

ANTIBIOTIC RESISTANCE AS AN EMERGING ENVIRONMENTAL HEALTH PROBLEM: SOURCES, PATHWAYS, HEALTH IMPACTS AND HYGIENE-BASED PREVENTION WITHIN A ONE HEALTH FRAMEWORK

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Abstract

Background: Antimicrobial resistance (AMR) is one of the leading global threats to public health. Although it has long been regarded as a problem of hospitals and clinical prescribing, a growing body of evidence shows that the natural environment acts as a reservoir, a transmission route and a breeding ground for antibiotic-resistant bacteria (ARB) and antibiotic resistance genes (ARGs).

Aim: This review explains why antibiotic resistance qualifies as an emerging environmental health problem, describes its main environmental sources and pathways, summarises its health and economic burden, and outlines hygiene-based and policy measures for its control.

Main findings: Bacterial AMR was directly responsible for an estimated 1.14 million deaths in 2021, and attributable deaths are forecast to reach 1.91 million per year by 2050. In 2023, about one in six laboratory-confirmed bacterial infections worldwide was resistant to antibiotics. Major environmental drivers include untreated or partially treated sewage, hospital effluent, pharmaceutical manufacturing waste, antibiotic use in livestock and aquaculture, and co-selection by heavy metals and biocides. Humans are exposed through drinking water, food, recreational water and direct contact.

Conclusion: Safe water, sanitation and hygiene (WASH), infection prevention, improved wastewater treatment, control of manufacturing pollution, prudent antibiotic use and environmental surveillance are essential, mutually reinforcing measures. A One Health approach that links human, animal and environmental health is required to slow the spread of resistance.

Keywords: antimicrobial resistance; antibiotic resistance genes; environmental health; wastewater; One Health; hygiene; sanitation; pharmaceutical pollution

Key Messages

- Antibiotic resistance genes are now recognised as environmental contaminants, not only clinical concerns.
- Sewage, hospital and factory effluents, and farm run-off carry antibiotics and resistant bacteria into water and soil.
- Poor sanitation and unsafe water help resistant bacteria spread from person to person, which makes hygiene a frontline defence.
- Controlling resistance requires a One Health approach that joins human, animal and environmental action.

1. Introduction

When Alexander Fleming received the Nobel Prize in 1945 for the discovery of penicillin, he warned that careless use of the drug could allow microbes to become resistant to it [1]. Eight decades later, that warning has become one of the defining health challenges of our time. Antimicrobial resistance (AMR), the ability of microorganisms to survive medicines that once killed them, is ranked by the World Health Organization (WHO) among the top global public health and development threats [2]. In 2019, bacterial AMR was directly responsible for an estimated 1.27 million deaths and was associated with 4.95 million deaths, a toll greater than that of HIV/AIDS or malaria [3]. The most recent WHO surveillance report found that one in six laboratory-confirmed bacterial infections worldwide in 2023 was resistant to antibiotic treatment, and that resistance increased in more than 40% of the pathogen-antibiotic combinations monitored between 2018 and 2023 [4].

For most of the antibiotic era, resistance was treated as a clinical problem confined to hospitals and prescribing practice. Over the past two decades, however, research has shown that the environment plays a central role in how resistance emerges and spreads. In 2006, Pruden and colleagues proposed that antibiotic resistance genes (ARGs) should be regarded as emerging environmental contaminants [5], and in 2023 the United Nations Environment Programme (UNEP) called for stronger environmental action as part of the One Health response to AMR [6]. Resistance itself is not new: genes conferring resistance to modern antibiotics have been found in 30,000-year-old permafrost [7]. What is new is the scale at which human activity is releasing antibiotics, resistant bacteria and resistance genes into water, soil and air.

This review has four objectives: (i) to explain why antibiotic resistance qualifies as an emerging environmental health problem; (ii) to describe its major environmental

sources and pathways of human exposure; (iii) to summarise its health and economic burden; and (iv) to highlight hygiene-based, technical and policy measures for its prevention and control.

