumpradit N,
596 et al. Antibiotic resistance—the need for global solutions. Lancet Infect Dis.
597 2013;13:1057–98. doi:10.1016/S1473-3099(13)70318-9
598 12. World Health Organization. Antimicrobial resistance: global report on
599 surveillance. Geneva: WHO; 2014. doi:1.4.2014

13. Kumarasamy KK, Toleman MA, Walsh TR, Bagaria J, Butt F, Balakrishnan R, et al. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. Lancet Infect Dis. 2010;10:597–602. doi:10.1016/S1473-3099(10)70143-2
14. Liu L, Johnson HL, Cousens S, Perin J, Scott S, Lawn JE, et al. Global, regional, and national causes of child mortality: An updated systematic analysis for 2010 with time trends since 2000. Lancet; 2012;379(9832):2151–61. doi:10.1016/S0140-6736(12)60560-1
15. Van Den Bogaard AE, Stobberingh EE. Epidemiology of resistance to antibiotics: Links between animals and humans. Int J Antimicrob Agents. 2000;14:327–35. doi:10.1016/S0924-8579(00)00145-X
16. WHO. Integrated Surveillance of Antimicrobial Resistance in Foodborne Bacteria: Application of a One Health Approach. Geneva: WHO. 2017. Pp87. http://apps.who.int/iris/bitstream/10665/91778/1/9789241506311_eng.pdf
17. Hasan B, Drobni P, Drobni M, Alam M, Olsen B. Dissemination of NDM-1. Lancet Infect Dis. 2012;12:99-100-2. doi:10.1016/S1473-3099(11)70333-4
18. Woerther P-L, Angebault C, Jacquier H, Hugede H-C, Janssens A-C, Sayadi S, et al. Massive increase, spread, and exchange of extended spectrum β-lactamase-encoding genes among intestinal enterobacteriaceae in hospitalized children with severe acute malnutrition in Niger. Clin Infect Dis. 2011;53:677–85. doi:10.1093/cid/cir522
19. Hawkey PM. Prevalence and clonality of extended-spectrum beta-lactamases in Asia. Clin Microbiol Infect. 2008;14(suppl):159–65. doi:10.1111/j.1469-0691.2007.01855.x
20. Karanika S, Karantanos T, Arvanitis M, Grigoras C, Mylonakis E. Fecal colonization with extended-spectrum beta-lactamase-producing Enterobacteriaceae and risk factors among healthy individuals: a systematic review and metaanalysis. Clin Infect Dis. 2016;63:310–8. doi:10.1093/cid/ciw283
21. Miao Z, Li S, Wang L, Song W, Zhou Y. Antimicrobial resistance and molecular epidemiology of ESBL-producing *Escherichia coli* isolated from outpatients in town hospitals of Shandong Province, China. Front Microbiol. 2017;8:1–8. doi:10.3389/fmicb.2017.00063
22. Zhang J, Zheng B, Zhao L, Wei Z, Ji J, Li L, et al. Nationwide high prevalence

of CTX-M and an increase of CTX-M-55 in *Escherichia coli* isolated from patients with community-onset infections in Chinese county hospitals. BMC Infect Dis. 2014;14:1–10. doi:10.1186/s12879-014-0659-0

23. Rutgersson C, Fick J, Marathe N, Kristiansson E, Janzon A, Angelin M, et al. Fluoroquinolones and qnr genes in sediment, water, soil, and human fecal flora in an environment polluted by manufacturing discharges. Environ Sci Technol. 2014;48:7825–32. doi:10.1021/es501452a

24. Amaya E, Reyes D, Vilchez S, Paniagua M, Möllby R, Nord CE, et al. Antibiotic resistance patterns of intestinal *Escherichia coli* isolates from Nicaraguan children. J Med Microbiol. 2011;60:216–22. doi:10.1099/jmm.0.020842-0

25. Randrianirina F, Ratsima EH, Ramparany L, Randremanana R, Rakotonirina HC, Andriamanantena T, et al. Antimicrobial resistance of bacterial enteropathogens isolated from stools in Madagascar. BMC Infect Dis 2014; 14:104. doi:10.1186/1471-2334-14-104

