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Quantifying the One Health Drivers of Antibacterial Resistance: Interactions Among Human, Animal, and Environmental Reservoirs, Transmission Pathways, and Global Knowledge Gaps

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Abstract

Antibacterial resistance (ABR) is no longer a clinical issue in a single sector, but a truly multisectoral phenomenon, influenced by use and transmission of antibiotics in human, animal, and environmental sectors. The Global Research on Antimicrobial Resistance (GRAM) Project estimated that, in 2021, 1.14 million deaths were directly caused by bacterial antimicrobial resistance (AMR), with 4.71 million deaths involving AMR, which is a contributing factor. GRAM Project estimates these figures could increase to 1.91 million and 8.22 million respectively by 2050 if current trends continue. This review reviews recent evidence (2020-2026) about the One Health drivers of ABR, quantifies the relative contribution of human, animal and environmental compartments by compartmental modelling and regional meta-analytical data, and describes the mobile colistin resistance (mcr) gene family as a case study of cross-sectoral spread. It also examines an important yet underappreciated aspect of the domain: the geographic skew in research investments in AMR, with Southeast Asia as a case study of a high-burden region that is chronically under-modelled. Lastly, the review assesses the state of global governance, based on the recently adopted WHO Global Action Plan on Antimicrobial Resistance 2026–2036, and a new, first-of-its-kind governance assessment across 193 countries, revealing that policy design has outstripped implementation, especially in the animal and environmental sectors. We suggest that the need to close the gap in One Health research and governance is now the limiting factor in the global AMR response, not the development of antibiotics.

Keywords: Antimicrobial resistance; One Health; Human–animal–environment interface; *mcr* genes; AMR governance**.**

Introduction

The concept of ABR lies at the crossroads of a complex One Health system: In addition to the individual's health-seeking behaviors, industrial, farming and veterinary activities, and environmental factors that influence the generation, selection and sharing of resistant bacteria, all of these impact health outcomes. In 2023, about 16% of all laboratory confirmed common bacterial infections were already resistant to the antibiotic used for treatment, according to the World Health Organization's Global Antimicrobial Resistance and Use Surveillance System (GLASS), which indicated that the situation will likely deteriorate if coordinated cross-sectoral action is not taken.The threat has been scaled up in a more precise manner. AMR-attributable deaths increased markedly among older adults, especially those aged 70 and over (+80% over the period 1990-2021), despite a reduction in child deaths under five by half due to better infection prevention. Governance and access, rather than drug discovery and development, may be the more important lever, as the model suggests that access and quality of care alone could avert nearly 92 million deaths due to antibiotic-resistant infections by 2050, bringing the total number of cumulative deaths projected by the reference case down to about 39 million.

In this context, 2026 will truly be a turning point for AMR policy. The Seventy-ninth World Health Assembly adopted the revised Global Action Plan on Antimicrobial Resistance (GAP-AMR) 2026-2036 on 23 May 2026, which was explicitly framed within a One Health approach, including human, animal, plant and environmental health sectors, and which fulfils a commitment made at the UN General Assembly High-Level Meeting on AMR in 2024. In parallel to this, the World Organisation for Animal Health (WOAH) adopted a similar plan in its 183 member countries two days before, and the Quadripartite alliance (FAO, UNEP, WHO and WOAH) is preparing operational guidance for

implementation together. This review takes that policy milestone as a point of departure to explore the science behind the spread of resistance in the human-animal-environment continuum and where the evidence is weak, and what constitutes a next step for a truly One Health research agenda.

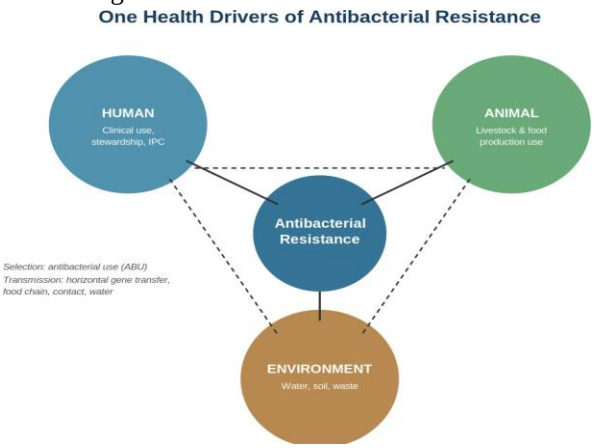


Figure 1. Conceptual One Health framework for antibacterial resistance, showing 'selection' (antibacterial use within each compartment) and 'transmission' (movement of resistant organisms and genes between compartments).