2. Methods

This article is a narrative review. Literature was drawn from peer-reviewed articles indexed in PubMed, including systematic analyses and reviews, together with reports and technical guidance from official public health and environmental bodies: WHO, the US Centers for Disease Control and Prevention (CDC), UNEP, the United Nations General Assembly and the World Bank. Search terms included combinations of “antibiotic resistance”, “antimicrobial resistance”, “environment”, “wastewater”, “antibiotic resistance genes”, “pharmaceutical pollution”, “One Health” and “water, sanitation and hygiene”. Priority was given to landmark studies, recent global burden estimates and current international policy documents. As this is a narrative rather than a systematic review, no formal quality scoring of individual studies was performed.

3. Understanding Antibiotic Resistance

3.1 How resistance arises and spreads

Bacteria become resistant in two main ways. First, random mutations in their own chromosomes may alter the target of an antibiotic or the way the drug enters or leaves the cell. Second, and more importantly for rapid spread, bacteria can acquire ready-made resistance genes from other bacteria through horizontal gene transfer: conjugation (transfer of plasmids between cells), transformation (uptake of free DNA from the surroundings) and transduction (transfer by bacteriophages). Resistance mechanisms include enzymes that destroy the drug (such as extended-spectrum β -lactamases and carbapenemases), efflux pumps that expel it, modification of the drug's target and reduced permeability of the cell wall. Because many resistance genes sit on mobile genetic elements such as plasmids, transposons and integrons, they can move from harmless environmental bacteria into human pathogens [8].

3.2 Why the environment matters

The environment contributes to resistance in three ways. It is a *reservoir*, holding an enormous diversity of bacteria and resistance genes. It is a *conduit*, carrying resistant organisms between people, animals and places through water, soil, food and air. It is also a *selection site*: even very low concentrations of antibiotics can favour resistant

bacteria. Laboratory work by Gullberg and colleagues showed that resistant strains can be selected at antibiotic concentrations far below those needed to inhibit bacterial growth [9]. On this basis, Bengtsson-Palme and Larsson proposed concentration limits for individual antibiotics in the environment, designed to stay below the level at which resistance is selected [10].

3.3 Pathogens of greatest concern

The 2024 WHO Bacterial Priority Pathogens List places carbapenem-resistant *Acinetobacter baumannii*, third-generation cephalosporin-resistant and carbapenem-resistant Enterobacterales, and rifampicin-resistant *Mycobacterium tuberculosis* in its critical priority group [11]. Enterobacterales such as *Escherichia coli* and *Klebsiella pneumoniae* normally live in the human and animal gut and are shed in large numbers in faeces. This creates a direct link between antibiotic resistance and sanitation, which is why the problem falls squarely within the field of hygiene.