26. Monira S, Shabnam SA, Ali SI, Sadique A, Johura FT, Rahman KZ, et al. Multi-drug resistant pathogenic bacteria in the gut of young children in Bangladesh. Gut Pathog 2017;9:19. doi:10.1186/s13099-017-0170-4

27. Shin H-H, Cho S-H. Prevalence of antimicrobial resistance in *Escherichia coli* strains isolated from fishery workers. Osong Public Heal Res Perspect; 2013;4:72–5. doi:10.1016/j.phrp.2013.03.001

28. Herindrainy P, Randrianirina F, Ratovoson R, Hariniana E, Buisson Y, Genel N, et al. Rectal carriage of extended-spectrum beta-lactamase-producing Gram-negative bacilli in community settings in Madagascar. PLoS One 2011;6. doi:10.1371/journal.pone.0022738

29. Arcilla MS, van Hattem JM, Haverkate MR, Bootsma MCJ, van Genderen PJJ, Goorhuis A, et al. Import and spread of extended-spectrum β-lactamase-producing Enterobacteriaceae by international travellers (COMBAT study): a prospective, multicentre cohort study. Lancet Infect Dis; 2017;17:78–85. doi:10.1016/S1473-3099(16)30319-X

30. Van Boeckel TP, Brower C, Gilbert M, Grenfell BT, Levin S a, Robinson TP, et al. Global trends in antimicrobial use in food animals. Proc Natl Acad Sci U S A. 2015;(16):1–6. doi:10.1073/pnas.1503141112

31. Laxminarayan R, Chaudhury RR. Antibiotic resistance in India: Drivers and

668 opportunities for action. PLoS Med. 2016;13:e1001974.
669 doi:10.1371/journal.pmed.1001974
670 32. Krishnasamy V, Otte J, Silbergeld E. Antimicrobial use in Chinese swine and
671 broiler poultry production. Antimicrob Resist Infect Control 2015;4:17.
672 doi:10.1186/s13756-015-0050-y
673 33. Shanta IS, Hasnat MA, Zeidner N, Gurley ES, Azziz-Baumgartner E, Sharker
674 MAY, et al. Raising backyard poultry in rural Bangladesh: financial and
675 nutritional benefits, but persistent risky practices. Transbound Emerg Dis.
676 2016;64:1454-1464. doi:10.1111/tbed.12536
677 34. van den Bogaard AE, London N, Driessen C, Stobberingh EE. Antibiotic
678 resistance of faecal *Escherichia coli* in poultry, poultry farmers and poultry
679 slaughterers. J Antimicrob Chemother. 2001;47:763–71.
680 doi:10.1093/jac/47.6.763
681 35. Graham JP, Eisenberg JNS, Trueba G, Zhang L, Johnson TJ. Small-scale
682 food animal production and antimicrobial resistance: mountain, molehill, or
683 something in-between? Environ Health Perspect. 2017;125:1–5.
684 doi:10.1289/EHP2116
685 36. Nguyen VT, Carrique-Mas JJ, Ngo TH, Ho HM, Ha TT, Campbell JI, et al.
686 Prevalence and risk factors for carriage of antimicrobial-resistant *Escherichia*
687 *coli* on household and small-scale chicken farms in the Mekong Delta of
688 Vietnam. J Antimicrob Chemother. 2015;70:2144–52. doi:10.1093/jac/dkv053
689 37. Brower CH, Mandal S, Hayer S, Sran M, Zehra A, Patel SJ, et al. The
690 prevalence of extended-spectrum beta-lactamase-producing multidrug-
691 resistant *Escherichia coli* in poultry chickens and variation according to farming
692 practices in Punjab, India. Environ Health Perspect. 2017;125:1–10.
693 doi:10.1289/EHP292
694 38. Andoh LA, Dalsgaard A, Obiri-Danso K, Newman MJ, Barco L, Olsen JE.
695 Prevalence and antimicrobial resistance of *Salmonella* serovars isolated from
696 poultry in Ghana. Epidemiol Infect. 2016;144:3288–99.
697 doi:10.1017/S0950268816001126
698 39. Braykov NP, Eisenberg JNS, Grossman M, Zhang L, Vasco K, Cevallos W, et
699 al. Antibiotic resistance in animal and environmental samples associated with
700 small-scale poultry farming in northwestern Ecuador. Msphere 2016
701 10;1:e00021-15. doi:10.1128/mSphere.00021-15

