**The Scope of the Antimicrobial Resistance Challenge and the Need for Sustainable Access to Effective Antibiotics**

Prof. Iruka N. Okeke, PhD1\*; Marlieke E.A. de Kraker, PhD2,3; Thomas P. Van Boeckel, PhD4,5; Prof. Heike Schmitt, PhD6,7; Prof. Ana Gales, MD PhD8; Silvia Bertagnolio, MD9; Prof. Mike Sharland, MD10; and Ramanan Laxminarayan, PhD5,11\*

1. Department of Pharmaceutical Microbiology, Faculty of Pharmacy, University of Ibadan, Oyo State, Nigeria
2. Infection Control Program, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland
3. WHO Collaborating Centre on AMR, Geneva, Switzerland
4. Health Geography and Policy Group, Department of Environmental Systems Science, ETH Zürich, Zürich, Switzerland
5. One Health Trust, Washington, D.C., United States of America
6. Centre for Zoonoses and Environmental microbiology, Dutch National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands
7. Environmental Biotechnology, Faculty of Applied Sciences, Delft University of Technology, Delft, the Netherlands
8. Division of Infectious Diseases, Escola Paulista de Medicina, Universidade Federal de São Paulo (EPM-UNIFESP), São Paulo, Brazil
9. Department of Control, Surveillance and Prevention of Antimicrobial Resistance, World Health Organization, Geneva, Switzerland
10. Centre for Neonatal and Paediatric Infection, St. George's University London, United Kingdom
11. High Meadows Environmental Institute, Princeton University, Princeton, NJ, United States of America

\*Corresponding authors

Dr. Iruka N. Okeke

Professor and Calestous Juma Science Leadership Fellow

Department of Pharmaceutical Microbiology

Faculty of Pharmacy

University of Ibadan,

Ibadan, Oyo State, 200284, Nigeria

Tel: +234 805 328 1714

Email: iruka.n.okeke@gmail.com

Dr. Ramanan Laxminarayan

One Health Trust

Obeya Pulse, First Floor, 7/1, Halasur Road

Bengaluru, Karnataka 560042

India

Tel: +91 97111 33491

Email: ramanan@onehealthtrust.org

**ABSTRACT**

Access to effective antimicrobials, when indicated, prolongs life, reduces disability, limits health care expenses, and enables access to other life-saving medical innovations. Antimicrobial resistance thwarts all these benefits and is a major barrier to the attainment of Sustainable Development Goals, including targets for newborn survival and to progress on healthy aging. Adverse consequences from resistance are seen in both healthcare- and community-associated infections, across the human life course, as well as in animals and the food chain. The limited set of effective antibiotics available has narrowed, and the very young, very old, and severely ill are particularly vulnerable to resistant infections because of the disproportionate burden of infectious diseases they carry. Those in resource-constrained settings are also vulnerable due to the lack of alternative medicines. This paper, the first in a series on the antimicrobial resistance challenge, considers the global scope of the problem and how it should be measured. Antibiotics are the most commonly prescribed medicines and the predominant selective force for resistant pathogens. Robust and actionable data are needed to drive changes and inform effective interventions to contain resistance. In particular, surveillance must cover all geographical regions, minimize biases towards hospital–derived data, and include non-human niches.

**[199 words]**

**KEY MESSAGES**

* Antimicrobial resistance (AMR) is compromising health and development targets and innovation. Everyone is at risk but especially vulnerable individuals and health systems.
* Rises in resistance among pathogens and indicator organisms in humans, animals, the food chain, and the environment have been documented in the past two decades.
* Antimicrobial use in medicine and agriculture, the selective force for resistance, is insufficiently documented, as are resistance rates, trends, and burden.
* Diagnostics that determine when antibiotics are needed, and provide AMR information, are essential for enhancing patient care and informing the public health response.
* Resistant organisms often disseminate through anthropomorphic pathways and can include non-human and inanimate intermediaries. Disseminated resistant microbial lineages endanger many more people and can become entrenched in healthcare facilities, in the community, and across food chains. These lineages spread in facilities across the world unless detected quickly and stopped through infection prevention and control.
* Every country needs a surveillance system to track antimicrobial resistance and use and must evaluate interventions to contain them.

**INTRODUCTION**

The burden from antimicrobial resistance (AMR) is untenably high, impacting more people and growing. AMR is typically presented, as a discreet problem and thus is invisible to many stakeholders. However, resistance currently impacts the health, well-being, and potential of most humans and of other species that inhabit our world. Today, humans begin and end life with a significant probability of contracting an antimicrobial-resistant infection and a decreasing likelihood of being able to access effective treatments. Infections from resistant bacteria are a health concern comparable to HIV and malaria, if not potentially more significant, and affect all regions (**Panel 1**).1 Antimicrobial resistance (AMR) threatens infectious disease management at all ages and limits medical progress.

In children younger than five, a dramatic decline in deaths—as much as 50% between 2000 and 2013—was enabled by improvements in water and sanitation, vaccination, and other public health interventions.32 However, Sustainable Development Goal (SDG) 3, to ensure healthy lives and promote well-being at all ages and to cut newborn mortality to less than 12 per 1,000 live births by 2030, is jeopardised when antibiotics fail to work (**Figure 2**). A third of newborn deaths are attributable to infection and half of those to sepsis,33 and increasingly, the pathogens no longer respond to most readily available antibiotics.

At the other end of life, the comorbidities and immuno-senescence that can accompany aging raise the propensity for infection—increasingly, antimicrobial-resistant infection (**Figure 3**). Roughly a 10th of the world’s population is older than 65, a proportion likely to double by 2050.38 Additionally, progress in treating noncommunicable diseases (NCDs), including diabetes and cancer, in people of all ages is constrained by AMR. Drug-resistant healthcare-acquired infections (HCAIs) in such patients complicate treatment, lengthen hospital stays, and increase cost of care.

AMR also threatens global health through food insecurity. Resistance restricts our ability to treat sick livestock, potentially increasing the cost and availability of animal protein. Overuse of antibiotics on farms and discharge of active antimicrobials into the environment selects resistant bacterial lineages in those settings and places humans and animals at risk of a future pandemic from an untreatable bacterial infection.40,41 Resistance drivers include antibiotic use, poor access to water and sanitation, lack of public health measures, insufficient vaccination, and failure of infection prevention in healthcare facilities. AMR is thus a One Health challenge that requires surveillance and interventions across human, animal, and environmental domains.

In the past decade, many countries have composed National Action Plans on how they plan to address antimicrobial resistance. Most of these plans are modelled on the WHO Global Action plan42 and emphasize the importance of expanding awareness of AMR, conducting surveillance to quantify the problem, preventing infections and the dissemination of antimicrobials, research to develop new antimicrobials and other strategies for overcoming or avoiding resistance as well as making the economic case for more support of resistance.

The 2024 *Lancet* Series on sustainable access to effective antimicrobials presents initiatives and targets to tackle the global health threat of AMR. This paper examines how AMR and antibiotic use have intersected with disease burden over the past decade. We draw from case studies of healthcare acquired infections, particularly in neonates and the elderly, as well as on select community-acquired infections. Paper 2 models the effectiveness of interventions to contain resistance in resource-limited settings.43 Paper 3 examines how research and development can address AMR.44 Finally, Paper 4 proposes achievable targets for a 10% reduction in disease burden from AMR by 2030.45

Here we present evidence on the growing effect of AMR on global health and examine options for pragmatic, rapid improvements in global AMR and antibiotic use surveillance. Our aim in this paper, and throughout the series, is to present the problem of AMR as a horizontal one that is exacerbated by inequitable access to antimicrobials. Our scope is restricted to non-tuberculosis bacterial and fungal pathogens, though drug resistance is a growing impediment to the treatment of tuberculosis, malaria, HIV infection, and other diseases as well. We begin by outlining the challenge posed by AMR to global goals for child survival, healthy aging, and food security. We review the state of resistance in infections caused by community-acquired pathogens that infect people across the courses of their lives, depending on exposure and risk. We then summarize recent progress and gaps in measuring and reporting of AMR and antimicrobial use, and we propose suggestions for improving surveillance.

**METHODS**

Thirty-eight experts in AMR and global health reviewed SDG targets, the current state data availability, and then elected the following focal areas for in-depth review: neonatal sepsis, healthcare-associated infection, typhoid, gonorrhoea, and pneumococcal infection (tuberculosis was excluded). Medline was searched via Pubmed for relevant review articles from 2003–2023 about antimicrobial or antibiotic resistance or antimicrobial or antibiotic consumption. Articles cited in the reviews were selected from the reference lists. Supporting data for the focal areas were retrieved from the following publicly available curated resistance databases: the 2019 GBD study and 2019 GRAM project,46 NeoOBS,47 CHAMPS,33 BARNARDS,48 DeNIS,34 ResistanceMap,49 Resistancebank,28 PathogenWatch,50 Typhinet,51 and the Medicine Quality Scientific Literature Surveyor.52 The expert group additionally listed relevant policy documents associated with the WHO Global Action Plan for Antimicrobial Resistance.42

**THREATS TO NEWBORN SURVIVAL**

Antimicrobial resistance stands in the way of meeting multiple health-related targets and neonatal sepsis remains a global concern, as it is the 8th most common cause of death in neonates and children under age five, with high rates in resource-limited settings.53,54 Babies with early-onset sepsis may be infected before or during birth because of premature rupture of maternal membranes; late-onset (age 3–28 days) sepsis commonly represents a health care associated infection (HCAI). Outbreaks of resistant bacteria attributable to poor infection prevention and control are increasingly detected, often only retrospectively. Babies born at a health facility can benefit from emergency obstetric or newborn care,37 but HCAIs could stall or reverse such child survival gains.

AMR constrains neonatal sepsis management: in an 11-country study, 18% of babies from whom a bacterial pathogen was cultured did not survive despite empirical antimicrobial therapy.55 Comparable neonatal sepsis outcomes due to resistance to first-line empirical treatment regimens recommended by the World Health Organization (WHO) have been reported elsewhere in the past two decades (**Supplementary Information pg 4**). Overall, an estimated 214,000 neonatal deaths were attributed to antimicrobial-resistant neonatal sepsis each year a decade ago.1,19,56,57 *Klebsiella* (particularly *pneumoniae*) *Staphylococcus, Acinetobacter,* and *Escherichia* spp. are the commonest causes of neonatal sepsis(not necessarily in that order), particularly in low-resource settings.1,56–59 In addition to these maternally-acquired *Streptococcus agalactiae* is a common cause of early-onset neonatal sepsis in higher-income settings.35,55,58 Real and perceived risk of mortality due to resistant bacteria causing sepsis has prompted overuse of carbapenems and consequent rising carbapenem resistance rates. Clinicians are increasingly compelled to use last-resort drugs like colistin,55 which has a more (and more serious) adverse effects than first-, second-, and third-line empiric drugs, and whose long-term effects for neonates are largely uncertain.