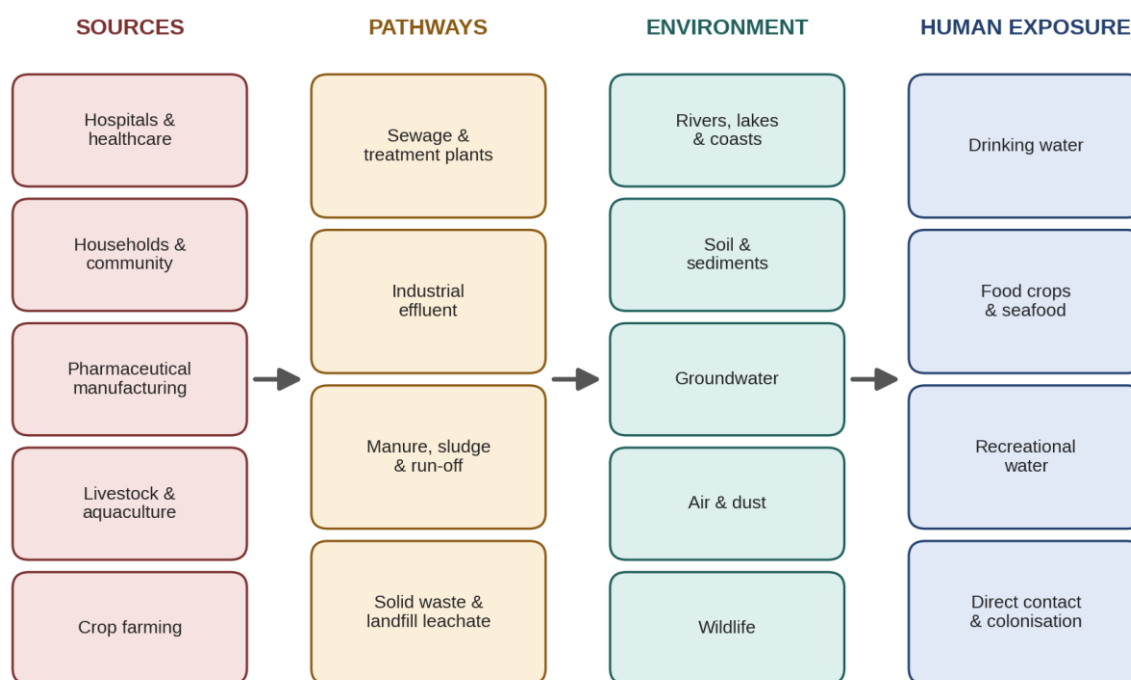
4. Why Antibiotic Resistance Is an Emerging Environmental Health Problem

An emerging environmental health problem is one that has only recently been recognised, is increasing in scale, poses a credible risk to human health and is not yet adequately covered by monitoring or regulation. Antibiotic resistance meets each of these criteria. ARGs and resistant bacteria are not included in most national drinking-water or effluent standards, yet they are now detected in rivers, sediments, soils and treated wastewater around the world [8].

Several landmark findings illustrate this. In 2011, bacteria carrying the NDM-1 gene, which confers resistance to carbapenems, were detected in public tap water and in seepage water from streets and pools in New Delhi [12]. In 2016, the plasmid-borne *mcr-1* gene, which confers resistance to colistin (a last-resort antibiotic), was reported in pigs, retail meat and patients in China and was subsequently detected in many other countries [13]. A global study of urban sewage from 79 sewage samples from 74 cities in 60 countries found that the abundance of resistance genes varied widely and was associated with socioeconomic, health and environmental factors, including sanitation [14]. Similarly, an analysis of data from over 100 countries found that poor infrastructure and governance were more strongly associated with resistance levels than antibiotic consumption alone, suggesting that the *spread* of resistant bacteria through inadequate sanitation is as important as antibiotic use itself [15].

5. Environmental Sources and Pathways

Figure 1 summarises how antibiotics, resistant bacteria and resistance genes move from their sources into the environment and back to people. Table 1 summarises the main sources and corresponding control measures.



Antibiotic residues, resistant bacteria and resistance genes move through every stage; horizontal gene transfer occurs within each compartment.

Figure 1. Simplified One Health model of the environmental dimension of antibiotic resistance, showing sources, environmental pathways and routes of human exposure. Original figure prepared by the authors based on [6,8].

5.1 Domestic sewage and wastewater treatment plants

A substantial proportion of many antibiotics taken by people passes through the body unchanged or as active metabolites and enters the sewer [16]. Wastewater treatment plants (WWTPs) therefore receive a continuous mixture of antibiotic residues, resistant bacteria from millions of human guts and free resistance genes. Conventional treatment reduces bacterial numbers but does not eliminate resistant organisms or genes, and the dense, nutrient-rich microbial communities in treatment tanks provide ideal conditions for gene exchange; for this reason WWTPs are described as hotspots of resistance [17]. A study of WWTPs in seven European countries found that the resistance genes in their

effluents mirrored the pattern of clinical resistance in each country [18], showing that sewage reflects the resistance carried by the population it serves. Where sewage is discharged without any treatment, as still occurs in many low- and middle-income countries, the load reaching rivers and coasts is far higher [6].

