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GLOBAL INFECTION PREVENTION AND MANAGEMENT IN HEALTHCARE

Antimicrobial resistance and One Health

VOLUME 1

Editors: Massimo Sartelli, Federico Coccolini, Fausto Catena and Leonardo Pagani

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GLOBAL INFECTION PREVENTION AND MANAGEMENT IN HEALTHCARE

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Editors

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The Global Antimicrobial Stewardship Partnership Hub

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Preface

Antimicrobial resistance (AMR) is a natural phenomenon that occurs as microbes evolve. However, misuse and overuse of antimicrobials, associated with ineffective infection prevention and control practices, are recognized as major drivers for the development and spread of AMR.

The substantial problem of AMR is especially relevant to antibiotic resistance, although antifungal resistance is increasing at an alarming rate and, in recent years, *Candida auris* has emerged worldwide as a MDRO.

Antibiotics can be lifesaving when treating patients with bacterial infections but are often used inappropriately, specifically when administered unnecessary or for excessive durations or without considering pharmacokinetic principles. Large variations in antibiotic consumption exist among countries worldwide, and while excessive use remains a major problem in some areas of the world, elsewhere there is a lack of access to many antibiotics.

AMR is not a disease for which we should expect to develop a cure. Instead, it is a complex phenomenon, involving multiple disciplines – working locally, nationally, and globally – to attain optimal health for people, animals, and the environment. It is a phenomenon that undermines the treatment of many infectious diseases affecting health systems all over the world. AMR is not something that you can identify easily, such as malaria or HIV. AMR is part of a larger phenomenon and is thus not amenable to easy technical interventions.

All prescribed antibiotics can contribute to the spread of AMR; therefore, it is important to understand how antibiotics in human health or animal health can drive the development and spread of AMR. Moreover, a vast majority of bacteria are essential for life and the health of humans, animals, and the ecosystem and only a very small percentage of them cause infectious diseases. This implies that the treatment of infections should be optimized in a way that does not make the cure worse than the disease.

Actions against AMR should focus firstly on local needs and national action plans because each country is different. However, resistance is everyone's problem and all countries have a role in solving the problem.

Some countries that have developed inclusive national plans have been successful in controlling AMR. These approaches include: improving awareness and understanding of AMR through effective communication, education, and training; strengthening the knowledge through surveillance and research; reducing the incidence of infection through effective sanitation, hygiene, and infection prevention measures; and optimizing the use of antimicrobial agents in human and animal health. These strategies demand patience and time to be organized. Furthermore, they require a comprehensive endorsement from the government authorities with ample funds.

However, AMR poses a global challenge. No single country, however effective it is at containing AMR within its boundaries, can protect itself from the importation of AMR through travel and trade. Working alone is not sufficient and international partnerships to seek global solutions are mandatory to tackle AMR.

By collaborating, there are opportunities for disseminating the best approaches for infection prevention and management. The global nature of AMR calls for a global response, both in the geographic sense and across the whole range of sectors involved. Nobody is exempt from the problem.

Responding to outbreaks of drug-resistant infections involves the coordination of efforts across national boundaries, varied health systems, and involving international agencies.

AMR has been often wrongfully considered purely a medical problem, presumably because of the direct and devastating consequences of patients with multidrug-resistant infections. Such a narrow perspective prevents the issue from being recognized as a systems failure and from getting the global attention that it requires.

There is no single “silver bullet” to address AMR. What we need to tackle the AMR problem is an adaptive and multipronged approach involving many stakeholders – working locally, nationally, and globally – to attain optimal health for people, animals, and the environment.

We need a multidisciplinary approach, considering also the great diversity of social, economic, political, and cultural contexts in which AMR develops or spreads. We need actions to increase awareness about AMR in order to implement more effective interventions. Finally, we need a comprehensive and solidaristic model as the only solution for a problem that knows no borders.

To tackle AMR, antimicrobial effectiveness needs to be recognized as a fundamentally important global public good and governed accordingly. AMR is a challenge to global development. Antimicrobial effectiveness must be looked upon as a limited global public good on the verge of becoming scarce, and the world has a collective responsibility to preserve it in order to avoid countless future victims of drug-resistant infections.

The COVID-19 pandemic has shown that despite all of our medical advances, we remain incredibly vulnerable to infections for which we have no therapies. However, it has shown that if sufficiently motivated, we can make huge changes in short time frames. Furthermore, the pandemic has highlighted the need for resilient health systems and has resulted in an unprecedented rate of collaboration in scientific, medical, social, and political dimensions. The pandemic has also created a renewed awareness of the importance of infectious diseases and is a substantial entry point for reigniting the momentum toward containing the silent pandemic of AMR.

We hope that this comprehensive global collection, involving a multidisciplinary group of experts with different background may raise awareness among all healthcare professionals about the issues with the increasing rate of AMR, and the ongoing efforts towards minimizing its rise.

Together we can make a difference!

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Foreword

On behalf of the International Society for Antimicrobial Chemotherapy (ISAC), I am honored to introduce this timely and essential resource, the Global Ebook on Optimal Antimicrobial Management in Hospital Settings. Published in collaboration with the Global Alliance for Infections in Surgery (GAIS), this book reflects our shared commitment to advancing the science and practice of antimicrobial stewardship, particularly in the context of surgical care.

As we mark the occasion of World Antimicrobial Resistance (AMR) Awareness Week, the importance of this work cannot be overstated. Antimicrobial resistance is one of the most pressing global health challenges of our time. It threatens to undo decades of medical progress, jeopardizing the effectiveness of treatments for infections and compromising patient outcomes across the world. The misuse and overuse of antibiotics in hospital settings, particularly in the context of surgery, is a key driver of this problem.

This ebook provides a comprehensive and evidence-based guide to optimizing antimicrobial practices in the perioperative and postoperative care of surgical patients. It offers valuable insights into the appropriate use of antibiotics, taking into account local epidemiology, patient risk factors, and the need for personalized treatment strategies. Through this collaborative effort, this book aims to provide healthcare professionals with the tools and knowledge to combat infection more effectively while preserving the efficacy of antibiotics for future generations.

The collaboration between several international partners underscores the global nature of the AMR crisis and the need for a unified response. We are proud to support initiatives like this ebook, which aim to bridge knowledge gaps and promote best practices that will ultimately save lives, reduce the burden of infections, and protect public health worldwide.

We congratulate Professor Massimo Sartelli and all the contributors and experts who have come together to share their expertise in this important publication. We also thank the Global Alliance for Infections in Surgery for their leadership in producing this resource, which will undoubtedly contribute to improving the quality of care for surgical patients and advancing the fight against antimicrobial resistance.

We hope that this ebook serves as both a practical guide to healthcare professionals everywhere, as we work together to tackle one of the greatest challenges facing modern medicine.

Souha S. Kanj
International Society for Antimicrobial Chemotherapy (ISAC)

The European Committee on Infection Control (EUCIC) was established by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) in 2014, recognizing the need to build a strong interdisciplinary network of professionals from different backgrounds in the field of infection prevention and control (IPC). Indeed, since its inception, EUCIC is continuously strengthening infection preventive measures in European countries to reduce the burden of infections. This is achieved through a network of resources, expertise exchange, collaborative networks, support structures and guidelines, and educational initiatives, including the accredited 2-year European training programme in IPC. To this end,

EUCIC supports and endorses the current global eBook collection "Global Infection Prevention and Management in Healthcare", an important initiative that connects professionals, scientific groups and societies towards raising awareness on the problems of AMR and healthcare-associated infections, and the need to enforce education and IPC practices across the globe.

Nico T Mutters, Constantinos Tsioutis and Gabriel Birgand
European Committee on Infection Control (EUCIC)

AMR is a barometer of many of the world's ills from poverty, corruption, civil unrest, geopolitical and climate strife and health inequality. We regard open access for all to high quality learning resources as a basic human right. This is particularly applicable to AMR. The Global Antimicrobial Stewardship Partnership Hub (GASPH) (https://global-asp-hub.com/), hosted by the British Society for Antimicrobial Chemotherapy (BSAC), aims to establish a truly cooperative global community dedicated to addressing the challenges of AMR, and particularly antimicrobial stewardship, through shared education, training and tacit learning. The mission of GASPH is to accelerate the PACE of action on AMR through Partnership, Advocacy, Commerce and investment, and Education. The provision of an open-access e-learning, knowledge-sharing platform will amplify, promote and enhance the work undertaken by a range of stakeholders now and in the future.
To date, the GASPH e-learning repository has 829 resources (https://global-asp-hub.com/ams-amr-repository/) from 38 countries across six continents (most are peer-reviewed) and includes 32 online courses. Therefore, it has been our privilege in partnership with the Global Alliance for Infection in Surgery in endorsing and supporting the creation and dissemination of this global digital e-textbook "INFECTION PREVENTION AND MANAGEMENT IN HEALTHCARE". Created by a diverse range of expert authors from many disciplines and from across the globe, it is a most welcome & stellar addition to the resource armoury to support our knowledge response to the AMR pandemic with a specific focus on surgical healthcare practice. We offer our heartiest congratulations to all involved and recommend it as a key resource for your library.

Dilip Nathwani
Global Antimicrobial Stewardship Partnership Hub (GASPH)

Infection prevention and control (IPC) is integral to modern healthcare systems, rooted in evidence-based approaches aimed at preventing the development of healthcare-associated infections (HAIs). Patients with HAIs require additional diagnostic and therapeutic procedures, have prolonged hospital stays, incur additional costs, and may have high morbidity and mortality. The occurrence of HAIs such as central line-associated bloodstream infections, catheter-associated urinary tract infections, surgical site infections, hospital-acquired/ventilator-associated pneumonia and *Clostridioides difficile* infection, continues to escalate at an alarming rate.
HAIs are closely linked to the challenge of antimicrobial resistance (AMR). The management of patients with HAIs frequently requires broader-spectrum antibiotic regimens due to the high risk of acquiring multidrug-

resistant organisms (MDROs) such as methicillin-resistant *Staphylococcus aureus* , vancomycin-resistant *Enterococcus faecium*, extended-spectrum beta-lactamase-producing *Enterobacterales*, carbapenemase-producing *Klebsiella pneumoniae*, and non-fermenting Gram-negative bacilli including *Pseudomonas aeruginosa*, *Acinetobacter baumannii,* and *Stenotrophomonas maltophilia*. Although antibiotic-resistant infections are a widely recognized public health threat, less is known about the burden of antifungal-resistant infections, and in recent years, *Candida auris* has emerged worldwide as a MDRO.

Improving patient safety in today's hospitals worldwide requires a systematic approach to combat HAIs and AMR, which go hand-in-hand.

As most HAIs are preventable, such infections are considered an important indicator of the quality of care provided to patients. Widely considered an essential component of all healthcare delivery, IPC can improve patients' safety and healthcare outcomes. Many different hospital disciplines are typically involved in IPC, making collaboration, communication and teamwork essential. There is evidence that a multidisciplinary approach in healthcare contributes to improving the quality of care. Leading international organizations acknowledge that collaborative practices are essential to achieve a concerted approach to providing care that is appropriate to meet the needs of patients, thus optimizing individual health outcomes and overall service delivery of healthcare. Such an approach reinforces the concept that each one brings their particular expertise and is responsible for their respective contributions to patient care.

IPC is a critical process requiring multidisciplinary collaboration. Bringing together health professionals from many fields, IPC improves decision-making, encourages a comprehensive action plan, optimizes the use of resources, allows for the exchange of knowledge, and consequently produces better results in the prevention of HAIs.

The Italian Multidisciplinary Society for the Prevention of Healthcare-associated Infections (Società Italiana Multidisciplinare per la Prevenzione delle Infezioni nelle Organizzazioni Sanitarie: SIMPIOS) endorses this global digital textbook promoted by the Global Alliance for Infections in Surgery, dealing with the prevention and management of infections in healthcare through a cohesive and multidisciplinary approach.

Maria Luisa Moro and Massimo Sartelli
Italian Multidisciplinary Society for the Prevention of Healthcare-associated Infections (SIMPIOS)

Antimicrobial resistance (AMR) and Healthcare-Associated Infections (HAIs) represent significant threats to public health worldwide, leading to increased morbidity, mortality, and healthcare costs.

Unfortunately, a strong increase in the number of deaths due to AMR has been estimated from 2022 to 2050. AMR involves the human, animal, and environmental sectors, and thus, the One Health approach plays a pivotal role in addressing this problem: to reduce the global threat of AMR, efforts should be focused on the development of inter-disciplinary and multi-sectorial interventions. Particularly, focusing on the human sector, scientific evidences demonstrated that a significant proportion of HAIs caused by multidrug-resistant organisms is preventable through effective IPC measures. Strategies combining Infection Prevention and Control (IPC) interventions, including hand hygiene and hospital environmental hygiene practices, vaccination, surveillance of AMR and HAIs, antimicrobial stewardship and good quality research, development and innovation are essential to mitigate the impact of AMR and to provide safe and high-quality patient care. This e-book addresses all the aspects related to this complex challenge of the 21st century and seeks to contribute

to a continuing scientific dialogue for improving knowledge and communication. The volume supports the importance of a constant action using a multidisciplinary approach, at all levels of the healthcare system, including policymakers, facility managers, health workers, patients and visitors. The contribution of the Italian Study Group of Hospital Hygiene of the *Italian* Society of Hygiene, Preventive Medicine and Public Health (GISIO-SItI) aims to provide an overview of the role of environmental hygiene in hospital settings that plays a crucial role in the prevention and control of HAIs and AMR, to ensure a healthy indoor environmental quality for patient safety and for the prevention of HAIs and AMR spread.

Roberta Siliquini and Martina Barchitta
Italian Study Group of Hospital Hygiene of the *Italian* Society of Hygiene, Preventive Medicine and Public Health

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In line with WSIS' mission "to bridge the gaps between safe surgery and infection prevention and control programs, with a focus on surgical infection reduction and safety where the need is greatest", we are delighted to endorse this freely available e-book which focuses on global infection prevention management in hospital settings. With a shared vocation of sharing information and improving patient outcomes, WSIS has often been involved in the projects of the Global Alliance for Infections in Surgery and once again has the great pleasure of being part of this initiative which will support health workers across the globe in making decisions to enhance patient care.

Robert G. Sawyer
World Surgical Infection Society (WSIS)

The mission of the Surgical Infection Society is to educate health care providers and the public about infection in surgical patients and promote research in the understanding, prevention and management of surgical infections. Several of our senior members have contributed to this freely-accessible eBook through chapter authorship. As we aim to reduce the incidence and impact of surgical infections globally, the Surgical Infection Society is pleased to lend endorsement to this worldwide collaboration to combat healthcare associated infections, address rising antimicrobial resistance, and to promote best practice in the care of infections in surgical patients.

Heather L. Evans
Surgical Infection Society

On behalf of the Surgical Infection Society Europe (SIS-E), it is my honor to introduce this multidisciplinary book covering a variety of topics on surgical infections, infection prevention and AMR.
Since its founding in 1987, SIS-E has been dedicated to promoting education and research in the prevention, diagnosis, and treatment of surgical infections. The endorsement of this book is a reflection of our commitment to advancing knowledge in this critical field and fostering global collaboration to address shared challenges.
Hospital-acquired infections and the growing threat of antimicrobial resistance (AMR) remain significant concerns in healthcare systems worldwide. This ambitious project aims to increase awareness of the need for rigorous infection prevention and effective management strategies. By bringing together the multidisciplinary perspectives of experts from various disciplines, we hope to provide a comprehensive resource that bridges the gap between research and practice.
For over three decades, SIS-E has been at the forefront of developments in surgical infection care. Through our annual congress, training workshops, and collaboration with international societies, we have created a robust network for sharing knowledge and experiences. This book represents another step in our mission to improve patient outcomes and enhance the global response to surgical infections and AMR, and we hope it will reach as many people as possible.
We thank the Global Alliance for Infectionsin Surgery and all contributors for their invaluable insights and dedication to this project. Together, we can advance the fight against surgical infections and contribute to a healthier future.

Ines Rubio Pérez
Surgical Infection Society Europe (SIS-E)

This e-book is an invaluable resource in the fight against antimicrobial resistance (AMR), providing essential guidelines to guide health professionals in infection prevention and control and antimicrobial stewardship. It also provides a quintessential focus on the impact of AMR on sustainable development and why a holistic, One Health approach is required. It further emphasises the critical role of advocacy, communication and awareness-raising as well as patient engagement as a core aspect to ensure informed, safety-focused decisions. By empowering healthcare teams and patients alike, the handbook supports efforts to reduce AMR, safeguard surgical outcomes and uphold the highest standards of care in every patient encounter.

Francesca Chiara and Vanessa Carter
The AMR Narrative

Antimicrobial Resistance (AMR) is a major global health security threat. Despite the huge dearth of evidence on the topic, there has been gradual progress in research and knowledge development. Most of this data, unfortunately, is quite dispersed which makes it difficult to access. The Global Alliance for Infections in

Surgery e-book on AMR will help address this gap since it is designed as a central platform where one can access knowledge from diverse topics related to AMR. Authored by diverse AMR experts from all over the world, it offers different perspectives, viewpoints, and key action points that could be undertaken to mitigate AMR. We are happy to endorse the e-book and hope you will find it of benefit.

Daniel Waruingi
Zihi Institute

I just returned from the 4th Global High-Level Ministerial Conference on AMR held on 15 and 16 November 2024 in Jeddah - The Kingdom of Saudi Arabia, where several commitments were announced under the theme From Declaration to Implementation, following the United Nations General Assembly (UNGA) High-Level Meeting (HLM) on AMR, held on 26 September 2024. Commitment, 12 of Jeddah called for “increased awareness of AMR and ways to curb it, notably through prudent and responsible use of antimicrobials and heightened infection prevention and control across all sectors by strengthening education and training initiatives”. Most of us agree that AMR is one of the most pressing challenges in global health today. It is a silent, escalating threat that undermines our ability to treat infections, disrupts healthcare systems, and compromises patient outcomes. The “Global Infection Prevention and Management In Healthcare” series is a comprehensive, evidence-based resource tailored for healthcare professionals, policymakers, and educators. This three-volume series, authored by many experts from all continents and edited by good samaritan doctors Massimo Sartelli Federico Coccolini Fausto Catena Leonardo Pagani, is designed to serve as a valuable guide for combating AMR through robust infection prevention and control practices. The first volume addresses foundational principles of infection prevention, emphasizing the critical role of adequate sanitation, hygiene, and antimicrobial stewardship in reducing the burden of drug-resistant infections. The subsequent volumes delve deeper into specialized topics, exploring advanced strategies for mitigating AMR in diverse healthcare settings and integrating the One Health approach, which recognizes the interconnectedness of human, animal, and environmental health. The series underscores the importance of a multidisciplinary and coordinated global response. By harnessing the collective expertise of international contributors, it offers practical tools, actionable insights, and case studies to support healthcare systems in preventing infections and optimizing antimicrobial use. The collaborative spirit behind these volumes reflects a shared commitment to safeguarding the efficacy of antimicrobials for future generations.
I sincerely hope this series will serve as an educational resource and inspire and empower health professionals worldwide to take decisive action against the growing AMR crisis. Together, through informed strategies and sustained efforts, we can work towards a future where infections are effectively prevented and managed and the devastating impacts of AMR are mitigated.

Ranga Reddy Burri
Infection Control Academy of India

Volume 1

Antimicrobial resistance and One Health

Chapter 1

Investing in strong healthcare systems protecting everyone

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Introduction

For decades, healthcare professionals, researchers, and advocacy groups have drawn attention to the sharp rise in antimicrobial resistance (AMR) globally. This alarm has gotten louder recently as AMR remains one of the World Health Organization's (WHO) top ten global health threats. AMR causes a significant number of deaths and disability globally, as well as socioeconomic challenges. An estimated five million deaths each year are related to bacterial antibiotic resistance. The economic burden of AMR is equally considerable, with projected annual losses to global gross domestic product ranging between US$ 1 trillion and US$ 3.4 trillion by 2030.

While the rise in AMR is multifactorial, the overuse and misuse of antimicrobial drugs, such as prescribing antibiotics for viral infections and not completing prescribed courses, is widely recognized as a top cause. The extensive use of antimicrobials in agriculture to promote livestock growth and prevent infections also leads to AMR in animals and humans. In addition, global travel and trade facilitate the spread of drug-resistant microbes across continents, while the widespread use of antibiotics in the food chain further exacerbates the issue. Additionally, new antimicrobial drugs are not being developed fast enough. The multifactorial nature of AMR determinants complicates our understanding of the burden and solutions to AMR globally. This complexity warrants a system-level intervention.

This chapter explores the critical components of a robust health system essential for addressing AMR, including strategies to reduce the spread of infections, improve patient outcomes, and decrease hospital costs. It explores the current challenges faced in combating AMR, such as global disparities, insufficient funding, and inadequate surveillance. The chapter also highlights the crucial role of investment, effective policies, and community engagement in mitigating AMR. By examining strategies for enhancing healthcare systems, such as developing diagnostic facilities, ensuring access to essential antimicrobials, and promoting research, this chapter aims to provide a roadmap for building resilient health systems capable of effectively tackling AMR.

Health systems and AMR

Role of health systems in combating AMR

Strong health systems ensure high standards of care, including accurate diagnostics and appropriate treatment, which reduce the misuse of antimicrobials. Awasthi *et al.* found that factors like governance quality, financial resources, and disease burden are closely linked to AMR levels. They equally found that improving access to vaccines, maternal care, and effective government policies can significantly reduce AMR. Their findings can be explained by the fact that well-trained healthcare professionals in robust health systems adhere to best practices in antimicrobial stewardship.

Effective health systems also establish and maintain comprehensive surveillance networks to track AMR patterns and outbreaks, enabling timely interventions and informed decision-making. Examples like the WHO's Global Antimicrobial Resistance and Use Surveillance System (GLASS) help countries collect, analyze, and share standardized AMR data. GLASS supports capacity building via training courses and the monitoring of national surveillance systems. GLASS tracks AMR in humans, the food chain, and the environment via epidemiological, clinical, and population sources. Less than half of countries submit AMR data to the GLASS database. On the other end of the spectrum, the National Database of Antibiotic-Resistant Organisms (NDARO), has seen more success. NDARO is a collaboration between the National Center for Biotechnology and Innovation, Food and Drug Administration, Centers for Disease Control and Prevention, United States Department of Agriculture, WHO, and Public Health England, that has created a detailed database of AMR genes, which can be accessed as raw data or through an interactive web interface to ensure consistency. The NDARO also equally developed interactive tools like AMRFinderPlus to identify AMR genes in bacterial genomes and MicroBIGG-E to help researchers and public health officials find bacterial genomes with AMR genes.