Review Approach

This is a narrative review that combines peer-reviewed literature, WHO/WOAH/FAO/UNEP policy documents, and pre-print/grey literature from targeted search in PubMed, Scientific Reports, The Lancet, Nature Medicine, and official repositories of WHO/WOAH/FAO/UNEP, with a focus on literature published between 2020 and 2026. Systematic reviews, meta-analyses, multi-country modelling studies and primary governance evaluations were given priority over single site case reports to support generalizable conclusions. Where possible, sources from 2025–2026 were favored, due to the dynamic nature of this field.

The One Health Framework: Selection and Transmission

In a One Health system, the drivers of ABR can be thought of as two interrelated processes. Selection is mostly due to ABU, which creates selection pressure for the appearance of resistant strains. Transmission is the spread of resistant organisms and resistance genes from one compartment to another (human to human, animal to animal, human to animal, through shared reservoirs in the environment like sewage, manure, soil, and water). It is interesting to note that the majority of global bacterial use, around 73%, is in food-producing animals rather than humans, and up to 50% of human antibacterial use is deemed unnecessary, thus highlighting that both human and animal use have significant, but not completely independent, pressures to choose antibacterials.

One of the more systematic attempts to quantify these relative contributions is by the OH-DART Study Group's compartmental modelling study in Thailand. The model connected the human, animal, and environmental compartments of ABR, using ODEs, and predicted the reductions in human ABR over a 20-year period (2020–2040) for various intervention scenarios. It found that on its own, the reduction of human ABU was the single most influential factor in reducing human colonisation with resistant bacteria (a maximum modelled reduction of 65.7–99.7%), with the Thailand's National Strategic Plan on AMR expected to yield a more modest 6.0–18.8% reduction, and this would increase to 8.5–24.9% if more ambitious 30% ABU-reduction targets are achieved. The authors found that interventions covering both human ABU and hygiene/sanitation have a significant effect when compared to either sector alone – and this has been backed by empirical evidence, not just theory, for a ‘cross-sectoral' (as opposed to ‘silo') approach.

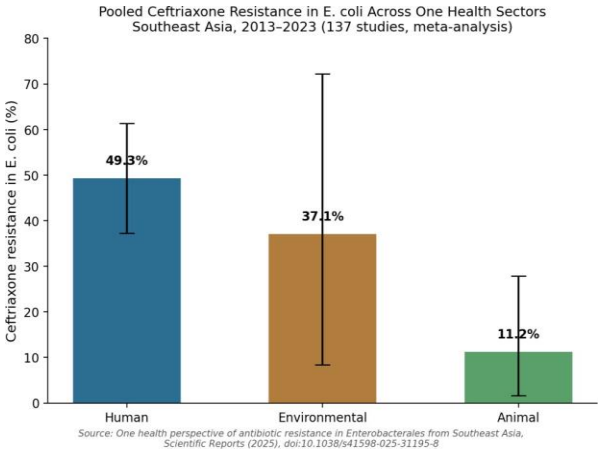
Regional Case Study: Antibacterial Resistance in Southeast Asia

A high-burden, chronically under-modelled region Southeast Asia is an example of both the potential and ongoing research gaps in One Health ABR. The prevalence of ABR is three times more common in LMICs than in high-income countries and there is growing evidence that the burden of ABR is even higher in LMICs despite limited access to effective antibacterials. However, modelling coverage does not capture burden: comparative analyses have revealed that, despite the high prevalence of extended-spectrum beta-lactamase (ESBL) producing Escherichia coli (E. coli) in Southeast Asia, there are only eight published ABR models in the region, compared to 35 for Africa and 42 for Europe. What the regional evidence shows

In 2025, a systematic review and meta-analysis published in Scientific Reports compiled data on resistance prevalence from 137 observational studies from across Southeast Asia from 2013 to 2023, explicitly taking a One Health approach by breaking down resistance data by human, animal, and environmental sample source. The highest resistance to ceftriaxone was observed in E. coli isolated from human samples (49.3%) followed by environmental (37.1%) and animal (11.2%)

sources. Although still low, carbapenem resistance was clearly increasing over time: meropenem resistance in Klebsiella pneumoniae increased to 13.0% and resistance rose significantly in humans (p = 0.009) and animals (p = 0.004) during the study period. All three sectors were positive for the blaCTX-M and blaTEM genes, supporting the notion of cross-compartment spread of resistance genes, and not sector isolated emergence.