40. Gondam Kamini M, Tatfo Keutchatang F, Yangoua Mafo H, Kansci G, Medoua Nama G. Antimicrobial usage in the chicken farming in Yaoundé, Cameroon: a cross-sectional study. Int J Food Contam. 2016;3:10. doi:10.1186/s40550-016-0034-6
41. Om C, McLaws ML. Antibiotics: Practice and opinions of Cambodian commercial farmers, animal feed retailers and veterinarians. Antimicrob Resist Infect Control. 2016;5:1–8. doi:10.1186/s13756-016-0147-y
42. Li P, Wu D, Liu K, Suolang S, He T, Liu X, et al. Investigation of antimicrobial resistance in *Escherichia coli* and Enterococci isolated from Tibetan pigs. PLoS One. 2014;9(4). doi:10.1371/journal.pone.0095623
43. Samanta I, Joardar SN, Das PK, Das P, Sar TK, Dutta TK, et al. Virulence repertoire, characterization, and antibiotic resistance pattern analysis of *Escherichia coli* isolated from backyard layers and their environment in India. Avian Dis 2014;58:39–45. doi:10.1637/10586-052913-Reg.1
44. Hussain A, Shaik S, Ranjan A, Nandanwar N, Tiwari SK, Majid M, et al. Risk of transmission of antimicrobial resistant *Escherichia coli* from commercial broiler and free-range retail chicken in India. Front Microbiol. 2017;8. doi:10.3389/fmicb.2017.02120
45. Roess AA, Winch PJ, Akhter A, Afroz D, Ali NA, Shah R, et al. Household animal and human medicine use and animal husbandry practices in rural Bangladesh: Risk factors for emerging zoonotic disease and antibiotic resistance. Zoonoses Public Health. 2015;62:569–78. doi:10.1111/zph.12186
46. Taylor NGH, Verner-Jeffreys DW, Baker-Austin C. Aquatic systems: Maintaining, mixing and mobilising antimicrobial resistance? Trends Ecol Evol. 2011;26:278–84. doi:10.1016/j.tree.2011.03.004
47. Pham DK, Chu J, Do NT, Brose F, Degand G, Delahaut P, et al. Monitoring antibiotic use and residue in freshwater aquaculture for domestic use in Vietnam. Ecohealth. 2015;12:480–9. doi:10.1007/s10393-014-1006-z
48. Jiang H-X, Tang D, Liu Y-H, Zhang X-H, Zeng Z-L, Xu L, et al. Prevalence and characteristics of beta-lactamase and plasmid-mediated quinolone resistance genes in *Escherichia coli* isolated from farmed fish in China. J Antimicrob Chemother. 2012;67:2350–3. doi:10.1093/jac/dks250
49. Zheng H, Zeng Z, Chen S, Liu Y, Yao Q, Deng Y, et al. Prevalence and characterisation of CTX-M β-lactamases amongst *Escherichia coli* isolates