Inadequate health systems enable the progression of AMR in several ways. For instance, the systematic overprescription of perioperative antibiotics, particularly in low- and middle-income countries (LMICs), can be motivated by mistrust of hospital infection prevention and control measures. Additionally, inadequate workforce density can lead to overworked healthcare professionals who may not have the time to adhere to proper antimicrobial stewardship practices. This can result in the inappropriate use of antibiotics, such as prescribing them prophylactically without clear indications, thereby promoting resistance. Low-quality service delivery can also exacerbate AMR as healthcare providers may resort to using broad-spectrum antibiotics without confirming bacterial infections, leading to the development of resistance. There are significant global disparities in AMR prevalence as Australasia accounts for the lowest AMR-directed and associated burden with 6.5 and 28.0 deaths per 100,000 people. On the other hand, Western sub-Saharan Africa has the highest burden, with 27.3 and 114.8 deaths per 100,000. Of the five regions with AMR death rates above 75 per 100,000, four are from sub-Saharan Africa. However, despite having the highest death rates, sub-Saharan Africa has the lowest percentage of infectious deaths attributable to AMR. The statistic suggests that although many people in sub-Saharan Africa die from antimicrobial resistance (AMR), there are also numerous other infectious diseases causing deaths. This means that the percentage of deaths specifically due to AMR is smaller compared to other regions. The lower percentage of deaths attributed to AMR in comparison to other infectious diseases in sub-Saharan Africa may help explain the difference in investments and emphasize the need for a balanced approach in addressing both AMR and other infectious diseases.

Health policy and governance

The lack of national databases tracking AMR events makes monitoring and responding to resistance patterns challenging. Without comprehensive surveillance systems, outbreaks of resistant infections in wards can go unnoticed and unmanaged, as seen in some LMICs. In some countries, despite having guidelines for the use of antibiotics in surgery, awareness and adherence among healthcare providers result in continued misuse.

Policymakers can play a major role in combating AMR by developing and implementing policies. However, their knowledge of and attitudes towards AMR can limit the impact of policies developed. A recent study of policymakers and politicians in HICs and LMICs found that although all participants had sufficient knowledge of AMR, LMIC participants demonstrated better knowledge of AMR. However, the survey found that LMIC policymakers had poorer perceptions and attitudes towards AMR compared to HIC policymakers. The study demonstrates a need to increase awareness of AMR to policymakers and politicians and the crucial need for political action to combat the escalating AMR crisis.

Poor-quality antimicrobial medications also play a significant role in the progression of AMR. In many regions, weak regulatory systems allow the circulation of substandard drugs, which can lead to treatment failures and the development of resistance. This is particularly problematic in surgical settings where the use of ineffective antibiotics can result in severe postoperative infections.

Health financing

Health financing can impact AMR prevalence. For example, public funding can provide greater control over healthcare providers and reassure patients about the financial implications of their antibiotic use decisions. In contrast, out-of-pocket payments can incentivize healthcare providers to prescribe and sell antibiotics more freely, as they often benefit financially from such transactions. Patients may also be more likely to demand antibiotics to avoid potential financial burdens from complications. Other financing modes, such as mandatory health insurance schemes, can have varying effects depending on their specific arrangements, while voluntary health insurance and company health schemes may also influence antibiotic stewardship, though their impact is less clear-cut. Overall, public spending can be beneficial for implementing effective AMR policies, as it can reduce the financial incentives for healthcare providers to overprescribe antibiotics and reassure patients about the financial risks associated with antibiotic stewardship measures. However, the specific arrangements of different financing modes can vary, and further research is needed to fully understand their impact on AMR.

Insufficient funding for AMR initiatives exacerbates regional disparities, leading to inequitable distribution of resources and inadequate surveillance and data collection. Recognizing this fact, the WHO created a tool to help countries estimate the costs of AMR national action plan activities. The tool guides users through entering costs, financing details, and inflation rates to create budget estimates for up to five years. Users need to find and calculate costs for different activities like meetings, consultants, field visits, human resources, and procurement separately. The tool also includes costs from other health programs, like vaccine initiatives. Unfortunately, there is evidence that every country but Austria has not adequately planned their budget needs.

National action plans and global initiatives

The AMR community has sought to control AMR-related disability and mortality goals through national action plans. Most countries have developed one, and these tend to build on four pillars: improving surveillance and research, reducing infections through better hygiene, optimizing antimicrobial use, and ensuring sustainable funding. The implementation levels of AMR national action plans vary widely globally. Norway is at one extreme, while the Federated States of Micronesia is at the opposing end. Specifically, the implementation has been frustrated by a lack of accountability and insufficient public education. Investing in robust health systems is essential for effectively addressing and mitigating the threat of AMR. Such investments enhance the response capacity, ensuring that health systems are better equipped to manage AMR threats through

coordinated efforts and resource allocation. Robust health systems contribute to sustainable health outcomes by preventing the spread of resistant infections, thereby reducing healthcare costs associated with prolonged illnesses and complex treatments. Strengthening health systems globally ensures a collective defense against AMR, which is crucial for maintaining global health security. Investing in health systems also yields economic benefits by decreasing the need for expensive second-line treatments and minimizing productivity losses due to illness.

Implementing stringent infection control measures and ensuring the rational use of antimicrobials can significantly reduce the spread of resistant infections. Additionally, a functioning health system can lead to economic benefits by reducing hospital costs associated with prolonged stays and complex treatments required for resistant infections. This alleviates the financial burden on healthcare facilities and patients and their families.

Stakeholder engagement and advocacy

Governments and international organizations are pivotal in formulating and enforcing these policies. Community and stakeholder engagement is equally important, as involving communities in AMR efforts can enhance public awareness and adherence to guidelines. Recognizing this, the global community has united to issue a call to world leaders asking that they make strong political commitments at the 2024 United Nations General Assembly high-level meeting on AMR.] Notably, the AMR community wants to see world leaders acknowledge the indispensable involvement of communities and civil society in national and global AMR responses. Moving forward, they hope to see clear, measurable targets for reducing the AMR burden. These goals would be supported by mechanisms ensuring meaningful, inclusive, and transparent participation of communities and civil society in AMR governance and accountability. The AMR global community wants to see Member States allocate the necessary financial and human resources to develop, implement, and monitor One Health AMR national action plans and adopt a people-centered approach for more effective, equitable, and sustainable interventions.

The complex nature of the causes of AMR warrants indirect investments that improve access to safe water, sanitation, and vaccines. Additionally, governments must enforce good practices and market regulations in the livestock, crops, and aquaculture sectors, including banning non-therapeutic antibiotic use, implementing disease prevention and control protocols, and developing transparent monitoring and surveillance systems. Waste management facilities should also be upgraded to reduce contact with fecal matter and other hazardous waste substances.

Logically, governments will have to implement environmentally sustainable waste treatment measures to prevent healthcare facilities, slaughterhouses, wastewater treatment plants, and antimicrobial manufacturing plants from releasing antimicrobials and resistant pathogens into the environment. Finally, they should support comprehensive AMR awareness, education, and community engagement activities, including artistic initiatives, and use behavioral and cultural insights to design interventions that resonate with community values and norms. Developing laboratories and diagnostic facilities is crucial for accurately detecting and monitoring resistant infections. Ensuring access to essential antimicrobials and implementing robust infection control measures can prevent the spread of resistance. Training and retaining a skilled workforce through education and training programs on AMR is vital. Providing incentives for healthcare professionals to specialize in infectious diseases can further enhance the capacity to manage AMR. Enhancing surveillance and research by establishing robust AMR surveillance systems and promoting the research and development of new antimicrobials and alternative therapies are also key strategies for addressing AMR effectively.

Local non-governmental organizations and civil society can also contribute significantly by advocating for AMR initiatives and supporting community-based interventions. Strengthening healthcare systems to combat AMR involves several strategic actions.

Investment plays a crucial role in combating AMR. Adequate financial investment is essential for developing and implementing effective AMR initiatives. This includes funding from various sources such as government budgets, private sector contributions, and international aid. Ensuring sustained and adequate funding can support the development of new antimicrobials, enhance diagnostic facilities, and improve infection control measures. Financial investment also enables the training and retention of a skilled healthcare workforce, vital for managing and preventing AMR.

Conclusion

In conclusion, addressing AMR requires a multifaceted approach that strengthens global health systems. By focusing on critical components such as reducing the spread of resistant infections, improving patient outcomes, and realizing economic benefits, we can mitigate the impact of AMR. Overcoming global disparities, insufficient funding, and lack of comprehensive surveillance requires substantial investment and robust policy frameworks. Engaging communities and stakeholders, alongside enhancing surveillance, research, and workforce training, are pivotal strategies. Through coordinated efforts and sustained commitment, we can build resilient health systems capable of effectively combating AMR and safeguarding public health.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 2

Gaining common knowledge about antimicrobial resistance: a patient's perspective

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A fatal accident in Johannesburg: 2004

In 2004, at the age of 25, fate had me fighting for my life on the side of a road in Johannesburg, South Africa. After spending the evening with friends at dinner, we were travelling home when another car overtook us from the opposite side of the road. As the second car veered into our lane, our driver swerved to avoid a collision, but the front wheel caught the curb. Our driver sharply applied brakes, but on a winding road with a slight incline, our car spun violently several times before crashing full force into a concrete wall (**Figure 1**).

Figure 1. Damage caused to the car.

Even though I was wearing a seatbelt, I was leaning forward at the time and locked into a position that resulted in multiple injuries to my abdomen, back, pelvis and neck, alongside several facial fractures as I struck

the dashboard with tremendous force. The car didn't have airbags, and a protruding radio casing ensured that I broke nearly every bone on the right side of my face.

Paramedics arrived on the scene within 30 minutes. Unconscious, and with the front of the car completely buckled because of the intense impact, I had to be removed through the back door. A few moments later the driver watched paramedics resuscitate me with a defibrillator. Because I had no private medical insurance, I was taken to the Charlotte Maxeke Johannesburg Academic Hospital where I was intubated and ventilated and waited for roughly 13 hours for a bed to become available in the high-care unit. My family waited anxiously while I drifted in and out of consciousness. I was told that cerebrospinal fluid leaked through my nose. Reports later verified that I had lacerations to my small intestine and bleeding into my peritoneal cavity which required two emergency laparotomies at the time. The first surgery was to repair the haemorrhage, the second was performed 48 hours later to wash out the abdomen which I believe was known as Damage Control Surgery (DCS) to reduce the risks of contamination. Further to this, I also fractured my pelvis and damaged my neck resulting in instability between the C1 and C2 vertebrae as well as damage to the L5 (lower back) region. According to CT scans I also had multiple facial fractures including to the nasal bone, lamina papyracea bilaterally, inferior and lateral walls of the right orbit, the maxillary sinus on the right and the zygomatic arch on the right. My right eye was completely distorted showing no normal anatomy and therefore had to be removed (**Figure 2**).

Figure 2. Vanessa Carter at the high-care unit of the Charlotte Maxeke Johannesburg Academic Hospital.

The only thing I remember is waking up in the high-care unit several days after the accident, staring at a white ceiling. I had no idea what had happened and felt confused as I listened to the sound of ventilators pushing air into my lungs and the eerie beeping of a heart monitor.

The nurses and my mother, realising I had woken up, explained where I was. My only way of responding was by writing notes on a piece of paper. To this day, I still don't remember the accident, which is probably for the best. A neurologist later confirmed that I had suffered from post-traumatic amnesia due to a primary diffuse and focal brain injury. My family was told that my chances of survival were low since I was a high-risk

patient due to various complications including infections like meningitis and sepsis. I was however fortunate to avoid them. My room was separated from other patients in the ward, and visitors were kept to a minimum. Following the two emergency laparotomies, the next step was a facial reconstruction to salvage what was left of my facial bones, remove the eye and implant a silicone ocular prosthetic. They also needed to repair my broken nose and jaw. I was given high doses of morphine and experienced seizures after the medication was discontinued.

I spent approximately three weeks in the intensive care unit (ICU) until being moved to the trauma ward and discharged about a week and a half later. I do not know which antibiotics I was prescribed when I was in Charlotte Maxeke Johannesburg Academic Hospital. Neither did I meet my treating doctors except for an ophthalmologist who visited my ward to ask for consent to remove the eye. I can only assume not meeting most of my treating surgeons was because the hospital was under-resourced. A few years later after obtaining my hospital record, I was able to learn their names. Most of my interaction at the time was with medical interns from the University of the Witwatersrand and nurses. I felt comfortable speaking with the young interns as most of them were my age.

A week after discharge, under the care of my mother, I had to be readmitted to Charlotte Maxeke Johannesburg Academic Hospital due to gallbladder complications. After a week, I was discharged again.

As a patient advocate two decades later, I often reflect on how nurses and interns could take a more active role in discussing the risk of infections and antimicrobial resistance (AMR) with patients and their families, as they were a significant part of my initial journey. During that stage, I had a limited understanding of infections. This is disturbing for me now as a patient who understands infections and particularly resistant strains better.

The aftermath: 2004 – 2011

I was relieved to be home, but I faced a challenging recovery. I needed to rebuild my strength to walk due to the fractured pelvis and was unable to eat solid foods because of the abdominal injuries and broken jaw. Adjusting to my new visual impairment also made me frequently unsteady. The facial swelling took several months to go down, and for at least a year, I experienced daily intense migraines, along with neck and back pain. It took me about six months to return to work part-time, doing computer work as a designer. Focusing on a computer screen was physically tiring as well as sitting in an office chair for long periods.

Anticipating the need for further facial surgeries, I applied for private medical insurance and was given a one-year exclusion period for any treatments related to my injuries.

Navigating the public health system in South Africa is challenging. On some days, visiting Charlotte Maxeke Hospital meant arriving at 6 a.m. and spending the entire day waiting to be seen. I recall arriving at the trauma outpatient ward with my mother and finding the lines so long that we doubted we would get an appointment that day, so we decided to leave. I was simply in too much pain and too tired to wait and felt if I couldn't cope anymore, I would try to find money to visit a private physician or return to the emergency department.

While awaiting my medical insurance to be approved, I tried to determine the surgeries I needed. I gradually realised that I required various specialist doctors. Having no previous complicated health history my initial step was to consult my GP and ophthalmologist to find out which specialists I should see. I was referred to a professor of ophthalmology with a sub-speciality in ocular plastic surgery. I was also referred to an ocularist, who made artificial eyes. The first surgery was to repair the orbital floor using a prosthetic made from a type of medical-grade porous polyethylene used in various surgical procedures, including reconstructive surgery.

The professor of ophthalmology performed this at the Pretoria Eye Institute about two years after the accident.

The outcome was positive, but further work was needed on the remaining bony structures in the maxilla and zygomatic areas, because facial symmetry had not yet been fully restored. In my sixth year, I then sought additional advice by consulting a plastic surgeon and a maxillofacial surgeon. The delay for this was because my life partner and I had planned to have a baby. This was achieved after a gynaecologist and general surgeon released adhesions on my ovaries, also caused by the accident. In addition, I was caught up in a six-year legal trial to claim compensation from the road accident fund (RAF) in South Africa to help pay for my medical costs and future loss of income as the long-term damage had been significant to my working career post-accident.

The maxillofacial surgeon implanted an alloplastic prosthetic to address the bony deficits. This was performed at a private hospital in Johannesburg.

Unfortunately, the incisions were made directly under my lower eyelid, and scar tissue adhered to the alloplastic implant, causing my lower eyelid to be pulled down. As a result, the plastic surgeon working in the same hospital needed to release the adhesions and correct the ectropion. An ectropion is a medical condition where the eyelid, usually the lower lid, turns outward away from the eye. This abnormal positioning exposes the inner lining of the eyelid and the surface of the eye. In my case, the ectropion was placing me at risk of infection which was problematic to the prosthetics in my face.

Two weeks after the surgery, when out shopping one day, I felt moisture on my face. When I arrived at my car, I pulled down the rear-view mirror and saw pus discharge seeping out of the lower eyelid down my cheek. I called my plastic surgeon's office to be told it was best to see the doctor as it may be an infection. Several days later I was admitted for an emergency surgery. That consisted of a debridement of the prosthetic and a minor reconstructive surgery to fix the damaged tissue. After being discharged, roughly two weeks later the infection reappeared, but this time worse. The skin was more inflamed, and the pus was now in a larger area above the cheek. I was readmitted to the hospital and a second debridement was performed alongside a cheek rotation flap to correct the damaged tissue.

Lo and behold, the infection reappeared for the third time. Both surgeons (maxillofacial and plastic surgeon) were now disagreeing about the prosthetic being removed. The plastic surgeon felt it was necessary and the maxillofacial surgeon felt the infection could be treated. As a patient I was confused. In between visits and after each surgery I was prescribed amoxicillin. One thing they both agreed on was that I should visit an Ear Nose and Throat (ENT) surgeon saying that the sinuses had been damaged severely on the right and that it may help to perform a sinus drainage.

Dealing with the infection and on another course of amoxicillin I managed to secure an appointment with the ENT surgeon a few days later. I was admitted to the same Johannesburg hospital to perform the sinus drainage. The ENT surgeon also corrected a deviated septum caused by the broken nose at the time of the accident. In the same surgery, the plastic surgeon repaired damaged tissue eaten away by the infection. I was placed on another course of antibiotics.

Two weeks later the infection was back for the fourth time. I'll never forget looking into the mirror after each surgery, wondering if by the end of it all, I would have a face left (**Figure 3**).

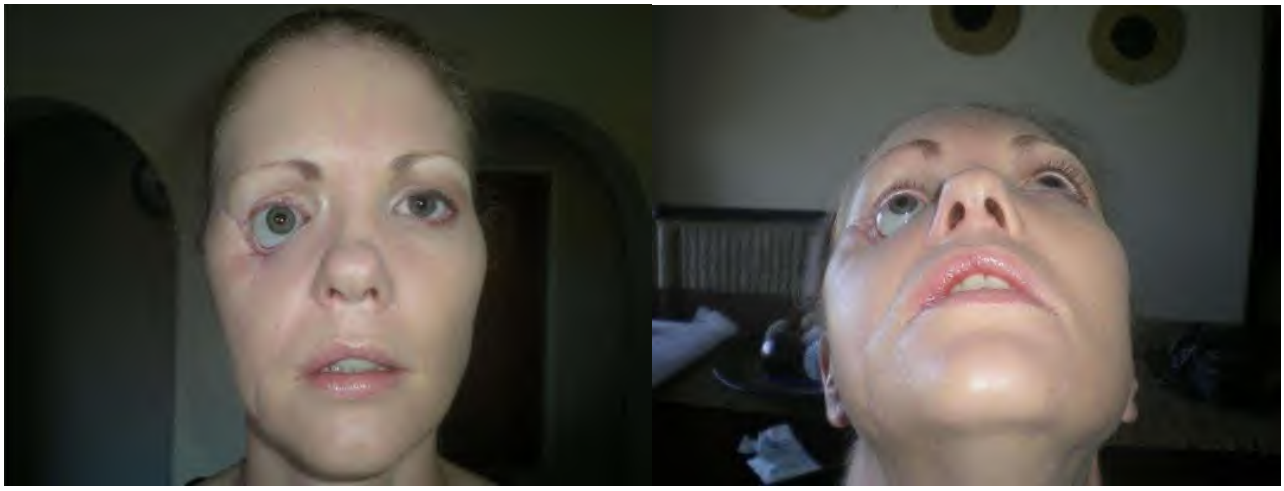

Figure 3. Tissue damage caused by methicillin-resistant *Staphylococcus aureus* after multiple surgeries.

The ENT surgeon and maxillofacial surgeon advised that we could try a second sinus drainage. The plastic surgeon on the other hand was adamant that the prosthetic needed to be removed to prevent it from becoming fatal, potentially leading to a bloodstream infection, sepsis, or worse. He planned to work closely with the ENT surgeon and mentioned that he would be in the operating theatre next door on the same day when we performed the second sinus drainage, and he would pay a visit. If he observed that the infection was still affecting the prosthetic, he would remove it. I took this with a pinch of salt, as I had not signed consent for the plastic surgeon to do so.

When I woke up from surgery, the ENT surgeon sitting at the bottom of my bed explained that the plastic surgeon had removed the prosthetic and sent it away for testing. That was the first time I heard the word "test". Alarm bells went off in my mind as I wondered why the plastic surgeon had taken such a risk. I also questioned why a test was necessary and what made this infection so unusual. By this point, 11 months had passed since the first infection appeared. My facial bones were now completely distorted on the right side, and a gaping hole under the eyelid meant that an artificial eye could no longer stay in the socket.

I called the pathology laboratories and requested a copy of the test to understand what was going on. The results displayed the acronym “MRSA” at the top with a group of antibiotic names on the left coupled with a line of “R’s” and “S’s” on the right. Like any confused patient desperately seeking answers, I turned to the internet. MRSA was a term I couldn’t pronounce at the time called methicillin-resistant *Staphylococcus aureus*. Accompanying that were the words, “antibiotic-resistant infection”. That made slightly more sense, but I still didn’t completely understand what that meant.

Feeling like I now trusted my plastic surgeon the most, I took the results to him and asked for an explanation. I also asked what I could be doing better as a patient to fight it. Even though we had removed the prosthetic, my face was still red and swollen with infection. To make matters more complicated, I had an orbital floor which could have been infected too. He explained the alloplastic prosthetic was colonised with MRSA and by removing it I had a better chance of treating the resistant infection. I could see on the test results that there were 5 antibiotics that I was susceptible to, one of them was Vancomycin. He prescribed a 7-day course. Day by day, over the next three months after removing the prosthetic, the infection started to clear. This time understanding what my role was I made sure I changed my eye pads close to three times a day and used only sterile products bought at the hospital pharmacy, including hand sanitiser and wash. I had to wait a year before we could perform any surgery to correct the damage.

There were days that I took my young son to nursery school and because my face was so swollen and red, and covered up with eye pads, his friends would say, “What happened to your mommy’s face, she looks like a zombie”. It was hard for me to explain to him at just under three years old why his mum looked different to the other parents. It was hard for me to do anything that involved people seeing my face because they would ask questions. But I persevered with a thought in the back of my mind that we would finally beat the infection.

