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ANTIMICROBIAL RESISTANCE: EXAMINING THE ENVIRONMENT AS PART OF THE ONE HEALTH APPROACH

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ABSTRACT

Antimicrobial Resistance (AMR) is a serious issue that is threatening the medical and agricultural advances of today. The connections that exist among human health, food production and the environment necessitate a One Health approach to address the challenge of AMR. Recent research points to the environment as an essential factor in the spread of AMR, as well as a possible reservoir of antimicrobial resistant bacteria and genes. The process, however, of the environmental transmission of resistance genes, along with their effects and how to mitigate them, is still being examined. As new research emerges, so to have new challenges regarding the selective pressure of antibiotics on the environment. AMR in the environment is not new, with resistance genes found even in isolated places (e.g. in permafrost or volcanoes) but understanding this natural process and its implications for tackling AMR continue to pose many questions. This paper aims to examine some of the emerging research on AMR from a One Health perspective and in particular to highlight the role of the environment. It will explore the use of antibiotics and their effects in different ecosystems, as well as the challenges they pose for developing countries: in particular, in designing policies to address antimicrobial resistance that take into account the connections among humans, animals and the environment.

La résistance aux antimicrobiens est un problème grave qui menace les avancées actuelles dans les domaines de la médecine et de l'agriculture. Du fait des liens qui existent entre la santé humaine, la production alimentaire et l'environnement, une approche globale, qui s'appuie sur l'initiative « Une seule santé », est nécessaire pour relever les défis qui y sont liés. Des recherches récentes montrent que l'environnement est un facteur essentiel dans la propagation de la résistance aux antimicrobiens, ainsi qu'un réservoir possible de bactéries et de gènes résistants. Elles n'ont pas encore permis cependant de comprendre le processus de transmission par l'environnement des gènes de résistance, ainsi que leurs effets et les moyens de les atténuer. À mesure que des recherches voient le jour, de nouveaux défis se posent concernant la pression de sélection que les antibiotiques exercent sur l'environnement. La question de la résistance aux antimicrobiens dans l'environnement n'est pas nouvelle, les gènes de résistance se trouvant même parfois dans des endroits reculés (par exemple dans le permafrost ou les volcans), mais la compréhension de ce processus naturel et de ses implications dans le cadre de la lutte contre la résistance aux antimicrobiens continue de soulever de nombreuses interrogations. Le présent document propose une analyse des recherches en cours concernant la résistance aux antimicrobiens dans l'optique d'une approche fondée sur l'initiative « Une seule santé » et souligne, en particulier, le rôle que joue l'environnement. Il dresse un état des lieux de l'utilisation des antibiotiques et de leurs effets dans différents écosystèmes, et des défis auxquels sont confrontés les pays en développement, qui doivent concevoir des politiques de lutte contre la résistance aux antimicrobiens qui tiennent compte des liens entre les humains, les animaux et l'environnement.

La resistencia a los antimicrobianos (RAM) es un problema grave que amenaza los avances médicos y agrícolas actuales. Las conexiones entre la salud humana, la producción de alimentos y el medioambiente requieren un enfoque «Una Salud» para afrontar el desafío de la RAM. Las investigaciones recientes señalan al medioambiente como un factor esencial en la propagación de la RAM, así como un posible reservorio de bacterias y genes resistentes a los antimicrobianos. Sin embargo, todavía se está examinando el proceso de transmisión

ambiental de los genes de resistencia, junto con sus efectos y la forma de mitigarlos. A medida que surgen nuevas investigaciones, se plantean nuevos retos en cuanto a la presión selectiva de los antibióticos en el medioambiente. La RAM en el medioambiente no es un fenómeno nuevo, ya que los genes de resistencia se encuentran incluso en lugares aislados (por ejemplo, en el permafrost o los volcanes), pero la comprensión de este proceso natural y sus consecuencias para hacer frente a la RAM siguen planteando muchas preguntas. El presente documento tiene por objeto analizar algunas de las investigaciones emergentes sobre la RAM desde la perspectiva «Una Salud» y, en particular, poner de relieve el papel del medioambiente. Asimismo, en él se exploran el uso de los antibióticos y sus efectos en diferentes ecosistemas, así como los desafíos que plantean a los países en desarrollo, en concreto, en la elaboración de políticas para abordar la resistencia a los antimicrobianos que tengan en cuenta las conexiones entre los seres humanos, los animales y el medioambiente.

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WHAT IS ANTIMICROBIAL RESISTANCE?

The World Health Organization (WHO) defines antimicrobial resistance as what

> happens when microorganisms (such as bacteria, fungi, viruses, and parasites) change when they are exposed to antimicrobial drugs (such as antibiotics, antifungals, antivirals, antimalarials, and anthelmintics). Microorganisms that develop antimicrobial resistance are sometimes referred to as "superbugs". As a result, the medicines become ineffective and infections persist in the body, increasing the risk of spread to others.[2]

Antimicrobial resistance is a natural phenomenon millions of years old and a natural defence mechanism that advantages bacteria in their competition for survival. Resistance mechanisms were found in environmental bacteria even before the introduction of antibiotics as medicines.[3]

The first antibiotic was discovered in 1928, when Alexander Fleming found a type of mould, which he later called penicillin, in a petri dish and realized it had antibacterial properties.[4] It wasn't until the late 1930s, however, with the help of two chemists from the University of Oxford, Howard Florey and Ernst Chain, that it was finally possible to stabilize and purify penicillin.[5] By the mid-1940s, penicillin was produced on a massive scale, inaugurating what we have come to know as the "antibiotic era."[6] Penicillin not only saved countless lives during World War II but also helped to reduce mortality for many other infections that were not previously treatable. It is essential to note that Fleming himself, in his Nobel Prize acceptance speech, warned of the emergence of antibiotic resistance. Today, there exists resistance to every antibiotic that we use.[7]

Losing antimicrobials will have severe implications for how modern medicine functions. In a recent article in the *Guardian*, Oliver Franklin-Walls explains:

> a world without antibiotics means returning to a time without organ transplants, without hip replacements, without many now-routine surgeries. It would mean millions more women dying in childbirth; make many cancer treatments, including chemotherapy, impossible; and make even the smallest wound potentially life-threatening.[8]

It is hard to imagine such a world. Therefore, it is critical to understand AMR and its effects.

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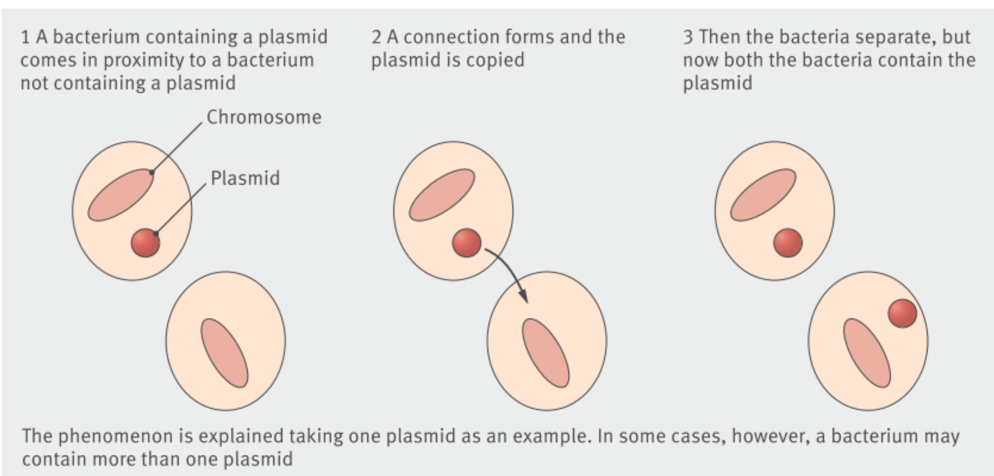
[2] World Health Organization, "Antimicrobial resistance", 15 February 2018. Available from https://www.who.int/en/news-room/fact-sheets/detail/antimicrobial-resistance (accessed 26 February 2019).
[3] ReAct, "How did we end up here?" Available from https://www.reactgroup.org/toolbox/understand/how-did-we-end-up-here/ (accessed 26 February 2019); B.A Wall and others, *Drivers, Dynamics, and Epidemiology of Antimicrobial Resistance in Animal Production* (Food and Agriculture Organization of the United Nations - FAO, 2016). Available from http://www.fao.org/feed-safety/resources/resources-details/en/c/452608/.
[4] Sally C. Davis, Jonathan Grant and Mike Catchpole, *The Drugs Don't Work: A Global Threat* (London, Penguin Group, 2013).
[5] Burcu Kilic, "Innovation and the pharmaceutical industry", in *Boosting Pharmaceutical Innovation in the Post-Trips Era* (Cheltenham, U.K., Edward Elgar Publishing Limited, 2014).
[6] Germán Velasquez, *Salud, Medicamentos y Tercer Mundo* (Madrid, Iepala Editorial, 1986).
[7] Gerard D. Wright, "Q&A: Antibiotic resistance: Where does it come from and what can we do about it?", *BMC Biology*, vol. 8, No. 1 (2010). Available from https://doi.org/10.1186/1741-7007-8-123.
[8] Oliver Franklin-Wallis, "The drugs don't work: What happens after antibiotics?," *The Guardian*, 24 March 2019. Available from https://www.theguardian.com/global/2019/mar/24/the-drugs-dont-work-what-happens-after-antibiotics.