5.2 Hospital effluent

Hospitals use large quantities of antibiotics, including last-resort agents, and treat patients colonised or infected with multidrug-resistant bacteria. Their wastewater is often discharged into the municipal sewer with little or no pre-treatment, adding concentrated antibiotic residues and highly resistant organisms to the general sewage stream [16].

5.3 Pharmaceutical manufacturing

Some of the highest antibiotic concentrations ever measured in the environment have come from factory effluents. Treated effluent from a plant near Hyderabad, India, which served around 90 bulk drug manufacturers, contained ciprofloxacin at concentrations exceeding those found in the blood of patients receiving the drug [19]. A global survey of pharmaceutical pollution in 258 rivers across 104 countries found active pharmaceutical ingredients at potentially harmful concentrations at about a quarter of sampling sites, with the greatest pollution in low- and middle-income countries [20]. In 2024, WHO issued its first guidance on wastewater and solid waste management for antibiotic manufacturing, setting targets intended to keep antibiotic concentrations in receiving waters below levels that select for resistance [21].

5.4 Agriculture and aquaculture

A large share of the world's antimicrobials is used in food-producing animals, often for growth promotion or routine disease prevention rather than treatment. Van Boeckel and colleagues estimated that antimicrobial use in food animals would rise by about two-thirds between 2010 and 2030, driven by growing demand for meat in middle-income countries [22]. Animal manure carrying residues and resistant bacteria is spread on fields as fertiliser, from where it can wash into rivers and groundwater or contaminate crops. In aquaculture, antibiotics are frequently added directly to water. The emergence of *mcr-1* in livestock is a clear example of resistance arising in agriculture and reaching humans [13].

5.5 Co-selection by heavy metals and biocides

Genes for resistance to heavy metals (such as copper, zinc and mercury) and to disinfectants are often located on the same mobile genetic elements as antibiotic resistance genes. Pollution by these substances can therefore maintain and select for antibiotic resistance even where no antibiotic is present, a process known as co-selection [23]. This links antibiotic resistance to wider problems of industrial and agricultural pollution.

5.6 Solid waste and the wider planetary context

Unused medicines discarded in household waste or flushed down toilets, and leachate from landfills, are further sources of contamination. UNEP places AMR within the “triple planetary crisis” of climate change, biodiversity loss and pollution, noting that environmental degradation and resistance are closely interconnected [6].

Table 1. Major environmental sources of antibiotic resistance and corresponding control measures. ARB, antibiotic-resistant bacteria; ARGs, antibiotic resistance genes; IPC, infection prevention and control; WWTP, wastewater treatment plant.

Source	What enters the environment	Key evidence	Hygiene and control measures
Domestic sewage	Antibiotic residues, gut-derived ARB, ARGs	WWTPs are resistance hotspots [17]	Universal safe sanitation; upgraded and advanced treatment; safe sludge handling
Hospitals	Last-resort antibiotics, multidrug-resistant bacteria	Concentrated residues in effluent [16]	On-site effluent pre-treatment; IPC; safe disposal of pharmaceutical waste
Pharmaceutical industry	Very high antibiotic concentrations	Ciprofloxacin above therapeutic levels [19]	WHO manufacturing guidance; discharge limits; responsible procurement [21]

Source	What enters the environment	Key evidence	Hygiene and control measures
Livestock and aquaculture	Residues, ARB and ARGs via manure and water	Rising animal antimicrobial use [22]	End growth promoters; vaccination; farm biosecurity; manure treatment
Metals and biocides	Co-selecting agents	Shared mobile genetic elements [23]	Industrial pollution control; prudent biocide use