Sepsis is a potentially lethal system-wide response to infection. Neonatal sepsis is most commonly secondary to a systemic bacterial infection, but fungal infections can also initiate sepses, particularly in low-birth-weight infants. Sepsis following fungal infection occurs worldwide but is best documented in high-income settings.56,60 *Candida albicans* and *C. parapsilosis* frequently feature, but since 2009, *C. auris* is of even greater concern.61 *C. auris* isolates are typically resistant to most or all known antifungals, infections have high mortality rates, and the organism was labelled critical on the 2022 WHO fungal priority pathogens list.62 A possibly ongoing fluconazole-resistant *C. auris* outbreak in a South African neonatal unit has involved 90 cases over four years.63

Identification and susceptibility information are critical to managing sepsis and to identify outbreaks. These data, generated in healthcare facilities, can feed into local, national, and regional surveillance at little extra cost. For neonatal sepsis and other infections caused by blood-borne bacteria, pathogen information derives from blood culture, which has a low yield (typically <20%) and a high contamination rate (perhaps >10% in low-resource settings).64 Blood culture sampling is most challenging from neonates and therefore contamination rates can he higher. Deep molecular diagnostics, like metagenomics, can yield an etiologic agent in almost four times as many cases, but cost presently precludes their routine use.56,58 Genomic enrichment methods and point-of-care aetiologic tests offer promise but are still under development. In high-income settings, a neonate with suspected sepsis typically undergoes more than one blood culture as well as supporting tests to confirm the diagnosis and guide care. The current goal for low-resource settings is that blood culture be available at referral centres,65 but even there, the required infrastructure, consumables, skilled personnel, and quality management systems are often lacking, and thus very few infections are cultured (Ondoa et al.; MAAP study).66 National and regional surveillance networks built around existing blood culture machines largely consist of tertiary sentinels, where resistance patterns of opportunistic pathogens differ markedly from primary- and secondary-care isolates, limiting the actionability of the data.56

Surveillance is increasingly uncovering outbreaks in neonatal intensive-care units.67,68 Applying whole genome sequencing, which will ultimately support tools to prevent mortality (see Paper 344), permits fine-level tracking of the opportunistic causes of neonatal sepsis, revealing routes through which bacteria are transmitted, whether directly among patients or via intermediaries, including medical devices and parenteral medications.63,69,70 Whole genome sequencing has revealed that specific lineages of *E. coli* (e.g., STs 69, 73, 95, and 131) and *K. pneumoniae* (STs 11, 15, and 17)71,72 are overrepresented in neonatal sepsis and HCAIs.35,73 A maternal vaccination strategy targeting these lineages could significantly lower neonatal sepsis rates.74 Surveillance using whole genome sequencing provides this information at no extra cost and offers more granularity than earlier genotypic methods. However, it falls short of achieving predictiveness to consistently guide empiric prescriptions or prevent HCAIs. Because turnaround times are typically long, few outbreaks have been shortened, stopped, or shrunk by sequencing. A short turnaround has in fact been achieved in some instances69; the barriers to genomic surveillance’s full potential arise from its use in large flagship initiatives too far removed from at-risk patients. Facility-based surveillance in neonatal intensive-care wards can help prevent infections by identifying and segregating infants colonised with potentially resistant pathogens, monitoring them for sepsis, and administering treatment based on actual susceptibility profiles.

**THREATS TO THE ELDERLY AND CHRONICALLY ILL**

People of any age can fall victim to HCAIs and the elderly face significant risk as aging populations benefit from advancements in medical care and enter hospitals and long-term care facilities. The UK national health service alone loses approximately £2 billion annually to HCAIs,75 mostly bacterial but, increasingly, fungal.62 Despite some improvements in infection prevention and control, treatment costs continue to rise. Drug resistance prolongs the need for infection management and requires more expensive medicines.76 Resistance is also a barrier to surgical care, directly affecting surgical outcomes. Evidence also suggests that some surgeries, particularly at older age, are deemed too risky given the likelihood of contracting an untreatable infection.

AMR undermines the effectiveness and value of organ transplants, joint replacements, cancer chemotherapy, and treatment of NCDs, which account for 80% of deaths and 70% of disability-adjusted life-years (DALYs) globally.77 Sub-optimally managed NCDs are poorly quantified but potentially a significant burden of AMR.78 AMR complicates treatment for chronic kidney disease,79 diabetes and associated urinary tract and foot infections,80 chronic obstructive pulmonary disease,81 and liver cirrhosis.82 Sepsis following HCAI in patients with NCDs urgently requires improved surveillance.

Cancer patients have a particularly high risk of infection. Cancer itself predisposes patients to malnutrition and psychological stress, and cancer treatments—invasive medical devices, surgery, chemotherapy, radiation, immunotherapy, and antibiotic use to prevent infection, which can then select for resistant infections—also present risk of infection.83,84 In a retrospective study, the mortality rate due to fatal infection in US cancer patients was 260·1/100,000 person-years, nearly three times that of the general population.85 In that cohort, patients aged 20 to 39 or over 80 years, as well as those receiving chemotherapy, showed a higher risk of fatal infections.85

Disparities in resources, infrastructure, organisation, and access to medical care will almost certainly raise cancer fatality rates in low- and middle-income countries (LMICs), where diagnoses are made at later stages and access to care remains a challenge.86 The most resistant ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *K. pneumoniae*, *A. baumannii*, *Pseudomonas aeruginosa,* and *Enterobacter* spp.) are frequent HCAIs in cancer patients.83,87 Bodro and collaborators reported increased persistence of bacteraemia (25% vs. 9·7%), metastatic infection (8% vs. 4%), and early case-fatality rates (23% vs. 11%) among cancer patients in Spain whose infections were caused by antimicrobial-resistant ESKAPE pathogens, compared with other, susceptible pathogens.88 Patients with infections caused by multidrug-resistant Gram-negative bacteria, especially non-fermentative bacteria like *Acinetobacter* spp., have particularly early mortality rates.89,90 To estimate the potential effect of AMR on the efficacy of antibiotic prophylaxis across a range of surgeries and cancer treatments,91 researchers modelled a 30% reduction in the efficacy of antibiotic prophylaxis and projected that an additional 6,367 infection-related deaths could occur annually in the United States, primarily among patients undergoing colorectal surgery (4,586 additional deaths), blood cancer chemotherapy (683), and total hip replacement (376).91 In the United States, declines in the efficacy of antibiotic prophylaxis agents in preventing surgical site infections following colorectal surgery have been reported.92

**ANTIMICROBIAL RESISTANCE IN COMMUNITY SETTINGS**

The vast majority of AMR infections are acquired in the community across most of the life course.1 Community-acquired urinary tract infections (UTIs) affected more than 404·6 million people globally and led to nearly 236,800 deaths in 2019.93 UTIs are the most common indication for antibiotic prescription in pregnancy,94 when the range of antibiotics that can be safely administered narrows, and are associated with maternal pre-eclampsia and low birth weight and/or pre-term infants if improperly treated.55 Although *E. coli* is the most frequent urinary tract pathogen in both community and hospital settings, ESKAPE pathogens are important UTI etiologic agents as well.95,96 Community-acquired UTIs are commonly caused by resistant *E. coli, K. pneumoniae, Proteus mirabilis,* and *S. saprophyticus.*95,96 Extended-spectrum beta-lactamase producers, such as CTX-M-15-producing *E. coli* ST131 strains, are globally disseminated and resistant to multiple antimicrobials.97,98 In certain regions, community-acquired UTIs caused by carbapenemase-producing *E. coli* increasingly necessitate intravenous antibiotics.99,100

Sexually transmitted bacteria cause considerable morbidity. The stigma associated with these infections, along with limited diagnostic resources, limits access to care and contributes to disease spread. In 2020, 82 million people contracted gonorrhoea.101 The incidence in middle-income settings and sub-Saharan Africa is estimated to be two and five times as high, respectively.102 In high-income settings, gonorrhoea infection rates have increased dramatically in the past two decades, largely among men who have sex with men—the demographic where concerns about AMR are greatest.103–105 Resistant clones rapidly become prominent and even pandemic because of high transmission rates and strong selection arising from empiric antibiotic use.106–108 Patients with suspected gonorrhoea typically receive empiric treatment, often from unsanctioned providers in settings with weak regulation.109

Rational gonorrhoea treatment consists of single doses or short courses of antibiotics known to be active against >95% of sentinel surveillance isolates.110 Culture and susceptibility tests take several days, and access to testing is severely limited because *Neisseria gonorrheae* requires specialized methods. The diagnosis and susceptibility profile would ideally be confirmed in a single healthcare visit so that appropriate treatment could begin immediately. Today, nucleic acid-based tests can guide therapy, but only where technical and human capacity is available.111 Currently, patients with gonorrhoea receive ceftriaxone alone or with azithromycin, which are effective for most patients.103,105 Recently trialled zoliflodacin, if approved, could offer a reserve option for resistant infections.112 Mathematical modelling shows that using rapid tests to screen for susceptibility to largely discontinued tetracycline and ciprofloxacin (seen in almost 70% of isolates in some settings) could, in addition to reducing the cost of treatment, prolong the usable lifespan of newer drugs.113 Sexually transmitted infections are best prevented with behavioural interventions, and gonorrhoeal vaccines in development offer additional promise.114,115

Typhoid fever is a life-threatening bloodstream infection caused by the Typhi serovariety of *Salmonella enterica* subsp. *enterica,* a feco-orally transmitted bacterium that only infects humans. Untreated or improperly treated infections are commonly fatal: 10–20% of those infected with *S.* Typhi in the pre-antibiotic era died.116 With little shift in incidence, antimicrobials dropped the mortality from typhoid to less than 1% in endemic regions.116 That success in typhoid control has been reversed by rapidly evolving resistance to every broad-spectrum antimicrobial treatment option that has been deployed (**Figure 4**). Typhoid is largely imported to Europe and North America by returning travellers but remains a major cause of febrile illness in parts of Africa and Asia with poor sanitation.117 Prevention is crucial because antibiotics treat infections but do not control transmission.117–119 After accounting for location, outbreaks attributable to multidrug-resistant strains are increasingly common and typically larger than outbreaks caused by antimicrobial-sensitive *S.* Typhi.120

Endemic-area surveillance would not only support treatment and sanitation priorities but also identify transmission chains and guide deployment of typhoid conjugate vaccine (see Paper 243). Genomic surveillance has identified major *S.* Typhi clones and their routes of local and global dissemination,121,122 including locations where drug-sensitive lineages continue to circulate. Typhi genomic surveillance is based on large numbers of genomes (disproportionately fewer from Africa) allows non-experts to contribute and interpret genomic information.122–124 Surveillance is inhibited by its dependence on blood culture, which is expensive, uncommon in many endemic areas, and insufficiently sensitive to detect most typhoid cases.125 Nevertheless, surveillance preceded adoption of the typhoid conjugative vaccines in all but one (Liberia) of the countries that had deployed them by 2023 (Liberia, Malawi, Nepal, Pakistan, Samoa, and Zimbabwe).126 Neighbouring countries commonly have little or no typhoid surveillance.

In contrast to *Salmonella* Typhi, good genomic surveillance resources exist for *Streptococcus pneumoniae,* a community-acquired cause of childhood illness and mortality that is also vaccine preventable. In 2009, an estimated 0·6 million deaths were associated with antimicrobial-resistant *S. pneumoniae*.1 Isolates can be retrieved from nasal-swab surveys in healthy populations and added to information from blood and cerebrospinal fluid cultures,127 compensating for limited access to microbiology resources. This in turn makes it possible to obtain lineage-specific information that can inform vaccine deployment and empiric treatment. For typhoid and other infections without easily accessible pathogenic or potentially pathogenic isolates, emerging surveillance approaches, including direct specimen testing and environmental surveillance, offer promise. Drug resistance monitoring and resistance mechanism identification need to be built into the new approaches, even at additional cost.

**ANTIMICROBIAL USE: A KEY DRIVER OF RESISTANCE**

Antimicrobials cure infections but also drive resistance by providing resistant microbes with a selective advantage over sensitive ones. Global antimicrobial/ antibiotic use (AMU) — the key driver of resistance—surged by 46% over the past two decades.128 Nevertheless, the *Lancet* AMR series of 2016 observed that more deaths were due to lack of access to antibiotics than to resistance.19 Although more patients now have access to antimicrobial drugs, resistance has made previously useful antimicrobials less effective, and access to previously second-line drugs has thus become more important. For example, affordable and safe antimicrobials (‘Access’ antibiotics in the AWaRe classification; see **Panel 2**129) were the mainstay of neonatal infection management in the mid to late 20thcentury. The close-to and actual last-resort options (‘Watch’ and ‘Reserve’ antibiotics) are increasingly used today. Most pathogens isolated from 19 facilities in a multi-country study55 were resistant to Access antibiotics. More than a third (37%) of neonates started on Watch regimens and 25% of infants started on Access or Watch courses had to be escalated to a higher level within 24 hours because their condition deteriorated and/or laboratory results indicated resistance. Thus, currently recommended neonatal sepsis regimens are commonly ineffective or undereffective empiric treatments because of resistance (**SI pg 5–6**).