The transmission of resistance and resistance genes occurs in two ways. Firstly, the bacterium passes it on vertically to its offspring. Secondly, the genes are transferred to other bacteria, including to other species of bacteria that differ from their offspring [9]. The latter process is called horizontal gene transfer and is one of the reasons that identical resistance genes have been identified in different species of bacteria, including crossover bacteria transmitted from animals to humans to the environment and *vice versa*.

Although resistance is a natural phenomenon, the increase in bacterial resistance that directly affects humans and animals is a result of the intensified use of antimicrobials in humans and agriculture, where it has been used for treating sick animals, disease prevention and growth promotion,[10] as well as for the treatment of plants.

Figure 1 illustrates one of the processes through which bacteria transfer resistant genes via plasmids through the process of conjugation. Figure 2 shows the multiple mechanisms through which gene transfer occurs: conjugation, transformation, transduction and gene transfer agents.

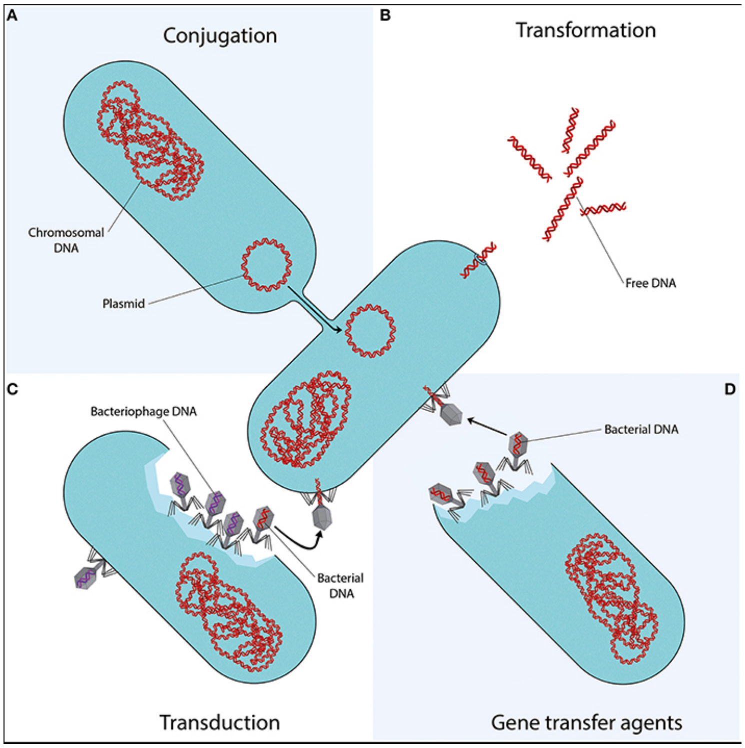
Figure 1: Horizontal gene transfer through plasmids



Source: Stålsby Lundborg and Tamhankar, “Antibiotic residues in the environment of South East Asia” (2017).

[9] Wright, "Q&A: Antibiotic resistance"; Cecilia Stålsby Lundborg and Ashok Tamhankar, "Antibiotic residues in the environment of South East Asia," *BMJ*, No. 358, Supp. 1 (5 August 2017).
[10] B. A. Wall, A. Mateus, L. Marshall, D. U. Pfeiffer, L. Lubroth, H. J. Ormel and others, *Drivers, Dynamics, and Epidemiology of Antimicrobial Resistance in Animal Production* (Food and Agriculture Organization of the United Nations - FAO, 2016).

Figure 2: Mechanisms of horizontal gene transfer



Source: Von Wintersdorff, C. J. H., Penders, J., Van Niekerk, J. M. and others, “Dissemination of antimicrobial resistance” (2016).

THE ENVIRONMENTAL DIMENSION OF AMR: WHY IS IT CRITICAL?

Antimicrobial resistance has attracted attention globally because of the threat it represents to modern medicine. The "One Health" approach aims to foster interdisciplinary collaboration to solve public health issues. This collaboration includes the intersections among humans, animals and the environment.[11] The environmental aspect of this approach and its contribution to AMR, however, have often lagged behind other areas of focus and therefore needs to be further understood and detailed.

In 2017, a report by the United Nations (UN) Environment Programme pointed out that "the genetic basis of antibiotic resistance in bacteria and how resistance can spread between environment and clinic are now subjects of enormous interest."[12] Furthermore, the report pointed out that the transmission of resistant bacteria, through either the food chain or direct contact with the environment is an area that is still being researched. Humans are constantly exposed to environmental bacteria and therefore to the resistance genes found in drinking water, food or soil, or directly in the environment.[13] The World Health Organization, in its 2015 Global Action Plan on Antimicrobial Resistance, acknowledged that AMR could circulate among humans, animals and the environment, adding that human and animal trade, travel and migration can further affect this circulation. Moreover, the fourth objective of the Global Action Plan on AMR calls for the WHO Secretariat to

> develop standards and guidance (within the tripartite collaboration with FAO and OIE), based on best available evidence of harms, for the presence of antimicrobial genes and their residues in the environment, especially in water, wastewater and food (including aquatic and terrestrial animal feed).[14]

Researchers have also been studying how human activities have affected natural habitats and wildlife, including the possible spread of AMR genes by wildlife.[15] A recent study on the discovery of resistance genes in the Arctic, where there is little human activity, seems to confirm the effect of human activity even in remote areas.[16] Researchers have also examined soil samples from the pre-antibiotic era as well as permafrost and noted that "clinically relevant resistance genes were rare in soils, and were not found on plasmids, prior to the 1940s."[17] This information has given scientists a starting point for trying to understand natural resistance versus the resistance observed as a product of human activity.[18]

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[11] Sabiha Y. Essack, "Environment: The neglected component of the One Health triad," *The Lancet Planetary Health*, vol. 2, No. 6 (June 2018), pp. e238–39. Available from https://www.thelancet.com/journals/lanplh/article/PIIS2542-5196(18)30124-4/fulltext.
[12] United Nations Environment Programme, *Frontiers 2017: Emerging Issues Of Environmental Concern*, *Frontiers* (2017). Available from https://www.unenvironment.org/resources/frontiers-2017-emerging-issues-environmental-concern.
[13] Ibid.
[14] World Health Organization, *Global Action Plan on Antimicrobial Resistance* (2015). Available from https://www.who.int/antimicrobial-resistance/global-action-plan/en/.
[15] Marion Vittecoq and others, "REVIEW: Antimicrobial resistance in wildlife," *Journal of Applied Ecology*, vol. 53, No. 2 (February 2016), pp. 519–29. Available from https://doi.org/10.1111/1365-2664.12596.
[16] Fiona Harvey, "Genes linked to antibiotic-resistant superbugs found in Arctic," *The Guardian* (28 January 2019). Available from https://www.theguardian.com/society/2019/jan/28/genes-linked-to-antibiotic-resistant-superbugs-found-in-arctic.
[17] Kornelia Smalla and others, "Environmental dimensions of antibiotic resistance: Assessment of basic science gaps", *FEMS Microbiology Ecology*, vol. 94, No. 12 (December 2018), pp. 1–6. Available from https://doi.org/10.1093/femsec/fiy195.
[18] Smalla and others (2018).