I wish I had known then what I know now. When the infection wasn’t clearing, I regret not asking my doctors if it might be due to antibiotic resistance. I wish I had requested a test. Perhaps tests were done, but I would have liked to know if they were. Once I finally understood what was happening to me, I felt empowered to take a more active role and make more informed decisions. I also wish that I hadn’t been the one responsible for keeping track of which type of antibiotics I was being prescribed and when between doctors. Why couldn’t this information have been shared more effectively between them? I also wish communication between them had been better, especially since their indecision left me confused. As a high-risk patient using countless antibiotics, resistance should have been common knowledge. It should be for any patient. Had the plastic surgeon not taken it upon himself, I dread to think where I would be today. Lastly, I had no idea how MRSA could have been a risk to my family, friends and community around me. This is also something that should be more clearly understood by patients at risk of infections.

A waiting game: 2011 – 2012

Waiting to heal teaches you the value of patience, and I was now in my seventh year of this journey since the accident. After the prosthetic was removed, I dedicated that year to learning more about antibiotic resistance, often staying up late into the night reading journal articles. Back in 2011, Although I could never fully understand antibiotic resistance, I needed enough knowledge to make more informed decisions about my upcoming surgeries. My doctors seemed uncertain about correcting the damage, and I couldn’t bear the thought of living with such a severe facial disfigurement for the rest of my life. I also knew I didn’t have the luxury of performing several surgeries, we needed to correct the damage in as few procedures as possible.

I researched facial surgeons in the UK and USA, spending hours compiling a photo history with notes about each one into a four-page Word document, which I then emailed to some of the top surgeons I could find. I must have emailed about 25 surgeons, and for weeks, no one replied. However, I did receive a response from a maxillofacial surgeon in New York who referred me to a maxillofacial professor in Johannesburg (Prof. Reyneke). About three months later, I received another email from one of the craniofacial surgeons I had found through a medical journal. He had written an article about his work in face transplant surgery and infection management (Dr. Caterson). He was based at Brigham and Women’s Hospital in Boston and was part of the Face Transplant team. In the email, his secretary explained that he had seen my plea for help and was willing to offer a 30-minute Skype call as he saw cases like mine all the time.

During that call, he explained that I needed to avoid using any more foreign materials and instead work with the remaining bone by performing a zygomatic osteotomy. We needed to correct the bone framework first, and only then proceed with minor plastic surgery touch-ups. The bony deficit was too large, and performing major plastic surgery procedures such as radial flaps without a proper framework could lead to multiple surgeries if the soft tissue settled. A radial flap involves using a section of tissue, including skin, muscle, and blood vessels, taken from the radial aspect of the forearm. I was further told by a different plastic surgeon in Johannesburg that I had a lack of blood supply to the facial area which meant a high risk of the soft tissue dying, which helped me further to decide. There was no room for error.

I visited multiple surgeons in Johannesburg but received differing opinions; one of them also referred me to Prof. Reyneke. My ocularist (Jack Bernard), who cared very much about my case, offered to accompany me to the appointments so that we could review the information together. He was elderly but a very active man who was determined to see me pull through. I visited Prof. Reyneke, and he echoed Dr. Caterson's advice. Prof. Reyneke performed the zygomatic osteotomy, and I was discharged a few days later. The result was perfect. The facial bones were finally looking symmetrical.

Sadly, like a bad case of *déjà vu*, the infection returned. I was readmitted to the hospital. This time my whole right face was covered with infection, now potentially both in the skin and bone. Tests revealed this time it was both an allergy and infection (**Figure 4**).

Figure 4. Osteomyelitis, skin infection and allergy to the topical antibacterial.

After all that hard work, pain and perseverance, my heart sank. I was ready to give up. No matter how patient and determined I was to fight this resistant infection, it felt out of my control. Professor Reyneke, just as dismayed but determined, began to work very closely with me. After being discharged, he said he was going to rotate my antibiotics. He would prescribe an antibiotic, then wanted me in his office weekly to check on the progress. If the infection worsened, even slightly, I was to call him immediately. He said that if I started an antibiotic course at 5 p.m., I needed to set my alarm for 5 a.m. in the morning so that I take it at precise, equal intervals. In his words, "You need to make sure there is no more than a 20-minute window, or these bacteria will continue to mutate." He also explained that I needed to be even more strict with infection care. No matter how often I washed my hands, it had to be done every time before they came near my face. I was so determined to follow this advice that my hands became almost raw, with skin peeling off from the constant washing and sterilising. We also discontinued the topical antibacterial ointment that I was using (chloramphenicol), which was like mupirocin, however meant for ophthalmic bacterial infections. We were using it for the surgical site on my face.

Over the course of three months, we rotated different antibiotics. I didn't record all their names, but I do remember that one was linezolid and another was clindamycin. After three months, the infection began to

clear up again. I could finally see the light at the end of the tunnel. During that time, I felt constantly ill, physically weak, and mentally drained, but we were making progress, and that was all that mattered.

Two steps forward, one step back: 2012

A few weeks after completing my last course of antibiotics, I became severely ill again. We had been discussing the possibility of almost being ready for touch-up plastic surgery as the facial infection cleared. I suddenly started vomiting intensely one day, which carried on to the following day until the vomit turned black. The abdominal pain was severe, so I was taken to the emergency department and admitted. I was under the care of a gastroenterologist this time, who wanted to try conservative treatment as far as possible as he advised I had an adhesive bowel obstruction (**Figure 5**).

Figure 5. Adhesive bowel obstruction after extensive antibiotic therapies.

Facing the future: 2013

By 2013, nine years had passed since my accident. Hospitals, pain, and uncertainty had become a normal part of life. My mind had become accustomed to hearing bad news repeatedly. Much like a cancer patient who is told the chemotherapy hasn't worked, I mentally prepared myself for every doctor's appointment so that I wouldn't break down if I received bad news again. I had one more surgery to get through and that was a minor plastic surgery using skin from my forehead to correct the lower eyelid with a rotation flap.
The infection seemed to be totally cleared. The plastic surgeon performed this in a private Johannesburg hospital. Like a miracle, the infection didn't reappear, and my face finally looked perfect! Well, good enough to remove the eye pad, and wear an artificial eye again (**Figure 6**).

Figure 6. Final result after a decade of facial surgeries, in 2013.

My ocularist had been working on my new eye, which I didn't feel 100% confident with, so he gave me an eye with a blue iris. He said, "Just try this, you always wanted blue eyes anyway." I felt comfortable with it, because I almost felt like it made a statement in terms of my imperfection and that I didn't need to hide my face anymore. He sadly passed away a few weeks later in 2013 having told me that he was proud that I was one of his greatest achievements during his 40 years as an ocularist. After nine years of working together with him, he was no longer just a treating specialist, he had become a friend. I still wear that same blue artificial eye today.

Raising my voice as an AMR patient survivor

In 2013, I set forward on a path to becoming a patient advocate for AMR. I felt there was so much more I could have done as a patient during my extensive journey. One of the biggest challenges I found was the lack of communication about the risks of resistant infections. These conversations should have been commonplace for a high-risk patient like me, but it wasn't. Even my community pharmacist couldn't answer all my questions when I collected my antibiotic prescriptions.

The internet became an important tool for me to empower myself as well as those few extra moments I had with my doctors to ask questions. When I didn't know about AMR, I couldn't have a conversation with my physician. Since 2013, I have served as a lay member of the Advisory Committee on Antimicrobial Prescribing, Resistance and Healthcare Associated Infection (APRHAI) in the UK, have been a member of the WHO Strategic Technical Advisory Group on AMR (2020-2023), served as Chair of the WHO Task Force of AMR Survivors (2023 – present) and founded a charity called The AMR Narrative which focuses on developing advocacy capacity around AMR, raising awareness and building a global community. I've also shared my story across the world at numerous events including the United Nations General Assembly Multistakeholder and High-Level Meetings in 2024, the 77th World Health Assembly and International Congress on Infection Prevention and Control. I've also won numerous awards including from Antibiotic Guardian, UK and FINDdx.

During those bedridden moments fighting for my life, I never could have imagined how purposeful my story was.
Patients and the public are crucial to tackling AMR. Unfortunately, many of them, still don't know how it can impact them and their communities. I certainly didn't. I was fortunate to have had the opportunity to take part in my own care once I learned what AMR was. I could never understand the multifaceted, scientific dimensionsbehind it, but basic knowledge ensured I could play an equal role in fighting for my survival. This should be the case for all patients. I believe I would not be here today had I not taken an active role in my care.

To learn more about my story, the WHO created a short video as part of the "AMR is Invisible, I am Not" campaign in 2024. Watch it here: https://youtu.be/GUw6fRhwt3Y?si=wlFp4hWdjQo_gt7c

Competing interests

The author has no financial and non-financial competing interests to declare.

Chapter 3

Uniting efforts against antimicrobial resistance

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Introduction

Antimicrobial resistance (AMR) is a serious public health threat that poses significant challenges, endangers human and animal health, compromises food safety and security, and could jeopardize economic stability. In 2019, bacterial AMR resulted in 1.27 million deaths worldwide. It is estimated that by 2050, AMR would cause up to 10 million deaths annually and in addition to health impacts, could add 1 trillion US $ to healthcare costs and lead to annual gross domestic product (GDP) losses of between 1-3.4 trillion US $ by 2030.
AMR has spread beyond national borders and across continents; this prompted the World Health Organization (WHO) and various international agencies to call for a coordinated, global response, as isolated efforts were proved to be inadequate to address this escalating worldwide crisis. In this chapter, we will present our perspective on unifying efforts to effectively tackle the challenges posed by AMR.

Securing global governance and leadership commitment

Addressing AMR requires rigorous international cooperation since unilateral endeavours are insufficient. Coordinated and sustained efforts among nations are essential to develop and implement comprehensive strategies to limit the spread of AMR and safeguard global health. Tackling AMR is also critical to achieving the Sustainable Development Goals (SDGs) adopted by all United Nations Member States. The SDGs call for global

partnerships, emphasizing that ending poverty and other deprivations must be coupled with strategies to improve health, and education, reduce inequality, spur economic growth, and tackle climate change.

Global governance involves the collective efforts of international institutions, nation-states, and diverse stakeholders to address challenges that transcend national boundaries. It necessitates coordinated action across multiple levels, incorporating institutional frameworks and processes that enable cooperation, regulatory mechanisms, and policymaking to manage and resolve transnational issues. During the 2010s, several international collaborations and high-level meetings were organized to address AMR. A significant milestone was the World Health Assembly's endorsement of the "Global Action Plan (GAP) on AMR" in 2015. This plan, developed by WHO in collaboration with the Food and Agriculture Organization (FAO) and the World Organization for Animal Health (OIE), called for coordinated action across sectors using a One Health approach. The first UN General Assembly High-Level Meeting on AMR in 2016 further elevated AMR to a global political priority, leading to the creation of the Interagency Coordination Group on AMR, which guides political leaders on sustainable AMR action. The second UN General Assembly High-Level Meeting on AMR took place in September of 2024.

Key components of global governance in combating AMR include the One Health approach, international collaboration, and national action plans. The One Health approach recognizes the interconnection between humans, animals, and the environment, promoting a collaborative, multisectoral, and transdisciplinary approach at local, national, regional, and global levels. International collaborations between key organizations such as WHO, FAO, and OIE involve sharing data, best practices, and resources to strengthen global and national responses. As such, countries have been encouraged to develop and implement national action plans that align with the GAP on AMR, ensuring that individual efforts contribute to a cohesive global response. These plans emphasize surveillance, antimicrobial stewardship (AMS), infection prevention and control (IPC), and advancing research and development (R&D) for new antimicrobials.

Enhancing surveillance and research

Surveillance programs are vital for identifying antimicrobial susceptibility patterns, tracking resistance trends, and detecting emerging threats, all of which are essential for combating AMR. The data generated from these programs supports the development and evaluation of AMS initiatives, informs treatment decisions, guides national and local policies, and directs efforts to develop new treatment options.

Several national and international initiatives were established to strengthen AMR surveillance systems such as the WHO’s Global Antimicrobial Resistance and Use Surveillance System (GLASS), the Central Asian and European Surveillance of Antimicrobial Resistance (CAESAR), the European Antimicrobial Resistance Surveillance Network (EARS-Net), and the Latin American Network for Antimicrobial Resistance Surveillance (ReLAVRA).

Additionally, pharmaceutical companies contribute to this effort, such as Merck & Co., Inc.’s “Study for Monitoring Antimicrobial Resistance Trends” (SMART), which monitors global resistance patterns. Despite these efforts, significant gaps remain. Therefore, global charitable foundations such as Wellcome created consortiums such as the Surveillance and Epidemiology of Drug–Resistant Infections Consortium (SEDRIC), aimed at taking actions to tackle the gaps in drug-resistant infections surveillance and epidemiology.

Significant knowledge gaps exist particularly in conflict-affected regions where disrupted healthcare systems, inadequate infection control, and unregulated antibiotic use exacerbate the spread of AMR. Extending surveillance efforts to these vulnerable areas is crucial for developing targeted interventions to address their unique challenges.

To enhance surveillance and research, WHO developed a global priority list of multi-drugresistant organisms (MDROs) to guide AMR research, surveillance, and interventions, targeting bacteria such as carbapenem-resistant *Acinetobacter baumannii* and carbapenem-resistant *Pseudomonas aeruginosa*, which contribute to healthcare-associated infections (HAIs), especially among immunocompromised patients. These critical priority pathogens are resistant to multiple antibiotics, including carbapenems, which makes their treatment challenging, increasing morbidity, mortality, and healthcare costs. Similarly, the Center for Disease Control and Prevention (CDC) has identified urgent threats like multidrug-resistant *Candida auris*, an emerging pathogenic fungus implicated in recent outbreaks.

Addressing the AMR crisis also requires increased investment in R&D and promoting innovation in new antibiotics, diagnostic tools, and vaccines. However, the slow uptake of new drugs and insufficient return on investment have led large pharmaceutical companies to cease antimicrobial R&D. To counter this, legislative initiatives in the United States, such as the DISARM (Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms) Act and the PASTEUR (Pioneering Antimicrobial Subscriptions to End Upsurging Resistance) Act, have been introduced. These initiatives incentivize the development and use of novel antimicrobials by providing financial incentives and enhancing AMS programs.

Developing and enforcing policies and regulations

Developing and enforcing regulations that limit the sale and misuse of antibiotics in both humans and animals is crucial to reducing AMR. In humans, restricting the dispensing of antibiotics except by a physician's prescription is not applied worldwide. This together with ensuring the good quality of generic antibiotics in the market should be governed by national policies developed by ministries of health and monitored closely.

The agricultural sector offers several examples that highlight the growing awareness of AMR and the need to unify efforts. Increasingly, policies are being introduced to prohibit the non-therapeutic use of antibiotics in livestock, particularly for growth promotion. For instance, in Europe, stricter regulations led to a 53% reduction in the sale of veterinary antibiotics between 2011 and 2022. Improving farming practices is also essential to reducing the need for antibiotics. This includes enhancing disease prevention, detection, and treatment through better biosecurity, nutrition, and access to vaccinations. Accurate monitoring and diagnostic tools are critical for early disease detection in animals and ensuring that antibiotics are used appropriately—only, when necessary, at the right dose, and through the correct route. Vaccination development is another critical aspect of combating AMR in agriculture. Pharmaceutical companies are central to this effort, creating new vaccines and innovative methods for administering them. For example, Phibro Animal Health developed 77 new vaccines across 18 countries over three years, including a live virus vaccine in an effervescent tablet, making it safe and convenient for use in remote locations. Vaccines reduce the need for antibiotics by preventing diseases like Bovine Respiratory Disease and Salmonellosis. Widespread vaccination can achieve herd immunity, limiting the spread of infectious diseases and reducing the reliance on antibiotics. Education is vital for the successful implementation of these practices. Both veterinarians and farmers must be educated on the proper and judicious use of antibiotics. Initiatives like the Center for Infectious Disease Research and Policy Antimicrobial Stewardship Program (CIDRAP-ASP) propose developing continuing education opportunities, educational tools, and partnerships with veterinary colleges to improve knowledge and confidence in antimicrobial prescribing.

Regulatory agencies and local governments play a crucial role in creating, executing, and enforcing these policies, particularly at the intersection of human and animal health. National health ministries and

departments should organize public awareness campaigns to educate both the public and professionals, especially farmers and veterinarians.

Enhancing infection prevention and control

IPC is essential in combating AMR, particularly within healthcare settings. Robust IPC programs in healthcare facilities are crucial for reducing the transmission of infectious agents among patients, healthcare workers, and visitors. Key measures include hand hygiene, the use of personal protective equipment (PPE), environmental cleaning, and surveillance, as highlighted during the COVID-19 pandemic. Effective IPC requires leadership support, education and training for healthcare personnel, and the use of advanced technologies like artificial intelligence, ultraviolet (UV) disinfection, and electronic hand hygiene monitoring. These practices help maintain adherence to IPC protocols and reduce the risk of acquisition and transmission of HAIs, particularly those caused by MDROs.

In conflict areas, weakened healthcare systems, infrastructure destruction, and population displacement severely hamper infection control efforts. These challenges lead to reduced surveillance, delayed diagnostics, interrupted vaccination campaigns, and limited healthcare access, increasing the risk of outbreaks of various diseases. Addressing these risks requires targeted interventions, strengthened healthcare for displaced populations, and collaboration between governments and international organizations.

Low- and middle-income countries (LMICs) face significant challenges in implementing IPC due to limited resources. The COVID-19 pandemic underscored these difficulties, making it clear that locally adapted guidelines, leadership advocacy, sustainable training systems, and enhanced monitoring are necessary for effective IPC implementation. For example, the ongoing Mpox outbreak in the Democratic Republic of Congo highlights how fragile healthcare systems struggle with effective IPC, exacerbating public health challenges.

Optimizing the use of antimicrobials

One of the most effective strategies for curbing antibiotic misuse in healthcare settings is the development and implementation of ASPs which play a crucial role in optimizing antimicrobial use. ASPs exemplify coordinated efforts to AMR. These multidisciplinary programs bring together healthcare providers from various specialties to implement proper individual treatments but also govern guidelines, pathways, and informatics to optimize antimicrobial use. The ASP primary goals are to enhance patient safety and outcomes, minimize resistance, and reduce unnecessary costs. Successful ASPs require strong leadership support for seamless integration into existing systems. These programs are best led by dedicated experts who oversee antimicrobial use, tailor interventions to local resources and resistance data, and prioritize ongoing education and training for all involved personnel. The effectiveness of ASPs relies on the involvement of multiple stakeholders: the administration, quality officers, healthcare providers from multiple disciplines (infectious diseases specialists, clinical pharmacists, nurses), infection control professionals, microbiologists, and information technologists. To optimize antimicrobial use, ASPs adopt several key strategies, primarily focused on continuous audits and monitoring, alongside strict regulations on antimicrobial usage. These efforts are complemented by ongoing education and training of healthcare workers (HCW) to promote responsible prescribing practices and improve patient outcomes. An important intervention that supports those two core strategies of ASPs is the development and implementation of evidence-based facility-specific clinical diagnostic and

treatment guidelines. These guidelines recommend antimicrobial choices, dosing, and therapy duration, to limit antimicrobial abuse. During the COVID-19 pandemic, the role of ASPs became more crucial in limiting the abuse of antibiotics in healthcare settings. Such is our experience at a tertiary care center in Lebanon where our ASP adapted to the challenges of the COVID-19 pandemic, maintained its operation, actively monitoring antibiotic consumption and providing targeted recommendations to limit antibiotic misuse. These efforts were necessary in mitigating the potential impact of the pandemic on AMR.

Using Electronic Health Records (EHR) facilitates and enhances the productivity of ASPs, especially when integrated with smart tools such as clinical decision support systems that can assist with the daily ASP activities, or the possibility to run reports that allow tracking of antimicrobial prescriptions, antimicrobial resistance trends, and rates of compliance to guidelines and order sets established and disseminated by ASPs. ASPs are also essential tools to combat AMR in ambulatory settings, including long-term care facilities, and nursing homes. In 2016, the CDC outlined the core elements of outpatient ASPs, and a few years later, the Joint Commission included ASP requirements for outpatient accreditation.

LMICs face higher resistance rates and have limited resources to establish comprehensive ASPs, despite their crucial need for such programs. The “Antimicrobial Stewardship Programs in Health-Care Facilities in LMICs” is a practical toolkit developed by the WHO to assist in that task.

Alongside AMS, diagnostic stewardship, which consists of ordering the right test for the right patient at the right time, is an auxiliary to ASP and an integral part of the fight against AMR. It can essentially be performed through novel diagnostic tools, such as point-of-care tests and molecular tools.

To ensure the optimization of the use of antimicrobials, it is essential to also invest heavily in public awareness campaigns targeting people from all backgrounds, ages, and occupations. As AMR becomes a social concern shared by all members of society, the pressure exerted on healthcare providers to prescribe unnecessary antibiotics is expected to subside. When designing awareness campaigns targeting AMR, the messages must be short, clear, unambiguous, relevant to the targeted country, and tailored to different audiences. Campaigns must focus on preventative measures, including vaccination and hand hygiene, as well as appropriate antibiotic use, such as indication for use, completion of antibiotic courses, and proper disposal of leftovers. Targeting school and college students must be a priority as this shall maximize the effect of awareness. Innovations are essential in such campaigns, such as resorting to movies and plays as those have a high impact, especially in younger audiences. Also, if used responsibly, social media platforms present endless opportunities to design widespread evidence-based messages that can be shared continuously and universally as constant reminders. Behavior change is expected to occur when adequate awareness campaigns are accompanied by regulatory modifications, changes in social structure, and a direct emotional and/or material impact on targeted populations.

Ensuring access and equity for all people

Aside from the well-known causes of AMR, an essential driver is often overlooked: substandard and falsified antimicrobials (SF). The composition of such medications is either intentionally manipulated or does not conform to quality standards. A recent systematic review suggested that almost 17.4% of the worldwide antibiotic supply might be SF, disproportionately present in LMICs. These low-quality antimicrobials contain subtherapeutic concentrations of antimicrobials selecting for AMR. This issue is compounded by the difficulty in detecting SF medications and the lack of regulatory enforcement in many regions. To address this, countries must collaborate in ensuring global access to reliable and high-quality antimicrobials, as well as to strengthen regulatory frameworks and surveillance systems to combat the proliferation of SF drugs.