Since 2016, WOAH has collected data on antibiotic sales for livestock from more 150 countries. Because the reporting countries are not specified and the national reports are aggregated by region (Europe, Africa, Americas, Middle East, and Asia–Far East–Oceania), the effect of national policies on AMU cannot be determined. Moreover, one country’s success in reducing AMU is diluted at the regional level if usage rises in neighbouring countries. In particular, between 2016 and 2018, WOAH reported a decline in global AMU, from 92,269 to 69,455 tonnes, that was largely attributable to China (where consumption fell from 44,186 to 29,774 tonnes). Modelling estimates of national-level AMU attempt to overcome such limitations. For 2020, one estimate named China, Brazil, India, and the United States as the top four countries for absolute AMU, measured in tonnes.130 From 2017 to 2020, AMU intensity in pigs fell slightly (from 193 to 173 mg/PCU), but in poultry, this measure fell sharply (from 68 to 35 mg/PCU) despite continued growth of the poultry sector.

AMU estimates assume that medication label claims of active ingredients are accurate, but an estimated 10% of antimicrobials marketed in LMICs are substandard or falsified.131 Medicines may contain less (sometimes more) than the labelled amount. Antibiotics may be incorrectly transported and stored, leading (particularly in the tropics) to physical and chemical degradation that affects shelf life and therefore efficacy. Falsified antimicrobials are particularly common where regulation and supply chains are weak and infection burdens (and therefore demand) are high. The Medicine Quality Scientific Literature Surveyor52 finds that substandard antibiotics are commonly reported from West and East Africa, South and East Asia, and Central America. Besides confounding consumption estimates, substandard medicines may exacerbate selection for AMR even when used according to prescription through a variety of mechanisms.131,132 Substandard or falsified antimicrobials also undermine the resistance-thwarting goals of combination regimens, and formulations containing no active ingredient, or the wrong active ingredient, can generate false impressions of resistance.

Overall, because of inertia and the difficulties of documentation (**Panel 3**), AMU in human clinical medicine, veterinary medicine, and agriculture is grossly underreported.

**THE NEED FOR ANTIMICROBIAL RESISTANCE SURVEILLANCE**

Paper 4 in this series proposes ambitious but achievable targets for containing AMR.45 These targets cannot be met, nor can progress towards them be measured, without robust surveillance of both resistance and its burden. In many parts of the world, however, surveillance is insufficient for the purpose. Surveillance strategies may be non-representative of the target population or may bias the responses, including prompting antibiotic overuse.145,146 Traditional laboratory-based resistance surveillance, which aggregates data from routine testing of patients in healthcare facilities, has obvious drawbacks: the data typically reflect the conditions of a selected sample of patients accessing health services and diagnostics, often from tertiary-care facilities where resistance rates may be high, and resistance patterns are often reported out of epidemiological and clinical context, thus limiting their utility to inform empiric treatment guidelines (**Panel 4**).147

The WHO *Antimicrobial Resistance: Global Report on Surveillance*161 observed that data on antimicrobial resistance were limited or lacking for more than half the world’s countries. The WHO Global Action Plan (GAP) on antimicrobial resistance, adopted in 2015,42 emphasized improving the evidence base of AMR and prompted the 68th World Health Assembly to recommend national action plans to tackle resistance.162 GLASS now supports countries in providing information on their national AMR surveillance system and shares aggregated data on AMR proportions and incidence data. GLASS has collaborated with existing AMR surveillance networks, such as the European Antimicrobial Resistance Surveillance Network (EARS-Net),163 the Central Asian and European surveillance of AMR (CAESAR),164 the Latin American Network for Antimicrobial Resistance Surveillance (Rede Latinoamericana de Vigilancia de la Resistencia a los Antimicrobianos, ReLAVRA),165 and the Western Pacific Regional Antimicrobial Consumption Surveillance System (WPRACSS). After the 2015–2019 early implementation phase, GLASS introduced indicators to assess countries’ AMR surveillance, including the number of reporting sites, participation in quality-assurance programmes, representativeness of the population and health system levels, and laboratory diagnostics standards. In 2020, GLASS added a module on monitoring of antimicrobial consumption (**Panel 3**). In addition, WHO has developed survey methods to generate reliable, representative data on the prevalence and attributable mortality of drug-resistant bloodstream infections, particularly where surveillance systems are suboptimal.10,166 These surveys have been rolled out in three African and Central Asian countries.

Surveillance has multiple purposes: supporting treatment guidelines, tracking the prevalence of AMR, identifying practices that exacerbate or ameliorate resistance, evaluating temporal trends, detecting outbreaks, enabling emergency preparedness, informing risk assessment. It enables benchmarking of AMR across regions, as has been undertaken through structured surveys in Europe.167–171 It can follow the evolution of novel resistance mechanisms and dangerous resistant clones. In 2016, for example, a new family of mobile colistin resistance genes, *mcr,* was observed during routine surveillance, of an unusual increase in colistin resistance in China.172 Surveillance data can inform policies for infection prevention and control and for antibiotic stewardship. Once interventions are implemented, surveillance can help evaluate their effectiveness prospectively (see Paper 243). It aids in assessing the risk and burden of disease and helps evaluate transmission between One Health reservoirs of antibiotic resistance. And it can be used to heighten awareness among health professionals, policymakers, and the general public. Modalities for surveillance can and should leveraged existing systems and programmes where possible to provide information at low cost (**Panel 5**).

Some parts of the world do not conduct enough susceptibility testing. The Mapping Antimicrobial Resistance and Antimicrobial Use Partnership (MAAP) reports that only 1·3% of diagnostic laboratories in sub-Saharan Africa were capable of bacteriological testing, and only a subset of those could perform susceptibility tests. Mycology expertise is truly scarce: fungal surveillance lags bacterial infection surveillance and is insufficient to support interventions to tackle the growing prevalence of resistant fungi responsible for both community- and healthcare-associated infections. For example, *Cryptococcus neoformans*, a difficult-to-treat, community-acquired opportunistic infection in people living with HIV, especially in Africa, and other immunocompromised patients, is typically diagnosed late, and susceptibility patterns are uncertain. *C. neoformans* isolates are reported as showing resistance to one or more of the antifungals; backup options are few.173,174

Electronic data capture systems are absent from the majority of African hospitals. WHONET offers laboratory data management that is the mainstay of strong surveillance systems in the Philippines and much of South America; it is compatible with the ACORN platform.175,176 Development of other open-access platforms tailored to microbiology data, such as SEDRI-LIMS, is expected to further mobilise laboratory antimicrobial susceptibility data for surveillance applications. Data intended to inform empiric prescribing guidelines must include details of the clinical presentation, underlying disease, empiric and subsequent switching of therapy, all relevant microbiology results, and in-hospital and 28-day mortality.131 ACORN enables clinical caregivers to collect such information electronically so that it can be merged with laboratory data and shared via easily interpretable dashboard displays.9

The ultimate value of a surveillance system depends on how the information is used. Does it resolve uncertainty? If we already have a good idea of the level of resistance—or if the surveillance is not accurate—then it adds little. Is the surveillance information actionable? If, for example, surveillance suggests a change in treatment, but the recommended drugs are unavailable, then it has little value. And finally, what is the benefit of the interventions informed by the surveillance data? Estimates of the value of surveillance can then help justify its cost.

**CONCLUSION**

Antibiotics have saved millions of lives but have also driven the accompanying resistance pandemic and its considerable attributable mortality. As is access to antimicrobials, the burden of resistance is enormous, growing, unevenly distributed; it is thwarting infectious disease control. Everyone is at risk from resistance, including those that have never taken an antibiotic, such as neonates, bear the consequences of antimicrobial selective pressure placed by generations before. In parts of Asia and sub-Saharan Africa, the burden is lack of access to effective antibiotics and infrastructural shortfalls that promote the spread of resistant pathogens. In all cases, AMR is inadequately documented because laboratory testing is insufficient, and its burden of disease is poorly measured. Strengthening surveillance is a prerequisite for halting antimicrobial resistance and measuring successes in its containment.

**DECLARATION OF INTERESTS**

A meeting held to coordinate this paper was supported by the Bill & Melinda Gates Foundation (BMGF) (INV-055356 to RL) and the Africa Centres for Disease Control and Prevention. Neither funder had any role in the decision to submit the paper for publication. RL has received grant funding from the National Science Foundation (CCF1918628). INO is a Calestous Juma Science Leadership fellow supported by BMGF (INV-036234); receives grant funding from the UK NIHR, Wellcome Trust, Public Health Alliance for Genomic Epidemiology, SEQAFRICA, Grand Challenges Africa Award (GCA/DD/rnd3/021), International Vaccine Institute Award; receives royalties from Oxford University Press, Cornell University Press, Springer; receives consulting fees from the Wellcome Trust, has received payment for lectures from the UK Microbiology Society; travel support from the BMGF, the European Society for Clinical Microbiology and Infectious Disease, the American Society for Microbiology; has paid leadership roles in the BMGF Surveillance Advisory group (2019-2021), the Thomas Bassir Biomedical Foundation Nigeria (2019-present), The International Centre for Antimicrobial Resistance Solutions Technical Advisory Forum (2021-present); has other financial/non-financial interests in the African Journal of Laboratory Medicine, Microbial Genomics, the Lancet Infectious Diseases, Nigeria Center for Disease Control, the Lancet Commission for Nigeria. SB is a staff of the World Health Organization (WHO); the views presented in this article are those of the authors and do not reflect those of the WHO or any funders. AG receives consulting fees from Aché, Eurofarma, União, and Química; payment for lectures from bioMérieux, Eurofarma, MSD, Pfizer, Sandoz; travel support from MSD and Pfizer; participates on the data monitoring board of Aché, Eurofarma, Hypera Pharma, MSD, Pfizer, Roche, Sandoz, United Medical, União, Química; is a member of the Scientific Advisory Committee of the Global Antibiotic Research and Development Partnership (GARDP), the Health 1 Area Coordination board, Fundação de Amparo à Pesquisa do Estado de São Paulo, and is a Researcher for the Brazilian National Council for Scientific and Technological Development. MS receives funding from the Wellcome Trust (222051/Z/20/Z), GARDP and EDCTP (NeoSep1); has unpaid leadership positions on the WHO Essential Medicine List Antibiotics Working Group and GARDP; has received equipment from Sandoz, InfectoPharm, and Shionogi. The other authors have no conflicts of interest to report.

**CONTRIBUTORS**

IO Conceptualization, Project administration, Formal Analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing; MdK Conceptualization, Writing – original draft, Writing – review & editing; TVB Conceptualization, Data curation, Methodology, Visualization, Writing – original draft, Writing – review & editing; HS Conceptualization, Writing – original draft, Writing – review & editing; AG Conceptualization, Writing – original draft, Writing – review & editing; SB Writing – review & editing; MS Writing – original draft, Writing – review & editing; RL Conceptualization, Data curation, Formal Analysis, Funding acquisition, Methodology, Project administration, Resources, Supervision, Visualization, Writing – review & editing

**ACKNOWLEDGEMENTS**

We thank John Stelling and Christiane Dolecek for helpful comments and are grateful to Ambika Lall, Isabella Impalli, Sally Atwater, and Chirag Kumar for figure and editorial assistance.

**Panel 1.** **Trends in the burden of antimicrobial resistance**

***AMR in humans***

Global 2020 AMR data reported to WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS) from 87 countries2 show that carbapenem resistance in *K. pneumoniae* was at least 8% in 2020, and resistance to ‘last-resort’ colistin was 5% or higher in some regions. Resistance to aminoglycosides in *A. baumannii* bloodstream infections—typically used with beta lactams for empirical treatment of sepsis—was reported for half of the cases, and over 60% reported resistance to carbapenems.2 More than 40% of *E. coli* bloodstream infections were resistant to third-generation cephalosporins across 76 countries.2

AMR trend analyses point to a rise in resistant infections, notably in Gram-negative organisms, in the past decade.3 In Europe in 2019–2021, increasing rates of resistance have been reported, particularly carbapenem-resistant *Acinetobacter* spp. causing bloodstream infections in 2017–2021.4 The substantial estimated burden of resistant infections in Europe increased between 2007 and 2015.5 In 2015, the 426,277 antimicrobial-resistant HCAIs accounted for an estimated 33,110 attributable deaths and 874,541 DALYs.5 Projections from high-income countries predict a 2·1-fold rise in resistance to third-line antimicrobials—the last-resort drugs—by 2035 compared with 2005.