The environment may also play a role as a plausible reservoir of antibiotic-resistant bacteria and resistance genes.[19] Gerard Wright, in his Q&A article on AMR, explains:

> The genes and proteins responsible for resistance in environmental bacteria are homologous to those found circulating in pathogens, strongly suggesting contemporary horizontal gene transfer. Opportunistic pathogens with environmental reservoirs—for example*, P. aeruginosa and A. baumannii*—are highly drug-resistant and have a remarkable capacity to acquire new resistance genes.[20]

This observation provides evidence of the role currently played by the environment in the spread of resistance genes to pathogens affecting humans, as well as its role as a reservoir of those genes. Other researchers have identified other vital vectors of environmental transmission, including "sewage, wastewater treatment plants, water bodies, and travel, but also air-borne aerosols, dust, and food colonized by bacteria."[21] Humans can come into contact with antibiotic resistance genes and bacteria through food, including raw vegetables, exposure to animals or biological substances and through water, soil and air.[22]

Because the environment plays multiple roles in the spread and storage of AMR genes, more research is needed, including examining not only how resistant bacteria and genes are disseminated but also how the emergence of resistance occurs in environmental bacteria and their role as a possible reservoir,[23] including an understanding of the pathways of transmission and what actions can be taken to prevent, mitigate exposure and assess the risk of this exposure and its implications for human health.[24]To further understand the connections among humans, the animals and the environment, the role played by antibiotic use in animal production and its effect also needs to be examined.

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[19] Christy Manyi-Loh and others, "Antibiotic use in agriculture and its consequential resistance in environmental sources: Potential public health implications," *Molecules*, vol. 23, No. 4 (April 2018). Available from https://doi.org/10.3390/molecules23040795.
[20] Wright, "Q&A: Antibiotic resistance."
[21] Johan Bengtsson-Palme, Erik Kristiansson and D. G. Joakim Larsson, "Environmental factors influencing the development and spread of antibiotic resistance," *FEMS Microbiology Reviews*, vol. 42, No. 1 (January 2018), pp. 68–80. Available from https://doi.org/10.1093/femsre/fux053.
[22] Smalla and others (2018); Manyi-Loh and others (2018).
[23] ReAct, *Addressing the Antibiotic Resistance Threat: The Role of Water, Sanitation and Hygiene* (2016).
[24] Chandan Pal and others, "The structure and diversity of human, animal and environmental resistomes," *Microbiome*, 4 (7 October 2016). Available from https://doi.org/10.1186/s40168-016-0199-5.

EXAMINING THE EFFECT OF THE USE OF ANTIBIOTICS IN ANIMALS ON THE ENVIRONMENT

A short background of the use of antibiotics in animals

Antibiotics are used extensively in the production of food animals. Some estimates indicate that at least 70 per cent of all the antibiotics produced in the world are used in animals,[25] and this number is expected to increase[26] unless urgent measures are taken. Chickens were the first animals to receive antibiotics as growth promoters. Through this process, scientists were able to demonstrate that daily antibiotic use could protect the birds from diseases, principally in closed, confined spaces. Moreover, this use of antibiotics generated benefits in the form of rapid weight gain and resulted in the cheaper and faster production of chickens.[27] The use of antibiotics as growth promoters in farming traces its origin to the 1940s.[28] Adding antibiotics to animal feed and water enabled agricultural producers to make meat more affordable and reduce production time. Early on, there were some warnings of the potential consequences of this newfound use of antibiotics, mainly related to the risk of exacerbating antibiotic resistance, but these concerns were largely dismissed.[29] Of the antibiotics that are routinely used to feed animals, it is estimated that about two-thirds contain similar compounds to those used to treat humans.[30]

A 2016 report pointed out that "in 2014 pharmaceutical companies sold nearly 21 million pounds of medically important antibiotics for use in food animals, more than three times the amount sold for use in people."[31] Antibiotics are used in animal production for treating and preventing disease and in some cases have become a substitute for more labour-intensive methods that would require individual care for animals. For this reason, Claas Kirchhelle, in his article on the history of antibiotic use in food production, points out that "many producers remain dependent on routine antibiotic use, and animal products from antibiotic-intensive productions systems are still being exported to other parts of the world."[32] Currently, large-scale farming practices rely on the routine use of antibiotics to ensure animals stay healthy and maintain productivity .[33,34] It has

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[25] Manyi-Loh and others (2018); Jacqui Thornton, "Where humans and animals collide: Emerging infections and newfound resistance," London School of Hygiene & Tropical Medicine (2017). Available from https://www.lshtm.ac.uk/research/research-action/features/where-humans-and-animals-collide-emerging-infections-and-newfound (accessed 28 February 2019).
[26] Johns Hopkins Center for a Livable Future and ReAct, A Framework for Costing the Lowering of Antimicrobial Use in Food Animal Production (2016). Available from https://amr-review.org/sites/default/files/ReAct_CLF_Hopkins_UKAMRReview_CommissionedPaper.pdf.
[27] Maryn McKenna, *Big Chicken: The Incredible Story of How Antibiotics Created Modern Agriculture and Changed the Way the World Eats* (2017).
[28] Ramanan Laxminarayan, Adriano Duse, Chand Wattal, Anita K. M. Zaidi, Heiman F. L. Wertheim, Nithima Sumpradit, Erika Vlieghe, Gabriel Levy Hara, Ian M. Gould and others,, "Antibiotic resistance: The need for global solutions," *The Lancet Infectious Diseases*, vol. 13, No. 12 (December 2013), pp. 1057–1098. Available from https://doi.org/10.1016/S1473-3099(13)70318-9.
[29] McKenna, *Big Chicken* (2017)*;* Megan Molteni, "Antibiotic-brined chicken and other bad ideas from US farming," *Wired* (2017). Available from https://www.wired.com/story/antibiotic-brined-chicken-and-other-bad-ideas-from-us-farming/ (accessed 28 February 2019).
[30] McKenna, *Big Chicken* (2017)*;* Wall and others (2016).
[31] Melinda Wenner Moyer, "How drug-resistant bacteria travel from the farm to your table," *Scientific American*, vol. 315, No. 6 (December 2016). Available from https://www.scientificamerican.com/article/how-drug-resistant-bacteria-travel-from-the-farm-to-your-table/.
[32] Claas Kirchhelle, "Pharming animals: A global history of antibiotics in food production (1935–2017)," *Palgrave Communications*, vol. 4, No. 96 (August 2018). Available from https://doi.org/10.1057/s41599-018-0152-2.
[33] Martin Khor, *When Medicines Don't Work Anymore. Antimicrobial Resistance: The World's Gravest Health Threat* (Penang, Malaysia, Third World Network and South Centre, 2018).
[34] Manyi-Loh and others (2018).

been observed, however, that using antibiotics in this manner can select for antibiotic resistance among commensal and pathogenic bacteria within the animals.

Selection for resistance can also occur in the environment as a result of exposure to the antibiotics animals release into the environment. Researchers have explained that this is happening because

> most of these antibiotics are not fully metabolized but released into the environment as waste products, [so] antibiotic resistance has an ecological impact since these waste products still have the potential to influence the bacteria population and promote antibiotic resistance.[35]

This is not unusual: a report prepared for the European Commission on the environmental risks of medicinal products estimates that "between 30 and 90% of the orally administered dose is generally excreted as active substance in the urine of animals and humans."[36] This percentage varies, however, according to the volumes and nature of the substance excreted.[37] This is another way antibiotics enter the environment that should be considered.