736 from healthy food animals in China. Int J Antimicrob Agents 2012;39:305–10.
737 doi:10.1016/j.ijantimicag.2011.12.001
738 50. Ma J, Liu JH, Lv L, Zong Z, Sun Y, Zheng H, et al. Characterization of
739 extended-spectrum β-lactamase genes found among *Escherichia coli* isolates
740 from duck and environmental samples obtained on a duck farm. Appl Environ
741 Microbiol. 2012;78:3668–73. doi:10.1128/AEM.07507-11
742 51. Abdissa R, Haile W, Fite AT, Beyi AF, Agga GE, Edao BM, et al. Prevalence of
743 *Escherichia coli* O157:H7 in beef cattle at slaughter and beef carcasses at
744 retail shops in Ethiopia. BMC Infect Dis. 2017;17:277. doi:10.1186/s12879-
745 017-2372-2
746 52. Liu Y-Y, Wang Y, Walsh TR, Yi L-X, Zhang R, Spencer J, et al. Emergence of
747 plasmid-mediated colistin resistance mechanism MCR-1 in animals and
748 human beings in China: a microbiological and molecular biological study.
749 Lancet Infect Dis. 2016;16:161–8. doi:10.1016/S1473-3099(15)00424-7
750 53. Jeannot K, Bolard A, Plésiat P. Resistance to polymyxins in Gram-negative
751 organisms. Int J Antimicrob Agents 2017;49:526-535.
752 doi:10.1016/j.ijantimicag.2016.11.029
753 54. Zhu YG, Johnson TA, Su JQ, Qiao M, Guo GX, Stedtfeld RD. Diverse and
754 abundant antibiotic resistance genes in Chinese swine farms. Proc Natl Acad
755 Sci U S A. 2013;110. doi:10.1073/pnas.1222743110
756 55. Nhung N, Cuong N, Thwaites G, Carrique-Mas J. Antimicrobial usage and
757 antimicrobial resistance in animal production in southeast Asia: A review.
758 Antibiotics. 2016;5:37. doi:10.3390/antibiotics5040037
759 56. Gao L, Hu J, Zhang X, Wei L, Li S, Miao Z, et al. Application of swine manure
760 on agricultural fields contributes to extended- spectrum ß-lactamase producing
761 *Escherichia coli* spread in Tai'an, China. Front Microbiol. 2015;6.
762 doi:10.3389/fmicb.2015.00313
763 57. Donkor ES, Newman MJ, Yeboah-Manu D. Epidemiological aspects of non-
764 human antibiotic usage and resistance: Implications for the control of antibiotic
765 resistance in Ghana. Trop Med Int Heal. 2012;17:462–8. doi:10.1111/j.1365-
766 3156.2012.02955.x
767 58. Addis Z, Kebede N, Worku Z, Gezahegn H, Yirsaw A, Kassa T. Prevalence
768 and antimicrobial resistance of Salmonella isolated from lactating cows and in
769 contact humans in dairy farms of Addis Ababa: A cross sectional study. BMC

Infect Dis. 2011;11:222. doi:10.1186/1471-2334-11-222

59. Woolhouse M, Ward M, Van Bunnik B, Farrar J. Antimicrobial resistance in humans, livestock and the wider environment. Philos Trans R Soc B; 2015;370(1670). doi:10.1098/rstb.2014.0083

60. Pruden A, Larsson JDG, Amézquita A, Collignon P, Brandt KK, Graham DW, et al. Management options for reducing the release of antibiotics and antibiotic resistance genes to the environment. Environ Health Perspect. 2013;121:878–85. doi:10.1289/ehp.1206446

61. Diwan V, Chandran SP, Tamhankar AJ, Stalsby Lundborg C, Macaden R. Identification of extended-spectrum beta-lactamase and quinolone resistance genes in *Escherichia coli* isolated from hospital wastewater from central India. J Antimicrob Chemother. 2012;67:857–9. doi:10.1093/jac/dkr564

62. Chandran SP, Diwan V, Tamhankar AJ, Joseph B V., Rosales-Klintz S, Mundayoor S, et al. Detection of carbapenem resistance genes and cephalosporin, and quinolone resistance genes along with oqxAB gene in *Escherichia coli* in hospital wastewater: A matter of concern. J Appl Microbiol. 2014;117:984-995 doi:10.1111/jam.12591

63. Lübbert C, Baars C, Dayakar A, Lippmann N, Rodloff AC, Kinzig M, et al. Environmental pollution with antimicrobial agents from bulk drug manufacturing industries in Hyderabad, South India, is associated with dissemination of extended-spectrum beta-lactamase and carbapenemase-producing pathogens. Infection 2017;45:479-491. doi:10.1007/s15010-017-1007-2

64. Islam MA, Islam M, Hasan R, Hossain MI, Nabi A, Rahman M, et al. Environmental spread of NDM-1-producing multi-drug resistant bacteria in Dhaka, Bangladesh. Appl Environ Microbiol. 2017;AEM.00793-17. doi:10.1128/AEM.00793-17