The Global Research on Antimicrobial Resistance (GRAM) study estimated that 4·95 million (3·62–6·57 million) deaths were associated with bacterial AMR in 2019 (resistant vs. no infections), including 1·27 million (0·91–1·71 million) deaths attributable to bacterial AMR (resistant vs. susceptible infections).1 The upper limit would place AMR in the top three causes of death, after ischemic heart disease, stroke, and chronic obstructive pulmonary disease. In addition to absolute AMR rates, the burden from resistance is driven by the overall infectious disease burden and access to second-line and reserve antimicrobials that can be used to treat resistant infections. Thus, estimated all-age death rate attributable to resistance was highest in West Africa (27·3 deaths/100,000) and lowest in Australasia (6·5 deaths/100,000). Such estimates have several limitations: the data come from a small number of countries; DALYs did not account for prolonged treatment effects, disability, or other sequelae; and burden estimates included non-hospitalized patients, but pathogen distributions and case fatality ratios were derived from hospital data. Also, because of sparse data, resistance proportions and relative risks were assumed equal across sub-populations, infection sites, and locations, affecting the reliability of the rankings.

Few studies have attempted to measure the AMR-attributable mortality. PANORAMA,6 a multinational cohort study, found that carbapenem-resistant Enterobacterales bloodstream infections in LMICs were associated with 3·7 days’ longer hospital stays and a 75% higher mortality rate compared with carbapenem-susceptible infections. A review of 109 studies showed similar findings,7 with longer hospital stays, doubled risk of admission to intensive care, 60% higher mortality from bloodstream infections by resistant pathogens, and increased direct medical and productivity costs. These estimates fail to adequately account for confounders, potentially overestimating the effect of AMR and underscoring the need for accurate data, especially in LMICs. In the MBIRA study,8 where models were adjusted for confounders, resistance to third-generation cephalosporins in Enterobacterales bloodstream infections was *not* associated with increased mortality risk compared with susceptible pathogens in multiple sites in Africa (aHR 6·79 vs. aHR 5·01; differential aHR 0·7 (0·42–1·30)). Confirmatory evidence is required, and ongoing initiatives (e.g., A Clinically Oriented Resistance Network (ACORN),9 aligned with WHO’s AMR attributable mortality protocol, and BALANCE study10,11) will offer more insights.

***AMR in domesticated animals***

In high-income countries, long-term, systematic surveillance of antimicrobial use (AMU) and resistance in animals12–14 has informed decisions to withdraw drug classes15 from animal production and end the use of antibiotics as growth promoters.16,17 However, surveillance has focused on the prevalence of resistance (percentage of resistant isolates) to the exclusion of disease burden, a gap now being addressed.18 Without systematically integrating antimicrobial resistance data with information on livestock production and disease, as is required in burden computation, the economic cost of resistance cannot be estimated.18 The European Food Safety Agency and the US National Antimicrobial Resistance Monitoring System for Enteric Bacteria have provided the template for surveillance in other regions, but variations in sampling schemes, laboratory guidelines, and susceptibility breakpoints complicate comparison of the data.

In the past decade in Europe, resistance of *Salmonella* and *E. coli* to ampicillin, tetracyclines, and sulfonamides was frequently detected (30–50%) but resistance to third-generation cephalosporins remained rare (0–1%).19 Resistance among poultry isolates is a growing problem, albeit with considerable variations between Eastern (high) and Western Europe (low) and among serovars. In the United States, *E. coli* and *Salmonella* quinolone resistance is substantially lower than in most of Europe. Low resistance rates for *Salmonella* in France and the United States could be associated with national control initiatives.20,21 For *Campylobacter*, resistance to quinolones (particularly ciprofloxacin) and tetracycline is high (>50%) in Europe, especially in poultry isolates; in the United States, quinolone resistance has remained at lower levels since the 2005 ban on using this class of drugs for animals.15

In LMICs, surveillance systems are largely nascent, and efforts to document the burden of AMR in animals have relied on second-best amalgamation of case studies and point prevalence surveys, often conducted using heterogeneous sampling schemes and laboratory protocols. A summary of 900 surveys,22 ranging from mixed farm-household surveys in Nigeria23 and Kenya24 to prospective surveys for new resistance genes in broilers in Pakistan25 and in salmon farms in Chile,26 quantified and mapped the prevalence of resistance for multiple antibiotics in chickens, cattle, and pigs. This geographic analysis identified likely hotspots for AMR in animals in southern India, north eastern China,27 southern Brazil, Ethiopia, and the peri-urban region of Johannesburg. Resistance levels in *E. coli* and *Salmonella* spp. to quinolones in LMICs were comparable to levels in Europe, but gentamicin resistance was higher in LMICs (5–38%) than in Europe (2·4–8·9%). In comparisons with LMICs and the United States, however, quinolone resistance was lower (2·4–4·6%) and gentamicin resistance higher (22·1% and 41·3% for *Salmonella* and *E. coli*, respectively). In *Campylobacter* spp., the highest resistance rates were identified for tetracyclines (60%) and quinolones (60%). Tetracycline resistance was also highest in the United States (49·1–100%). In 2020, researchers sought to quantify the relative prevalence of AMR in aquaculture in Asia, identifying China as the current hotspot of resistance and using an open-access repository (resistancebank.org) (**Figure 1**) for reporting new point prevalence surveys of AMR in animals in LMICs.

Initiatives to ramp up surveillance in LMIC animal sectors have been undertaken by several countries29 and supported by international funders30 but have not yet reported AMR prevalence in an integrated international platform. The need for a globally harmonised surveillance system and reporting platform for human AMR was requested by WHO member states in the 2015 World Health Assembly resolution, leading to the development of GLASS. The World Organization for Animal Health (WOAH, formerly the Office International des Epizooties) started collecting data on the extent and reasons for antimicrobial use in animals (ANIMUSE) in 2015, and in 2022 the UN Food and Agriculture Organization (FAO) began developing the International FAO Antimicrobial Resistance Monitoring (InFARM) platform. WHO GLASS focuses on pathogens relevant to human health but also includes organisms relevant to other sectors, such as *E. coli* and *Salmonella* spp. In addition, WHO supports the country implementation of the integrated TriCycle module of extended-spectrum beta-lactamase (ESBL)–producing *E. coli*,31 which surveys the prevalence of these resistant bacteria in sick and healthy humans, livestock and food, and the environment. TriCycle was developed by WHO, in collaboration with WOAH and FAO.

**Panel 2. AWaRe: A traffic light approach to antibiotic use**

In 2017, the WHO developed the AWaRe system for categorising the more than 250 antibiotics used in humans according to their clinical efficacy, safety, selection of resistance or impact on microbiome, and cost. “Access” antibiotics (e.g., amoxicillin) are generally older, often narrow-spectrum drugs that are still effective in treating common infections, particularly in primary care. They have a good safety profile and are inexpensive (where widely available). “Watch” antibiotics (e.g., third-generation cephalosporins) have a broader spectrum of activity against resistant organisms, are still widely effective against more severe infections in hospitals, generally are more likely to select for resistance, and typically have higher toxicity and higher cost. “Reserve” antibiotics (e.g., colistin) are used as a last resort to treat multidrug-resistant infections in severely ill patients. The WHO Essential Medicines List (EML) includes about 30 Access and Watch antibiotics and 10 in the Reserve class. The WHO recently added a Not Recommended category of antibiotics, mainly inappropriate fixed-dose combinations.

The WHO 2022 EML AWaRe Book guides on the optimal choice of drug, dose, and duration for about 35 common infections in adults and children in primary care and hospital settings, with a strong universal healthcare focus.129 The recommendations now underpin the development of future policy goals. For example, Access antibiotics (most commonly amoxicillin) are the first-choice recommendation for 90% of the most common infections seen in primary care. The AWaRe Book also takes a risk-based approach, giving guidance on when an antibiotic is not recommended, usually for minor respiratory infections. AWaRe-based quality indicators, quality metrics, and educational and stewardship interventions have been developed. The AWaRe system’s traffic light approach has simplified AMU surveillance and monitoring and will dictate in the future which Access antibiotics should be universally available to meet SDG 3·8 (to achieve universal health coverage). Many older Watch antibiotics with little utility are still widely produced, and further guidance on unnecessary antibiotics is needed. Developing policy goals based on absolute levels of Access, Watch, and Reserve antibiotics at a country level will require risk adjustment for burden of disease, demography, mortality, and rates of AMR.

**Panel 3. Challenges in measuring antibiotic use**

The 2023 G20 New Delhi Leader’s Declaration calls for implementing antimicrobial stewardship efforts in national action plans through antibiotic use surveillance, but global surveillance of antibiotic use in humans has seen less progress than surveillance for resistance. The GLASS guide to collecting and reporting resistance data was launched in 2016; its antibiotic use modules did not start until 2020, and most of its data sources do not measure actual antibiotic use by patients. The 2022 GLASS report2 noted that 109 countries were enrolled in GLASS AMR, with 87 providing data; only 36 were enrolled in GLASS-AMC (Antimicrobial Consumption), and only 27 countries were providing data, although information was available from other sources (e.g., ESAC-Net). GLASS reports that about 95% of overall antibiotic use is oral; the rest is parenteral. To be useful at a country level, surveillance data should be representative of the target population and without substantial bias. Improved macro-, mid-, and micro-level data are needed to enable robust country-level attribution of total and AWaRe levels (see **Panel 2**) of antibiotic use to inform evidence-based goals.

Macro-level data on global antibiotic trade—a complex market involving imports, manufacturing, and exports—are limited. Countries provide their own data to GLASS. The World Customs Organisation Harmonised System is used by the World Trade Organisation to monitor global trade in active pharmaceutical ingredients and pharmaceutical products. In this system, the two main subcategories monitored are (i) penicillins and streptomycins and (ii) all other antibiotics, whose mass production and export started more recently.133 Interestingly, Thailand has detailed and publicly available use data broken down by antibiotic because it mandates annual reporting of the total volume of imported and manufactured medicines, including antibiotics, by all market authorisation holders.134 By following this example, other countries could gain insights in the global antibiotic manufacturing and trade landscape.

Pharmaceutical production is concentrated predominantly in China and India, but also occurs in the European Union.135 The International Federation of Pharmaceutical Manufacturers and Associations and the AMR Industry Alliance have clear statements on industry’s role in supporting antibiotic use and stewardship policies, but they represent only a small portion of the estimated $50 billion/year antibiotic manufacturing sector, which grows at an estimated annual rate of more than 5%. A large data set of antibiotic wholesale distribution and sales, covering about 75 countries from 2000 onwards, is available (commercially) from IQVIA MIDAS. It provides estimates of country-level sales based on an IQVIA confidential in-house algorithm. Many caveats are required when estimating population-level exposure, but MIDAS reports data on tens of billions of defined daily doses/year. Some (predominantly high-income) countries have access to national pharmacy data or insurance claims and procurement data. In LMICs, estimates of use can be obtained from major donors or non-governmental organisations like Oxfam and Médecins sans Frontiers.

At a micro level, primary care data collection is inadequate in most LMICs. Patterns of use can be assessed through facility exit interviews, prescription audits, household surveys, and point prevalence surveys. Global-PPS (point prevalence survey)136 is a voluntary hospital survey without a representative sampling frame, and other methods have been developed, including by GLASS. Patient-level data collection is problematic because many patients taking unprescribed antibiotics do not know the identity of their medication.137 As we learned during COVID-19, just having a representative sampling frame is often insufficient because estimates can still be biased by non-response if this is not accounted for through weighting and/or post-stratification.138

Despite widespread antibiotic use in primary healthcare and the doubling of use in LMICs over the past decade,139 little surveillance below tertiary care has been undertaken. The ABACUS project140 and others141–143 have reported the wide variation in primary healthcare provision globally. Antibiotics in the community may be obtained from public facilities, pharmacies, private providers, and the informal sector. Other sources of data are facility and exit surveys from demographic and health surveys and service provision assessments. Electronic data systems are rarely available in most LMIC primary care facilities, so novel point prevalence survey tools are in development, including the ADILA project Antibiotic Prescribing in Primary Healthcare PPS.144

Global AWaRe targets will likely encourage improved surveillance, but a comprehensive approach is required, given that countries’ data sources vary and will change over time. In the short term, models could use a wider range of existing data sources and impute or predict missing data to provide better estimates. A single, standard method of evaluating and monitoring country-level antibiotic use is needed. Because most antibiotics are used in primary care, a facility-sampling framework, with appropriate adjustments and integration of multiple data sources, should be developed to provide overall country estimates that can be used as SDG indicators. Future surveillance methods should include a wider, standardised assessment of costs across all levels of the supply and distribution sectors to guide target development and programme funding. Existing surveillance structures could be amended to align more closely with future targets. This could include extending current data fields collected in DHS Service Provision Assessments Sick Child Visits to AWaRe antibiotic use in both adults and children. Data on AWaRe antibiotic sales, manufacturing, and trade are required. Country-level commercial sales of older generic antibiotics should become an integral part of GLASS outputs, and aggregated data should be included in the global health observatory this information is already available open access, through GRAM and other sources.