A Food and Agriculture Organization (FAO) study also concluded that "there is a substantial body of evidence to support the view that the emergence of antimicrobial resistance in bacteria in livestock populations is connected to the emergence of AMR in bacterial populations that colonize and infect humans."[38] Other researchers have observed that the use of antimicrobials as growth promoters at sub-therapeutic levels encourages resistance to emerge. Antibiotic use in animals for non-therapeutic purposes has been linked to an increase in resistant bacteria and resistance genes, some of which have been transferred to humans.[39] Furthermore, other studies have looked at the rise of infections in humans originating in animals,[40] making addressing the interface between humans and animals even more critical.

To illustrate this interface, it is worth examining the case of colistin, an old antibiotic that was not used in humans because of its toxicity, but that now has become a last-resort antibiotic. Since this antibiotic was not used in humans, it came to be commonly used in animals as a growth promoter. In 2013 a group of Chinese researchers discovered in pigs a gene, MCR, that conferred resistance to colistin. This gene could be transferred from one bacterium to another. Later, this gene was found around the world in animals, the environment and people. To date it has been detected in over 30 countries across five continents.[41] Colistin resistance was first identified in animals and then transferred to humans.[42] This is not the only case; there is also evidence showing how Methicillin-resistant Staphylococcus (MRSA) was also directly spread from animals to people.[43] These cases illustrate the links between humans and animals and the need to explore this relationship further but, as this evidence suggests, the effects are already

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[35] Ibid.
[36] BIO Intelligence Service, *Study on the Environmental Risks of Medicinal Products, Final Report Prepared for Executive Agency for Health and Consumers* (Paris, Executive Agency for Health and Consumers, 2013).
[37] Ibid.
[38] Wall and others (2016).
[39] Wall and others (2016); Manyi-Loh and others (2018).
[40] Thornton (2017).
[41] McKenna (2017); Wang and others (2018).
[42] ReAct, *Addressing the Antibiotic Resistance Threat: The Role of Water, Sanitation and Hygiene* (2016).
[43] Ramanan Laxminarayan, Adriano Duse, Chand Wattal, Anita K. M. Zaidi, Heiman F. L. Wertheim, Nithima Sumpradit, Erika Vlieghe, Gabriel Levy Hara, Ian M. Gould and others, "Antibiotic Resistance: The Need for Global Solutions", *The Lancet Infectious Diseases*, vol. 13, No. 12 (2013), pp. 1057–98. Available from https://doi.org/10.1016/S1473-3099(13)70318-9.

starting to emerge clearly. It is also important to point out that in many cases antibiotics are being used as substitutes for incorrect or inadequate farming practices despite increasing evidence that it is possible for agricultural production not to use antibiotics routinely without affecting overall production.[44]

For example, antibiotics for growth promotion have been banned in the European Union since 2006,[45] and the Global Action Plan on AMR, endorsed by all WHO member states, recognizes the need to phase out the use of antibiotics as growth promoters.[46] Still, antibiotics for growth promotion continue to be used in many countries. Claas Kirchhelle rightly argues that it is important

> not to displace blame for drug overuse on middle-and low-income countries. Having pioneered and exported antibiotic-dependent production and consumption since the 1940s, high-income countries have a moral responsibility to contain the fallout of these systems in other parts of the world.[47]

As illustrated above, the current model of production requires the use of antibiotics, so unless there is widespread adoption of more sustainable practices and support for countries to transition to them, change will be difficult.

Furthermore, the loss of effective antibiotics is a problem not only for humans: the increase in drug-resistant infections also means losing the antimicrobials needed to treat sick animals, leading to losses in production. Moreover, farmers and others involved in meat production are at higher risk of coming into contact with resistant bacteria.[48] Antibiotic-resistant bacteria that have been identified in farm animals can then spread to humans, either directly or through contact with food, water, air and soil;[49] therefore, addressing transmission pathways and prevention is essential. Effective antibiotics are needed to treat animals, so safeguarding their effectiveness is also in the interest of farmers**.** Augmenting productivity while at the same time reducing antibiotic use is a challenge that needs to be acknowledged, and alternatives need to be sought.[50] Investment in improving farm productivity while safeguarding medically important antibiotics will be vital in responding to AMR.

Additionally, the ecological effects of the exposure to antibiotics in animals and how this can provoke changes in the ecosystem with which it comes in contact is another important angle to examine. One study on the routine use of antibiotics in cattle found that their use can have unintended ecological consequences, including changes in the microbiota of dung beetles due to their exposure to antibiotics as well as an increase in greenhouse-gas emissions due to the routine exposure of cattle to broad-spectrum antibiotics.[51] The study highlights the critical nature

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[44] Maarten van der Heijden and others, *When the Drugs Don't Work: Antibiotic Resistance as a Global Development Problem* (2019); Anthony D. So and others, “An Integrated Systems Approach Is Needed to Ensure the Sustainability of Antibiotic Effectiveness for Both Humans and Animals,” *Journal of Law, Medicine & Ethics*, No. 43, Supp. 3 (Summer 2015).
[45] van der Heijden and others (2019); Wall and others (2016).
[46] WHO (2015).
[47] Kirchhelle (2018).
[48] Wall and others (2016).
[49] ReAct, *Addressing the Antibiotic Resistance Threat* (2016); Johns Hopkins Center for a Livable Future and ReAct (2016).
[50] van der Heijden and others (2019).
[51] Tobin J. Hammer and others, “Treating cattle with antibiotics affects greenhouse gas emissions and microbiota in dung and dung beetles," *Proceedings of the Royal Society B: Biological Sciences*, vol. 283, No. 1831 (2016), pp. 1–7. Available from https://doi.org/10.1098/rspb.2016.0150.

of research in better understanding the ecological interactions between the use of antibiotics in animals and their surrounding ecosystems.

Use in aquatic environments

Aquaculture is an important industry that has become more intensive in recent decades, principally for the production of shrimp and fish. This intense production has increased bacterial diseases and therefore escalated the use of antimicrobials.[52] The use of antimicrobial drugs in the aquaculture industry, however, is different from their use in other animals because the medicines are generally added to the feed that goes directly into the water. This direct contact with the environment through water could result in the exposure of a wider variety of bacteria to antimicrobials and therefore generate resistance.[53] A report from the UN Environment Programme (UNEP) noted that,

> once consumed, most antibiotic drugs are excreted unmetabolized, along with resistant bacteria. They can then pass either through sewage systems or more directly into water and soils, and mix with environmental bacteria in the presence of other pollutants that may add further pressure to help select for antibiotic resistance, directly or indirectly.[54]

In the case of fish, around 75 per cent of the antibiotics given to fish are excreted into the water unmetabolized; therefore, this could result in the spread of antimicrobial-resistant bacteria and resistance genes through the water environment. This could also potentially increase the risk of the fish pathogens' developing resistance.[55] Moreover, the antibiotics used in aquaculture are usually the same ones as the ones used in animals and humans,[56] and these resistance genes can flow from aquatic environments into the ocean,[57] where humans can come into contact with them.