6. Routes of Human Exposure

People come into contact with environmental resistance through several routes. **Drinking water** is a key route wherever water treatment and distribution are inadequate, as illustrated by the detection of NDM-1-carrying bacteria in tap water [12]. **Food** is another: crops irrigated with wastewater or fertilised with manure, as well as meat and seafood, can carry resistant bacteria. **Recreational water** also matters. In the United Kingdom, a study of surfers and other coastal water users found that regular surfers were several times more likely than non-surfers to have their guts colonised by *E. coli* resistant to third-generation cephalosporins [24]. Finally, **occupational exposure** affects farmers, abattoir staff, sanitation workers and wastewater treatment personnel. Colonisation is usually silent, but colonised people can later develop resistant infections or pass resistant bacteria to others.

7. Health and Economic Burden

The Global Research on Antimicrobial Resistance (GRAM) project estimated that, in 2021, 1.14 million deaths were directly attributable to bacterial AMR and 4.71 million were associated with it. Without further action, attributable deaths are forecast to rise to 1.91 million per year by 2050, with a cumulative 39 million deaths attributable to AMR between 2025 and 2050. South Asia is expected to bear the largest share, with 11.8 million attributable deaths over that period [25]. WHO surveillance data show marked regional differences, with resistance highest in the South-East Asia and Eastern Mediterranean Regions (Figure 2) [4]. Even in high-income countries the burden is

substantial: the CDC estimated that more than 2.8 million antibiotic-resistant infections and over 35,000 deaths occur each year in the United States [26].

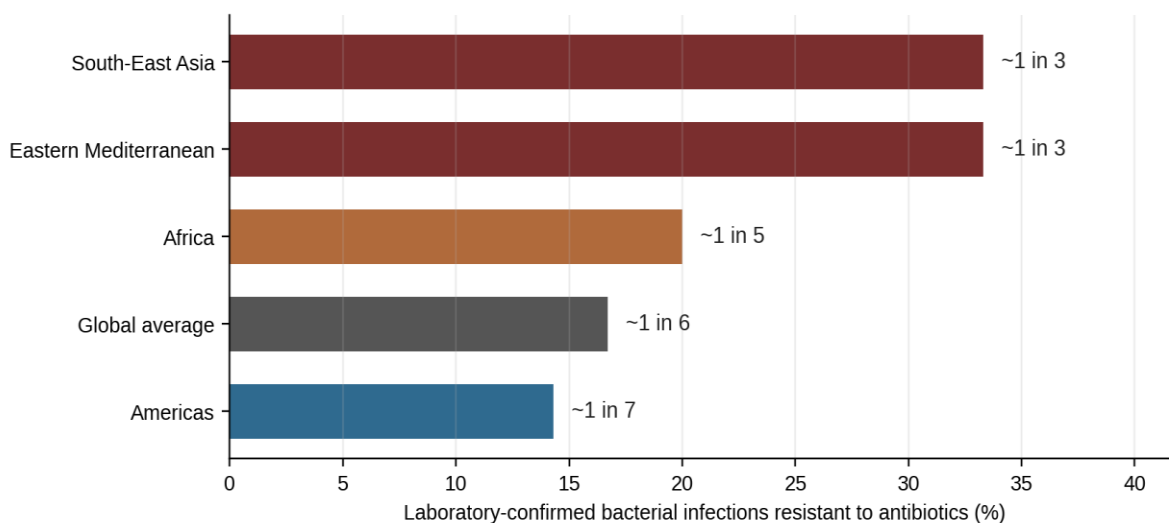


Figure 2. Approximate proportion of laboratory-confirmed bacterial infections resistant to antibiotics in 2023, by WHO region (regions with reported summary estimates shown). Figure prepared by the authors from data in [4].