Country-level data on AWaRe antibiotic use will require a more detailed and transparent assessment of global trade flows. Current methods of bridging data between countries with varying data inputs (e.g., IQVIA MIDAS in GRAM) have considerable bias and uncertainty. Improved modelling approaches could provide more representative estimates of population-level antimicrobial exposure, making maximal use of multiple data sources.

**Panel 4. Pathways to more actionable AMR surveillance**

Additional investment and innovation in surveillance of AMR is essential. To investigate AMR prevalence in the community and avoid the clinical isolate bias, active sampling of healthy populations is required. Cost is a key consideration, particularly in LMICs. An exemplary approach for community sampling that can be used with limited resources is included in the WHO TriCycle protocol on integrated AMR surveillance through analysis of the prevalence of ESBL-producing *E. coli* in healthy pregnant women.148 For identification of emerging resistance of low community prevalence, active sampling requires considerable resources. Wastewater analysis can complement human surveillance: resistance rates in isolates retrieved from wastewater have been shown to be highly correlated with those of the associated human community.149,150 However, international validation of wastewater analysis of AMR, especially for the quantitative relationship between wastewater outcomes and population carriage and for non-sewered situations, is required before wastewater sampling can be recommended for wide application.

Available clinical and microbiological information needs to be collated and conveyed to policymakers in easily interpretable forms so that it is used in decision-making. During the COVID-19 pandemic, several platforms—some of them pre-existing—that distilled information about the epidemiological distribution and trajectory of genetic variants were used by policymakers.151 Similar tools are emerging for AMR. They include pathogen-specific platforms, such as Typhinet and Klebnet, as well as the ResistanceMap database and amr.watch and amr net dashboards in development.123

Efforts linking surveillance activities in the human and animal domains are still in their infancy, and even less developed for the intersection with the environmental and plant domain. Transmission of AMR between domains does occur, underpinning the need for integrated, One Health AMR surveillance. For example, restricting the use of antibiotics in food animals is associated with a reduction in the presence of antibiotic-resistant bacteria in humans, predominantly in those with close animal contact,152 probably mediated through transmission of resistant bacteria. Ecologically, resistance levels to specific antibiotics in food animal *Campylobacter* isolates have been associated with those in humans across European countries,153 again pointing to animal-human transmission.

Studies on the relevance of environmental exposures alone are mainly limited to recreational activities.154 In local studies in Malawi applying a One Health sampling approach, human colonisation with ESBL-producing *E. coli* was found associated with the presence of animals in the household and the wet season, suggesting a major influence of exposure to animals and the environment for ESBL colonisation.155 Higher prevalence of ESBL–*E. coli* has also been found in pregnant women in Madagascar156 during the wet season and rainfall, probably related to higher fecal-oral dissemination through environmental transmission. Last, according to a systematic review of African studies, drinking water quality can also affect ESBL carriage. Information on the exact transmission routes of resistant bacteria in LMICs is needed to guide interventions. Studies in this field require simultaneous—and ideally longitudinal—sampling of human populations and environmental matrices and can be informed by systematic environmental surveillance.157

Data on human exposure to AMR from different domains is one output of Integrated One Health surveillance. Other purposes are evaluating trends in AMR or AMU in several domains, monitoring new forms of antimicrobial resistance, and analysing the effectiveness of interventions. These goals require different sample sources and analysis endpoints. Among the efforts to develop guidance on integrated surveillance are Joint Actions within the European Union and the Quadripartite Technical Group on Integrated Surveillance.158 A blueprint for a harmonised sampling effort with ESBL–*E. coli* as one common indicator has been put forward by WHO.31 This integrated TriCycle protocol includes resistance in bloodstream infections and in the community, poultry and poultry wet market or slaughterhouse wastewater, human wastewater, and river water.31 First TriCycle iterations have been completed in Indonesia,159 Madagascar,156 Ghana,160 and Pakistan, and the protocol is being applied in several other countries.

Where surveillance data on resistance and use are lacking, how can we derive the evidence we need? Modelling is associated with uncertainty because it assumes that a relationship between AMR and risk factors is valid across similar geographies, which it often is not. Nevertheless, filling data gaps can help synthesise evidence to estimate a burden for comparison across regions or diseases and can thus help set priorities. Filling gaps can also motivate surveillance by calling on doubters to challenge a model with data. Extrapolation has greater uncertainty than gap filling because it assumes that a relationship between AMR and risk factors will remain valid beyond the temporal or geographic domains used for training the model. Extrapolations can nevertheless serve a purpose for ‘what if’ scenarios. For example, what happens if the animal sector continues to grow, and antibiotics are used with the same intensity as today? It is crucial to differentiate scenarios (what could happen) from projections (what will happen).

**Panel 5.** **Bringing AMR surveillance into the 21st century: Recommendations**

* Every country should have a national surveillance system that tracks antimicrobial resistance and use, with in-country granularity, and can be used to evaluate programmes to meet goals for addressing resistance.
* Diagnostic testing for patients suspected of having a bacterial or fungal infection should be supported at all levels of care, to promote rational antimicrobial use and enhance surveillance.
* Data from routine clinical bacteriology laboratories can and should contribute to antimicrobial resistance surveillance but should form only part of the national surveillance picture. Countries should use available surveillance modules. The TriCycle protocol generates information on resistance in the clinic, the community, the food chain, and the environment at low cost. Point prevalence surveys can supplement laboratory-based surveillance that covers too few geographic areas or only tertiary care.
* Efforts should link resistance rates in pathogens to disease outcomes, to measure the actual burden of AMR. ACORN9,145 offers one model that has been piloted in resource-limited settings.
* Surveillance that incorporates information from isolates from animals, the environment, and healthy people is critical to provide a One Health picture of antimicrobial resistance.
* Regulations on antimicrobial distribution must be strengthened to reduce selection for resistance, improve access for patients for need antimicrobials, and permit antimicrobial use surveillance.
* Electronic data capture is essential for collating and sharing surveillance information and making it available, in a timely manner and in easily used formats, to clinical, antimicrobial stewardship, and public health decision-makers.
* The value of existing surveillance systems should be evaluated, and the methods honed to increase cost-effectiveness and the quality and actionability of the information gleaned.

**References**

1 Murray CJ, Ikuta KS, Sharara F, *et al.* Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet* 2022; **399**: 629–55.

2 World Health Organization. Global antimicrobial resistance and use surveillance system (GLASS) report: 2022. 2022. https://www.who.int/publications/i/item/9789240062702 (accessed Nov 24, 2023).

3 Langford BJ, So M, Simeonova M, *et al.* Antimicrobial resistance in patients with COVID-19: a systematic review and meta-analysis. *The Lancet Microbe* 2023.

4 Kinross P, Gagliotti C, Merk H, *et al.* Large increase in bloodstream infections with carbapenem-resistant Acinetobacter species during the first 2 years of the COVID-19 pandemic, EU/EEA, 2020 and 2021. *Eurosurveillance* 2022; **27**: 2200845.

5 Cassini A, Högberg LD, Plachouras D, *et al.* Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *The Lancet infectious diseases* 2019; **19**: 56–66.

6 Stewardson AJ, Marimuthu K, Sengupta S, *et al.* Effect of carbapenem resistance on outcomes of bloodstream infection caused by Enterobacteriaceae in low-income and middle-income countries (PANORAMA): a multinational prospective cohort study. *The Lancet Infectious Diseases* 2019; **19**: 601–10.

7 Allel K, Stone J, Undurraga EA, *et al.* The impact of inpatient bloodstream infections caused by antibiotic-resistant bacteria in low-and middle-income countries: A systematic review and meta-analysis. *Plos Medicine* 2023; **20**: e1004199.

8 Aiken AM, Rehman AM, de Kraker ME, *et al.* Mortality associated with third-generation cephalosporin resistance in Enterobacterales bloodstream infections at eight sub-Saharan African hospitals (MBIRA): a prospective cohort study. *The Lancet Infectious Diseases* 2023; **23**: 1280–90.

9 Turner P, Ashley EA, Celhay OJ, *et al.* ACORN (A Clinically-Oriented Antimicrobial Resistance Surveillance Network): a pilot protocol for case based antimicrobial resistance surveillance. *Wellcome Open Research* 2020; **5**.

10 World Health Organization. GLASS method for estimating attributable mortality of antimicrobial resistant bloodstream infections. 2020.

11 Burden of AMR and treatment failure in low-, middle- and high-income countries. BALANCE. Ineos Oxford Institute for Antimicrobial Research. https://www.ineosoxford.ox.ac.uk/balance (accessed Nov 18, 2023).

12 Mölstad S, Löfmark S, Carlin K, *et al.* Lessons learnt during 20 years of the Swedish strategic programme against antibiotic resistance. *Bulletin of the World Health Organization* 2017; **95**: 764.

13 Food and Drug Administration. National Antimicrobial Resistance Monitoring System—Enteric bacteria (NARMS): 2007. Executive Report. US Department of Health and Human Services. *FDA, Rockville, MD* 2010.

14 European Food Safety Authority, European Centre for Disease Prevention and Control. The European Union summary report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2016. *EFSA Journal* 2018; **16**: e05182.

15 US Food and Drug Administration. Enrofoxacin for poultry; final decision on withdrawal of new animal drug application following formal evidentiary public hearing; availability. *FR Doc* 2005; : 05–15224.

16 US Food and Drug Administration. FDA’s Strategy on Antimicrobial Resistance - Questions and Answers. http://www.fda.gov/animalveterinary/guidancecomplianceenforcement/guidanceforindustry/ucm216939.htm (accessed Sept 30, 2023).

17 Millet S, Maertens L. The European ban on antibiotic growth promoters in animal feed: from challenges to opportunities. *Veterinary Journal* 2011; **187**: 143–4.

18 Rushton J, Huntington B, Gilbert W, *et al.* Roll-out of the Global Burden of Animal Diseases programme. *The Lancet* 2021; **397**: 1045–6.

19 Laxminarayan R, Matsoso P, Pant S, *et al.* Access to effective antimicrobials: a worldwide challenge. *The Lancet* 2016; **387**: 168–75.

20 DGCCRF. Plan de surveillance des salmonelles dans les matières premières et les aliments pour volailles. Direction générale de la concurrence, de la consommation et de la répression des fraudes, 2018. https://www.economie.gouv.fr/dgccrf/plan-surveillance-et-controle-des-antibiotiques-coccidiostatiques-et-additifs-en-alimentation.

21 Food Safety and Inspection Service, UDSA. Pilot Projects: Salmonella Control Strategies. http://www.fsis.usda.gov/inspection/inspection-programs/inspection-poultry-products/reducing-salmonella-poultry/pilot.

22 Van Boeckel TP, Brower C, Gilbert M, *et al.* Global trends in antimicrobial use in food animals. *Proceedings of the National Academy of Sciences* 2015; **112**: 5649–54.

23 Okpara EO, Ojo OE, Awoyomi OJ, Dipeolu MA, Oyekunle MA, Schwarz S. Antimicrobial usage and presence of extended-spectrum β-lactamase-producing Enterobacteriaceae in animal-rearing households of selected rural and peri-urban communities. *Veterinary microbiology* 2018; **218**: 31–9.

24 Muloi DM, Wee BA, McClean DM, *et al.* Population genomics of Escherichia coli in livestock-keeping households across a rapidly developing urban landscape. *Nature microbiology* 2022; **7**: 581–9.

25 Azam M, Mohsin M, Saleemi MK. Virulence-associated genes and antimicrobial resistance among avian pathogenic Escherichia coli from colibacillosis affected broilers in Pakistan. *Tropical animal health and production* 2019; **51**: 1259–65.