65. Amaya E, Reyes D, Paniagua M, Calderón S, Rashid MU, Colque P, et al. Antibiotic resistance patterns of *Escherichia coli* isolates from different aquatic environmental sources in León, Nicaragua. Clin Microbiol Infect. 2012;18:E347-54. doi:10.1111/j.1469-0691.2012.03930.x

66. Graham DW, Olivares-Rieumont S, Knapp CW, Lima L, Werner D, Bowen E. Antibiotic resistance gene abundances associated with waste discharges to the Almendares river near Havana, Cuba. Environ Sci Technol. 2011;45:418–24. doi:10.1021/es102473z

804 67. Talukdar PK, Rahman M, Rahman M, Nabi A, Islam Z, Hoque MM, et al.
805 Antimicrobial Resistance, Virulence factors and genetic diversity of *Escherichia*
806 *coli* isolates from household water supply in Dhaka, Bangladesh. PLoS One.
807 2013;8(4). doi:10.1371/journal.pone.0061090
808 68. Hassan MM, Ahmed SA, Rahman KA, Biswas TK. Pattern of medical waste
809 management: existing scenario in Dhaka City, Bangladesh. BMC Public Health.
810 2008;8:36. doi:10.1186/1471-2458-8-36
811 69. Patwary MA, O'Hare WT, Sarker MH. An illicit economy: Scavenging and
812 recycling of medical waste. J Environ Manage. 2011;92:2900-2906.
813 doi:10.1016/j.jenvman.2011.06.051
814 70. Chethana T, Thapsey H, Gautham MS, Sreekantaiah P, Suryanarayana SP.
815 Situation analysis and issues in management of biomedical waste in select
816 small health care facilities in a ward under Bruhat Bengaluru Mahanagara
817 Palike, Bangalore, India. J Community Health. 2014;39:310–5.
818 doi:10.1007/s10900-013-9761-2
819 71. Ahammad ZS, Sreekrishnan TR, Hands CL, Knapp CW, Graham DW.
820 Increased waterborne bla NDM-1 resistance gene abundances associated with
821 seasonal human pilgrimages to the Upper Ganges River. Environ Sci Technol.
822 2014;48:3014–20. doi:10.1021/es405348h
823 72. Diwan V, Tamhankar AJ, Khandal RK, Sen S, Aggarwal M, Marothi Y, et al.
824 Antibiotics and antibiotic-resistant bacteria in waters associated with a hospital
825 in Ujjain, India. BMC Public Health. 2010;10:414. doi:10.1186/1471-2458-10-
826 414
827 73. Dhaka P, Vijay D, Vergis J, Negi M, Kumar M, Mohan V, et al. Genetic
828 diversity and antibiogram profile of diarrhoeagenic *Escherichia coli* pathotypes
829 isolated from human, animal, foods and associated environmental sources.
830 Infect Ecol Epidemiol 2016;18:31055. doi:10.3402/iee.v6.31055
831 74. Dulo F, Feleke A, Szonyi B, Fries R, Baumann MPO, Grace D. Isolation of
832 multidrug-resistant *Escherichia coli* O157 from goats in the somali region of
833 Ethiopia: A cross-sectional, abattoir-based study. PLoS One. 2015;10:
834 doi:10.1371/journal.pone.0142905
835 75. Pehrsson EC, Tsukayama P, Patel S, Mejía-Bautista M, Sosa-Soto G,
836 Navarrete KM, et al. Interconnected microbiomes and resistomes in low-
837 income human habitats. Nature. 2016;533:212–6. doi:10.1038/nature17672