Over the years, various efforts have been made to address this issue including the establishment of the "Global Antibiotic Research and Development Partnership" (GARDP) by the WHO in 2016. It focuses on the development of novel therapeutic antimicrobials and ensures their accessibility to all populations. In 2019, the GARDP succeeded in producing and distributing cefiderocol to around 135 countries including numerous LMICs. Cefiderocol is a potent antibiotic that targets serious infections with resistant Gram-negative bacteria. It has been recognized by the WHO as an essential medicine and is used to treat multiple Gram-negative pathogens identified as high-priority pathogens. In addition, with the support of the WHO and UNICEF, GARDP created another initiative; SECURE, aimed at increasing worldwide access to antibiotics including those with limited availability and newly approved 'reserve' antibiotics. It also collaborates with organizations to create sustainable antibiotic markets by developing new strategies, such as proving effective use, securing innovative funding, and increasing market availability. They have managed to build a portfolio of essential antibiotics and integrated older and novel treatments into health policies; thus, improving antibiotic access and availability at low cost in LMICs. Currently, this initiative is in the development stage which includes refined adjustments to the framework for better preparation for an effective global launch. The implementation phase will extend from 2024 to 2027.

In addition to securing antimicrobials, equitable access to vaccines is essential to prevent individual bacterial and viral infections and create herd immunity ultimately leading to less use of antibiotics and reduction in AMR. For instance, the pneumococcal conjugate vaccine has been found to reduce the incidence of *Streptococcus pneumoniae* resistant to penicillin. Likewise, a recent study predicted that a vaccine targeted against extraintestinal *Escherichia coli* could prevent 22,000 deaths linked to AMR. Challenges to access to vaccines gained global attention during the COVID-19 pandemic. The Vaccines Global Access (COVAX) was created to ensure fair global distribution of the COVID-19 vaccine. However, challenges like "vaccine nationalism" hindered these efforts, leading to what has been described as vaccine inequity. Thus, efforts should be made to increase the production of vaccines in LMICs and decrease their reliance on donations. Achieving this goal requires strong political commitment and adequate funding. While COVAX played a role in improving vaccine distribution, sustainable, long-term solutions are necessary. Diagnostics also represent a crucial, yet often overlooked, factor in reducing AMR. In LMICs, people are frequently prescribed antibiotics for fever without supporting diagnostic tests for bacterial infections. For example, bacteriologic cultures are only available in 1.3% of southern Africa's labs. Consequently, "Médecins Sans Frontières" has established programs to improve diagnostic capacities in LMICs. The "Mini-Lab" project is a portable microbiology laboratory designed for use by trained technicians. It utilizes manual detection methods to identify organisms and their resistance patterns. Another example is "The Foundation for Innovative New Diagnostics" (FIND) established in 2003. FIND collaborates with approximately 200 international partners to develop diagnostic tools tailored to LMICs. It also ensures equitable access to diagnostics through quality assurance and laboratory strengthening. Most recently, they developed and distributed 20 novel testing tools in LMICs, thereby preventing antibiotic misuse and reducing the risk of AMR. Unfortunately, sustaining such initiatives remains challenging. Therefore, through strengthening the healthcare systems worldwide, it is necessary to ensure equitable access to vaccines, diagnostics, and preventive measures, especially in LMICs.

The WHO has developed the AWaRe book to guide HCW in their empiric use of antibiotics including in LMICs. In addition, the International Society of Antimicrobial Chemotherapy is in the process of developing a publicly accessible pathogen-directed antibiotic guide (AbX Guide) that provides evidence-based, specific therapy guidelines adapted to resource-limited countries. Similar initiatives should be encouraged to aid healthcare professionals decrease antibiotic misuse.

Fostering multisectoral partnership

To effectively reduce the burden of AMR, collaboration across multiple sectors is essential. By pooling efforts and expertise, sectors such as healthcare, agriculture, and regulatory bodies can develop more comprehensive and coordinated strategies to combat AMR. For instance, governments can collaborate with educational institutions to raise public awareness. Partnerships with industries are necessary to ensure better outreach of vaccines. Other strategies to combat AMR are listed in **Figure 1**. World AMR Awareness Week (WAAW) is a perfect example of collaboration between governments, civil society and academia. This global campaign calls for cross-sectoral collaboration to prevent AMR. Governments and policymakers are encouraged to involve civil society and reinforce regulations to decrease the overuse of antibiotics, while the academic sector is urged to include AMR in their school curricula. The private sector is further encouraged to implement policies in workplaces such as the appropriate disposal of wastewater to prevent the spread of resistant pathogens.

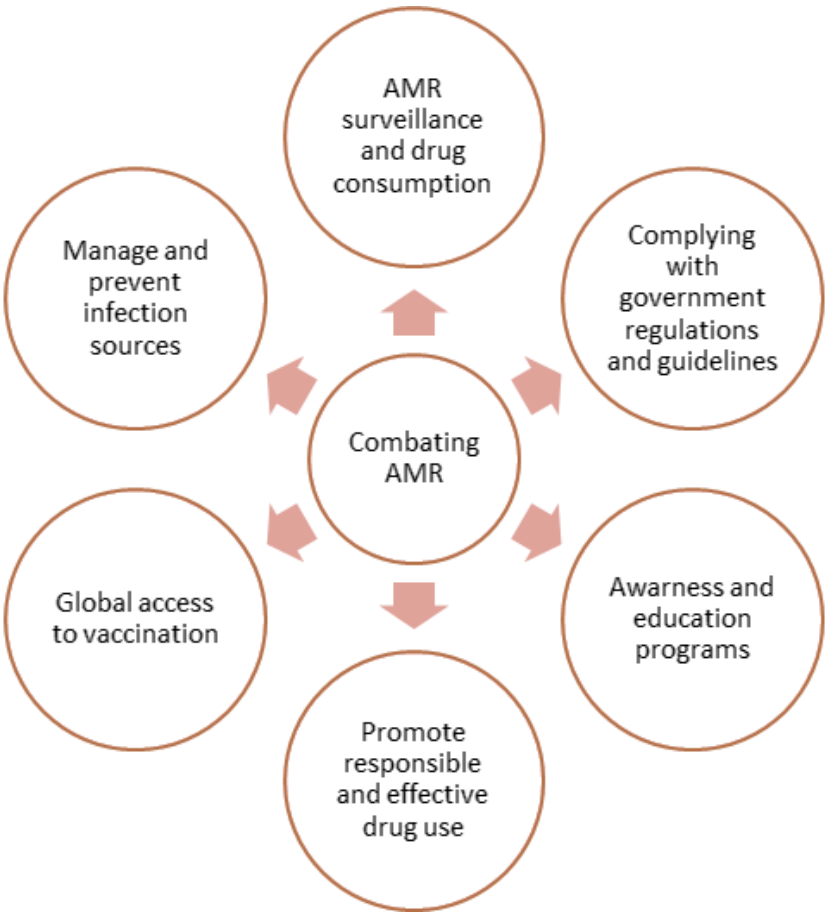

Figure 1. Proposed solutions for combatting AMR (Adapted from Sharma A, *et al.* 2022).

Conclusion

Local awareness campaigns in LMICs through educational interventions and community engagement are as crucial as global awareness for the fight against AMR. Significant gaps in knowledge have been described in

several countries such as Jordan and Ethiopia. Information brochures, posters, and electronic platforms can successfully achieve changes, expand public understanding, and promote responsible antibiotic use.

Furthermore, research is an imperative tool for advancement in medicine, especially regarding developing clinical trials on the prevention and treatment of resistant pathogens. After evaluating five principal medical journals, a recent study highlighted that LMICs are under-represented in these trials. For instance, the ME-RINO trial, one of the most impactful clinical trials, only included 3 participating sites from LMICs. Thus, global cooperation in the execution of clinical trials is necessary to ensure the generalizability of the results and their impact on healthcare settings.

Conducting impactful research and implementing global actions against AMR requires financial support. Initiatives such as the "Multi-Partner Trust Fund" (MPTF) and the "AMR Action Fund" were established. The former reached 13 million dollars to support multi-sector activities in LMICs as well as activities at the global levels to combat AMR through a One Health approach. Meanwhile, the AMR Action Fund has invested more than 140 million dollars since July 2020 to develop novel antimicrobials. Although achievements were witnessed in certain domains, a lack of consistent funding impeded their progress.

Due to the exponential advancement in technology, the necessity to develop novel solutions to reduce AMR has become unavoidable. Therefore, machine learning (ML) and artificial intelligence have gained interest throughout the last 5 years. Applying ML against AMR can be achieved by predicting resistance phenotypes using genomic data, understanding the antibiotic mechanism of action to guide novel antibiotic development, and finally, guiding AMS utilizing data retrieved from patients' electronic records.

AMR is a daunting global health challenge that requires a unified and comprehensive approach. The rapid spread of resistant pathogens across borders and the potential for severe health, economic, and social impacts underscore the urgency of addressing this issue collectively. Global governance, through coordinated efforts like the WHO's GAP and the One Health approach, provides frameworks for nations to collaborate effectively. Surveillance and research are pivotal in understanding resistance patterns and guiding interventions, while the development and enforcement of policies are crucial to controlling the misuse of antimicrobials in both human and animal health.

The role of ASP cannot be overstated. These programs optimize the use of antimicrobials, reduce the spread of resistance, and are essential in both inpatient and outpatient settings. Moreover, IPC measures, especially in healthcare settings, are vital in preventing the transmission of MDROs. The COVID-19 pandemic has highlighted the importance of robust infection control practices and the need for global solidarity in health crises. Ensuring access to high-quality antimicrobials, diagnostics, and vaccines is critical, particularly in LMICs where SF drugs exacerbate the AMR crisis. Sustained efforts are needed to ensure equitable access and to safeguard global health.

In conclusion, tackling AMR requires a multifaceted approach that includes global cooperation, enhanced surveillance and research, stringent regulations, effective AMS, robust infection prevention, and equitable access to quality healthcare. By uniting these efforts, we can mitigate the threat of AMR and protect the health and well-being of populations worldwide.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 4

Time for action: addressing the global AMR crisis

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Introduction

Antimicrobial resistance (AMR) kills and debilitates millions of people annually and turns back progress, particularly in global health, food safety and security, economic growth, poverty alleviation, and the environment.
While many technical targets have been proposed to mitigate AMR, it is important that these initiatives be spearheaded – even at the local level – by unifying global targets that:

- Engage public and political support globally.
- Easily communicate progress on AMR mitigation.
- Focus on stewardship programs (diagnostic and clinical), surveillance and IPC.
- Use a One Health (human, animal and planetary health) approach.
- Investments in new drugs and new strategies.

AMR: numbers and predictions

AMR presents significant challenges to public health - not only in strictly clinical settings but also for those who work with antimicrobials on a daily basis, and by extension, to the global economy. One of the most recent reports published in Lancet and cited by the 2023 World Health Organization (WHO) report on AMR, indicates that there were 1.27 million deaths in a single year directly caused by AMR infections, a number that rises to 4.95 million when including deaths indirectly associated with AMR. Currently, the most affected continent is Africa, with over 100 deaths per 100,000 inhabitants, though Europe also has a mortality rate of approximately 75 deaths per 100,000 inhabitants. The leading cause of these deaths is lower respiratory tract infections caused by resistant microorganisms, followed by bloodstream infections. The pathogens with the highest resistance rates are all members of the ESKAPE group (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Escherichia coli*), along with *Mycobacterium tuberculosis* and *Streptococcus pneumoniae*.
Based on recent studies regarding antibiotic resistance rates, infection incidence, ease of transmission, and the availability of preventive measures and alternative therapies, the WHO released a new report in 2024

identifying antibiotic-resistant bacteria that require increased attention. The report confirmed the inclusion of rifampicin-resistant *Mycobacterium tuberculosis* in the critical priority group, alongside *A. baumannii* and third-generation cephalosporin- or carbapenem-resistant *Enterobacterales* (with *K. pneumoniae* KPC occupying the top spot in this ranking of bacteria of greatest concern). Similarly, ceftriaxone- or fluoroquinolone-resistant *Neisseria gonorrhoeae* is now part of the high-priority group, along with methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant *E. faecium* (VRE), and carbapenem-resistant *P. aeruginosa*. Macrolide- or penicillin-resistant streptococci remain in the medium-priority group, along with ampicillin-resistant *Haemophilus influenzae*.

Without a change in direction, the WHO estimates that by 2050, resistant infections could lead to approximately 10 million deaths annually worldwide. Although the African and Asian continents are expected to be most affected due to the ease with which infections spread there, Europe will also face severe consequences, with annual deaths equating to the population loss of a city like Bologna, which has around 400,000 inhabitants.

Addressing the problem is mandatory

The primary reason why the AMR phenomenon must be addressed is that resistance somewhere is resistance everywhere. As the recent rapid and widespread transmission of the SARS-CoV-2 pandemic has reminded us, in our globalized and borderless world microorganisms can easily "travel" with us, our goods, and our animals, or simply spread through the environment. This, combined with the ability of bacteria to exchange genetic material, including resistance determinants, allows that resistance to an antibiotic class rarely remains confined to its place of origin, and often not even to the species in which it first emerged. A relevant example among Gram-negative bacteria - a group in which horizontal gene transfer (HGT) occurs more frequently and where beta-lactamase genes were first identified - is represented by the first case of isolation of a carbapenemase-producing *K. pneumoniae* (KPC) in Italy. The bacterium, isolated from a patient with an intra-abdominal infection, appears to have been introduced by an Israeli doctor who was completing part of their residency at the University Hospital of Florence. Another emblematic case is represented by the entry of New Delhi Metallo-beta-lactamase (NDM) into Sweden, where the gene was first isolated from an Indian patient with a urinary tract infection caused by *K. pneumoniae* acquired during a trip to India. Both those cases occurred in 2009, and since then, NDM and KPC-carrying strains, not limited to *K. pneumoniae*, have spread globally, becoming endemic in different countries. Thus, the more bacteria become resistant, the more resistant bacteria will circulate.

The most evident consequence of AMR is the inability to successfully treat infectious diseases. It is important to emphasize that it is not only multidrug-resistant (MDR) strains that pose a threat to public health. Sometimes, resistance to just one or two antibiotic classes is enough to necessitate the use of less effective therapies or those with more severe side effects - assuming alternatives exist and the patient is not allergic to the options to which the microorganism remains sensitive. The risk of certain antibiotics becoming unusable, combined with the complexity of the patient, means that the treatment pipelines for infectious diseases could soon become obsolete, without sufficient time to replace ineffective drugs and propose validated alternatives.

Although every effort to reduce AMR is commendable, some authors have already highlighted that individual strategies, such as reducing the use of a single antibiotic, do not always achieve the desired outcome.

One health approach to AMR

Since the emergence, persistence, and spread of AMR are multifactorial and also correlate with anthropological factors (such as low GDP and investments in public health) and environmental factors (such as temperature and sanitation practices), it is not unreasonable to assume that without global actions, we are approaching a point of no return, beyond which we may need to speak of a post-antibiotic era.
Among the anthropological and environmental factors, the impact of antibiotic use in agriculture and animal husbandry on AMR is substantial because the same classes of antibiotics are often used in both veterinary and human medicine, contributing to the maintenance of resistance gene in all settings. This cross-application creates a reservoir of resistance genes in animal populations that can transfer to human pathogens, complicating treatment options for infections. Studies estimate that the agricultural and farming sector accounts for a large proportion of global antibiotic consumption - over 70% in some countries. This widespread use contributes to a significant portion of the global AMR burden, making it a critical area for intervention in global efforts to control resistance. Wastewater treatment plants, hot spots for AMR, also play a crucial role in containing AMR. It has been demonstrated, by our group, that wastewater serves as a reservoir for antibiotic-resistant bacterial species, such as *A. baumannii* and *P. aeruginosa*, as well as resistance genes. It is clear that effectively combating AMR is not just a matter of timing; it requires addressing the problem with a One Health approach, which integrates human, animal, and environmental health considerations along with actions targeted at every local level.

Antimicrobial stewardship programs

In parallel with the One Health approach, collaboration between professionals who deal with microorganisms and antibiotics on a daily basis is critically important in containing AMR. The clinical microbiologist and the infectious disease specialist play key roles in this collaboration. The appropriate use of antibiotics is inseparable from a rapid clinical microbiological diagnostic approach to identify the etiological agent and to reduce to turn-around time for antimicrobial susceptibility testing (AST). Only in this way can antibiotic stewardship be effectively implemented, allowing the specialist to adjust an effective antibiotic therapy with benefits to the patient and the community, by reducing the risk of selecting resistant microorganisms and preserving the efficacy of the remaining active compounds, including the new ones. Proper training of healthcare personnel through infection control and prevention (IPC) programs - including hand and hospital hygiene, surgical site infections, injection safety, and how hospitals operate during and outside of emergencies - is another important strategy for containing AMR, as a significant factor in the spread of antibiotic resistance is attributable to healthcare-associated infections (HAIs), especially in low- and middle- income countries, due to the vulnerability of the patients in hospital settings. Once again, robust IPC measures are cost-saving because AMR can thrive in healthcare facilities.

Research and development

However, stewardship and IPC programs will not be sufficient to prevent us from reaching the aforementioned "point of no return". Forward-thinking governments and scientific societies must invest in and prioritize research into new molecules with more potent antimicrobial activity - especially those effective against MDR strains such as carbapenem-resistant *A. baumannii* (CRAB), KPC producers, and Gram-positive bacteria

resistant to vancomycin or daptomycin. Additionally, they should explore novel strategies that can complement traditional antimicrobial therapy, such as bacteriocins, antimicrobial peptides, the use and engineering of bacteriophages, probiotics, immunomodulators, techniques that target the enzymes or proteins responsible for AMR (including the CRISPR-Cas system), and new drug delivery systems.
Today, we can leverage artificial intelligence, which enhances high-throughput screening performance and allows for the modelling of new molecules and their interactions with microbes.
Educating the general public is crucial in combating AMR. Everyone must understand that adherence to prescribed therapy is not only essential for ensuring recovery from the infectious disease but also for minimizing the risk of relapse caused by resistant strains of the microorganism selected by inadequate treatment. Therefore, initiatives aimed at educating the public about the correct use of antimicrobials are highly valuable.

Political and economic actions

For these reasons, there is a critical need for dedicated funding not only for surveillance but also for the development of new antibiotics and innovative strategies. Such financial support is vital to fuel research, foster advancements in treatment options, and explore alternative methods to address AMR. By doing so, the global community can better address this silent but growing threat, ensuring a healthier future for generations to come. It has been 10 years since the Obama administration initiated a task force in the U.S. to combat AMR. Since then, other countries around the world have also shown increased awareness of the issue, and Europe has allocated part of the NextGenerationEU funds to allow member states to finance research on AMR. For instance, the Italian INF-ACT project (One Health Basic and Translational Actions Addressing Unmet Needs on Emerging Infectious Diseases) has been addressing AMR from multiple angles in Italy for the past two years, using a One Health approach that includes not only antibiotic resistance in bacteria but also studies on fungi, viruses, parasites, and vectors.
Similarly, since 2015, the United Nations has established World AMR Awareness Week to raise global awareness about this critical issue. These commendable initiatives cannot and must not remain standalone activities, nor should they be short-lived or considered sufficient to combat a problem of such vast scope. Governments worldwide and international organizations need to invest more time, energy, and funds into researching new strategies that can mitigate the damage caused by AMR and, in some way, reverse its course. Additionally, better education is needed for both the general public, as consumers, and specialists in microbiology and infectious diseases.

Conclusion

In conclusion, addressing AMR demands a comprehensive and global response that transcends isolated efforts and short-term measures. The multifactorial nature of AMR, exacerbated by human actions across various sectors, requires a coordinated One Health approach that integrates human, animal, and environmental health. Collaboration among professionals, investment in research for new antibiotics, and innovative treatment strategies are all crucial to overcoming the growing threat of AMR. Global awareness initiatives, such as World AMR Awareness Week, highlight the importance of sustained commitment and action from governments, international organizations, and the scientific community to safeguard public health and prevent a post-antibiotic era. This and many other initiatives must be declined at national, regional and local levels.

Without decisive intervention, AMR will continue to escalate, putting millions of lives at risk and undermining the effectiveness of modern medicine.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 5

Striking the balance in the 21st century: optimizing effective antimicrobial therapy while preserving efficacy

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Introduction

The most worrisome cause of fever for every clinician is that of a serious bacterial infection leading to sepsis, septic shock, and death. When U.S. Surgeon General Dr. William H. Stewart made his observations on the dramatic shift in human disease from early death due to infections to chronic illnesses, his remarks were misinterpreted to have declared "the war against pestilence won". He was quite cognizant in his writings and speeches that while major inroads had been made in the Antibiotic Era, bacterial diseases had not been conquered. The urban legend, however, took over the public imagination. To this day, a prescription for antibiotics remains a source of reassurance for many a patient seeking care for a viral illness and many a clinician faced with ever-more-limited time.

In many areas of the world, antibiotics and their counterfeits are available at pharmacies without healthcare professional involvement and without regulatory oversights of their quality and safety. Public health campaigns against using antibiotics in the case of viral infections have failed to stem their overuse in wealthier countries. In a spatial modeling study including multiple data sources between 2000 to 2018, covering over 208,000 children across over 200 countries, Browne AJ *et al.* estimated a 46% increase in daily global antibiotic consumption rate for lower respiratory infection symptoms by 2018. Disquietingly, fluoroquinolone use, associated with the rapid development of resistance across a range of important pathogens (e.g. *Neisseria gonorrhea*, *Pseudomonas aeruginosa*), was noted to increase significantly. Third-generation cephalosporins, associated with extended-spectrum beta-lactam resistance, rose as well. A pattern of disparity also emerged, with most consumption occurring in eastern Europe and central Asia, while Sub-Saharan Africa was lowest.

The multifactorial problem of antimicrobial resistance (AMR)

We know that it is critical to balance life-saving access to antibiotics across the spectrum of high- to low-income areas with discerning use that limits the spread of resistance. Tackling the problem of AMR, however, is fraught with barriers both known and unknown to the clinician at the point of care. In addition to the critical decisions behind prescribing, it is impacted by declining antimicrobial research and development, supply chain disruptions and shortages, agricultural overuse and run-off, global travel and human migrations, economic inequity, and climate change. Economic disincentives to pursuit public health professions and

physicians electing specialization in Infectious Diseases threaten both clinically informed public health policy-making and antimicrobial stewardship at the critical care bedside.