26 Shah SQ, Cabello FC, L’Abée‐Lund TM, *et al.* Antimicrobial resistance and antimicrobial resistance genes in marine bacteria from salmon aquaculture and non‐aquaculture sites. *Environmental microbiology* 2014; **16**: 1310–20.

27 Zhao C, Wang Y, Tiseo K, Pires J, Criscuolo NG, Van Boeckel TP. Geographically targeted surveillance of livestock could help prioritize intervention against antimicrobial resistance in China. *Nature Food* 2021; **2**: 596–602.

28 ResistanceBank. https://resistancebank.org (accessed Nov 24, 2023).

29 National Steering Committee on Antimicrobial Resistance of Thailand. Thailand’s First One Health Report on Antimicrobial Consumption and Antimicrobial Resistance in 2017. 2020 https://rr-asia.woah.org/wp-content/uploads/2020/10/thailand\_s-one-health-report-in-2017.pdf.

30 The Fleming Fund. The Fleming Fund Phase I: A Summary. 2022 https://www.flemingfund.org/publications/the-fleming-fund-phase-i-a-summary/ (accessed Nov 13, 2023).

31 World Health Organization. WHO integrated global surveillance on ESBL-producing E. coli using a “One Health” approach: implementation and opportunities. 2021.

32 Liu L, Oza S, Hogan D, *et al.* Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. *The lancet* 2015; **385**: 430–40.

33 Mahtab S, Madhi SA, Baillie VL, *et al.* Causes of death identified in neonates enrolled through Child Health and Mortality Prevention Surveillance (CHAMPS), December 2016–December 2021. *PLOS Global Public Health* 2023; **3**: e0001612.

34 Chaurasia S, Jeeva Sankar M, Agarwal R, *et al.* Characterisation and antimicrobial resistance of sepsis pathogens in neonates born in tertiary care centres in Delhi, India: a cohort study. *Lancet* 2016; **4**: e752–60.

35 Sands K, Carvalho MJ, Portal E, *et al.* Characterization of antimicrobial-resistant Gram-negative bacteria that cause neonatal sepsis in seven low-and middle-income countries. *Nature microbiology* 2021; **6**: 512–23.

36 Ingle DJ, Levine MM, Kotloff KL, Holt KE, Robins-Browne RM. Dynamics of antimicrobial resistance in intestinal Escherichia coli from children in community settings in South Asia and sub-Saharan Africa. *Nature microbiology* 2018; **3**: 1063–73.

37 Sievert DM, Ricks P, Edwards JR, *et al.* Antimicrobial-resistant pathogens associated with healthcare-associated infections summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009–2010. *Infection Control & Hospital Epidemiology* 2013; **34**: 1–14.

38 Statista Research Department. Proportion of selected age groups of world population and in regions in 2022. Statista. 2023; published online Oct 5. https://www.statista.com/statistics/265759/world-population-by-age-and-region/#:~:text=Globally%2C%20about%2025%20percent%20of,over%2065%20years%20of%20age.

39 Murray CJ, Aravkin AY, Zheng P, *et al.* Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The lancet* 2020; **396**: 1223–49.

40 Ikhimiukor OO, Odih EE, Donado-Godoy P, Okeke IN. A bottom-up view of antimicrobial resistance transmission in developing countries. *Nature Microbiology* 2022; **7**: 757–65.

41 Bouiller K, Bertrand X, Hocquet D, Chirouze C. Human infection of methicillin-susceptible Staphylococcus aureus CC398: a review. *Microorganisms* 2020; **8**: 1737.

42 World Health Organization. Global action plan on antimicrobial resistance. 2016 https://www.who.int/publications/i/item/9789241509763 (accessed Feb 11, 2024).

43 Lewnard JA, Gleason A, Hsu LY, *et al.* Burden of bacterial antimicrobial resistance in low- and middle-income countries avertible by existing interventions: an evidence review and modeling analysis. *Lancet* Forthcoming.

44 Laxminarayan R, Impalli I, Rangarajan R, *et al.* Expanding Antibiotic, Vaccine, and Diagnostics Development and Access to Tackle Antimicrobial Resistance. *Lancet* Forthcoming.

45 Mendelson M, Lewnard JA, Sharland M, *et al.* Ensuring Progress on Sustainable Access to Effective Antibiotics at UNGA 2024: A Target-Based Approach. *Lancet* Forthcoming.

46 Global Research on Antimicrobial Resistance (GRAM). https://www.tropicalmedicine.ox.ac.uk/gram (accessed Dec 7, 2023).

47 NeoOBS. Penta. https://penta-id.org/severe-infections-and-antimicrobial-resistance/neoobs/ (accessed March 19, 2024).

48 Burden of Antibiotic Resistance in Neonates from Developing Societies (BARNARDS). Cardiff University. https://www.cardiff.ac.uk/research/explore/research-units/burden-of-antibiotic-resistance-in-neonates-from-developing-societies-barnards (accessed March 19, 2024).

49 One Health Trust. ResistanceMap. https://resistancemap.onehealthtrust.org (accessed Dec 7, 2023).

50 Pathogenwatch. https://pathogen.watch (accessed Nov 24, 2023).

51 Global Overview of Salmonella Typhi. https://www.typhi.net (accessed Nov 24, 2023).

52 Infectious Diseases Data Observatory. Medicine Quality Scientific Literature Surveyor. https://www.iddo.org/mqsurveyor/ (accessed Nov 24, 2023).

53 Stoll BJ, Puopolo KM, Hansen NI, *et al.* Early-onset neonatal sepsis 2015 to 2017, the rise of Escherichia coli, and the need for novel prevention strategies. *JAMA pediatrics* 2020; **174**: e200593–e200593.

54 UNICEF. Levels and trends in child mortality 2023. 2024 https://data.unicef.org/resources/levels-and-trends-in-child-mortality-2024/ (accessed March 19, 2024).

55 Russell NJ, Stöhr W, Plakkal N, *et al.* Patterns of antibiotic use, pathogens, and prediction of mortality in hospitalized neonates and young infants with sepsis: A global neonatal sepsis observational cohort study (NeoOBS). *PLoS Medicine* 2023; **20**: e1004179.

56 Saha SK, Schrag SJ, El Arifeen S, *et al.* Causes and incidence of community-acquired serious infections among young children in south Asia (ANISA): an observational cohort study. *The Lancet* 2018; **392**: 145–59.

57 Breiman RF, Blau DM, Mutevedzi P, *et al.* Postmortem investigations and identification of multiple causes of child deaths: An analysis of findings from the Child Health and Mortality Prevention Surveillance (CHAMPS) network. *PLoS medicine* 2021; **18**: e1003814.

58 Mduma E, Halidou T, Kaboré B, *et al.* Etiology of severe invasive infections in young infants in rural settings in sub-Saharan Africa. *PloS one* 2022; **17**: e0264322.

59 Mashau RC, Meiring ST, Dramowski A, *et al.* Culture-confirmed neonatal bloodstream infections and meningitis in South Africa, 2014–19: a cross-sectional study. *The Lancet Global Health* 2022; **10**: e1170–8.

60 Cook A, Ferreras-Antolin L, Adhisivam B, *et al.* Neonatal invasive candidiasis in low-and middle-income countries: data from the NeoOBS study. *Medical Mycology* 2023; **61**: myad010.

61 Lockhart SR, Etienne KA, Vallabhaneni S, *et al.* Simultaneous emergence of multidrug-resistant Candida auris on 3 continents confirmed by whole-genome sequencing and epidemiological analyses. *Clinical Infectious Diseases* 2017; **64**: 134–40.

62 World Health Organization. WHO fungal priority pathogens list to guide research, development and public health action. 2022 https://www.who.int/publications/i/item/9789240060241 (accessed Sept 29, 2023).

63 Kekana D, Naicker SD, Shuping L, *et al.* Candida auris Clinical Isolates Associated with Outbreak in Neonatal Unit of Tertiary Academic Hospital, South Africa. *Emerging Infectious Diseases* 2023; **29**: 2044.

64 Obeng-Nkrumah N, Labi A-K, Addison NO, Labi JEM, Awuah-Mensah G. Trends in paediatric and adult bloodstream infections at a Ghanaian referral hospital: a retrospective study. *Annals of clinical microbiology and antimicrobials* 2016; **15**: 1–10.

65 Fleming KA, Horton S, Wilson ML, *et al.* The Lancet Commission on diagnostics: transforming access to diagnostics. *The Lancet* 2021; **398**: 1997–2050.

66 Okeke IN. Divining without seeds: the case for strengthening laboratory medicine in Africa. Cornell University Press, 2011 https://books.google.com/books?hl=en&lr=&id=m6ZX-iwg3VQC&oi=fnd&pg=PR1&dq=Divining+without+seeds+:+the+case+for+strengthening+laboratory+medicine+in+Africa&ots=tl5EM7ofaX&sig=tx-0JgcHQb8o5gG2nZKbI3tdj4c (accessed March 29, 2016).

67 Köser CU, Holden MT, Ellington MJ, *et al.* Rapid whole-genome sequencing for investigation of a neonatal MRSA outbreak. *New England Journal of Medicine* 2012; **366**: 2267–75.

68 Okomo U, Senghore M, Darboe S, *et al.* Investigation of sequential outbreaks of Burkholderia cepacia and multidrug-resistant extended spectrum β-lactamase producing Klebsiella species in a West African tertiary hospital neonatal unit: a retrospective genomic analysis. *The Lancet Microbe* 2020; **1**: e119–29.

69 Harris SR, Cartwright EJ, Török ME, *et al.* Whole-genome sequencing for analysis of an outbreak of meticillin-resistant Staphylococcus aureus: a descriptive study. *The Lancet infectious diseases* 2013; **13**: 130–6.

70 Jauneikaite E, Baker KS, Nunn JG, *et al.* Genomics for antimicrobial resistance surveillance to support infection prevention and control in health-care facilities. *The Lancet Microbe* 2023; **4**: e1040–6.

71 Hu Y, Yang Y, Feng Y, *et al.* Prevalence and clonal diversity of carbapenem-resistant Klebsiella pneumoniae causing neonatal infections: A systematic review of 128 articles across 30 countries. *PLoS Medicine* 2023; **20**: e1004233.

72 Hetland MA, Hawkey J, Bernhoff E, *et al.* Within–patient and global evolutionary dynamics of Klebsiella pneumoniae ST17. *Microbial genomics* 2023; **9**: 001005.

73 Lipworth S, Vihta K-D, Davies T, *et al.* Molecular epidemiology and antimicrobial resistance phenotype of paediatric bloodstream infections caused by Gram-negative bacteria. *Communications Medicine* 2022; **2**: 101.

74 Kumar CK, Sands K, Walsh TR, *et al.* Global, regional, and national estimates of the impact of a maternal Klebsiella pneumoniae vaccine: A Bayesian modeling analysis. *Plos Medicine* 2023; **20**: e1004239.

75 Guest JF, Keating T, Gould D, Wigglesworth N. Modelling the annual NHS costs and outcomes attributable to healthcare-associated infections in England. *BMJ open* 2020; **10**: e033367.

76 Serra-Burriel M, Keys M, Campillo-Artero C, *et al.* Impact of multi-drug resistant bacteria on economic and clinical outcomes of healthcare-associated infections in adults: Systematic review and meta-analysis. *PloS one* 2020; **15**: e0227139.

77 The Institute for Health Metrics and Evaluation. VizHub - GBD Compare. https://vizhub.healthdata.org/gbd-compare/.

78 Hocking L, Ali G-C, d’Angelo C, *et al.* A rapid evidence assessment exploring whether antimicrobial resistance complicates non-infectious health conditions and healthcare services, 2010-20. *JAC Antimicrob Resist* 2021; **3**: dlab171.

79 Miranda MV, González FC, Paredes-Godoy OS, Maulén MA, Vásquez CC, Díaz-Vásquez WA. Characterization of metal(loid)s and antibiotic resistance in bacteria of human gut microbiota from chronic kidney disease subjects. *Biol Res* 2022; **55**: 23.

80 Signing AT, Marbou WJT, Penlap Beng V, Kuete V. Antibiotic Resistance Profile of Uropathogenic Bacteria in Diabetic Patients at the Bafoussam Regional Hospital, West Cameroon Region. *Cureus* 2020; **12**: e9345.