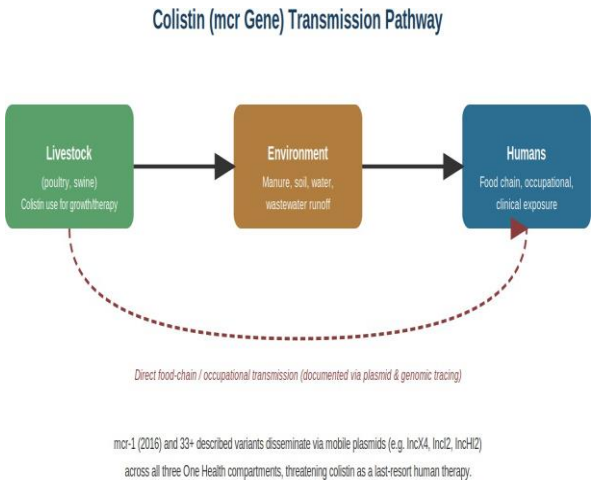
Figure 2. Pooled ceftriaxone resistance in E. coli across One Health sectors in Southeast Asia, 2013–2023, based on meta-analysis of 137 observational studies. Error bars represent 95% confidence intervals.



The modelling gap is worsened by labour capacity limitations. Between 2021 and 2024, the EQASIA External Quality Assessment programme, funded by the Fleming Fund, assessed the capacity of the participating laboratories to identify ESBL-, AmpC-, and carbapenemase-producing E. coli from a simulated food matrix in South and Southeast Asian countries, in line with the WHO Tricycle protocol. Technical variability in laboratory performance was documented in the programme, and in some rounds, the accuracy in species identification as low as 23.1%, highlighting that regional surveillance data should be treated with caution, and investing in laboratory proficiency is a key requirement for reliable One Health surveillance. Mechanistic Case Study: Colistin and the mcr Gene Family.

Colistin (polymyxin E) is considered a highest-priority critically important antimicrobial (HPICA) by the WHO and is a last-resort drug for Gram-negative infections that are resistant to multiple antimicrobials in humans, such as Acinetobacter baumannii, Pseudomonas aeruginosa and Klebsiella pneumoniae. But in many LMICs, colistin was also widely applied in unregulated animal farming, especially in raising poultry and pigs, for more than 60 years. The discovery of the plasmid mediated mobile colistin resistance gene mcr-1 in 2016 marked a shift in the landscape of resistance: mcr genes are not chromosomally mediated, but instead are on mobile genetic elements that can be horizontally transmitted between bacterial species and across host compartments. Since then, over 30 variants of mcr-1 have been described and other gene family members (mcr-1 to mcr-10) have been described.

In the ABR literature, some of the most clear-cut evidence of cross-compartment spread is available through the use of genomic tracing studies. An analysis of colistin resistance in E. coli on a single holding in Spain showed the simultaneous presence of mcr-1 and mcr-3 in E. coli from cattle origin, suggesting transmission dynamics within the farm between



livestock. In a separate study, genomic analysis of the more widespread mcr-1.26 type in human and poultry E. coli revealed that the plasmid genome was highly similar, and that the temporal distribution of isolates was the same, suggesting that the common source of this variant and the spread of this variant into the human population was likely to be the poultry industry. Regulatory interventions demonstrate the potential for intervention: Germany's DART 2020 One Health strategy has led to a 53% drop in the sale of veterinary colistin from 2011 to 2020, still, in 2022, six member states of the EU Were identified as not achieving the consumption limit of less than 5 mg/PCU

Figure 3. Schematic transmission pathway of mobile colistin resistance (mcr) genes across the livestock, environment, and human compartments.

Governance: Policy Design Has Outpaced Implementation

The most direct evidence for the effectiveness of AMR policy so far gathered is from a study published in the

journal Nature Medicine in 2026, which created a multidimensional One Health governance index via structured expert (Delphi) consultation, and assessed AMR governance over the period 2017-2022 by analysing 269 policy documents, alongside surveillance and antimicrobial-use data, across 193 countries. While global governance successfully improved significantly during this period (from 30.7 to 44.5 out of 100), the implementation and monitoring of governance always fell short of policy design, especially in the animal and environmental sectors. The analysis revealed that a statistically significant decrease in the prevalence of AMR became apparent only after approximately five years of implementing a national action plan (NAP), and that multisectoral involvement and antimicrobial-use surveillance systems early on were the most important factors in achieving better outcomes over time.