The pharmaceutical "pipeline"

Since the 1960s, public and private health goals shifted research and development investments towards the management of chronic diseases. In the 1980s, the global AIDS pandemic shifted attention to the development of antiretrovirals, costly but reimbursed by health insurers after years of public activism. Investment in developing antibacterial agents, however, has lagged. A few novel agents targeting resistant organisms have been successful, others less so--"me-too" beta-lactams with greater cost and limited benefit over existing ones have failed to succeed in the market. From 2010 to 2021, 12 new antimicrobials were approved by the U.S. Food and Drug Administration primarily targeting resistant Gram-negative bacilli. Globally, the World Health Organization (WHO) began analyzing the preclinical and clinical development of antibacterials in 2017. This data is published online on the Global AMR R&D Hub's Dynamic Dashboard. Investments in therapeutics for hospital-associated Gram-negative bacilli of critical or high importance totaled approximately US$340 million between 2107 to the present. This is roughly equally divided between the development and discovery stages. Government and public funding remain the majority contributors to active projects in the discovery and development stages, with public-private funders at approximately 20% of the total. Many projects closed during the COVID-19 pandemic and remain active as of 2024.

Ironically, the problem of evolving resistance and returns on private investment may be exacerbated by both antimicrobial stewardship programs and healthcare costs in resource-rich countries. Newer intravenous antibiotics are necessarily "restricted" by hospital pharmacy formularies, third-party payers, and Infectious Disease specialists in favor of cost-efficiency and targeted evidence-based use. In addition, over the past two decades, prescribing of newer antibiotics may have been impacted by conflict-of-interest policies restricting pharmaceutical detailing, particularly at academic medical centers, in addition to the open-access publication of physician payments by pharmaceutical companies. While the latter has helped to curb healthcare costs and adverse events, an unintended consequence may be reduced attention to newer antibiotics that may not be available on a hospital formulary or that require additional effort to prescribe. Another important limitation in clinician prescribing of newer agents is the lack of susceptibility testing to inform the use of newer agents, whether by lack of development by commercial laboratories or by limitations of hospital budgets. Given the financial aspects, private pharmaceutical firms have shifted priorities to higher yield, long-term investments in the chronic diseases of aging populations, such as cancers, autoimmune diseases, and atherosclerosis.

Supply chain disruptions and shortages

Over the past decade, shortages of essential antimicrobials, previously unprecedented, now regularly disrupt health care. Manufacturing supply and distribution chains have become increasingly fractured and complex, and a break in the chain may create a far-reaching crisis. Over 80% of the active pharmaceutical ingredients used by U.S. manufacturers are sourced from over 4,000 manufacturing facilities in China and India. These facilities are registered with the U.S. Food and Drug Administration (FDA), yet regular inspections that might foreshadow interruptions have been challenging due to staffing vacancies, administrative barriers, funding, and most recently, a global pandemic. One of the earliest shortages most keenly felt in hospital medicine involved the widely used beta-lactam drug, piperacillin-tazobactam. In 2016, the Qilu Pharmaceutical firm in China was the sole producer of several pharmaceutical components critical to the manufacture of piperacillin-tazobactam. Already in short supply, an explosion ground production of this drug to a halt. A key first-line antibiotic in guidelines for serious and nosocomial infections across the world, hospital clinicians of almost

every specialty scrambled and developed alternative treatment regimens and alternative suppliers. Since then, clinicians have had to alter treatment pathways for several first-line antimicrobials across the range of human infections, including penicillin, cefazolin, ceftolozane–tazobactam (a key agent against resistant Gram-negative bacilli), acyclovir, among others. No sooner than one shortage resolves, than another (or two) begins when a key point in the manufacturing and distribution chain is broken. Thus, clinicians may be left with suboptimal or less evidence-based drug options, some of which may be favoring antimicrobial resistance in ways yet to be understood.

Pressures at the point-of-care

Clinicians and surgeons across the healthcare spectrum fully recognize the importance of the judicious use of antimicrobials and the growing threat of multidrug-resistant organisms. For many, however, it remains a risk that looms somewhere in a nebulous future. The threat of AMR seems theoretical faced with the immediacy of the patient in the clinic who took time off from work expecting a curative prescription or who presents in florid septic shock. There are numerous considerations at the point of care. Time and again, in peer-reviewed studies of ambulatory and primary care practices, where the bulk of antibiotics are prescribed, the greatest determinant of inappropriate prescriptions is actual or perceived patient expectation. Time, communication skills, and workload constraints in both ambulatory and hospital settings may limit opportunities for patient education. Employers, third-party fee-for-service payers, and hospital administrations increasingly impose patient satisfaction metrics on clinician credentialling. Moreover, for some practices, third-party income and fear of litigation add undeniable fiscal pressures to medical decision-making. Unsurprisingly, some prescribers do not recognize (intentionally or not) their own role in antimicrobial resistance, preferring to blame hospital prescribers and other sources. On the patient's part, drivers include preconceived ideas about their diagnosis, expectations or perceived benefit from prior inappropriate prescriptions, pressures to return to school and work, and the placebo effect of a prescription. Lastly, in some areas, access to antimicrobials is unregulated. Anyone can buy antibiotics or antifungals without a prescription and at low cost at the corner kiosk (**Figure 1**).

Ways forward at the bedside or examination room

The weight of choosing wisely for one's patient is sometimes heavy early in the face of uncertain diagnosis, especially when the risk of failure may include sepsis or even death. It is especially easy to over-prescribe in healthcare settings where continuity-of-care and personal observation or feedback about outcomes are limited. For clinicians with access to medical records or who provide longitudinal care, the negative consequences of repeated antibiotic therapy become clear, immediate, costly, and complicated. In my practice as an infectious disease subspecialist, longitudinal medical records often document a progressive loss of treatment options over time that I must then explain to a frustrated or very ill patient or family member. The fear of under-treating a bacterial infection is often so overwhelming that antibiotics may be continued by the patient or the prescriber for extended periods of time despite a clear lack of benefit and in the face of obvious adverse effects. Ironically, one of the most common (and rewarding) aspects of daily infectious disease practice is the discontinuation of unnecessary antibiotics. Early in my career, I learned the invaluable aphorism, "Antibiotics are not antipyretics" (credit to Larry Lutwick MD, Professor of Medicine, Mayo Clinic, U.S.). In many situations, both prescriber and patient simply need validation of the decision or "permission to stop". Whether it is a matter of validation or of shifting the burden of risk to the infectologist, this discomfort is

fear-driven and socially constructed. Fortunately, knowledge is the antidote to fear. Or at least it allows evidence to inform and balance risk aversion in both patient and clinician.

Figure 1. Pharmacy kiosk, Los Cabos, Mexico, 2022.

Non-bacterial causes of acute neutrophilia and fever in the ambulatory and surgical setting

Fever and acute leukocytosis are concurrent non-specific reactions and are typically the first clue of an inflammatory or damaging event. In general, a leukocyte count above 11,000 cells/µL in adults is considered a leukocytosis and prompts concern for bacterial infection. It is important to obtain a white blood cell differential with the complete blood count to ensure that this reflects neutrophilia and an acute reactive event. Normally, neutrophil precursors reside in the bone marrow and mature over approximately two weeks to maintain a reserve of polymorphonuclear of about two-thirds of that in the peripheral blood. Neutrophils circulate in blood for less than half a day when released from bone marrow before entering peripheral tissues. Mature neutrophils are the predominant white blood cell in adults, ranging from 40 to 60% of the differential. The expected range given by laboratories is up to 2 standard deviations from the mean in a population. About 2.5% of normal individuals will fall above the bell curve and remain healthy. Individuals with Down syndrome or familial genetic factors may have above-average leukocyte counts.

Ward HN and Reinhard EH reviewed 35 healthy individuals followed for unexplained persistent neutrophilia over 7 years of their Hematology practice. Ages ranged from 22 to 65, neutrophils averaged 14,965 per cubic mm, and this finding persisted for an average of 34.8 months. Over an average of 7 years, 11 developed no significant illness or symptoms and 19 developed a wide range of unassociated illnesses. Only 4 developed conditions that might have been related to their leukocytosis—none was an acutely life-threatening bacterial infection. In our practice, we may have the benefit of access to a decade or more of our patients' laboratory

reports. An unexplained neutrophilia of less than 20 cells per cubic mm of one month or greater speaks reassuringly against most urgent conditions requiring an antibiotic.

Neutrophils can be produced and released into the circulation very rapidly in response to acute bacterial infection, but also in response to tissue damage, thrombosis, inflammatory conditions, metabolic disorders, stressors, hemolysis or hemorrhage, and malignancies (**Table 1**)**.**

Table 1. Non-infectious causes of fever and neutropenia.

Non-infectious causes of fever and neutropenia
Direct tissue damage ● Surgery, burns ● Necrosis ● Infarction, ischemia (including cardiac) ● Carcinoma, carcinomatosis
Hemorrhage, hemolysis
Thrombosis ● Superficial or deep thrombophlebitis, pulmonary embolus ● Chemical phlebitis ● Vasculitis
Asplenia
Metabolic conditions ● Diabetic ketoacidosis ● Gout
Collagen vascular diseases, vasculitis

Asplenia is often associated with moderate neutrophilia. While corticosteroid therapy is a well-known cause, other pharmacologic causes include lithium and nicotine. Chemical phlebitis may cause fever when peripheral intravenous catheter sites extravasate medications. While bacterial sepsis may cause a very high neutrophilia with counts above 50,000 cells per cubic mm, sepsis causing this level of inflammation is rarely missed and justifies the rapid initiation of antibiotics. Most other infectious causes are indolent and require focused diagnostics and treatment, such as tuberculosis. Neutrophilia in the setting of watery stools commonly alerts us to *Clostridioides difficile* colitis, for which the most immediate therapy is cessation of broad-spectrum antibiotics. A leukocytosis greater than 100,000 cells per cubic mm is almost invariably caused by hematologic malignancy rather than infection requiring antibiotics.

A common cause of persistent or recurrent fever in the hospital during treatment for a diagnosed bacterial infection is inadequate source control rather than a need for broader spectrum antibiotic coverage or another infection. Aseptic pneumonic effusion may lead to empyema with recurrent fever despite appropriate antibiotics for pneumonia. Surgical site infections generally follow a clear progression from superficial wound infection to dehiscence and deep tissue infection to organ or implant infection and abscess. If a non-surgical skin and soft tissue infection is failing to improve, the patient should be assessed for an unrecognized abscess or necrotizing infection. Cellulitis due to *Staphylococcus aureus* not uncommonly organizes into phlegmon and abscess. Inadequately relieved chronic lymphedema is ripe grounds for streptococcal soft tissue infection, which further worsens edema and delays lymphatic drainage of inflammatory toxins and infected tissue fluids. Uninfected chronic decubitus ulcers are unlikely to cause fever even in the setting of exposed bone or

chronic osteomyelitis, but a septic or infected decubitus is readily diagnosed by the presence of increased wound drainage, peri-wound cellulitis, pain (unless insensate), and malodor. In the setting of bacterial pyelonephritis, hydronephrosis or obstruction to urinary flow should be sought before declaring antibiotic failure. Bacterial prostatitis may be complicated by abscess.

Asymptomatic bacteriuria

A common condition that frequently results in unnecessary antibiotics in the ambulatory, preoperative, and operative setting is chronic bacteriuria and pyuria in the absence of other symptoms or signs of acute cystitis or pyelonephritis. Asymptomatic bacteriuria and pyuria are well-recognized as common with advancing age and comorbidities, occurring in 20% of ambulatory 80-year-olds and up to 50% of long-term care residents. ASB and pyuria develop within days of bladder catheter insertion. Antibiotic therapy of asymptomatic bacteriuria (ASB) may temporarily clear bacteria without evidence of reduced urinary tract infection rate nor prevention of sepsis or death. On the contrary, treatment without symptoms has been associated with increased reinfection and with increasingly resistant organisms. In addition, treatment of ASB adverse drug events hypersensitivity reactions, and collateral damage to the gut microbiome leading to *Clostridium difficile* colitis and colonization with more pathogenic Gram-negative flora. The U.S. Infectious Disease Society of America (IDSA) published its original Clinical Practice Guideline for the Management of Asymptomatic Bacteriuria in 2005, updated in 2019 to balance evidence, benefits, and adverse and economic costs. In adults, evidence supports the potential benefit of screening for ASB in pregnancy and treating for the shortest effective course, no more than 7 days. Otherwise, screening for ASB should be avoided in older individuals living in the community or long-term residences, in diabetic patients, in those requiring chronic bladder catheterization post non-renal transplant or beyond the initial 30 days post renal transplant. The IDSA guidelines recommend screening and treating for ASB prior to invasive urologic procedures and suggest a short course of antibiotics targeting the organisms in culture starting 30 to 60 minutes before surgery. A maximum of 1 to 2 doses is suggested in the absence of symptomatic cystitis or pyelonephritis postoperatively. Lastly, the IDSA guideline recommends against screening or treating for ASB prior to non-urologic surgery.

In the surgical setting, preoperative screening with urinalysis and culture remains highly prevalent despite guidelines and the absence of supportive data outside of procedures directly involving the urologic tract. Treatment of ASB or colonization is best associated with reduced post-procedure symptomatic urinary tract infection (UTI), bacteremia, and sepsis in the setting of more invasive urologic procedures, including flexible ureteroscopy, percutaneous nephrolithotomy, and transurethral resection of the prostate (TURP). A recent retrospective study of 264 patients undergoing urologic procedures found a postoperative febrile UTI rate of 3.9% and 0.5% of surgical site infection. Fifty-eight percent of patients developing postoperative UTI or SSI had documented preoperative ASB. The authors note that prior studies, however, have suggested otherwise. The odds ratio of postoperative infection was highest for isolation of one or two organisms on urine culture, but notably, not much more so than for polymicrobial cultures, which are often rejected for culture by microbiology laboratories as “contaminated” or difficult to speciate. There remains no data defining the duration and benefit of preoperative antibiotic therapy in urologic procedures.

The association of ASB with postoperative infections is much lower in other surgical procedures. However, given the significant morbidity and healthcare costs associated with prosthetic joint infections (PJI, primarily total prosthetic knee and hip arthroplasties), all efforts should be made to reduce perioperative risks for PJI, including screening and treating for ASB should evidence support it. Risk factors for PJI include those associated with both ASB and SSI: impaired nutrition, uncontrolled hyperglycemia, obesity, and immunosuppression, all common in advancing age. A recent meta-analysis of 12 studies involving over 42,000 patients found an increased incidence of PJI associated with ASB, but no correlation between urine colonizers and

subsequent SSI or PJI, and no significant effect of preoperative treatment for ASB. Another reviewing 14 studies also found increased odds ratio of 1.84, but no significant influence of treatment of ASB preoperatively. Four studies found no correlation between baseline ASB microorganisms and subsequent PJI, the majority of which reflect skin flora.

Vertebral infections arise hematogenously via vertebral arteries and the valve-less venous plexus, with several case reports suggesting urologic origin presumably via venous drainage from the pelvis. The overall incidence of discitis is 0.4-2.4 per 100,000 per year. A few studies have documented a 4-10% incidence of asymptomatic, transient bacteremia within 24 hours of exchanging a bladder catheter, with one study estimating that 1 in 14 chronically catheterized adults in the community. Urologic sources of discitis, however, are rare and are often associated with bacteremia. Given the low incidence of vertebral infections related to urine and the fact that capillary arterial pressure is typically 20 mmHg higher than slower venous flow, ASB is less likely to be a source of neurosurgical infection even assuming bidirectional flow across Batson's plexus. That said, it is an understandable concern that neurosurgical procedures might be at risk. A retrospective review of 716 patients undergoing vertebroplasty for osteoporotic compression fracture identified preprocedural ASB in 14.1%. The odds ratio of PVI was highest in smokers (16.26) and malignancy (7.27) and lowest with ASB (5.61). Despite the frequency of ASB, the incidence of post-vertebroplasty infection was reassuringly low at 1.26%, and there was no correlation between ASB flora and PVI.

Outside of more invasive urologic procedures, the association of ASB with post-operative SSI within 30 days of procedures is inconsistent. After statistical balancing of patient characteristics (88.9% males and 11% females in the U.S. veterans' healthcare system), a recent cohort study of over 250,000 patients undergoing over 288,000 surgical procedures found no correlation between preoperative urine culture and subsequent UTI or SSI within 30 days afterward. Preoperative culture was performed within 30 days prior to surgery in 10.5%, with SSI occurring in 1.3% having a urine culture, and 1.5% in those who did not. In addition, no difference was observed when analyzing orthopedic and neurosurgical procedures.

In addition to concerns related to monitoring of infection rates and medicolegal liability, cognitive bias induced by "positive tests" has been repeatedly confirmed in health care professionals. A persistent prevalence of inexpensive urine dipsticks used routinely to detect leukocyte esterase (produced by neutrophils) and nitrite (produced by coliforms) contributes significantly to the inappropriate treatment of asymptomatic bacteriuria and pyuria. The positive predictive value of urine dipsticks and pyuria is well below 50% in several studies. Despite this, a positive urine dipstick or a positive urinalysis with or without culture is associated with an increased probability of an antibiotic prescription. Public Health England has launched effective efforts to educate and discourage health professionals from routine use of urine dipsticks in asymptomatic older patients, including a quality control study in nursing homes that led to a 56% drop in antibiotic prescriptions for suspected urinary tract infections.

Guidance for striking the most effective balance

Pre-test probability and medical evidence form the basis of appropriate, effective use of diagnostic tools and antibiotics. In 2011, the Antibiotic Stewardship and Resistance Working Groups (ASRWG) of the International Society for Chemotherapy proposed ten key points for the appropriate use of antibiotics in hospital settings, updated in 2016. In 2023, the Worldwide Antimicrobial Resistance National/International Network Group (WARNING) Collaborators, a consensus of nearly 300 experts from 115 nations, published 10 "golden rules" for optimal antibiotic use (**Figure 2**). These guidelines generally agree. Chief among them is order cultures only when the clinical picture supports it (high pre-test probability). Few body fluids are truly sterile, thus

treat the patient, not the positive test. In our practice, we discontinue empiric antibiotics at 48 hours if there is no clear evidence of bacterial infection. Furthermore, we discontinue antibiotics with persistent fever if there is no documented bacterial infection. Empiric treatment accounts for local resistance patterns and individual risk factors for resistance. Third through sixth are best summarized to treat with the optimal dose, optimal route, and optimal duration. Shorter courses are increasingly favored by data. ASRWG speaks to limiting overexposure without supportive data, e.g. dual beta-lactam combinations or other synergistic or additive combinations, or indiscriminate or recurring use of the same agents, such as carbapenems or quinolones. Seventh in both: Source control. Antibiotics do not sterilize tissue, and efficacy may depend on the size of the inoculum. Abscesses, necrotic tissue and bone must be debrided. Infected catheters, devices, and implants colonized with bacteria must be removed. Equally crucial, knowledge empowers. Surveillance, monitoring, education, and (importantly) collegial, respectful, objective feedback, are keys to engaging staff and changing practice. These form the heart of our center's antimicrobial stewardship program. Lastly, preventing antimicrobial resistance and ensuring optimal outcomes in the 21st century involves team-based collaboration between infectious disease specialists, the microbiology laboratory, the hospital epidemiologist or infection preventionist, clinical pharmacists, and the clinicians involved in direct care. In our practice, infectious disease-trained clinical pharmacists play an integral role in optimizing our treatment, managing adverse effects, selecting alternatives when necessary, and de-escalating therapy.

Conclusion

To some degree, antimicrobial resistance is an inevitable part of the co-evolution of microbes and humans. In the end, whether we as healthcare providers know what to do or need support or validation to do it, at the end of the day "the hand holding the pen" (or on the keyboard) carries the responsibility of balancing timely, beneficial antimicrobial therapy and reducing antimicrobial resistance. A multidisciplinary antimicrobial stewardship approach offers an important opportunity for all levels of expertise and clinical experience to optimize outcomes while minimizing or delaying the loss of effective therapies. Collaborative approaches can lead to realistic and achievable goals at the individual bedside, as well as institutional, and community levels.

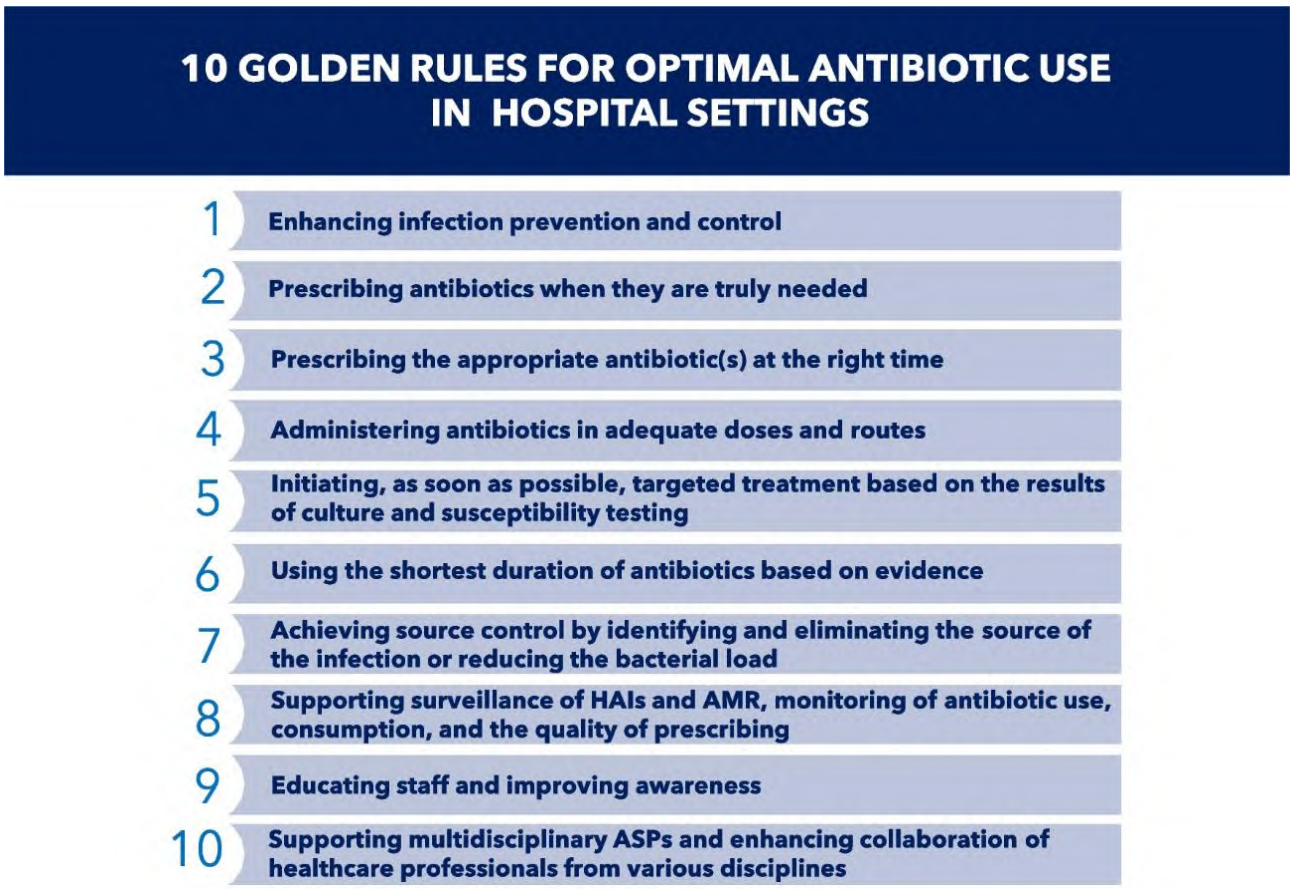

Figure 2. The 10 "golden rules" for optimal antibiotic use in hospital settings (Adapted from Worldwide Antimicrobial Resistance National/International Network Group (WARNING) Collaborators, 2023).