81 Ronconi G, Dondi L, Calabria S, *et al.* [Community acquired pneumoniae and chronic obstructive pulmonary disease: the RWE analysis of events that required hospitalizations, and healthcare integrated costs.]. *Recenti Prog Med* 2023; **118**: 204–21.

82 Sonkoue Lambou JC, Noubom M, Djoumsie Gomseu BE, Takougoum Marbou WJ, Tamokou J-D-D, Gatsing D. Multidrug-Resistant Escherichia coli Causing Urinary Tract Infections among Controlled and Uncontrolled Type 2 Diabetic Patients at Laquintinie Hospital in Douala, Cameroon. *Can J Infect Dis Med Microbiol* 2022; **2022**: 1250264.

83 Nanayakkara AK, Boucher HW, Fowler VGJ, Jezek A, Outterson K, Greenberg DE. Antibiotic resistance in the patient with cancer: Escalating challenges and paths forward. *CA Cancer J Clin* 2021; **71**: 488–504.

84 AMR Control. AMR Control Supplement: The Challenge for the Cancer Community. 2022 http://resistancecontrol.info/amr2022/ (accessed Nov 24, 2023).

85 Zheng Y, Chen Y, Yu K, *et al.* Fatal infections among cancer patients: a population-based study in the United States. *Infectious diseases and therapy* 2021; **10**: 871–95.

86 Barrios CH. Global challenges in breast cancer detection and treatment. *The Breast* 2022; **62**: S3–6.

87 Cornejo-Juárez P, Vilar-Compte D, Pérez-Jiménez C, Ñamendys-Silva S, Sandoval-Hernández S, Volkow-Fernández P. The impact of hospital-acquired infections with multidrug-resistant bacteria in an oncology intensive care unit. *International Journal of Infectious Diseases* 2015; **31**: 31–4.

88 Bodro M, Gudiol C, Garcia-Vidal C, *et al.* Epidemiology, antibiotic therapy and outcomes of bacteremia caused by drug-resistant ESKAPE pathogens in cancer patients. *Supportive Care in Cancer* 2014; **22**: 603–10.

89 Scheich S, Weber S, Reinheimer C, *et al.* Bloodstream infections with gram-negative organisms and the impact of multidrug resistance in patients with hematological malignancies. *Annals of hematology* 2018; **97**: 2225–34.

90 Tang Y, Xu C, Xiao H, Wang L, Cheng Q, Li X. Gram-negative bacteria bloodstream infections in patients with hematological malignancies–the impact of pathogen type and patterns of antibiotic resistance: a Retrospective Cohort Study. *Infection and Drug Resistance* 2021; : 3115–24.

91 Teillant A, Gandra S, Barter D, Morgan D, Laxminarayan R. Potential burden of antibiotic resistance on surgery and cancer chemotherapy antibiotic prophylaxis in the USA: a literature review and modelling study. *Lancet Infectious Diseases* 2015; **15**: 1429–37.

92 Gandra S, Trett A, Alvarez-Uria G, Solomkin JS, Laxminarayan R. Is the efficacy of antibiotic prophylaxis for surgical procedures decreasing? Systematic review and meta-analysis of randomized control trials. *Infection Control & Hospital Epidemiology* 2019; **40**: 133–41.

93 Yang X, Chen H, Zheng Y, Qu S, Wang H, Yi F. Disease burden and long-term trends of urinary tract infections: A worldwide report. *Frontiers in Public Health* 2022; **10**: 888205.

94 Ansaldi Y, de Tejada Weber BM. Urinary tract infections in pregnancy. *Clinical microbiology and infection* 2022.

95 Foxman B, Manning SD, Tallman P, *et al.* Uropathogenic Escherichia coli are more likely than commensal E. coli to be shared between heterosexual sex partners. *American journal of epidemiology* 2002; **156**: 1133–40.

96 Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. *Nature reviews microbiology* 2015; **13**: 269–84.

97 Gibreel TM, Dodgson AR, Cheesbrough J, Fox AJ, Bolton FJ, Upton M. Population structure, virulence potential and antibiotic susceptibility of uropathogenic Escherichia coli from Northwest England. *Journal of Antimicrobial Chemotherapy* 2012; **67**: 346–56.

98 Nicolas-Chanoine M-H, Bertrand X, Madec J-Y. Escherichia coli ST131, an intriguing clonal group. *Clinical microbiology reviews* 2014; **27**: 543–74.

99 Kumarasamy KK, Toleman MA, Walsh TR, *et al.* Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. *The Lancet infectious diseases* 2010; **10**: 597–602.

100 Lee J, Sunny S, Nazarian E, *et al.* Carbapenem-Resistant Klebsiella pneumoniae in Large Public Acute-Care Healthcare System, New York, New York, USA, 2016–2022. *Emerging Infectious Diseases* 2023; **29**: 1973.

101 World Health Organization. Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021. 2021 https://www.who.int/publications/i/item/9789240027077 (accessed Feb 11, 2024).

102 Rowley J, Vander Hoorn S, Korenromp E, *et al.* Chlamydia, gonorrhoea, trichomoniasis and syphilis: global prevalence and incidence estimates, 2016. *Bulletin of the World Health Organization* 2019; **97**: 548.

103 Mortimer TD, Pathela P, Crawley A, *et al.* The distribution and spread of susceptible and resistant Neisseria gonorrhoeae across demographic groups in a major metropolitan center. *Clinical Infectious Diseases* 2021; **73**: e3146–55.

104 Centers for Disease Control and Prevention. Sexually Transmitted Disease Surveillance 2018. 2019 https://www.cdc.gov/std/stats18/STDSurveillance2018-full-report.pdf (accessed Feb 11, 2024).

105 Kakooza F, Golparian D, Matoga M, *et al.* Genomic surveillance and antimicrobial resistance determinants in Neisseria gonorrhoeae isolates from Uganda, Malawi and South Africa, 2015–20. *Journal of Antimicrobial Chemotherapy* 2023; **78**: 1982–91.

106 Yahara K, Ma KC, Mortimer TD, *et al.* Emergence and evolution of antimicrobial resistance genes and mutations in Neisseria gonorrhoeae. *Genome medicine* 2021; **13**: 1–12.

107 Fifer H, Cole M, Hughes G, *et al.* Sustained transmission of high-level azithromycin-resistant Neisseria gonorrhoeae in England: an observational study. *The Lancet Infectious Diseases* 2018; **18**: 573–81.

108 Lahra MM, Martin I, Demczuk W, *et al.* Cooperative recognition of internationally disseminated ceftriaxone-resistant Neisseria gonorrhoeae strain. *Emerging infectious diseases* 2018; **24**: 735.

109 Attram N, Dela H, Behene E, *et al.* Antimicrobial use of patients with sexually transmitted infection symptoms prior to presentation at five health facilities in Southern Ghana. *Antimicrobial Resistance & Infection Control* 2023; **12**: 146.

110 Bolan GA, Sparling PF, Wasserheit JN. The emerging threat of untreatable gonococcal infection. *The New England journal of medicine* 2012; **366**: 485.

111 Gaydos CA, Melendez JH. Point-by-point progress: gonorrhea point of care tests. *Expert review of molecular diagnostics* 2020; **20**: 803–13.

112 Bradford PA, Miller AA, O’Donnell J, Mueller JP. Zoliflodacin: an oral spiropyrimidinetrione antibiotic for the treatment of Neisseria gonorrheae, including multi-drug-resistant isolates. *ACS Infectious Diseases* 2020; **6**: 1332–45.

113 Yaesoubi R, Xi Q, Hsu K, *et al.* The Impact of Rapid Drug Susceptibility Tests on Gonorrhea Burden and the Life Span of Antibiotic Treatments: A Modeling Study Among Men Who Have Sex With Men in the United States. *American Journal of Epidemiology* 2024; **193**: 17–25.

114 Lyu Y, Choong A, Chow EP, *et al.* Vaccine value profile for Neisseria gonorrhoeae. *Vaccine* 2023.

115 Padeniya TN, Hui BB, Wood JG, Seib KL, Regan DG. The potential impact of a vaccine on Neisseria gonorrhoeae prevalence among heterosexuals living in a high prevalence setting. *Vaccine* 2023; **41**: 5553–61.

116 Stuart BM, Pullen RL. Typhoid: clinical analysis of three hundred and sixty cases. *Archives of Internal Medicine* 1946; **78**: 629–61.

117 Willis LD, Chandler C. Quick fix for care, productivity, hygiene and inequality: reframing the entrenched problem of antibiotic overuse. *BMJ global health* 2019; **4**: e001590.

118 Mintz ED, Guerrant RL. A lion in our village—the unconscionable tragedy of cholera in Africa. *New England Journal of Medicine* 2009; **360**: 1060–3.

119 Andrews JR, Qamar FN, Charles RC, Ryan ET. Extensively drug-resistant typhoid—are conjugate vaccines arriving just in time? *New England Journal of Medicine* 2018; **379**: 1493–5.

120 Kim S, Lee KS, Pak GD, *et al.* Spatial and temporal patterns of typhoid and paratyphoid fever outbreaks: a worldwide review, 1990–2018. *Clinical Infectious Diseases* 2019; **69**: S499–509.

121 Wong VK, Baker S, Pickard DJ, *et al.* Phylogeographical analysis of the dominant multidrug-resistant H58 clade of Salmonella Typhi identifies inter-and intracontinental transmission events. *Nature genetics* 2015; **47**: 632–9.

122 Carey ME, Dyson ZA, Ingle DJ, *et al.* Global diversity and antimicrobial resistance of typhoid fever pathogens: Insights from a meta-analysis of 13,000 Salmonella Typhi genomes. *Elife* 2023; **12**: e85867.

123 Carey ME, Dyson ZA, Argimón S, *et al.* Unlocking the potential of genomic data to inform typhoid fever control policy: supportive resources for genomic data generation, analysis, and visualization. Oxford University Press US, 2023: S38–46.

124 Baker KS, Jauneikaite E, Hopkins KL, *et al.* Genomics for public health and international surveillance of antimicrobial resistance. *The Lancet Microbe* 2023; **4**: e1047–55.

125 Mogasale V, Ramani E, Mogasale VV, Park J. What proportion of Salmonella Typhi cases are detected by blood culture? A systematic literature review. *Annals of clinical microbiology and antimicrobials* 2016; **15**: 1–8.

126 Coalition Against Typhoid. Typhoid Vaccines. https://www.coalitionagainsttyphoid.org/the-issues/typhoid-vaccines/ (accessed Feb 15, 2024).

127 Bentley SD, Lo SW. Global genomic pathogen surveillance to inform vaccine strategies: a decade-long expedition in pneumococcal genomics. *Genome Medicine* 2021; **13**: 84.

128 Browne AJ, Chipeta MG, Haines-Woodhouse G, *et al.* Global antibiotic consumption and usage in humans, 2000–18: a spatial modelling study. *The Lancet Planetary Health* 2021; **5**: e893–904.

129 World Health Organization. The WHO AWaRe (access, watch, reserve) antibiotic book. Geneva: World Health Organization, 2022.

130 Mulchandani R, Wang Y, Gilbert M, Van Boeckel TP. Global trends in antimicrobial use in food-producing animals: 2020 to 2030. *PLOS Global Public Health* 2023; **3**: e0001305.

131 Cavany S, Nanyonga S, Hauk C, *et al.* The uncertain role of substandard and falsified medicines in the emergence and spread of antimicrobial resistance. *Nature Communications* 2023; **14**: 6153.

132 Weinstein ZB, Zaman MH. Evolution of rifampin resistance in Escherichia coli and Mycobacterium smegmatis due to substandard drugs. *Antimicrobial agents and chemotherapy* 2019; **63**: 10–1128.

133 Bjerke L. Antibiotic geographies and access to medicines: Tracing the role of India’s pharmaceutical industry in global trade. *Social Science & Medicine* 2022; **312**: 115386.

134 Health Policy and Systems Research on Antimicrobial Resistance (HPSR-AMR) Network. Thailand One Health Dashboard on Antimicrobial Resistance. https://www.thaiamrwatch.net (accessed Nov 24, 2023).

135 Kumar V, Bansal V, Madhavan A, *et al.* Active pharmaceutical ingredient (API) chemicals: a critical review of current biotechnological approaches. *Bioengineered* 2022; **13**: 4309–27.