Antimicrobial resistance can also have effects on the marine environment. A recent study on dolphins in the United States found patters of resistance to commonly used antibiotics among coastal dolphin populations. The findings could be explained by the transfer of resistance genes and bacteria from humans or terrestrial animals to the marine environment and then to the dolphins. Another possible route of transmission could be the direct discharge of antibiotics into the marine environment, resulting in the development of resistant bacteria that is later transferred to the dolphins.[58] The study shows that there could be multiple routes for antimicrobial resistance to be transferred to the marine ecosystem. Therefore, more research is

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[52] Jaime Romero, Carmen Gloria Feijoo and Paola Navarrete, *Antibiotics in Aquaculture: Use, Abuse and Alternatives, Health and Environment in Aquaculture*, Edmir Carvalho, ed. (InTech, 2012). Available from https://www.intechopen.com/books/health-and-environment-in-aquaculture/antibiotics-in-aquaculture-use-abuse-and-alternatives.
[53] Romero, Feijoo and Navarrete (2012).
[54] UNEP, *Frontiers 2017: Emerging Issues Of Environmental Concern* (2017).
[55] Romero, Feijoo and Navarrete (2012); UNEP, "Antimicrobial Resistance from Environmental Pollution among Biggest Emerging Health Threats, Says UN Environment" (5 December 2017). Available from https://www.unenvironment.org/news-and-stories/press-release/antimicrobial-resistance-environmental-pollution-among-biggest [accessed 27 February 2019].
[56] Wall and others (2016).
[57] van der Heijden and others (2019).
[58] Adam M. Schaefer and others, "Antibiotic-resistant organisms cultured from Atlantic bottlenose dolphins (Tursiops truncatus) inhabiting estuarine waters of Charleston, SC and Indian River Lagoon, FL," *EcoHealth*, vol. 6, No. 1 (2009), pp. 33–41. Available from https://doi.org/10.1007/s10393-009-0221-5.

needed to understand the possible implications and transmission routes of antibacterial resistance.

The effect of antibiotic use in agriculture on the soil and aquatic environment

The use of antimicrobials in animal production, including in aquaculture, has also effects on the environment. Soil studies from the last 100 years have presented evidence showing, beginning in the mid-1970s, an increase in antibiotic resistance closely related to the exposure of soils to manure-based fertilizers in which the manure is from food animals exposed to antimicrobials. The types of resistance genes identified in these studies were found to be similar to the ones in clinical isolates in hospitals.[59] Antibiotics are released into the environment through many pathways, including through human waste, waste from farms, water, manure, irrigation and runoff from farms.[60]

The UN Environment Programme reports that there is

> clear evidence that the release into the environment of antimicrobial compounds from households, hospitals and pharmaceutical facilities and in agricultural run-off, combined with direct contact between natural bacterial communities and discharged resistant bacteria, is driving bacterial evolution and the emergence of more resistant strains.[61]

Moreover, the UN Environment Programme also observed that other antimicrobial compounds, such as disinfectants and heavy metals, could potentially have an effect on the evolution of resistant bacteria in the environment.[62]

Researchers in Sweden observed that “sewage treatment plants (STPs) provide an obvious setting that offers interaction opportunities for a range of different bacterial species, and also may present sufficient conditions for resistance selection.[63] They explained that

> opportunistic pathogens usually thriving in soil may be intermediary organisms that can act as recipients of resistance genes from human-associated bacteria and which could transfer those genes back at a later point, or even re-infect humans themselves.[64]

Therefore, understanding the effects that antibiotics are having on the bacteria in soil and water and their transmission routes to humans is necessary to improve overall understanding of antimicrobial resistance and develop strategies to reduce exposure to it. Moreover, the presence of antimicrobial-resistant bacteria and resistant genes in water can contaminate water sources that humans depend on, particularly in developing countries, where a single source of water is generally used for multiple purposes and where, therefore, antimicrobial resistant

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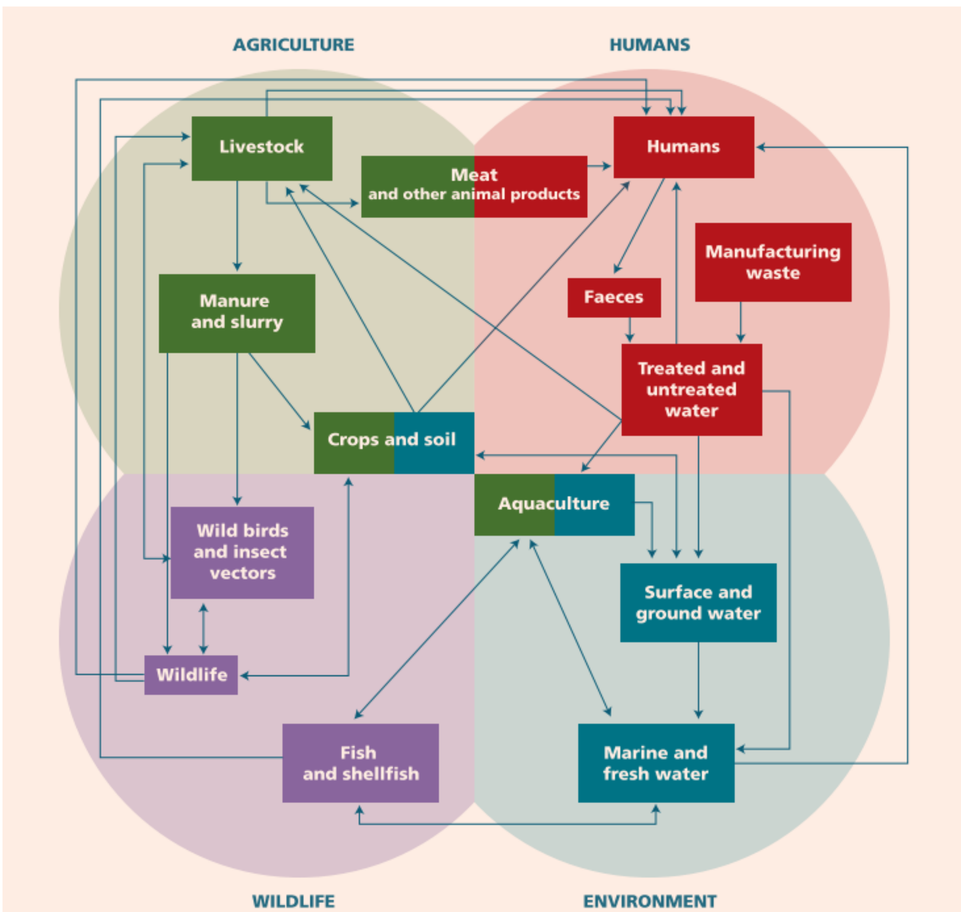
[59] Dusan Jasovsky and others, “Antimicrobial Resistance. A Threat to the World's Sustainable Development,” *Development Dialogue Paper* (2016); Pal and others (2016).
[60] Manyi-Loh and others (2018).
[61] United Nations Environment Programme, “Antimicrobial Resistance” (2018).
[62] UNEP, *Frontiers 2017* (2017).
[63] Bengtsson-Palme, Kristiansson and Larsson (2018).
[64] Ibid.

bacteria and genes can be easily transmitted to humans.[65] Water is one of the ways AMR is spreads, not only because of its direct consumption but also because it is used in irrigation.[66] Antibiotics can enter the aquatic environment through wastewater, the improper disposal of antibiotics and farm runoffs.[67] This drives bacteria to select for resistance.

Current agricultural practices are also affecting the natural soil microbiome[68] and therefore changing the bacteria found there. The future effects of these alterations are difficult to estimate but are nevertheless crucial for understanding the full effect of the use of antibiotics, both in humans and agriculture, on the environment. Figure 3 below provides a visual representation of the different interactions that can be found among agriculture, humans and the environment, including wildlife. It also provides an idea of the various transmission pathways that should be considered.

Figure 3: AMR transmission routes



Source: Wall and others (2016)

[65] Wellcome, U.S. Centers for Disease Control and Prevention and UK Science & Innovation Network, *Initiatives for Addressing Antimicrobial Resistance in the Environment Current Situation and Challenges* (2018).
[66] Wall and others (2016).
[67] The Lancet Planetary Health, "The Natural Environment and Emergence of Antibiotic Resistance", *The Lancet Planetary Health*, vol. 2, No. 1 (2018), p. e1. Available from https://doi.org/10.1016/S2542-5196(17)30182-1.
[68] Smalla and others (2018).

ANTIBIOTIC EXPOSURE VIA FARMS, HOSPITALS AND WASTE

Interactions among the environment, humans and animals are not the only way antimicrobials are used in clinical practice. In animal husbandry, they enter into contact with the environment. Antimicrobials are also spread in the environment via other routes, including runoff from farms, discharge from pharmaceutical manufacturing facilities and hospital and waste-management disposal. These routes have consequences for the bacterial ecosystems, as well as for the current increase in resistance genes.