Competing interests

The author has no financial and non-financial competing interests to declare.

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Chapter 6

Global research priorities for antimicrobial resistance in human health

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Introduction

Antimicrobial resistance (AMR) poses a greater health burden than TB, HIV, and malaria, with major economic repercussions. To combat this, WHO coordinated the 2015 Global Action Plan on AMR, which calls for a research agenda to address key knowledge gaps on AMR, including assessing its health and economic impacts, the cost-effectiveness of interventions, and developing new treatments, diagnostics, and vaccines, while also monitoring and reporting implementation progress.

To concentrate efforts on generating evidence for the pathogens that pose the greatest public health risk associated with AMR, WHO released a priority list of bacterial pathogens in 2017 (updated in 2024) and fungal pathogens in 2022. Additionally, WHO conducts an annual review of the pipeline for agents targeting bacteria to help set priorities and inform policy for research and development (R&D). As of 2021, out of 46 antibiotics and 61 candidate vaccines in clinical development, only 28 antibiotics and 10 vaccines were aimed at WHO's bacterial priority pathogens.

Although attention to AMR has grown in recent years, knowledge gaps hinder an effective response. This is evident from the slow progress many countries have made in implementing their National Action Plans on AMR. Low- and middle-income countries seem to bear the highest burden of bacterial AMR. However, significant data gaps due to limited laboratory capacity and data collection systems affect the reliability of these estimates.

Previous attempts to compile research gaps for resistant bacterial infections have not succeeded in identifying crucial research priorities for human health. Some initiatives have concentrated only on specific aspects of AMR or solely on the one-health interface, often neglecting priorities relevant to resource-limited settings. A prioritised, multidisciplinary research agenda on AMR can be instrumental in guiding investments by governments and funders and attracting the interest of policymakers, researchers, and the private sector towards significant knowledge gaps that need evidence generation, thereby supporting the effective implementation of AMR policies and interventions. This represents the first comprehensive effort focusing specifically on infections caused by drug-resistant bacteria, including *Mycobacterium tuberculosis* and fungi, based on a robust and validated approach for prioritising research topics.

The WHO research agenda for AMR in human health

The research agenda sought to identify the most urgent global research priorities linked to human health, with significant potential to impact policies, interventions, and tools addressing AMR in WHO's priority bacterial and fungal pathogens, as well as resistant *M. tuberculosis* (**Box 1**). The evidence produced could help guide the prioritization of interventions within AMR National Action Plans.

Box 1. Research agenda development framework.

Objectives The research agenda has two objectives: 1. to advance the evidence on antimicrobial resistance through the identification and prioritization of research topics encompassing the prevention, diagnosis, treatment, and care, the burden and determinants of antimicrobial resistance, as well as optimizing intervention delivery, and 2. To catalyse increased investment and scientific interest among researchers, donors, and public health professionals.
Scope and focus The research agenda is global in its scope, focuses on antimicrobial resistance in the human health sector, and specifically on infections caused by WHO bacterial priority pathogens, WHO fungal priority pathogens with critical importance for antimicrobial resistance, and resistant *Mycobacterium tuberculosis*. Other pathogens such as drug-resistant HIV and malaria are out of scope.
Population The research agenda aims to define priorities for research applicable to the general population, including vulnerable populations, neonates and children.
Geographic context While the research agenda is global in its scope, it places a particular focus on identifying knowledge gaps and prioritizing research topics relevant for low-resource settings.
Time frame In line with the Sustainable Development Goals, the research agenda aims to catalyse research by 2030.
Research investment strategy The research agenda aims for investments in antimicrobial resistance research to be balanced and diversified across the prioritized research topics (i.e., not focusing on one or a few high-risk and/or expensive research ideas) and encompassing the four domains of research (i.e. descriptive, delivery, discovery, development).

The research agenda emphasizes addressing crucial knowledge gaps by 2030, in line with the Sustainable Development Goals. It focuses on research pertinent to low-resource settings, recognizing disparities in the availability of diagnostics, antimicrobials, and infection prevention measures compared to high-resource settings. The agenda covers all four key research domains—description, delivery, development, and discovery—to tackle the multifaceted challenges of AMR in human health.

An internal WHO steering group with expertise in key AMR areas was formed to oversee the development of the agenda and define the objectives, scope, population, geographic focus, time frame, AMR sectors, and prioritization criteria. The agenda was developed using the Child Health and Nutrition Research Initiative (CHNRI) method, a systematic, transparent, and repeatable method ideal for prioritizing research topics from a broad selection and reducing individual bias through independent expert scoring (**Box 2**).

Box 2. Metric-based and consensus-based approaches for agenda priority setting (Adapted from World Health Organization, 2020).

Metric-based approaches

- *Description*: metric-based approaches generate priorities based on an algorithm that pools individual scoring of research questions.
- *Strengths*: systematic and repeatable. Reduces the risk of an individual opinion dominating over others. More feasible for a larger number of stakeholders to participate and dampens down the dominance of minority but vocal stakeholders.
- *Weaknesses*: scoring can be very demanding for participants. Individuals score in isolation, can limit opportunities for dialogue.
- *Examples*: Child Health and Nutrition Research Initiative (CHNRI) and Delphi techniques.
- *Usage*: more suitable for global prioritization exercises.

Consensus-based approaches

- *Description*: consensus-based approaches lead to priorities decided by group consensus.
- *Strengths*: priorities are decided by group consensus which improves acceptability.
- *Weaknesses*: not strictly systematic. Might result in "obvious" priorities without strong evidence. Priorities might reflect the views and biases of a limited number of experts and, potentially, those more vocal in the discussions. Not feasible for prioritization of a large number of research topics.
- *Examples*: combined Approach Matrix (CAM) and Priority-setting Partnerships (PSP).
- *Usage*: more often used for national prioritization exercises.

A semi-structured approach was used to form an informal group of global experts. Researchers were identified via Web of Science, seeking varied expertise across research fields, AMR areas, regions, income levels, and populations, alongside referrals and open calls. The group also included policymakers and program managers. Of the 562 experts found, 261 contributed to the development of the research agenda. Declarations of interest were reviewed independently, and no one was compensated by WHO. Experts from 69 countries participated: European (41%), Americas (24%), African (15%), Western Pacific (8%), South-East Asian (7%), and Eastern Mediterranean (4%), with most from the UK, USA, South Africa, Switzerland, Canada, India, Brazil, and Australia.

The initial CHNRI phase involves experts submitting their research proposals or concepts. This step was enhanced by conducting an extensive scoping review of both peer-reviewed and grey literature from the past decade (2012-2021). This included a systematic search for systematic reviews indexed in PubMed, Embase, and Web of Science using an exhaustive list of terms, as well as manual searches of data repositories and the websites of 92 key organizations. The review revealed 2,340 knowledge gaps (**Box 3**) from over 3,000 documents regarding the burden, drivers, technologies, tools, and interventions for preventing, diagnosing, treating, and caring for resistant pathogens within this research agenda's scope. These gaps were then sorted into research topics or subtopics. The topics were further structured into the PICO/PECO (population, intervention/exposure, comparator, outcome) format and consolidated into 177 thematic research topics. The research topics were organized into a "knowledge matrix," categorizing them into the four CHNRI-defined domains (descriptive, delivery, development, and discovery research) as well as three themes according to WHO's people-centered approach for AMR: prevention, diagnosis, and treatment and care. An online survey gathered feedback from 257 expert group members on the 177 research topics identified in the scoping review. One-hundred and fifty-six (61%) participated. Experts could accept, suggest text improvements, or recommend removing each topic. Removal was considered if the topic was (a) noncritical due to existing evidence; (b) unlikely to inform policies or interventions; or (c) unfeasible to address by 2030.

Box 3. Definitions.

Knowledge gaps Areas for further research identified from an extensive scoping review and through an expert survey.
Research topics Thematic areas which encompass common themes emerging from identified knowledge gaps and associated research questions.
Research priorities The top research topics prioritized by the global expert group.
Research domains Four research domains often used by the Child Health and Nutrition Research Initiative (CHNRI) knowledge matrix to categorise research topics: descriptive (have greater understanding of AMR burden and drivers), delivery (provide ways to deliver existing interventions with better quality), development (improve existing interventions, reduce their costs, or optimise their implementation), and discovery (new interventions to prevent, treat, and diagnose antimicrobial resistance).
Themes The research topics and priorities cover three themes: antimicrobial resistance prevention, diagnosis, treatment and care, plus a cross-cutting theme, in accordance with the WHO people-centered approach for addressing antimicrobial resistance.
Areas The research topics and priorities encompass the antimicrobial resistance relevant areas: WASH (water, sanitation and hygiene); infection prevention and control; immunization; diagnosis/diagnostics; antimicrobial stewardship; antimicrobial use and consumption; antimicrobial medicines; epidemiology, burden, and drivers of antimicrobial resistance; awareness and education; policies and regulations; prevention of drug-resistant tuberculosis; diagnosis of drug-resistant tuberculosis; and treatment and care of drug-resistant tuberculosis.
WHO steering group A group of WHO experts with technical expertise spanning the different AMR areas which defined the objectives and scope of the agenda. This group supported the consolidation of research topics and the development of the criteria for prioritisation, and guided the prioritisation process.
Expert group An informal group of global experts external to WHO identified through a semi-structured review of publication output in Web of Science as well as policymakers with a mix of expertise from across research disciplines and AMR areas, geographical representation, income settings, and paediatric expertise. The expert group participated in the identification of knowledge gaps (Survey 1) and prioritization of research topics (Survey 2).

To ensure comprehensive coverage of critical knowledge gaps on AMR in human health, expert group members were encouraged to suggest up to two additional topics, based on specific criteria, including avoidance of duplication, filling a critical gap in knowledge, relevance to human health, potential policy relevance, and feasibility for evidence generation by 2030.

Each research topic in Survey 1 was recommended for removal by at least one expert, with a median of 7 removal suggestions per topic (ranging from 1 to 34). Additionally, 158 new topics were proposed by 90 experts, while 54 experts provided recommendations for improving existing topics. Concurrently, a call for expert contributions was opened on the WHO website to involve the wider research community. The open call enabled individuals to review current topics, suggest new ones, and evaluate the proposed topics based on the provided criteria. This process resulted in 18 individuals recommending the removal of 58 topics and suggesting 7 new topics.

In total, 165 new topic proposals were received from the expert survey and the open call, which underwent a thorough review by at least two reviewers. Reviewers utilized a semi-structured consensus method, consulting with subject area experts in the WHO steering group to determine acceptance or rejection. This process added 65 new topics, removed 100 topics (new or from the scoping review list), merged 22 topics, and

reclassified 70 topics as subtopics. To streamline prioritization, similar topics with slightly different perspectives were combined into composite research topics, which would require multiple studies to address all underlying gaps. The steering group assessed the revised list, resolving disagreements through meetings or email, resulting in a final list of 175 consolidated topics.

In Survey 2, a total of 328 experts were invited, with 234 (71%) participating in scoring the 175 consolidated research topics. Notably, 129 of these experts had also contributed to Survey 1. Participants identified their primary viewpoint (high-income, low- and middle-income, or all-income settings) and target age group (adults, children, or all age groups). When evaluating the topics, 93 out of 234 (40%) applied an "LMIC perspective," 86 (37%) considered "all income settings," while the remaining 55 (23%) used a "high-income settings" perspective. Additionally, 78 (33%) focused solely on adults, 38 (16%) on neonates/children only, and 118 (50%) considered all age groups in their evaluation. Among the 234 experts in Survey 2, 114 (49%) identified as women, and 84 (36%) were affiliated with institutions in LMICs.

Within their self-designated AMR areas of expertise, experts evaluated whether each research topic met five criteria (**Box 4**) and recorded their answers as: "yes" (score 1 point), "no" (score 0 points), or "don't know." Intermediate criterion scores for each topic were then calculated by summing the scores for each criterion and dividing by the number of experts who evaluated This calculation was repeated using input solely from experts assessing topics from the perspective of LMICs. Following this, a research priority score (RPS) for each topic was calculated from both global and LMIC viewpoints. The RPS was determined as a weighted average of the five criterion scores, with "feasibility by 2030" and "health equity" each given a 10% weight, and the remaining three criteria each assigned a 27% weight. This distribution of weights was based on feedback from experts who acknowledged the complexity of the topics and the challenges in evaluating them against the "feasibility by 2030" and "health equity" criteria. The topics were ranked by weighted RPS into two distinct lists: one considering "global" perspectives (regardless of income setting) and another based solely on the responses from experts evaluating topics from an LMIC setting.

Box 4. Criteria for scoring and prioritizing research topics.

Filling critical knowledge gaps Is the research likely to fill critical knowledge gaps on antimicrobial resistance?
Answerability and feasibility by 2030 Can a research study be designed and carried out by 2030 to address at least some components of the research topic? (Availability of funding should not be considered).
Potential for translation into policy Do findings have the potential to inform evidence-based policy and practices aimed at mitigating the public health impact of antimicrobial resistance?
Impact to mitigate antimicrobial resistance Is the research likely to result in an intervention that is effective, efficacious and/or efficient in mitigating the impact of antimicrobial resistance? (Effective: producing a desired effect in a real-world environment; efficacious: providing a desired effect in a controlled environment; efficient: providing the highest value for the available resources).
Promoting health equity Is the research likely to promote health equity (i.e., leading to interventions that will reduce the inequitable impact of antimicrobial resistance across diverse socioeconomic contexts and underprivileged populations)?

Among the 175 research topics, the median RPS was 0.85 (ranging from 0.62 to 0.95), with 130 (74%) having an RPS of 0.80 or higher. For LMICs, the median RPS was 0.90 (ranging from 0.70 to 0.97), with 162 (92%) scoring 0.80 or above. After ranking topics by RPS, the topics in the top 20th percentile were assessed for

inclusion in the priority list, resulting in 35 global and 35 LMIC topics. Removing duplicates left 40 research priorities addressing global and LMIC perspectives. These results were shared with the WHO steering group and experts via email and presented at a WHO global webinar.

Overview of the research priorities

The research agenda comprises 40 priorities: seven on drug-resistant tuberculosis and 33 on drug-resistant bacterial and fungal infections. The latter are categorised into prevention (n=4), diagnosis (n=6), treatment and care (n=11), and cross-cutting themes like AMR epidemiology, awareness, education, and policies (n=12) (**Table 1**).

Within the theme of prevention, two research priorities in water, sanitation, and hygiene (WASH) investigate the effects and implementation of WASH-related interventions on outcomes such as the burden of AMR and antimicrobial prescribing in both community and healthcare settings. The priority for infection prevention and control aims to identify multimodal intervention strategies and assess the relative impact of their components. The research priority on immunization emphasizes evaluating vaccines' impacts on colonisation and infections with resistant organisms, along with their indirect benefits in enhancing stewardship efforts and reducing prescribing.

Six priorities under the diagnosis theme aim to improve accessible and affordable diagnostics, such as point-of-care tests for distinguishing bacterial from viral infections, aiding treatment decisions, and reducing antibiotic use. Enhanced rapid phenotypic and molecular methods for bacterial identification and antimicrobial susceptibility testing are also prioritized. Nearly half of the global population lacks access to diagnostics, and only about a fifth of LMICs can access primary care diagnostic tests. These tests should expedite critical specimen analysis like blood cultures and test multiple pathogens simultaneously. Two priorities focus on better detection and susceptibility testing of WHO fungal priority pathogens crucial for AMR. Another priority seeks to understand the performance and implementation of point-of-care tests for Neisseria gonorrhoeae, improving the identification and management of potentially asymptomatic STIs, decreasing unnecessary antibiotics, and identifying AMR emergence.

Focusing on treatment, three key priorities in antimicrobial stewardship are interventions to reduce misuse and strategies to optimise empirical treatments. This focus is especially critical in areas with limited diagnostic facilities and healthcare access. The research emphasizes the necessity for studies on pharmacy-level interventions and overarching frameworks to regulate antimicrobial dispensing, aiming to improve stewardship in primary care. Three priorities concern antimicrobial use and consumption, stressing the need to identify optimal methods and metrics for monitoring them, including unnecessary use. The agenda highlights the importance of utilizing facility, national, and surveillance data on antimicrobial consumption to inform treatment guidelines and stewardship programs. Additionally, five research priorities include investigating new and existing antimicrobials, with a focus on improving the treatment of resistant *Enterobacterales*, including typhoidal and non-typhoidal salmonellae. There is also a focus on infections from sexually transmitted and fungal priority pathogens, as well as bloodstream infections caused by Gram-negative bacteria in neonates and young children.

Table 1. Global research priorities for antimicrobial resistance in human health
(Adapted from World Health Organization, 2023).

RESISTANT BACTERIAL AND FUNGAL INFECTIONS
PREVENTION
● Water, sanitation, and hygiene (WASH). ● Investigate the impact, contribution, utility, effectiveness and cost-effectiveness of interventions to ensure safely managed WASH (including hand hygiene) and waste management practices in the community setting on reducing the burden and drivers of AMR, such as unnecessary antibiotic use for diarrhoeal diseases in low- and middle-income countries (LMICs). ● Investigate implementation strategies of WASH-related interventions in healthcare settings (including ensuring access to safely managed water and sanitation, safe hand hygiene, safe management of waste and environmental cleaning), and assess their impact, acceptability, equity and cost-effectiveness on the burden and transmission of resistant healthcare-associated infections and antimicrobial medicine prescribing across socioeconomic settings.
Infection prevention and control
● Identify the most effective, cost-effective, acceptable and feasible multimodal IPC strategies (such as hand hygiene, contact precautions, and patient isolation) and the relative effect of their components in reducing different types of healthcare-associated infections caused by multidrug-resistant pathogens across geographical and socioeconomic settings.
Immunization
● Assess the impact of vaccines on preventing colonization and infection by resistant pathogens (whether specifically targeted by the vaccine or not) and on reducing the overall use of antimicrobial medicines, health-care encounters, and health system costs among adults and children and across socioeconomic settings.
DIAGNOSIS
Diagnosis and diagnostics
● Investigate and evaluate rapid point-of-care diagnostic tests (including biomarker-based tests) and diagnostic algorithms to discriminate between bacterial and viral infections and non-infectious syndromes that are feasible for use in limited-resource settings and among different subpopulations (including children and newborns) and their impact on clinical outcomes. ● Investigate and evaluate diagnostic tests for isolating and identifying antimicrobial susceptibility testing and/or detecting resistance of bacterial pathogens (including multiplex panel-based tests and tests using novel technologies) that are rapid, (near) point of care, affordable, feasible for use in limited-resource settings and among different subpopulations and from a variety of specimen types and for how they affect clinical outcomes. ● Investigate and evaluate phenotypic and genotypic methods of rapid antimicrobial susceptibility testing and resistance detection directly from positive blood culture bottles, especially for use in LMICs, and how they affect clinical outcomes. ● Investigate and evaluate rapid, (near) point-of-care diagnostic tests (including antigen and multiplex panel-based tests) for detecting WHO fungal priority pathogens with critical importance for antimicrobial resistance (such as *Candida auris, Aspergillus fumigatus* and *Cryptococcus neoformans*) feasible for use in limited-resource settings and among different subpopulations and their impact on clinical outcomes. ● Investigate and evaluate the clinical utility and diagnostic accuracy of phenotypic antifungal susceptibility testing, including determining minimal inhibitory concentration breakpoints and testing for *in vitro* and *in vivo* synergy between antifungal medicines, and its impact on clinical outcomes. ● Investigate, assess the performance and evaluate the implementation of novel rapid point-of-care molecular and non-molecular assays and optimal testing and screening approaches (including self-testing) for *Neisseria gonorrhoeae* and antimicrobial resistance detection to reduce inappropriate antibiotic prescribing and emergence of antimicrobial resistance.

(cont.)