This imbalance in sector is supported by the independent regional analysis. The EU-JAMRAI 2 needs-assessment survey of 30 EU/EEA countries revealed that only 25 % 1. of countries had an integrated, well-developed One Health national action plan, and more than half of the respondents identified financial and governance challenges as the main barriers to implementation. A• parallel scoping review of national AMR performance indicators revealed more than 2,300 distinct academic indicators, but these were disproportionately focused on human health (surveillance and stewardship), with a relatively small number of indicators available for animal and environmental health, which the authors believe actively undermines multisectoral coordination.

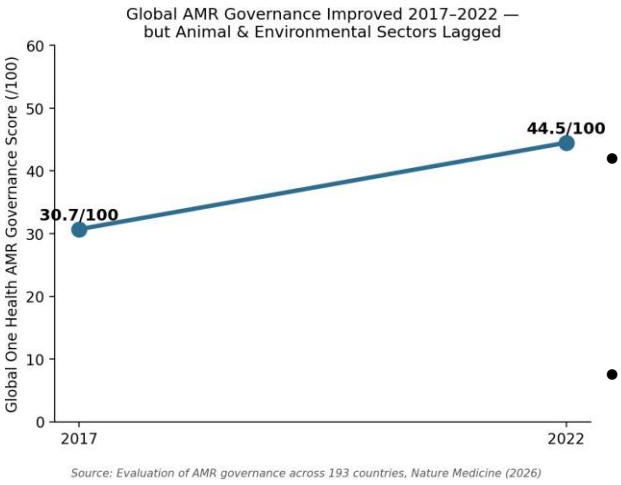


Figure 4. Global One Health AMR governance scores improved between 2017 and 2022 across 193 countries, though implementation and monitoring especially in animal and environmental sectors lagged behind policy design.

This design-implementation gap is directly attempted to be solved by the newly adopted GAP-AMR 2026–2036. It establishes commitments for enhanced surveillance, infection prevention and control, water and sanitation/hygiene (WASH), antimicrobial stewardship, and sustainable financing and asks for progress reports to the World Health Assembly every two years until 2031. The plan's modelling estimates economic benefits of around US$1 trillion between 2025 and 2050 could be achieved if the targets are met and the UN 2024 target of cutting bacterial AMR-related deaths by 10% by 2030 is also achieved. If this second generation plan succeeds where parts of the first (2015) plan failed, then it will likely depend on the ability to bridge the identified animal and environmental governance gaps during the first implementation phase, which is now underway, and not yet over.

Research Priorities and Recommendations

Combining the evidence presented above, four research and policy priorities emerge for the future of One Health ABR research and policy:

- Re-align investment in research geographically. The eight published ABR models in Southeast Asia, alongside the highest burden of resistance documented anywhere in the world, is indicative of a deeper gap in funding for research in LMICs that needs to be an explicit goal of Quadripartite research financing for GAP-AMR 2026-2036.
- Focus on indicators for the environment and animal sectors, and not just the human sector, as there is evidence that indicators are less available in these sectors than in others and that governance data indicates that these are the sectors furthest behind.
- Increase genomic/mobile plasmid surveillance of mobile resistance determinants, including mcr genes, which provide clear mechanistic evidence of cross-compartment transmission and may be expanded to other priority resistance mechanisms (e.g., carbapenemases and ESBLs).
- Support laboratory quality assurance programmes, e.g. EQASIA, in high burden, lower-resourced areas because surveillance data is only as good as the laboratory capacity that produces it. Taken together, these priorities suggest a clear conclusion which may be jarring for a drug discovery-driven field: The evidence base and the follow-through on existing governance commitments are

the most pressing global need for the AMR response, not the absence of new antibiotics.

Conclusion

These studies, from compartmental modelling in Thailand to tracing the mcr-gene to the genome of bacteria found in human, animal and environmental samples across Europe and to the evaluation of mcr-gene governance across 193 countries, all demonstrate that the drivers of human, animal and environmental sources of resistance are interconnected, not independent. The World Health Organization (WHO) Global Action Plan on Antimicrobial Resistance (2026-2036) is a promising and timely step toward bridging the policy ambition and implementation gap that has been prevalent over the past decade since the first Global Action Plan on Antimicrobial Resistance (2015-2025). The likelihood of that opportunity being realized will rely strongly on whether research investment and surveillance infrastructure is shifted to the animal and environmental sectors, and whether to those areas that have been under-researched and under-surviled like Southeast Asia for long periods.

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