It is important to point out that the concentration of antibiotics in natural environments changes depending on the area examined. For example, environmental exposure to antibiotics due to pharmaceutical pollution or sewage outlets from hospitals has a particularly high concentration. Evidence shows, however, that even at low concentrations of antibiotics, selection of resistant bacteria is still possible.[69]

The role of farms

The direct use of antimicrobials as growth promoters and animal treatments is not the only way bacteria are exposed to antimicrobials in animal production. Farms also produce runoff and wastewater that sometimes is used for crop irrigation. Additionally, waste from farms is sometimes used as manure, and it has been confirmed that antibacterial resistance genes from manure used as fertilizer do transfer to soil bacteria.[70] A study from the *Lancet* pointed out that "agricultural waste such as animal faces can release antibiotics into the soil, leading to concentrations as high as the ones used to treat infections."[71] These high concentrations probably result in a selective pressure that increases the presence of resistance genes that may be acquired by bacteria in the soil. The presence of these genes and antibiotic-resistance bacteria can result in their direct and indirect transmission to humans.[72]

Therefore, how solid waste and water leaves farms may be an essential factor to consider when designing AMR-containment strategies. Furthermore, another aspect of the use of antimicrobials on farms—their use in plants and crop production—needs further exploration. In 2018, *The Atlantic* reported on the use in flower production of certain fungicides made of the same chemical compounds as those used to treat humans with fungal infections. As a result of this practice, there was an increase in fungal infections resistant to treatment, even though patients had never been exposed to those chemical compounds.[73] These findings have implications not only for human health but possibly for crop production too.

The broad-spectrum antibiotic oxytetracycline is used in apple, peach, pear and nectarine production, and an expansion of its use on citrus plants in Florida has recently been proposed . A submission from *Consumer Reports* to the United States Food and Drug Administration

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[69] Erik Gullberg and others, "Selection of resistant bacteria at very low antibiotic concentrations", *PLoS Pathogens*, vol. 7, No. 7 (2011), pp. 1–9. Available from https://doi.org/10.1371/journal.ppat.1002158.
[70] BIO Intelligence Service (2013).
[71] The Lancet Planetary Health (2018).
[72] Manyi-Loh and others (2018).
[73] Maryn McKenna, "Killer Tulips Hiding in Plain Sight," *The Atlantic* (November 2018). Available from https://www.theatlantic.com/science/archive/2018/11/when-tulips-kill/574489/?utm_source=newsletter&utm_medium=email&utm_campaign=newsletter_axiosscience&stream=science
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Agency (FDA) on the expansion of the use of this antibiotic noted the increased risk due to antimicrobial resistance and the effect of this use on non-targeted species, such as honeybees. The report explains that exposure to antibiotics can disrupt the bees' gut microbiome, with potentially deadly consequences for this important pollinator, as well as the risk of spreading mobile genetic resistance genes.[74]

Discharge from manufacturing facilities and hospitals

Discharge from hospitals and pharmaceutical manufacturing facilities usually contains high levels of antimicrobials and therefore plays a role in the exposure of bacteria to antimicrobial agents. In the case of hospitals, this discharge usually ends up in landfills and wastewater treatment plants, where antimicrobial agents can be found. The hospital's environment, however, could also contribute to the spread of pathogens with multi-drug-resistance and therefore pose a risk not only for patients but also for people living nearby, who could be exposed through water and air.[75]

Pharmaceutical production facilities are also a primary source of contamination because good manufacturing practices are currently defined only for production within a facility and not the fate of wastewater, air and other materials leaving the facility. Environmental regulations that are weak, or lacking entirely, especially for antibiotic residue, allow local pollution at the source. This practice has consequences for selection for resistance. High concentrations of antibiotics in the environment surrounding factories provide a breeding ground for resistance. In its 2016 report, the European Public Health Alliance explains that

> antibiotics released from factories into water bodies combine with runoff from farms and human waste including sewage exposes bacteria to sharing and exchanging genes with resistance but also exposes environmental bacteria to this and could potentially turn them into reservoirs of resistance material.[76]

When antibiotics and their active pharmaceutical ingredients are manufactured, their residue is often discharged into water, where they enter into direct contact with the environment. This has an effect on the surrounding ecosystems and in turn increases resistant bacteria.[77]

There is not enough publicly available information, however, to know the extent of the discharge of antibiotics into the water and therefore the environment.[78] Unless there are procedures in place to ensure that manufacturing practices take care of not only toxic substances but also antibiotic residues, the effect on the environment will be harmful and the selection pressure will become a source of contamination to animals and humans. Current regulatory systems related

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[74] Michael Hansen, *Consumer Reports Comments on EPA's Registration Review Proposed Interim Decisions for Several Pesticides: Oxytetracycline* (2019). Available from https://advocacy.consumerreports.org/wp-content/uploads/2019/05/CR-comments-to-EPA-on-oxytetracycline-PID-final-5.17.19-1.pdf.

[75] Aimee K Murray and others, "Novel Insights into Selection for Antibiotic Resistance in Complex Microbial Communities", *American Society for Microbiology*, vol. 9, No. 4 (2018), pp. 1–12.

[76] European Public Health Alliance and Changing Markets, *Drug Resistance Through the Back Door: How the Pharmaceutical Industry Is Fuelling the Rise of Superbugs Through Pollution in Its Supply Chains* (2016).

[77] Adela Maghear and Maja Milkowska, *The Environmental Impact of Pharmaceutical Manufacturing: How Does Industry Address Its Own Waste?* (Brussels, HCWH Europe, 2018).

[78] Madlen Davies and Sam Loewenberg, "Big Pharma Fails to Disclose Antibiotic Waste Leaked from Factories", *Ecologist* (24 January 2018).

to handling pharmaceutical pollution do not include any regulations related to antimicrobial resistance.[79]

In a study conducted on the diversity of resistomes, it was found that “environments affected by pollution from pharmaceutical manufacturing were not only rich in ARGs [antibiotic resistance genes] but also carried the highest relative abundance of ARGs of all investigated environments.”[80] Extremely high concentrations of antibiotics have been found in waterways near antibiotic manufacturing sites.[81] Currently, there are no appropriate regulations for manufacturing sites regarding the disposal of antibiotic residue. Environmental regulations are designed and implemented nationally, and at the moment no international agreement provides standards other than some voluntary commitments by manufacturers.[82] In most cases, good manufacturing practices have not included the safe disposal of antimicrobial waste,[83] which will need to be addressed, given its effects on the environment and on transmission.

The life cycle of medicinal products and their possible routes of release into the environment is illustrated in Figure 4 below.

Figure 4: The basic life cycle of a medicinal product and possible routes of release into the environment

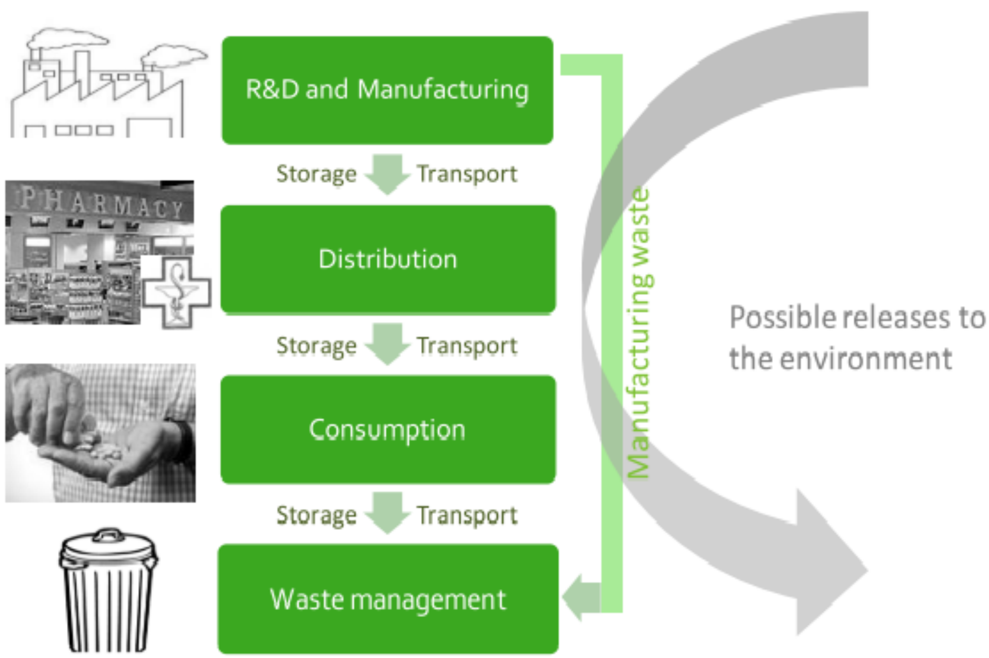

Figure 1: Life-cycle steps

Source: BIO Intelligence Service (2013)