Resistance also threatens the foundations of modern medicine. Surgery, caesarean sections, cancer chemotherapy, organ transplantation and the care of premature infants all depend on effective antibiotics to prevent and treat infection. Resistant infections lead to longer hospital stays, the use of more expensive and more toxic second-line drugs, and higher mortality. The World Bank estimated that, in a high-impact scenario, AMR could reduce global economic output by 3.8% by 2050 and push up to 28 million additional people into extreme poverty [27]. The earlier Review on Antimicrobial Resistance had projected that AMR could cause 10 million deaths a year by 2050 [28]; although subsequent estimates have refined this figure, it was instrumental in placing AMR on the global political agenda.

8. Prevention and Control: The Central Role of Hygiene

Because resistant bacteria spread through the same routes as other faecal and environmental pathogens, many of the most effective defences against AMR are classic hygiene and public health measures. Every infection prevented is an antibiotic course that is never needed.

8.1 Water, sanitation and hygiene (WASH)

Universal access to safe drinking water, safely managed sanitation and handwashing with soap reduces the transmission of resistant gut bacteria within communities and lowers the overall burden of infection, and therefore the demand for antibiotics. The association between poor sanitation infrastructure and high resistance levels makes WASH investment one of the most powerful, and most neglected, AMR interventions [6,15].

8.2 Infection prevention and control in healthcare

In hospitals and clinics, hand hygiene, environmental cleaning and disinfection, screening and isolation of patients carrying multidrug-resistant organisms, and safe management of medical and pharmaceutical waste limit both patient-to-patient spread and release into the environment. Pre-treatment of hospital effluent before it reaches municipal sewers is an additional safeguard [16].

8.3 Improved wastewater treatment

Advanced treatment technologies such as ozonation, ultraviolet disinfection, membrane filtration and activated carbon can further reduce resistant bacteria and genes in treated effluent, while careful handling of sewage sludge prevents contamination of agricultural land [17,29]. Where centralised treatment is not yet affordable, expanding basic sanitation coverage remains the priority.

8.4 Controlling pollution from manufacturing

Applying the WHO manufacturing guidance, introducing enforceable discharge limits based on resistance-selection thresholds, and rewarding cleaner production in public procurement can sharply reduce one of the most concentrated sources of environmental antibiotics [10,21].

8.5 Antibiotic stewardship in humans and animals

Prudent use reduces the quantity of antibiotics excreted into the environment. WHO's AWARe classification groups antibiotics into Access, Watch and Reserve categories to guide prescribing [30], and the 2024 UN political declaration set the target that at least 70% of antibiotics used in human health should come from the Access group [31]. In animal production, ending growth promotion, improving vaccination and farm biosecurity, and restricting antibiotics that are critically important for human medicine are central measures.

8.6 Environmental surveillance

Monitoring of sewage offers a low-cost, non-invasive way to track resistance across entire populations, including healthy people who are never tested in clinics [14]. Integrating environmental data with human and animal surveillance allows earlier detection of emerging resistance and better targeting of interventions.

8.7 Public awareness and education

Individuals can contribute by:

- not demanding or using antibiotics for viral illnesses such as colds and influenza;
- taking antibiotics only when prescribed by a qualified health professional and following the prescriber's instructions;
- never sharing antibiotics or using leftover medicines;
- returning unused medicines to pharmacies or take-back schemes instead of flushing them or throwing them away;
- practising good hand hygiene and safe food preparation.

9. Global and National Policy Responses

The WHO Global Action Plan on Antimicrobial Resistance, adopted in 2015, set five strategic objectives: improving awareness and understanding, strengthening surveillance and research, reducing infection through sanitation, hygiene and infection prevention, optimising antimicrobial use, and increasing sustainable investment [32]. Its implementation is coordinated through the Quadripartite partnership of the Food and Agriculture Organization (FAO), UNEP, WHO and the World Organisation for Animal Health (WOAH). In September 2024, world leaders at the UN General Assembly adopted a political declaration committing to reduce the estimated 4.95 million deaths associated with bacterial AMR by 10% by 2030, to ensure that at least 60% of countries have funded national action plans, to meaningfully reduce antimicrobial use in agrifood systems, and to prevent and address the discharge of antimicrobials into the environment [31]. Nevertheless, the environmental dimension remains one of the least developed components of many national action plans [6].