838 76. Stålsby Lundborg C, Diwan V, Pathak A, Purohit MR, Shah H, Sharma M, et al.
839 Protocol: a “One health” two year follow-up, mixed methods study on antibiotic
840 resistance, focusing children under 5 and their environment in rural India. BMC
841 Public Health. 2015;15:1321. doi:10.1186/s12889-015-2632-2
842 77. UNICEF and ICDDRB. Evaluation of avian influenza communication for
843 development initiative- Improving biosecurity in live bird markets. 2015. Dhaka:
844 icddr,b. Pp160.
845 78. Finley RL, Collignon P, Larsson DGJ, Mcewen SA, Li XZ, Gaze WH, et al. The
846 scourge of antibiotic resistance: The important role of the environment. Clin
847 Infect Dis. 2013;57:704–10. doi:10.1093/cid/cit355
848 79. Carruth L, Roess AA, Terefe Y, Hosh FM, Salman MD. Antimicrobial
849 resistance and food safety in Africa. Lancet Infect Dis. 2017;17:575–6.
850 doi:10.1016/S1473-3099(17)30273-6
851 80. Grundmann H, Klugman KP, Walsh T, Ramon-Pardo P, Sigauque B, Khan W,
852 et al. A framework for global surveillance of antibiotic resistance. Drug Resist
853 Updat 2011;14:79–87. doi:10.1016/j.drup.2011.02.007
854 81. Donado-Godoy P, Castellanos R, León M, Arevalo A, Clavijo V, Bernal J, et al.
855 The establishment of the colombian integrated program for antimicrobial
856 resistance surveillance (COIPARS): A pilot project on poultry farms,
857 slaughterhouses and retail market. Zoonoses Public Health. 2015;62(s1):58–
858 69. doi:10.1111/zph.12192
859 82. Zaidi MB, McDermott PF, Campos FD, Chim R, Leon M, Vazquez G, et al.
860 Antimicrobial-resistant *Campylobacter* in the food chain in Mexico. Foodborne
861 Pathog Dis. 2012;9:841–7. doi:10.1089/fpd.2012.1127
862 83. Carrique-Mas JJ, Rushton J. Integrated interventions to tackle antimicrobial
863 usage in animal production systems: The ViParc project in Vietnam. Front
864 Microbiol. 2017 13;8:1062. doi:10.3389/fmicb.2017.01062
865 84. Van Cuong N, Nhung NT, Nghia NH, Mai Hoa NT, Trung NV, Thwaites G, et al.
866 Antimicrobial consumption in medicated feeds in Vietnamese pig and poultry
867 production. Ecohealth 2016;13:490–8. doi:10.1007/s10393-016-1130-z
868 85. Wuijts S, van den Berg HHJL, Miller J, Abebe L, Sobsey M, Andremont A, et al.
869 Towards a research agenda for water, sanitation and antimicrobial resistance.
870 J Water Health 2017;15:175–84. doi:10.2166/wh.2017.124
871 86. O’Neill J. Tackling drug-resistant infections globally: final report and

recommendations. the Review on Antimicrobial Resistance. London. 2016. Available at: https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf

87. Founou LL, Founou RC, Essack SY. Antibiotic resistance in the food chain: A developing country-perspective. Front Microbiol 2016 23;7:1–19. doi:10.3389/fmicb.2016.01881

88. Huijbers PMC, Blaak H, De Jong MCM, Graat EAM, Vandenbroucke-Grauls CMJE, De Roda Husman AM. Role of the Environment in the Transmission of Antimicrobial Resistance to Humans: A Review. Environ Sci Technol. 2015;49:11993–2004. doi:10.1021/acs.est.5b02566

89. Laxminarayan R, Sridhar D, Blaser M, Wang M, Woolhouse M, Laxminarayan R, et al. Achieving global targets for antimicrobial resistance. Science. 2016;353:1057–875. doi:10.1126/science.aaf9286

90. Wernli D, Jørgensen PS, Harbarth S, Carroll SP, Laxminarayan R, Levrat N, et al. Antimicrobial resistance: The complex challenge of measurement to inform policy and the public. PLoS Med. 2017;14:1–9. doi:10.1371/journal.pmed.1002378

Acknowledgements

The authors gratefully acknowledge funding support from the UK Antimicrobial Resistance Cross Council Initiative (NERC/BBSRC/MRC) grant number NE/N019555/1 with additional support from the EPSRC Bridging the Gaps in AMR award EP/M027341/1.

Ethics statement: No ethical clearances were required for the purposes of the review.

Competing interests statement: The authors declare no competing interests

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

Authors' contributions statement: All authors contributed to the intellectual conception for the paper, the search, retrieval and synthesis of information presented and the writing and editing of the manuscript. All authors approved the final version.