[79] Johan Bengtsson-Palme and D. G. Joakim Larsson, “Concentrations of Antibiotics Predicted to Select for Resistant Bacteria: Proposed Limits for Environmental Regulation,” *Environment International*, No. 86 (2016), pp. 140–49. Available from https://doi.org/10.1016/j.envint.2015.10.015.
[80] Pal and others (2016), p. 15.
[81] ReAct, *Addressing the Antibiotic Resistance Threat: The Role of Water, Sanitation and Hygiene*.
[82] Maghear and Milkowska (2018); Madlen Davies, “Big pharma's pollution is creating deadly superbugs while the world looks the other way,” *The Bureau of Investigative Journalism* (2017). Available from https://www.thebureauinvestigates.com/stories/2017-05-06/big-pharmas-pollution-is-creating-deadly-superbugs-while-the-world-looks-the-other-way.
[83] Davies and Lowenberg, "Big Pharma" (2018).

Waste management

The disposal of antibiotics also plays a role in how antimicrobial substances end up in the environment. This includes how antibiotics are discharged from homes and hospitals. These often end up in landfills, in contact with soil, as well as in water treatment plans.[84] Moreover, studies have observed the emergence of resistance due to the discharge of unused drugs into landfills that often end up filtering into water bodies or accumulate in the environment, generating resistance.[85] Through this process, animals and other organisms can come into contact with bacteria carrying resistance genes and become potential reservoirs of resistance, making this a possible route of transmission.[86] When waste is not appropriately handled, primarily because of the lack of basic sanitation, the environment can become a reservoir and vehicle for the carriage of antimicrobial resistant pathogens that can cause untreatable infections.[87] Still, scientists continue to work on understanding how resistance genes are transmitted between bacteria in the environment and those that may affect humans. Bengtsson-Palme, Kristiansson and Larsson explained that:

> even less is known about how resistance-carrying, non-pathogenic environmental bacteria disperse and interact with human-associated bacteria. In this process, opportunistic pathogens with the environment as their chief habitat may play a very important role in mediating resistance from environmental bacteria to the human microbiome.[88]

Studies have recently been conducted on water-treatment plants and the effect of antibiotic residues in those environments, primarily because treatment plans have not been designed to treat antibiotic residue.[89] Moreover, in many developing countries, there are no water-treatment plants, and wastewater is directly released into water bodies, increasing the possibility of contact, including through the food chain.[90] There are no specific regulations on antibiotic residues in wastewater because no clear consensus exists on what constitutes a safe concentration of antibiotic residue in the environment, a level beyond which resistance is exacerbated.[91]

Bengtsson-Palme and Larsson, however, have studied the "upper boundaries for selective concentrations for all common antibiotics"[92] and concluded that "emission limits for antibiotics must be set individually for each compound and that different antibiotics have very different potential to be selective."[93] This study provides data that could be used as a starting point for regulators in trying to establish limits on antibiotic discharge in the environment.

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[84] UNEP, *Frontiers 2017* (2017).
[85] Durgesh Nandan Jha, "Antibiotics you throw away may be breeding superbugs," *The Times of India* (29 August 2018). Available from https://timesofindia.indiatimes.com/india/antibiotics-you-throw-away-may-be-breeding-superbugs/articleshow/65585501.cms.
[86] Bengtsson-Palme, Kristiansson and Larsson (2018).
[87] Wellcome, U.S. Centers for Disease Control and Prevention and U.K. Science & Innovation Network (2018).
[88] Bengtsson-Palme, Kristiansson and Larsson (2018). p 72
[89] UN Environment, *Frontiers 2017: Emerging Issues Of Environmental Concern* (2017).
[90] Stålsby Lundborg and Tamhankar (2017).
[91] Ibid.
[92] Bengtsson-Palme and Larsson (2016).
[93] Ibid.

WATER AND SANITATION

Clean water and sanitation are essential for health, food security and people's livelihoods. This is why they are one of the UN Sustainable Development Goals (SDGs). Moreover, clean water and sanitation are also critical in preventing infections and water-borne diseases, and it is therefore vital to address antimicrobial resistance, not only because of the role it plays in preventing infections but also because it is one way that resistance genes can be transferred. A recent article on the centrality of sanitation has pointed out that

> sanitation, defined as the collection and treatment of human sewage, is a cornerstone of reducing the global burden of infectious disease, including those caused by antibiotic-resistant pathogens. Adequate water and sanitation practices, therefore, must be central to any AMR action plan.[94]

Even though the critical nature of water and sanitation has been widely recognized, when addressing the AMR data that WHO and the United Nations Children's Fund (UNICEF) collected in 54 countries found that, of the 66,101 health care facilities surveyed, 38 per cent did not have an improved water source, 19 per cent lacked improved sanitation, and 35 per cent lacked water and soap for handwashing[95]. This lack of services compromises the ability to provide essential routine services, such as child delivery, and jeopardizes the ability of health workers to prevent and control infection.[96]

In many countries, antibiotics are incorrectly used to treat diarrhoea. It is estimated that universal access to improved water and sanitation could significantly reduce the use of antibiotics and prevent not only diarrhoea but also other infections, such as typhoid fever.[97] Reducing infection will lower the use of antibiotics. Ensuring access to clean water and sanitation will have a significant effect on lowering infections and preventing illness, particularly for newborns and mothers,[98] and improving sanitation and health would help decrease the burden on AMR.[99]

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[94] Helmut Bürgmann and others, "Water and Sanitation: An Essential Battlefront in the War on Antimicrobial Resistance," *FEMS Microbiology Ecology*, vol. 94, No. 9 (2018), pp. 1–14. Available from https://doi.org/10.1093/femsec/fiy101.

[95] WHO and UNICEF, *Water, sanitation and hygiene in health care facilities: Status in low- and middle-income countries and way forward* (2015). Available from https://apps.who.int/iris/bitstream/handle/10665/154588/9789241508476_eng.pdf;jsessionid=1C9FA467A169F9A9F12D025A5DA6F85D?sequence=1.

[96] Wellcome, U.S. Centers for Disease Control and Prevention and U.K. Science & Innovation Network (2018).

[97] ReAct, *Addressing the Antibiotic Resistance Threat: The Role of Water, Sanitation and Hygiene* (2016).

[98] Ibid.

[99] Rene S. Hendriksen and others, "Global Monitoring of Antimicrobial Resistance Based on Metagenomics Analyses of Urban Sewage," *Nature Communications*, vol. 10 (2019). Available from https://doi.org/10.1038/s41467-019-08853-3.