10. Challenges and Research Gaps

Important gaps remain. There are as yet no widely adopted regulatory limits for resistance genes in drinking water or effluents, and methods for measuring them are

not fully standardised. The dose-response relationship between environmental exposure and human infection is still poorly understood [8]. Surveillance capacity is weakest in the regions with the highest burden, and many countries still do not report data to global systems [4]. The pipeline of new antibiotics, particularly against Gram-negative bacteria, remains thin [11]. Addressing these gaps will require sustained funding, interdisciplinary research and closer cooperation between the health, environmental, agricultural and industrial sectors.

11. Implications for Hygiene and Public Health Practice

For students and professionals in hygiene and public health, antibiotic resistance reinforces a simple principle: preventing infection is better than treating it. Health workers can lead by example in hand hygiene and rational prescribing, educate patients and communities, advocate for safe water and sanitation, support environmental monitoring, and promote the One Health perspective in their institutions. Annual campaigns such as World AMR Awareness Week offer opportunities for student-led outreach in schools, communities and healthcare facilities.

12. Conclusion

Antibiotic resistance is no longer only a hospital problem. Antibiotics, resistant bacteria and resistance genes are released into the environment from homes, hospitals, factories and farms, and they return to people through water, food and everyday contact. This makes antibiotic resistance a genuine and growing environmental health problem. The tools to slow it are largely known: safe water and sanitation, good hygiene, infection prevention, cleaner manufacturing, better wastewater treatment, prudent antibiotic use and integrated surveillance. Applying them together, through a One Health approach, is essential to preserve effective antibiotics for future generations.

Declarations

Author contributions: All authors contributed to the conception of the review, literature search, drafting and critical revision of the manuscript. All authors read and approved the final version and agree to be accountable for its content.

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References

1. Fleming A. Penicillin. Nobel Lecture; 1945 Dec 11; Stockholm. Available from: <https://www.nobelprize.org/prizes/medicine/1945/fleming/lecture/> [cited 2026 Oct 7]
2. World Health Organization. Antimicrobial resistance [Fact sheet]. Geneva: WHO; 2023 Nov 21. Available from: <https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance> [cited 2026 Oct 7]
3. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet*. 2022;399(10325):629-55.
4. World Health Organization. Global antibiotic resistance surveillance report 2025: WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS). Geneva: WHO; 2025.
5. Pruden A, Pei R, Storteboom H, Carlson KH. Antibiotic resistance genes as emerging contaminants: studies in northern Colorado. *Environ Sci Technol*. 2006;40(23):7445-50.
6. United Nations Environment Programme. Bracing for superbugs: strengthening environmental action in the One Health response to antimicrobial resistance. Geneva: UNEP; 2023.
7. D'Costa VM, King CE, Kalan L, Morar M, Sung WW, Schwarz C, et al. Antibiotic resistance is ancient. *Nature*. 2011;477(7365):457-61.
8. Larsson DGJ, Flach CF. Antibiotic resistance in the environment. *Nat Rev Microbiol*. 2022;20(5):257-69.