Table 1. Global research priorities for antimicrobial resistance in human health (Adapted from WHO, 2023) *(cont.)*

RESISTANT BACTERIAL AND FUNGAL INFECTIONS
TREATMENT AND CARE
Antimicrobial stewardship
● Investigate antimicrobial stewardship interventions (such as implementing the WHO AWaRe antibiotic book, guidelines, clinical algorithms, education and training, audit and feedback), alone or in combination, that are context-specific, feasible, sustainable, effective and cost-effective to avoid antimicrobial misuse in outpatient and inpatient settings, especially where diagnostic capacity may be limited.
● Identify feasible, effective and scalable pharmacist dispensing practices for antimicrobial medicines in community pharmacies, along with related regulatory frameworks (such as incentives and disincentives) to improve antimicrobial stewardship in the community, especially in LMICs.
● Investigate criteria and strategies to optimize empirical antimicrobial therapy (such as antimicrobial spectrum, dose, the timing of initiation, de-escalation and stopping), weighting the benefits (such as improving outcomes and reducing costs) *versus* potential harm (such as clinical failure, infection relapse, resistance emergence and adverse events) for main community and healthcare-associated infectious syndromes among adults and children, especially in settings with limited access to medicine, diagnostics and healthcare services.
Antimicrobial use
● Determine optimal (feasible, accurate and cost-effective) methods and metrics to monitor antimicrobial use in the community and health-care settings and appropriate targets to monitor progress in reducing inappropriate antimicrobial use.
● Determine the levels, patterns, trends and drivers of appropriate and inappropriate prescribing and use of AWaRe antibiotics across countries and community and healthcare settings, with data disaggregated by sex, age, socioeconomic status and subpopulations, including those experiencing vulnerability and with comorbidities (such as people living with HIV, people with TB and people with malaria).
● Investigate optimal approaches to effectively use the facility- and/or national-level data on antimicrobial use and AMR surveillance to inform antimicrobial stewardship programmes and treatment guidelines.
Antimicrobial medicines
● Investigate efficacious and safe antibiotic treatment regimens based on old and new agents and combinations for infections, especially for extended-spectrum beta-lactamase-producing and/or carbapenem-resistant *Enterobacterales*, with minimum selection and transmission risk for AMR, especially among children and other subpopulations experiencing vulnerability.
● Investigate efficacious and safe antibiotic treatment regimens for infections by drug-resistant typhoid and non-typhoidal salmonellae (including for pathogens resistant to cephalosporins and fluoroquinolones) across socioeconomic settings.
● Investigate efficacious and safe empirical antibiotic treatment (drug choice, drug combination, route, dose and duration) for Gram-negative bacteria causing bloodstream infections or sepsis among newborns and young children, especially in settings with high AMR prevalence and limited diagnostic capacity and antimicrobial medicine availability.
● Investigate antifungal regimens optimized for efficacy, cost, safety and duration for the treatment of infections caused by WHO fungal priority pathogens that are critically important for AMR (such as *Candida auris*, *Aspergillus fumigatus* and *Cryptococcus neoformans*) in settings with increasing or high prevalence of antifungal resistance.
● Investigate efficacious and safe regimens based on new or existing antimicrobial medicines for urogenital and extragenital STIs (such as resistant *N. gonorrhoeae* and resistant *Mycoplasma genitalium*) in the context of increasing AMR levels, including in populations experiencing vulnerability (such as people living with HIV, pregnant women and adolescents)

(cont.)

Table 1. Global research priorities for antimicrobial resistance in human health (Adapted from WHO, 2023) *(cont.)*

RESISTANT BACTERIAL AND FUNGAL INFECTIONS
CROSS-CUTTING AREAS
Antimicrobial resistance epidemiology, burden and drivers
● Investigate the prevalence, incidence, mortality, morbidity and socioeconomic impact of community-acquired infections (respiratory tract infections, urinary tract infections and bloodstream infections) and healthcare-associated infections (bloodstream infections, urinary tract infections, surgical site infections and respiratory tract infections) caused by resistant WHO bacterial priority pathogens, with data disaggregated by sex, age, socioeconomic status and subpopulations (such as populations experiencing vulnerability or with comorbidities, including people living with HIV, people with TB and people with malaria) and across socioeconomic settings, especially in LMICs.
● Investigate the prevalence, incidence, morbidity, mortality and socioeconomic impact and identify and quantify the routes and dynamic of infections by resistant WHO fungal priority pathogens that are critically important for AMR (such as *C. auris, A. fumigatus* and *C. neoformans*) across geographical and socioeconomic settings and in populations experiencing vulnerability.
● Investigate the association, contribution and impact of structural and health system factors (such as hospital microbiome, sanitation infrastructure, waste management, health expenditure, governance, distribution of resources, population displacement, conflict and disruptions in the care continuum) on colonization (selection, persistence and spread or loss of bacterial populations) and infection by WHO bacterial and fungal priority pathogens in subpopulations, including those experiencing vulnerability (such as migrants and refugees) and people with comorbidities, across socioeconomic settings.
● Identify optimal (efficient, effective and cost-effective) surveillance methods to generate accurate and reliable data on the epidemiology and burden of AMR among WHO bacterial and fungal priority pathogens (including determining the molecular mechanisms of resistance) in community and health-care settings and disaggregated by sex, age and subpopulations that are relevant and actionable at the local and national levels, especially in LMICs.
● Assess how the programmatic use of antimicrobial medicines in mass administration affects AMR in the short and long term, focusing on subpopulations experiencing vulnerability in low-income settings.
● Evaluate the public health benefits, cost, impact on unnecessary or inappropriate antibiotic prescribing and potential AMR consequences of currently recommended syndromic STI management and treatment of people with asymptomatic STIs (including *N. gonorrhoeae*) in settings with variable diagnostic capacity.
Antimicrobial resistance awareness and education
● Determine the most (cost-)effective behavioural change interventions to mitigate the emergence and spread of AMR by targeting and engaging the general public, young people, mass media, healthcare workers and policy-makers across socioeconomic settings.
Policies and regulations related to antimicrobial resistance
● Evaluate the implementation of AMR-related policies and regulations at the national level and how effective they are in mitigating AMR and improving health outcomes in the community and healthcare settings across socioeconomic contexts.
● Investigate strategies for the sustainable and (cost-)effective implementation of national policies, legislation and regulations (including sustainable financing and optimal governance structures) to improve infection prevention and patient care practices and the use of antimicrobial medicines in the community and health-care settings across socioeconomic contexts.
● Identify the most (cost-)effective interventions to mitigate AMR in the human health sector, globally and within countries or regions, and determine the rationale, costs, benefits, feasibility, sustainability and potential returns on investment to achieve the greatest benefit.
● Investigate strategies to integrate AMR interventions into broader health, health financing, development, welfare structures and national policies and evaluate their impact on mitigating AMR, enhancing health system efficiency, reducing people's out-of-pocket expenses and improving equitable access to and use of diagnostics and antimicrobial medicines.
● Investigate how existing regulatory frameworks, marketing incentives (or their absence) and sustainable financing models affect the development and availability of new antimicrobial medicines and identify effective strategies to adapt these approaches to low-income settings to improve availability for adults and children.

(cont.)

Table 1. Global research priorities for antimicrobial resistance in human health (Adapted from WHO, 2023) *(cont.)*

DRUG-RESISTANT TUBERCULOSIS
Prevention
● Investigate effective preventive TB vaccines that meet WHO preferred product characteristics criteria and demonstrate impact on preventing infection, disease and recurrence (relapse or reinfection), thereby preventing or reducing the incidence of drug-resistant TB.
Diagnosis
● Investigate how the diagnostic performance of molecular assays can be improved to detect drug resistance among people with extrapulmonary and pulmonary TB, from non-respiratory specimens, including among children and adolescents. ● Determine optimal diagnostic and treatment delivery models to improve the access, effectiveness, cost-effectiveness, feasibility and acceptability of drug-resistant TB testing and treatment across settings and subpopulations (such as people living with HIV, prisoners and children and adolescents) and evaluate their impact on reducing drug-resistant TB at the population level.
Treatment and care
● Investigate better tolerated, optimally dosed, more effective and shorter combination regimens, using a stratified risk approach, for treating people with all forms of drug-resistant TB, including in populations experiencing vulnerability (such as children, pregnant and breastfeeding women and people living with HIV). ● Determine the optimal, (cost-)effective, shortest duration and safest TB preventive treatment for the contacts of people with drug-resistant TB, especially among people at high risk of TB infection and disease, as identified in WHO guidance, and eligible populations experiencing vulnerability (such as children, adolescents, people living with HIV and pregnant women). ● Investigate strategies for improving treatment outcomes among people with drug-resistant TB who have known risk factors and co-occurring conditions (such as HIV, undernutrition, diabetes mellitus, tobacco use, alcohol and other substance use and mental health disorders) and populations experiencing vulnerability (such as pregnant and breastfeeding women, children, adolescents and prisoners) in various geographical and socioeconomic settings. ● Investigate the programmatic effectiveness, safety and tolerability of currently used WHO-recommended treatment regimens for drug-resistant TB (including combinations with bedaquiline, delamanid and/or pretomanid) on patient outcomes and drug-resistant TB emergence across populations and settings and identify the drivers of treatment failure.

The availability of AMR surveillance data and therefore our understanding of AMR is disparate between high- and low-resource settings. Six research priorities focus on understanding the burden, drivers, and transmission pathways of resistant bacterial and fungal pathogens and on identifying optimal surveillance methods for obtaining accurate and representative data. These are central for developing treatment guidelines and for implementing interventions aimed at reducing resistance emergence and dissemination. Furthermore, the impact on antimicrobial prescribing and AMR of different management strategies for people with suspected or confirmed sexually transmitted infections needs exploring. An additional priority raises the question of the impact of the programmatic use of antimicrobials in mass administration on resistance development and persistence.

The five research priorities related to policies and regulations highlight the need for comprehensive monitoring and evaluation of AMR interventions. While studies have assessed gaps and opportunities to strengthen national-level governance efforts and AMR National Action Plans, the agenda emphasizes the need for context-specific evidence on effective strategies to implement national AMR policies and programs and inform a more tailored approach to policy implementation. Knowledge gaps are especially evident in low-resource settings, where actions are often based on evidence from high-income countries, while the availability of resources, the socio-economic and political context, as well as cultural drivers of antimicrobial use differ.

Furthermore, information on cost-saving or cost-effective AMR interventions both in the hospital and community setting would inform rational policy design. While evidence from modelling studies in high-income settings exists, data from real-world observational studies and low-resource settings are limited. Evidence and practical strategies for countries to integrate AMR interventions into existing health system structures can further ensure the efficient use of resources and financial sustainability of the AMR response. An important research priority relates to evaluating the impact of regulatory frameworks, marketing incentives (including 'pull incentives'), and sustainable financing models on antimicrobial R&D pipelines, given that 'push incentives' alone are deemed insufficient to ensure a healthy pipeline. While high-income countries such as Sweden and the UK have been experimenting with novel economic incentives, ensuring equitable access to antimicrobials globally would require research into mechanisms that are also feasible in low-income settings.

The five research priorities concerning policies and regulations underscore the necessity for thorough monitoring and evaluation of AMR interventions. Although some studies have identified gaps and opportunities to bolster national governance and AMR National Action Plans, the agenda stresses the importance of acquiring context-specific evidence on effective strategies for implementing national AMR policies and programs to facilitate a more tailored policy execution. This is particularly crucial in low-resource settings where actions are often extrapolated from high-income country evidence, despite differences in resource availability, socio-economic and political contexts, as well as cultural influences on antimicrobial use. Additionally, understanding the cost-saving or cost-effective nature of AMR interventions in both hospital and community settings would support rational policy formulation. While modelling studies from high-income settings provide some insights, real-world observational data, especially from low-resource environments, remain scarce.

Moreover, evidence and practical strategies for integrating AMR interventions into existing health system frameworks can promote efficient resource utilization and financial sustainability of AMR responses. Another key research priority involves assessing the impact of regulatory frameworks, marketing incentives (including 'pull incentives'), and sustainable financing models on antimicrobial R&D pipelines, given that 'push incentives' alone are considered inadequate for maintaining a robust pipeline. While innovative economic incentives are being tested in high-income countries like Sweden and the UK, equitable global access to antimicrobials demands research into mechanisms suitable for low-income settings.

Seven research priorities address the need to enhance the prevention, diagnosis, and treatment of drug-resistant tuberculosis. These focus areas include developing effective vaccines, developing safer and shorter treatment regimens for all forms of drug-resistant tuberculosis, preventing infection in vulnerable populations, and developing point-of-care tests for tuberculosis detection.

Overall, the research priorities reflect the need for evidence to enhance the effectiveness of existing tools and refine service delivery models to ensure equitable access to diagnostics, drug-susceptibility tests, and treatment. The research agenda also aims to strengthen the reliability and use of programmatic data for assessing the benefits, safety and cost-effectiveness of interventions, along with broader strategies to improve health outcomes.

Discussion

This is the first WHO research agenda setting global research priorities for AMR in human health, relevant to resistant bacterial and fungal infections of critical importance for AMR, as well as drug-resistant *M. tuberculosis*. The priorities encompass the complete people-centred journey, from prevention to diagnosis and

treatment, while also addressing overarching knowledge gaps in AMR epidemiology, burden and drivers, policy and regulations, awareness and education, with a focus on low-resource settings and people experiencing vulnerability such as migrants and refugees.

The research agenda is expected to guide policymakers, the global research community, industry, and funders in coordinating and aligning research efforts and investments on the most critical global knowledge gaps. An essential criterion for prioritization was the potential for translation of research outputs into policy, so that addressing the research priorities is likely to have a significant impact on AMR prevention practices, the diagnosis, treatment, and management of infections, and national and global policies aiming to mitigate AMR. Evidence from well-designed, large-scale, multidisciplinary studies on the drug-resistant tuberculosis research priorities will support the attainment of Member State's ambitious declaration to expand coverage of rapid diagnostic testing, treatment and tuberculosis preventive treatment to reach 90%, and coverage of health and social benefits package for people with tuberculosis to reach 100% by 2027.

Investment in AMR research has shown inconsistency to date. From January 2017 to September 2021, the Global AMR R&D Hub (https://globalamrhub.org/) documented investments totaling $8.9 billion across 12,093 projects financed by 214 worldwide organizations specializing in AMR. Approximately one-third of the funds allocated to priority bacterial pathogens, equivalent to $4.3 billion, were directed toward developing new therapeutics. In comparison, only 12% was allotted to vaccines, 6% to diagnostics, and a mere 1% to policy research. Furthermore, fungal research across all sectors received just 6% of total investments. While investment remains limited compared to other disease areas, 90% of funding is channeled towards R&D activities targeting bacterial pathogens. The top three research areas receiving the highest funding volumes across all sectors are basic research, therapeutics, and operational R&D. However, funding for product-related R&D, including diagnostics and vaccines, lags significantly behind.

Recognising the critical role of R&D in the fields of vaccination, diagnosis, and treatment, the agenda calls for enhanced efforts to develop new agents for extended-spectrum beta-lactamase-producing and/or carbapenem-resistant *Enterobacterales* and for sexually transmitted infections. It also highlights the need to investigate how marketing incentives (or their absence) and sustainable financing models can affect the development and availability of new antimicrobial medicines, particularly in LMICs. This emphasizes the need to continue investing in product-related R&D, but also to expand funding support across the entire research spectrum from descriptive studies to delivery, development, and discovery.

Efforts to implement this research agenda have the potential to ensure a more balanced approach to AMR research funding, i.e. one that is not only focused on developing an arsenal of therapeutic options, but also tools to promptly and accurately diagnose infections, generate evidence for policy-makers on the most cost-effective prevention and antimicrobial stewardship interventions, on how interventions should be implemented, and policies that are also feasible in low-resource settings. This can ensure that countries are well-equipped to address the complex causes of AMR through a multidisciplinary approach.

This research agenda complements and is broadly aligned with two parallel AMR research agendas. The One Health Priority Research Agenda for AMR, which addresses the intricate interactions between humans, animals, plants, and their shared environment, was developed through a collaborative effort involving the Quadripartite—comprising the Food and Agriculture Organization, the UN Environment Programme), WHO, and the World Organization for Animal Health. The Strategic Research and Innovation research agenda from the future European Partnership on One Health AMR, co-funded by Member States and the European Commission under the Horizon Europe funding programme, is currently being developed and is expected to guide future investments in AMR over the next years on topics encompassing both the One Health continuum and human health. The agenda also aligns with the evidence gaps identified by Guideline Development Groups

in the WHO tuberculosis guidelines. These priorities aim to drive scientific interest and investment, guiding global and national health policies and supporting evidence-based interventions for AMR control.

The approach used in the development of the agenda ensured that the topics chosen for prioritization were highly relevant for future research and investment by combining a comprehensive scoping review to identify knowledge gaps with an expert survey. The metric-based CHNRI priority-setting approach is a transparent, reproducible, rigorous, and inclusive method. Its use reduced bias by minimizing the influence of a few individuals, unlike consensus-based methods.

The participation of AMR experts globally ensured geographical diversity and the validity of outcomes. With 261 experts from 69 countries and a 71% survey response rate, this effort reflects extensive global expertise. While 23% of the experts focused on high-income perspectives, 40% brought insights from low-resource settings, highlighting research relevant to LMICs. The research priorities balance broad thematic topics with focused research questions, striking a balance between thematic, high-level topics that capture the essence of multiple sometimes overlapping knowledge gaps *versus* more granular, focused research questions that could be used to design a study. Each priority will need multiple studies to be fully addressed.

Conclusion

The research agenda outlines 40 key research priorities aimed at catalyzing research, improving treatments and diagnostics, supporting evidence-based National Action Plans for AMR, and ensuring the feasibility of interventions in resource-limited settings. The research agenda serves as a compelling call to action for the global AMR research community to intensify investments and initiatives in AMR research aligned with the research agenda's priorities, striving to reverse the increase of AMR and reduce its related morbidity and mortality by 2030.

Role of the funding source

WHO funded the study and was responsible for study design, collection, analysis, and interpretation of the data, writing of the report, and the decision to submit the paper for publication. The first and corresponding authors had full access to all data and shared the final responsibility to submit for publication.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 7

Framing antimicrobial resistance as a sustainable issue

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Introduction

Antimicrobial resistance (AMR) is often referred to as a "silent pandemic," a term that underscores its gradual yet profound impact on global health. Unlike more overt health crises, AMR has been slowly building, often unnoticed until it started reaching a critical juncture.
Antimicrobials made an impressive almost century-long evolutionary journey from the revolutionary 1928 penicillin discovery in human medicine to current times when agricultural and food systems around the globe are unimaginable without this public good. This extensive use of antibiotics, which speeds up the emergence of resistant strains, coupled with a lack of new antimicrobials development since the 1980s, global travel and trade facilitating the rapid spread of resistant bacteria across borders, and the COVID-19 pandemic leading to heightened antibiotic usage, collectively underscore AMR as a pressing planetary issue.
This issue goes beyond straight health parameters. In its complexity, it involves multiple interconnected disciplines and factors and opens for more sophisticated, balanced, and sustainable solutions.

Bad news, good news

AMR death toll is hard to assess. In 2019, WHO estimated that antibiotic resistance is killing around 700,000 people every year, while the results of predictive statistical models published in a 2022 Lancet study indicated that in 2019 there were almost 5 million deaths globally associated with bacterial AMR, with 1.27 million deaths as the direct result of drug-resistant bacterial infections. This far exceeds the annual global deaths attributable to tuberculosis (1.5 million), malaria (643,000), and HIV/AIDS (864,000). If no action is taken, this number could increase to 10 million by 2050, matching the current annual global death toll of cancer, with around 2.4 million deaths projected in high-income countries between 2015 and 2050.
Low- and middle-income countries (LMIC) will bear the bulk of the clinical burden. Climate change in these regions is rapidly altering the geographic range of zoonotic and vector-borne disease vectors and pathogens and impacts transmission dynamics, sustaining microbial resistance. The African region (in particular, the western sub-Saharan Africa) is already reporting the highest AMR mortality rates despite the relatively low prevalence of resistance. In 2019, over 1.05 million deaths were associated with AMR and 250,000 deaths were attributable to AMR there, surpassing deaths from HIV/AIDS (639,554) and malaria (594,348) in the region. The largest fatal AMR burden was attributed to lower respiratory infections, bloodstream infections, intra-abdominal infections, and tuberculosis (TB).

In recent months, countries worldwide have witnessed a concerning surge in cases of antibiotic-resistant mycoplasma pneumonia ("walking pneumonia"), some reported outbreaks of various multi-drug-resistant infections (**Figure 1**), highlighting increased mortality rates and complications due to resistant strains and emphasizing the need for enhanced infection control measures, international collaboration and innovative strategies to combat antibiotic resistance.

China: *"China's children battling pneumonia shows the dangers of drug resistance. The once mild disease caused prolonged illness. Global threat stems from rise of superbugs and novel pathogens"* – Bloomberg, 11 November, 2023
United Kingdom: *"In the UK, antibiotic resistance is once again on the rise after declines in the pandemic, with more dangerous strains of bacteria spreading in communities and hospitals., highlighting the urgent need for new antibiotics and enhanced infection control measures"* - Gov.Uk, November, 2023
Russia: *"Болеют дети: в России выросло число случаев микоплазменной пневмонии"* – Izvestiya, 6 December 2023
India: *"India facing a pandemic of antibiotics-resistant superbugs. AMR impacts everyone, from newborns to elders. Only 43% of the pneumonia infections caused by one pathogen in India could be treated with first line of antibiotics in 2021, down from 65% in 2016"* – BBC, October 2022, Times of India, January, 2023
Brazil: *"Aumenta nos hospitais brasileiros a presença de bactérias resistentes a antibióticos. Os cientistas identificaram bactérias resistentes na água dos rios Tietê e Pinheiros, que cortam a capital, e infectando tartarugas, pinguins, baleias e golfinhos, além de aves marinhas, no litoral brasileiro"* – Pesquisa, January 2024
France: *"Après plus de trois années à un niveau très bas de circulation dans le contexte de la pandémie de Covid-19, recrudescence des infections à Mycoplasma pneumoniae en lien avec la levée des mesures sanitaires et la baisse de l'immunité de la population contre l'infection"* – Santepubliquefrance.fr, January 2024
United States: *" Seattle Reports Outbreak of Rare, Drug-Resistant Fungal Infection. Experts warn its high mortality, ability to easily spread in healthcare facilities, labeling it an "urgent antimicrobial resistant threat"* – Forbes, February 2024

Figure 1. Outbreaks of various multi-drug-resistant infections worldwide.

Ongoing scientific advances in microbiology and ancient genetics offer promising novel therapeutic approaches. These unconventional ideas share a common line: seeking innate defenses against antibiotics, which could provide more sustainable foundations for addressing AMR.
Researchers at the New York University School of Medicine have made significant strides in understanding bacterial metabolism, particularly focusing on hydrogen sulfide (H_2S), a toxic byproduct generated by antibiotic-resistant bacteria. Their findings have led to the development of small molecules that inhibit bacterial enzymes responsible for H_2S production, thereby enhancing the efficacy of existing antibiotics against resistant strains. Concurrently, a team from the Perelman School of Medicine at the University of Pennsylvania is working with molecular resurrection, exploring genomes of our ancestors, including those of Neanderthals and Denisovans, using artificial intelligence to identify potential antimicrobial peptides. These peptides, when tested against modern pathogens in animal models, have demonstrated strong antimicrobial properties, suggesting a new frontier in antibiotic development distinct from traditional sources.
The reality is that the commercial incentives for developing new antibiotics remain limited. Pharmaceutical companies face significant financial risks in bringing novel treatments to market, despite the critical need.