CHANGES IN THE ENVIRONMENT AND THE HUMAN MICROBIOTA

Antimicrobials do not affect only the outside ecosystem. They also have an effect on the microbiome. In recent years, there have been increased efforts made to understand the microbiome and how antimicrobials produce changes in it. A recent report from the London School of Hygiene and Tropical Medicine explains that

> the human gut contains a diverse range of "good bacteria" called the microbiome, which ensures healthy digestion. Unfortunately, widespread antibiotic use and changing diets have wreaked havoc on the delicate ecosystem of human guts, depleting good bacteria and leaving many people with digestion problems and reduced immunity to infection.[100]

Because of this imbalance, several studies have looked at the importance of a diverse microbiota for human health. The bacteria living in our bodies experience many changes, at birth as well as due to the diet we consume.[101] Antibiotics also clearly affect the diversity of and produce changes in the composition of the microbiome, and some studies have been conducted on the long-term effects that these changes can have on the immune system and metabolic functions of the body.[102] This is another reason antibiotics should be used prudently.[103,104] It is also important to note that the human microbiome comprises bacteria and microorganisms in the body not only in the gastrointestinal tract but also in the skin, respiratory tract and genital tract, where bacteria perform many functions critical to life.[105,106] More research is needed on the dynamics within the microbiome and how resistance is transferred.[107] For example, people can acquire antibiotic-resistant bacteria from the environment, which then become part of the microbiome in the gut without necessarily affecting their health.[108] Researchers have found that the human microbiome in the gut contains a higher abundance of resistance genes than is found in the outside environment, except for in wastewater and pharmaceutically polluted environments that also contain high concentrations of resistance genes.[109]

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[100] David Lewis, "Gene Editing, Predatory Bacteria and Zebrafish: Getting Creative to Control Infection," *London School of Hygiene & Tropical Medicine* (2019). Available from https://www.lshtm.ac.uk/research/research-action/features/gene-editing-predatory-bacteria-and-zebrafish?utm_source=Twitter-press&utm_medium=Social&utm_campaign=Gene%2520editing,%2520predatory%2520bacteria%2520and%2520zebrafish:%2520Getting%2520creative%25 (accessed 15 March 2019).
[101] "Microbiome: Your body houses 10x more bacteria than cells," *Discover* (2010). Available from http://discovermagazine.com/galleries/zen-photo/m/microbiome.
[102] Peter Søgaard Jørgensen and others, "Antibiotic and pesticide susceptibility and the anthropocene operating space," *Nature Sustainability*, vol. 1, No. 11 (2018), pp. 632–41. Available from https://doi.org/10.1038/s41893-018-0164-3.
[103] Smalla and others (2018).
[104] Amy Langdon, Nathan Crook and Gautam Dantas, "The Effects of Antibiotics on the Microbiome throughout Development and Alternative Approaches for Therapeutic Modulation," *Genome Medicine*, vol. 8, No. 1 (2016). Available from https://doi.org/10.1186/s13073-016-0294-z.
[105] Ileseung Cho and Martin J Blaser, "The Human Microbiome: At the Interface of Health and Disease," *Nat Rev Genet*, vol. 13, No. 4 (2012), pp. 260–70. Available from https://doi.org/10.1038/nrg3182.
[106] ReAct, "UNDERSTAND – BACTERIA Essential for Human Life" (2016). Available from https://www.reactgroup.org/toolbox/understand/bacteria/bacteria-are-essential-for-human-life/ (accessed 13 March 2019).
[107] Wall and others (2016).
[108] van der Heijden and others (2019).
[109] Pal and others (2016).

With the use of antimicrobials in medicine, the human microbiome has been exposed to many antimicrobial agents over the decades, which has led to changes in the microbiome. After extensive, continuous exposure to antibiotics, the modifications to the microbiome may be permanent, and a person's microbiome may not be able to recover its diversity of organisms.[110] This can affect our health. Furthermore, babies' exposure to antibiotics can modify their developing microbiome and therefore affect their digestive function, resulting in issues such as malnutrition or obesity.[111] Early exposure to antibiotics may be a contributing factor in the development of obesity as adults because of the vulnerability of the microbiome to selection pressure and permanent changes.[112] More research in this area is necessary to build a more robust understanding of the effects that antibiotic use has in the human microbiome and its link with aspects of our health and the environment. A recent article published by *Nature* examining the microbiota of newborns born vaginally versus by Caesarean section found that

> babies delivered by caesarean section were deprived of maternally transmitted commensal bacteria, but had a substantially higher relative abundance of opportunistic pathogens that are commonly associated with the hospital environment.[113]

This demonstrates the importance of the environment in establishing the gut microbiota in babies and the hospital environment as a place of possible colonization with antimicrobial resistance.

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[110] Cho and Blaser (2012).
[111] Langdon, Crook and Dantas (2016).
[112] Cho and Blaser (2012); Langdon, Crook and Dantas (2016).
[113] Yan Shao and others, "Stunted microbiota and opportunistic pathogen colonization in Caesarean-section birth," *Nature*, No. 574 (September 2019). Available from https://doi.org/10.1038/s41586-019-1560-1.

CHALLENGES FOR DEVELOPING COUNTRIES AND POLICY RECOMMENDATIONS

This paper has examined the effects of the use of antimicrobials in animals, including in aquaculture, on the soil and water environments, including the exacerbation of antimicrobial resistant bacteria due to selection pressure. The bacteria and resistance genes are then hosted in the environment and can potentially be transferred to animals and humans. This paper has also reviewed the role played by waste management, pharmaceutical manufacturing practices and water and sanitation in understanding and tackling antimicrobial resistance. The effect of antimicrobial use is not limited to the environmental ecosystems in water and soil but extends to the diversity and functions of our microbiome. It is, therefore, important that the efforts to tackle antimicrobial resistance include building a better understanding of the role of the environment. To this end, the "One Health" approach continues to be strengthened. As this paper has argued, the environment is closely linked with the human and the animal dimension of AMR. Resistance genes are exchanged through multiple pathways within the environment.[114]

Ensuring that the environmental factor is an integral part of the AMR containment response requires many different measures to be taken. These include support for developing countries financially and technically in building infrastructure for clean water and sanitation, increased investment in better animal husbandry practices, a transition to more sustainable agricultural practices not reliant on the routine use of antibiotics and the design of appropriate environmental standards. Additionally, it will be necessary to ensure access to technologies that can reduce pharmaceutical manufacturing pollution.

The environmental dimension of antimicrobial resistance brings to the forefront some of the development challenges faced by developing countries and adds to the many competing priorities for action. There are many measures developing countries must investigate in order to adequately address AMR.

Challenges include:

- Phasing out antibiotics as growth promoters and eliminating the use of medically important antibiotics in agriculture and aquaculture while ensuring productivity and retaining livelihoods.
- Investing in infrastructure for clean water, sewage and sanitation.
- Reducing and eventually eliminating the release of antimicrobials into the environment through improvements in waste management and better regulations for hospitals and drug-manufacturing facilities.
- Increasing understanding, research and knowledge of how the environment facilitates the emergence, persistence and transmission of antimicrobial resistance and finding ways to mitigate them.
- Developing the laboratory capacity, surveillance and training of veterinary and healthcare staff or other professionals in the optimal use of antimicrobials.
- Facilitating access to affordable vaccinations to prevent infections in animals and improving biosecurity, appropriate nutrition and the use of alternative treatments for animals and plants.
- Implementing infection, prevention and control measures for humans and animals to reduce infections.

[114] Smalla and others (2018).

- Ensuring prudent antibiotic use for humans and animals.

Policy recommendations:

- Integrating the environmental dimension into National Action Plans on antimicrobial resistance.
- Supporting the WHO, FAO, the World Organisation for Animal Health (OIE) and UNEP in undertaking research on AMR and One Health and providing guidelines and standards to limit the exposure to and management of antibiotic residues.
- Providing financial and technical support for small-scale farmers to transition into more sustainable production practices without the routine use of antibiotics.
- Supporting, through international finance, developing countries in building infrastructure for clean water, sanitation and the use of infection, prevention and control measures.
- Elaborating and implementing environmental regulations and standards to reduce or eliminate pharmaceutical pollution.
- Incorporating antimicrobial resistance as part of the plan to achieve the Sustainable Development Goals.
- Researching developing affordable technologies that can help eliminate antibiotic residue and improve monitoring, particularly in the developing-country context.
- Researching and developing alternatives to antibiotics.

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