9. Gullberg E, Cao S, Berg OG, Ilback C, Sandegren L, Hughes D, et al. Selection of resistant bacteria at very low antibiotic concentrations. *PLoS Pathog.* 2011;7(7):e1002158.
10. Bengtsson-Palme J, Larsson DGJ. Concentrations of antibiotics predicted to select for resistant bacteria: proposed limits for environmental regulation. *Environ Int.* 2016;86:140-9.
11. World Health Organization. WHO bacterial priority pathogens list, 2024: bacterial pathogens of public health importance to guide research, development and strategies to prevent and control antimicrobial resistance. Geneva: WHO; 2024.
12. Walsh TR, Weeks J, Livermore DM, Toleman MA. Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study. *Lancet Infect Dis.* 2011;11(5):355-62.
13. Liu YY, Wang Y, Walsh TR, Yi LX, Zhang R, Spencer J, et al. Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. *Lancet Infect Dis.* 2016;16(2):161-8.
14. Hendriksen RS, Munk P, Njage P, van Bunnik B, McNally L, Lukjancenko O, et al. Global monitoring of antimicrobial resistance based on metagenomics analyses of urban sewage. *Nat Commun.* 2019;10(1):1124.
15. Collignon P, Beggs JJ, Walsh TR, Gandra S, Laxminarayan R. Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis. *Lancet Planet Health.* 2018;2(9):e398-405.
16. Kraemer SA, Ramachandran A, Perron GG. Antibiotic pollution in the environment: from microbial ecology to public policy. *Microorganisms.* 2019;7(6):180.
17. Rizzo L, Manaia C, Merlin C, Schwartz T, Dagot C, Ploy MC, et al. Urban wastewater treatment plants as hotspots for antibiotic resistant bacteria and genes spread into the environment: a review. *Sci Total Environ.* 2013;447:345-60.
18. Parnanen KMM, Narciso-da-Rocha C, Kneis D, Berendonk TU, Cacace D, Do TT, et al. Antibiotic resistance in European wastewater treatment plants mirrors the pattern of clinical antibiotic resistance prevalence. *Sci Adv.* 2019;5(3):eaau9124.
19. Larsson DGJ, de Pedro C, Paxeus N. Effluent from drug manufactures contains extremely high levels of pharmaceuticals. *J Hazard Mater.* 2007;148(3):751-5.

20. Wilkinson JL, Boxall ABA, Kolpin DW, Leung KMY, Lai RWS, Galban-Malagon C, et al. Pharmaceutical pollution of the world's rivers. *Proc Natl Acad Sci U S A*. 2022;119(8):e2113947119.
21. World Health Organization. Guidance on wastewater and solid waste management for manufacturing of antibiotics. Geneva: WHO; 2024.
22. Van Boeckel TP, Brower C, Gilbert M, Grenfell BT, Levin SA, Robinson TP, et al. Global trends in antimicrobial use in food animals. *Proc Natl Acad Sci U S A*. 2015;112(18):5649-54.
23. Baker-Austin C, Wright MS, Stepanauskas R, McArthur JV. Co-selection of antibiotic and metal resistance. *Trends Microbiol*. 2006;14(4):176-82.
24. Leonard AFC, Zhang L, Balfour AJ, Garside R, Hawkey PM, Murray AK, et al. Exposure to and colonisation by antibiotic-resistant *E. coli* in UK coastal water users: environmental surveillance, exposure assessment, and epidemiological study (Beach Bum Survey). *Environ Int*. 2018;114:326-33.
25. GBD 2021 Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance 1990-2021: a systematic analysis with forecasts to 2050. *Lancet*. 2024;404(10459):1199-226.
26. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2019. Atlanta (GA): US Department of Health and Human Services, CDC; 2019.
27. World Bank. Drug-resistant infections: a threat to our economic future. Washington (DC): World Bank; 2017.
28. O'Neill J. Tackling drug-resistant infections globally: final report and recommendations. London: Review on Antimicrobial Resistance; 2016.
29. Berendonk TU, Manaia CM, Merlin C, Fatta-Kassinos D, Cytryn E, Walsh F, et al. Tackling antibiotic resistance: the environmental framework. *Nat Rev Microbiol*. 2015;13(5):310-7.
30. World Health Organization. The WHO AWaRe (Access, Watch, Reserve) antibiotic book. Geneva: WHO; 2022.
31. United Nations General Assembly. Political declaration of the high-level meeting on antimicrobial resistance. New York: United Nations; 2024.
32. World Health Organization. Global action plan on antimicrobial resistance. Geneva: WHO; 2015.