136 Homepage. Global-PPS. https://www.global-pps.com (accessed Nov 24, 2023).

137 Monnier AA, Do NT, Asante KP, *et al.* Is this pill an antibiotic or a painkiller? Improving the identification of oral antibiotics for better use. *The Lancet Global Health* 2023; **11**: e1308–13.

138 Bradley VC, Kuriwaki S, Isakov M, Sejdinovic D, Meng X-L, Flaxman S. Unrepresentative big surveys significantly overestimated US vaccine uptake. *Nature* 2021; **600**: 695–700.

139 Klein EY, Milkowska-Shibata M, Tseng KK, *et al.* Assessment of WHO antibiotic consumption and access targets in 76 countries, 2000–15: an analysis of pharmaceutical sales data. *The Lancet Infectious Diseases* 2021; **21**: 107–15.

140 Wertheim HF, Chuc NTK, Punpuing S, *et al.* Community-level antibiotic access and use (ABACUS) in low-and middle-income countries: finding targets for social interventions to improve appropriate antimicrobial use–an observational multi-Centre study. *Wellcome Open Research* 2017; **2**.

141 Morgan DJ, Okeke IN, Laxminarayan R, Perencevich EN, Weisenberg S. Non-prescription antimicrobial use worldwide: a systematic review. *The Lancet infectious diseases* 2011; **11**: 692–701.

142 Whyte SR, Van der Geest S, Hardon A. Social lives of medicines. Cambridge University Press, 2002.

143 Okeke IN, Lamikanra A, Edelman R. Socioeconomic and behavioral factors leading to acquired bacterial resistance to antibiotics in developing countries. *Emerging infectious diseases* 1999; **5**: 18.

144 The Global Health Network. Antibiotic Prescribing in Primary Healthcare Point Prevalence Survey (APC-PPS). https://amr.tghn.org/adila/apc-pps/ (accessed Nov 24, 2023).

145 van Doorn HR, Ashley EA, Turner P. Case-based surveillance of antimicrobial resistance in the ACORN (A Clinically Oriented Antimicrobial Resistance Surveillance Network) study. *JAC-Antimicrobial Resistance* 2020; **2**: dlaa018.

146 Laupland K. Defining the epidemiology of bloodstream infections: the ‘gold standard’of population-based assessment. *Epidemiology & Infection* 2013; **141**: 2149–57.

147 Hasegawa S, Livorsi DJ, Perencevich EN, Church JN, Goto M. Diagnostic accuracy of hospital antibiograms in predicting the risk of antimicrobial resistance in enterobacteriaceae isolates: a nationwide multicenter evaluation at the Veterans Health Administration. *Clinical infectious diseases* 2023; **77**: 1492–500.

148 Sintondji K, Fabiyi K, Hougbenou J, *et al.* Prevalence and characterization of ESBL-producing Escherichia coli in healthy pregnant women and hospital environments in Benin: an approach based on Tricycle. *Frontiers in public health* 2023; **11**.

149 Blaak H, Kemper MA, de Man H, *et al.* Nationwide surveillance reveals frequent detection of carbapenemase-producing Enterobacterales in Dutch municipal wastewater. *Science of The Total Environment* 2021; **776**: 145925.

150 Hutinel M, Huijbers PMC, Fick J, Åhrén C, Larsson DGJ, Flach C-F. Population-level surveillance of antibiotic resistance in Escherichia coli through sewage analysis. *Eurosurveillance* 2019; **24**: 1800497.

151 Argimón S, Abudahab K, Goater RJ, *et al.* Microreact: visualizing and sharing data for genomic epidemiology and phylogeography. *Microbial genomics* 2016; **2**: e000093.

152 Tang KL, Caffrey NP, Nóbrega DB, *et al.* Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: a systematic review and meta-analysis. *The Lancet Planetary Health* 2017; **1**: e316–27.

153 European Centre for Disease Prevention and Control (ECDC), European Food Safety Authority (EFSA), European Medicines Agency. Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) Report. 2017; **15**: e04872.

154 Leonard AF, Morris D, Schmitt H, Gaze WH. Natural recreational waters and the risk that exposure to antibiotic resistant bacteria poses to human health. *Current opinion in microbiology* 2022; **65**: 40–6.

155 Cocker D, Chidziwisano K, Mphasa M, *et al.* Investigating One Health risks for human colonisation with extended spectrum β-lactamase-producing Escherichia coli and Klebsiella pneumoniae in Malawian households: a longitudinal cohort study. *The Lancet Microbe* 2023.

156 Milenkov M, Rasoanandrasana S, Rahajamanana LV, *et al.* Prevalence, risk factors, and genetic characterization of extended-spectrum beta-lactamase Escherichia coli isolated from healthy pregnant women in Madagascar. *Frontiers in Microbiology* 2021; **12**: 786146.

157 Hooban B, Fitzhenry K, O’Connor L, *et al.* A longitudinal survey of antibiotic-resistant Enterobacterales in the Irish environment, 2019–2020. *Science of the Total Environment* 2022; **828**: 154488.

158 Quadripartite Technical Group on Antimicrobial Resistance and Use Integrated Surveillance (QTG-AIS). World Health Organization. https://www.who.int/groups/quadripartite-technical-group-on-integrated-surveillance-on-antimicrobial-use-and-resistance (accessed Nov 30, 2023).

159 Puspandari N, Sunarno S, Febrianti T, *et al.* Extended spectrum beta-lactamase-producing Escherichia coli surveillance in the human, food chain, and environment sectors: Tricycle project (pilot) in Indonesia. *One Health* 2021; **13**: 100331.

160 Banu RA, Alvarez JM, Reid AJ, *et al.* Extended Spectrum Beta-Lactamase in River Waters Collected from Two Cities in Ghana, 2018-2020. 2021.

161 World Health Organization. Antimicrobial resistance: global report on surveillance. 2014 https://www.who.int/publications/i/item/9789241564748 (accessed Feb 13, 2024).

162 68th World Health Assembly. SIXTY-EIGHTH WORLD HEALTH ASSEMBLY, WHA68.7, Global action plan on antimicrobial resistance. 2015; published online May 26. https://apps.who.int/gb/ebwha/pdf\_files/WHA68/A68\_R7-en.pdf (accessed Feb 11, 2024).

163 European Centre for Disease Prevention and Control. European Antimicrobial Resistance Surveillance Network (EARS-Net). European Centre for Disease Prevention and Control. https://www.ecdc.europa.eu/en/about-us/networks/disease-networks-and-laboratory-networks/ears-net-data (accessed Feb 14, 2024).

164 World Health Organization. Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR). World Health Organization. https://www.who.int/europe/groups/central-asian-and-european-surveillance-of-antimicrobial-resistance-(caesar) (accessed Feb 14, 2024).

165 Pan American Health Organization. Latin American and Caribbean Network for Antimicrobial Resistance Surveillance - ReLAVRA+. Pan American Health Organization. https://www.paho.org/en/topics/antimicrobial-resistance/latin-american-and-caribbean-network-antimicrobial-resistance (accessed Feb 14, 2024).

166 World Health Organization. Methodological principles of nationally representative surveys as a platform for global surveillance of antimicrobial resistance in human bloodstream infections. 2023 https://www.who.int/publications/i/item/9789240067004 (accessed Feb 11, 2024).

167 Grundmann H, Aanensen DM, van den Wijngaard CC, Spratt BG, Harmsen D, Friedrich AW. Geographic distribution of Staphylococcus aureus causing invasive infections in Europe: a molecular-epidemiological analysis. *PLoS medicine* 2010; **7**: e1000215–e1000215.

168 David S, Reuter S, Harris SR, *et al.* Epidemic of carbapenem-resistant Klebsiella pneumoniae in Europe is driven by nosocomial spread. *Nature microbiology* 2019; **4**: 1919–29.

169 De Kraker M, Wolkewitz M, Davey P, *et al.* Burden of antimicrobial resistance in European hospitals: excess mortality and length of hospital stay associated with bloodstream infections due to Escherichia coli resistant to third-generation cephalosporins. *Journal of Antimicrobial Chemotherapy* 2011; **66**: 398–407.

170 Esteban-Cantos A, Aracil B, Bautista V, *et al.* The carbapenemase-producing Klebsiella pneumoniae population is distinct and more clonal than the carbapenem-susceptible population. *Antimicrobial Agents and Chemotherapy* 2017; **61**: 10–1128.

171 Grundmann H, Glasner C, Albiger B, *et al.* Occurrence of carbapenemase-producing Klebsiella pneumoniae and Escherichia coli in the European survey of carbapenemase-producing Enterobacteriaceae (EuSCAPE): a prospective, multinational study. *The Lancet infectious diseases* 2017; **17**: 153–63.

172 Liu Y-Y, Wang Y, Walsh TR, *et al.* Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study. *The Lancet Infectious Diseases* 2015; published online Nov. DOI:10.1016/S1473-3099(15)00424-7.

173 Ordaya EE, Abu Saleh OM, Vergidis P, Deml SM, Wengenack NL, Fida M. Temporal trends in antifungal susceptibility of Cryptococcus neoformans isolates from a reference laboratory in the United States, 2011–2021. *Mycoses* 2024; **67**: e13691.

174 Bongomin F, Oladele RO, Gago S, Moore CB, Richardson MD. A systematic review of fluconazole resistance in clinical isolates of Cryptococcus species. *Mycoses* 2018; **61**: 290–7.

175 Argimón S, Masim MA, Gayeta JM, *et al.* Integrating whole-genome sequencing within the National Antimicrobial Resistance Surveillance Program in the Philippines. *Nature communications* 2020; **11**: 2719.

176 O’Brien TF, Stelling JM. WHONET: an information system for monitoring antimicrobial resistance. *Emerging infectious diseases* 1995; **1**: 66.

**FIGURE CAPTIONS**

**Figure 1. Change in prevalence of antimicrobial resistance in animals in low- and middle-income countries between 2000-2010 vs 2011-2020.** Points prevalence surveys obtained from resistancebank.org28 for chicken (A, n = 565), pigs (B, n= 303), and cattle (C, n = 407). AMP, Ampicillin; CHL, Chloramphenicol; CIP, Ciprofloxacin; CTX, Cefotaxime; GEN, Gentamicin; SXT, Sulfamethoxazole-Trimethoprim; TET, Tetracycline.

**Figure 2. AMR retards progress towards global childhood survival targets**. (A) Progress in reducing under five mortality, neonatal mortality, and neonatal sepsis since 2000 (solid lines) in comparison to the Sustainable Development Goal targets for neonatal and under five mortality (dotted lines). Dashed lines present a counterfactual scenario were there to be no AMR-attributable deaths (see Supplement for details). The counterfactual scenario’s shift from the reported values is based on the Global Burden of Disease Antimicrobial Resistance study1 and the rate of change is calculated from cohort studies on antimicrobial resistance.34–36 (B) Reported percent changes in the last decade of neonatal sepsis isolates by drug resistance. Source data is the same as that informing the rate of change in the no AMR counterfactual scenario in (A). Multidrug resistance (MDR) is defined akin to Sievert et al.37 to mean drug resistance to a majority of the currently prescribed antibiotic treatments at time of data analysis. (C) Progress in reducing bacterial mortality stratified by age group. All Global Burden of Disease syndromic causes that have bacterial underpinnings are summed for the two age groups.

**Figure 3. Drug-resistant infections present a significant burden on aging populations.** (A) Estimated number of AMR-attributable deaths (i.e., infection from a drug-resistant pathogen that is in the causal chain of death) stratified by the top five pathogens among individuals over 65 years. The height of the bars represents the total number of all-cause over 65 deaths that are attributable to an AMR pathogen while the colored section of each bar represents the contribution of each pathogen. Data are shown by geographic GBD super region. (B) Percent of all-cause over 65 mortality that are attributable to AMR by pathogen. Same as **SI pg 6** but for individuals over 65. Source data on the burden of AMR pathogens are from the GRAM study,1 and estimates for the total number of all-cause over 65 deaths for scaling in (B) are from the GBD study.39 Estimates reflect the situation as of 2019.

**Figure 4. Evolution of antimicrobial resistance in *Salmonella* enteric serovar. Typhi and consequently mandated shifts in treatment over three-quarters of a century.** We illustrate the evolution of AMR in an extended figure adapted from Andrews et al. 2018.119