Additional questions arise about patenting ancient genetic sequences and the ethical implications of resurrecting molecules from extinct organisms.
While the regulatory landscape is evolving, one thing remains clear. These examples of the ongoing foundational research into AMR- microbial physiology, largely publicly funded, highlight the crucial role of government and academic institutions in advancing scientific understanding. These efforts equally underscore the need for continued collaboration between academia, industry, and policymakers to effectively address antibiotic resistance.
Innate qualities, like natural resilience that is being explored, contribute to sustainability. Achieving and maintaining sustainability involves intentional efforts, policies, and practices that promote responsible resource use, equitable development, and environmental stewardship to ensure that social, economic, and environmental needs are balanced over the long term.

What do we know about sustainability?

Ensuring sustainability involves creating systems and practices that meet current needs without compromising the ability of future generations to meet their own needs.
Throughout recent history, there have been numerous efforts to devise sustainable agendas that garner consensus among diverse nations, organizations, sectors, and individuals. These initiatives have aimed to tackle global challenges like poverty, health inequities, and environmental issues. National priorities have been critical in shaping these agendas, as each country had to address its specific needs and resources while also supporting international objectives. Successes and shortcomings of past endeavors bring valuable insights into addressing complex challenges like AMR sustainably.
At the global level: sustainability is about sustained financial support and continued political commitment. It also requires robust international collaboration to address complex issues effectively.
Examples of Global Agendas that faced sustainability challenges:

- Millennium Development Goals (2000-2015): while the MDGs made significant strides in poverty reduction, health improvement, and education, their sustainability was limited by challenges in addressing environmental concerns and systematic inequalities, and ensuring lasting impacts beyond the 2015 deadline. The transition to the Sustainable Development Goals (SDGs) aimed to build on these achievements but faced challenges in achieving inclusive development due to differing levels of commitment and implementation capacity among member states.
- Global Polio Eradication Initiative: despite being framed as a sustainable global health initiative, the Global Polio Eradication Initiative faced obstacles such as vaccine hesitancy, logistical challenges in conflict zones, and political resistance in some regions. These factors compromised the initiative's ability to achieve its eradication goals within anticipated timelines, highlighting the complexities of sustaining global health efforts amidst diverse socio-political landscapes.
- Global Response to HIV/AIDS: although there has been substantial progress in treating and preventing HIV/AIDS, challenges remain in achieving universal access to treatment and eliminating stigma and discrimination associated with HIV/AIDS.
- Doha Development Agenda (WTO): the Doha Development Agenda aimed to address global trade imbalances and promote sustainable development through fairer trade rules and improved market access for developing countries. However, negotiations stalled over issues such as agricultural subsidies, intellectual property rights, and market liberalization, underscoring the difficulty of reconciling diverse national interests and achieving consensus on sustainable trade practices.

- Kyoto Protocol (1997): while not a complete failure, the Kyoto Protocol struggled to achieve its ambitious goals of reducing greenhouse gas emissions globally. Many countries did not meet their targets, and some major emitters, including the United States, withdrew from the agreement.

Examples of Global Agendas with sustainable outcomes:

- Smallpox eradication (1959-1980): the eradication of smallpox is widely regarded as a sustainable success in public health. Comprehensive eradication involved completely removing the virus from the human population rather than merely controlling it, providing lasting benefits to global health. The achievement was the result of a coordinated global effort led by the World Health Organization (WHO), which included extensive international collaboration, vigilant surveillance, mass vaccination campaigns, and rapid response to outbreaks. Although the initial costs were high, the long-term savings and reallocation of resources to other public health initiatives have proven substantial. The smallpox eradication effort also provides valuable lessons for future disease elimination campaigns, such as those targeting polio and guinea worm disease. While the strategies used for smallpox may not be directly applicable to other diseases due to their unique characteristics, the experience and infrastructure developed during this campaign continue to support global public health efforts, underscoring the enduring impact of this achievement.
- Global Alliance for Vaccines and Immunization (GAVI) (2000-present): GAVI is a public-private global health partnership focused on increasing access to immunization in poor countries. Since its inception in 2000, GAVI has contributed to significant increases in vaccine coverage and has helped save millions of lives. Continuous innovation, recurring financial support, and collaboration to guarantee equitable vaccine access drive sustainable advancements in global health.

These examples demonstrate that global initiatives often encounter obstacles if they lack holistic approaches that address the complex interplay of social determinants of health, environmental systems, and systemic inequalities, lose momentum for continued political and financial commitment. On the other hand, they can succeed in ensuring long-term impact if they develop an adaptive approach to sustainability, consider unintended consequences and innovative financing solutions and involve continuous evaluation and improvement of practices.

At the national level: sustainability at the national level is often the most volatile and challenging to navigate, yet it is where real change occurs, driven by communities and their members. Sustainability here can be projected through a few straightforward approaches:

Multidisciplinary and inter-sectorial approach - by integrating efforts across various sectors and engaging multiple stakeholders, many countries have successfully demonstrated how these policies have contributed to sustainable solutions to the most complex socio-economic and public health issues.

Here are a few examples:

By combining education with social services, prioritizing extensive teacher training, and implementing a holistic curriculum, a number of countries have developed equitable and high-performing education systems that led to improved outcomes in diverse areas such as health, education, sustainability, and urban development: ex. South Korea’s Smart City Initiative; New Zealand’s Whānau Ora Approach; Canada’s Social Determinants of Health Approach; Singapore’s Public Health Policy; Finland's Education Reform, etc.

Multiple countries have adopted diverse, cross-disciplinary strategies to tackle childhood obesity, blending regulatory actions, school-based initiatives, community involvement, and public health awareness campaigns to achieve better health outcomes for children: ex. Mexico’s National Strategy for the Prevention and Control

of Overweight, Obesity, and Diabetes, France's "Nutrition and Health" Policies; Sweden's "Health on Equal Terms" Policy; "Health Japan 21" Initiative; United Kingdom's "Healthy Schools" Program, etc.
Human-centred policies - findings from fundamental research on the innate protection mechanisms mentioned above, although not specifically intended for this purpose, strongly highlight the increasing natural shift toward human-centered policies. This trend can uncover opportunities for personalized interventions and tailored solutions. Such insights help identify and address specific needs and challenges, leading to more effective and equitable outcomes across various sectors.

Can AMR become a new global sustainable agenda?

AMR can have good chances to become a sustainable public health achievement. Making it sustainable means developing and implementing strategies that preserve the effectiveness of antimicrobials, promote their responsible use, encourage multidisciplinary research, support global health and environmental systems, and contribute to broader human development goals over the long term.
As AMR is not just a biomedical challenge but also a social, economic, and environmental issue, it will require ongoing investment in human capital to sustain progress in a harmonious and enduring manner at both global and national levels.
Despite its complexities, AMR can be effectively managed globally and nationally by adopting a holistic approach that prioritizes interdisciplinary community engagement, human-centered strategies, accountability, and continuous monitoring and evaluation. Sustained political commitment, investment in health infrastructure, innovative approaches to antimicrobial research and development, and strong multisectoral collaboration are crucial for long-term impact and sustainability.

Integrating AMR at every level: from research to policy and practice

Addressing AMR as a core component of human development at the national scale requires a broad, multisectoral approach for sustained progress and targeted fund allocation strategies.
Comprehensive multidisciplinary research is an ongoing commitment. Understanding resistance mechanisms, developing new antimicrobials, and improving surveillance and public health interventions are essential components of this effort. At the policy level, robust regulatory frameworks for antimicrobial use in humans, animals, and agriculture are essential. These frameworks should also promote the surveillance and reporting of AMR to track progress and identify emerging threats and support new treatment development. The health sector must implement strong antimicrobial stewardship programs and enhance infection control measures. Agriculture should promote responsible use of antimicrobials in food production and ensure sustainable farming practices. Education plays a crucial role in raising awareness and integrating AMR topics into school curricula and professional training. Additionally, the environmental sector must manage waste and pollution to limit the spread of resistant bacteria. Economic policies should incentivize new antimicrobial development.
The transportation sector needs to ensure safe handling of pharmaceuticals, and the food industry must support responsible antimicrobial use. Legal frameworks should enforce regulations on antimicrobial use, while public communication should promote awareness of responsible practices. Finance and investment should focus on funding AMR research and public health initiatives. Technology and innovation can advance

diagnostics and surveillance, while community development efforts engage local populations in AMR prevention and education. The national security sector also has a role in protecting antimicrobial supply chains and preventing bioterrorism-related misuse. Integrating these diverse sectors ensures a comprehensive strategy for managing AMR.

Linking AMR to the life course perspective

With the recently released WHO's Core Package of Interventions to Support AMR national action plans, the international expertise puts forward the people-centered approach to addressing AMR in the human health sector, based on (1) prevention of infections; (2) access to essential health services; (3) timely, accurate diagnosis; and (4) appropriate, quality-assured treatment.

The life course perspective would offer a more comprehensive framework to understand how AMR impacts individuals from infancy through old age. At each stage of life, from childhood infections to chronic diseases in adulthood, the threat of AMR necessitates tailored approaches to antimicrobial use and infection control. By linking AMR clinical management to the life course concept, stakeholders can develop targeted interventions that address specific health needs and vulnerabilities across different age groups, ultimately improving the sustainability and overall impact of AMR strategies.

Childhood and adolescence - early exposure to antibiotics and vaccinations are critical in shaping immune responses and susceptibility to infections later in life. AMR interventions should focus on promoting vaccination coverage, improving hygiene practices, and reducing unnecessary antibiotic prescriptions in pediatric care settings.

Reproductive years - maternal health and management of sexually transmitted infections are pivotal during reproductive years. AMR poses challenges in treating these infections effectively, underscoring the need for comprehensive sexual and reproductive health services that prioritize antimicrobial stewardship.

Adulthood - chronic diseases and surgical procedures in adulthood often require antimicrobial interventions. Sustainable practices include optimizing antibiotic use in hospital settings, promoting infection prevention protocols, and investing in rapid diagnostic technologies to guide treatment decisions.

Older adults - elderly populations are particularly vulnerable to infections and the complications of AMR due to age-related declines in immune function. AMR strategies for older adults should prioritize appropriate antibiotic use, vaccination programs, and integrated care approaches that enhance antimicrobial stewardship in long-term care facilities.

Building on existing foundations for stronger health crisis preparedness

The COVID-19 pandemic has highlighted key lessons for tackling AMR, including the need for robust surveillance, advanced diagnostics, and rapid research. For example, multifunctional TB lab networks, with their infrastructure for monitoring cases of TB, HIV, STI and NTDs, proved to be highly instrumental in detecting drug-resistant strains, and providing essential data, including to address AMR. As climate change alters disease dynamics, these labs based in LMIC are crucial for adapting strategies to manage AMR-associated diseases effectively. Strengthening multifunctional laboratory networks not only enhances global health security but also enables a comprehensive approach to linking AMR with specific diseases, ensuring that the same urgency and efficiency applied to COVID-19 are directed toward tackling broader AMR challenges.

Achieving SDGs through AMR mitigation

The 2030 Agenda for Sustainable Development provides a framework to ensure healthy lives and promote well-being for all. Addressing AMR is crucial for achieving several SDGs, particularly those related to health (SDG 3), poverty reduction (SDG 1), and sustainable cities and communities (SDG 11). AMR challenges the sustainability and effectiveness of the public health response to various communicable diseases and threatens the gains made in health and development. By integrating AMR efforts further into the broader SDG framework, we can ensure a more comprehensive and sustainable approach to combating AMR.

Political commitment, international collaboration and sustained investment

Sustained political commitment is essential for addressing AMR effectively. Despite 178 countries having developed AMR national action plans, fewer than 20% are funded or implemented. National governments, in collaboration with international organizations like the World Bank, WHO, FAO, and OIE, should continue refining their tailored national action plans that adopt a systemic, intersectoral approach, fostering cohesion and collaboration. Investing in the long-term sustainability of health systems, including strengthening veterinary services, is critical, along with raising awareness through education and communication to gain stakeholder and population support.

One of the promising recent initiatives is the World Bank's "Stopping the Grand Pandemic: A Framework for Action" which provides a strategic roadmap for tackling global health crises, with a focus on pandemic preparedness and response. This initiative aims to mobilize international cooperation and resources to bolster healthcare systems, enhance surveillance capabilities, and accelerate the development of medical interventions. By emphasizing the need for sustained investment in public health infrastructure, innovative technologies, and capacity-building, the framework aligns financial resources with strategic priorities to mitigate future pandemics' impacts and ensure global readiness to address emerging health threats effectively.

Conclusion

Antimicrobial resistance (AMR) presents a multifaceted global challenge, transcending mere biomedical concerns. Addressing AMR as a sustainable issue requires a holistic approach that ensures the health of people, animals, and the environment, while also reinforcing socio-economic systems and national security. The transition towards a human-centered paradigm, reflected by research into the innate resilience of the human body against AMR, further emphasizes the need to integrate AMR management into all aspects of human health, well-being, and productivity, thereby enhancing sustainability.

Framing AMR as a sustainable issue demands adaptive strategies that learn from past initiatives. Effective solutions involve consistent financial support, political commitment, and the integration of various sectors and stakeholders. A comprehensive approach stems from ongoing multidisciplinary research and will require robust regulatory frameworks and continuing antimicrobial stewardship to ensure the responsible use of antimicrobials and support global health, environmental, and security systems. Moreover, linking AMR clinical management to the life course perspective highlights the importance of tailored clinical interventions across different age groups to maintain antimicrobial effectiveness throughout an individual's life.

Sustainable approaches should equally take hold of existing foundations. Bringing in already available assets such as national multifunctional lab networks and further strengthening their capacities are crucial for tackling AMR as part of the health crisis preparedness framework. Aligning AMR strategies further with the Sustainable Development Goals and integrating them into broader human development agendas will enhance societal resilience and health outcomes.
Addressing AMR effectively demands continuous investment, political commitment, and collaborative efforts to safeguard the effectiveness of antimicrobials and promote a healthier, more sustainable world.

Key messages

1. AMR as a contemporary concept: AMR is not a curable disease but a complex, global issue involving multiple disciplines. Addressing it as a sustainable issue highlights the importance of holistic and innovative approaches to ensure optimal health for people, animals, and the environment, resilient agricultural and socio-economic systems, and stronger national security.
2. Transition to a human-centered paradigm: inadvertently spearheaded by microbiological research that explores innate resilience characteristics of our human body to AMR, the concept of AMR could draw on more fundamental resources of human potential and needs, integrating it more deeply with all facets of human health, well-being, and productivity to enhance sustainability.
3. How to achieve sustainability: lessons from past initiatives across diverse fields demonstrate that successful strategies often develop adaptive approaches, consider unintended consequences and involve continuous evaluation and improvement of practices. Globally, sustainability requires consistent financial support and political commitment. Nationally, success relies on integrating diverse sectors and stakeholder engagement. Ensuring sustainability for AMR means that antimicrobial stewardship is prioritized at every level of governance and practice, globally and nationally, as a holistic, human-centered concept.
4. Multidisciplinary and inter-sectorial approach: a comprehensive strategy to combat AMR involves integrating efforts across various sectors and disciplines. To ensure longer-term impact, national and global efforts should focus on sustained research, robust regulatory frameworks, continuous collaboration and antimicrobial stewardship to maintain antimicrobial effectiveness, promote responsible use, and support global health, environmental and security systems.
5. Life course perspective: linking AMR clinical management to the life course perspective underscores the importance of tailored interventions that address specific health needs and vulnerabilities across different age groups. This approach ensures that antimicrobial use remains effective throughout an individual's lifespan.
6. Building on existing foundations: linking AMR to existing initiatives is crucial for stronger health crisis preparedness. Multifunctional TB lab networks at the national level, already monitoring TB, HIV, STI, and NTDs, are well-equipped to tackle AMR by detecting drug-resistant strains and providing essential data. Addressing AMR is also key to achieving SDGs. Integrating AMR efforts into the SDG framework ensures a comprehensive and sustainable approach to health, poverty reduction, and sustainable communities. Initiatives like the World Bank's "Stopping the Grand Pandemic: A Framework for Action" emphasize the need for continuous investment in public health infrastructure and capacity-building to address emerging health threats effectively.
7. Challenges and opportunities: overcoming governance gaps, enhancing international cooperation, and fostering innovation in antimicrobial research are critical for addressing AMR effectively. Sustainable

solutions require long-term political commitment, investment in health infrastructure, and collaborative efforts across sectors and nations.

Competing interests

The author has no financial and non-financial competing interests to declare.

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Chapter 8

Setting up an antimicrobial resistance surveillance system

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Introduction

Antibiotics are among the most groundbreaking medical innovations of the 20th century, revolutionising healthcare and saving millions of lives. Surgical operations, cancer treatments, and immunosuppressive therapies often depend on antibiotic prophylaxis to prevent infectious complications. However, the optimism with Sir Alexander Fleming's discovery of penicillin in 1928 and US Surgeon General William H. Stewart's 1967 proclamation that it was "time to close the book on infectious diseases" has faded. While antimicrobial resistance (AMR) is a natural evolutionary process, it has been exacerbated by various man-made conditions, including the overuse of antimicrobials, low vaccination coverage, poor access to water, sanitation and hygiene infrastructure, in human and animal health and agricultural sectors, and creation of favourable environments for microbe interactions through poor wastewater management practices.

In 2014, an estimated 700,000 deaths were attributed to AMR, including deaths from HIV, tuberculosis (TB), and malaria. In 2019, bacterial AMR alone was directly responsible for 1.27 million deaths (20% of whom were children under five), with 4.95 million deaths associated with drug-resistant bacterial infections. Economically, AMR is projected to cause healthcare costs of up to $1.2 trillion annually in a high-resistance scenario and $0.33 trillion in a low-AMR scenario.

Pharmaceutical companies are shifting focus away from infectious disease treatments due to the rapid evolution of microbial resistance and low returns on investment. As a result, the AMR crisis is set to worsen unless urgent action is taken through a One Health approach, which recognises the interconnectedness of human, animal, and environmental health.

The United Nations High-Level Meetings on AMR are key events that drive international cooperation. In September 2024, a Political Declaration set a target to reduce global AMR-related deaths by 10% by 2030. Effective surveillance systems are essential for informing this effort and providing critical data on the burden of AMR. This chapter outlines a programmatic approach to setting up an AMR surveillance system adaptable to any setting.

Setting up an AMR surveillance system

Microbes possess a variety of resistance mechanisms, many of which remain unknown to science, making it difficult to quantify AMR fully. Additionally, several challenges—such as insufficient testing facilities and

diagnostics, manpower shortages, non-compliance with testing standards, and reliance on paper-based records—exist across many settings. These obstacles hinder a comprehensive understanding of human health and agriculture resistance patterns, limiting effective treatment evaluation and understanding of resistance drivers.

While modeling studies estimate the burden of drug-resistant infections and their complications, they are often one-time assessments and can lack accuracy. Establishing baseline resistance data and tracking trends over time requires robust information technology systems for data capture and efforts to strengthen laboratory infrastructure and surveillance systems. Retrieving clinical data and antibiotic usage (AMU) records from healthcare facilities can reveal critical drivers of AMR, enabling the development of evidence-based policies to optimise antimicrobial stewardship and improve patient care.

The following are the key steps to set up an AMR surveillance system.

Team formulation

At the outset, a diverse team should be assembled with clearly defined roles and responsibilities for each member to ensure smooth coordination and accountability. A team leader should be appointed to provide direction, make critical decisions, and maintain focus on project goals. Open communication is essential for leveraging the strengths of each member, fostering collaboration, and ensuring all voices are heard. Roles and responsibilities should be flexible, adapting as needed to address evolving project demands, challenges, or changing circumstances. This adaptability ensures the team remains responsive and effective throughout the project lifecycle.

Problem statement & objectives

The problem statement and key objectives are the foundation of any surveillance project. A well-defined problem statement clarifies the issue's importance and establishes why it must be addressed, providing clear direction for the project. Key objectives, on the other hand, serve as measurable, actionable targets that align with the problem statement. These objectives guide allocating resources, time, and funding toward the project's priority areas. Surveillance studies can be based on analysing existing data or designed as prospective studies to gather new information over time.

Stakeholder engagement

Stakeholder engagement builds trust, enhances decision-making, and significantly improves the chances of project success by ensuring that all perspectives are considered. It fosters collaboration by addressing differing opinions and potential conflicts through negotiation and compromise. This is particularly critical in externally funded studies, where local and regional health authorities must be informed at every stage. At the outset, kick-off workshops followed by regular in-person and online meetings are crucial for maintaining ongoing communication and ensuring alignment as the project progresses.

Data Sharing Agreement (DSA)

A well-structured Data Sharing Agreement (DSA) is critical for protecting all parties involved by ensuring legal compliance, safeguarding data, and promoting transparency in data management. It ensures that data is shared securely and ethically, per relevant legal and regulatory requirements. A robust DSA fosters trust among stakeholders by clearly outlining responsibilities, data handling protocols, and security measures to prevent misuse or unauthorised access.

Methodologies for laboratory selection and data management (collection, standardisation, analysis)

The success of a study or project heavily depends on the robustness of the methodology. In an AMR surveillance study, the following vital methodologies are essential for reliable outcomes.

a. *Laboratory identification.*

The in-house laboratory typically serves as the identified site when establishing an AMR surveillance system at a single hospital. However, for a multicentric study, the preferred approach is to map microbiology laboratories initially and then select those with acceptable quality. Available budgets and timelines often guide this selection.

An AMR surveillance program aims to estimate microbial resistance, so laboratory quality is a critical factor in the selection of laboratories and is assessed through an objective evaluation. While there is no one-size-fits-all selection plan, the role of a microbiologist is crucial in designing questionnaires to evaluate the eligibility and readiness of laboratories for inclusion in the study.

Key factors to consider include:

- General information. Level of service, affiliations and co-location with pharmacy and clinical units.
- Quality management system implementation. This includes personnel, biosafety measures, sample management, quality control practices, participation in external quality assessments, accreditation and certifications, inventory management, audits, and laboratory information systems. All these components must be carefully considered when selecting laboratories or facilities to collect data.

b. *Data collection & standardization.*

This step is extremely critical for any AMR surveillance study since the final results rest on the data collected. The first task is identifying the variables of interest to achieve the study's objectives. These include patient identification number, specimen type, date of specimen collection, culture results, antimicrobial susceptibility test results for relevant pathogen-drug combinations, patient demographics, diagnosis, indwelling devices, and antimicrobial usage history. The data are collected at the patient level, as available in laboratory and clinical records.

Handheld electronic devices should be procured and customised for data entry, ensuring simultaneous anonymisation of patient details. Data collection is labour-intensive, especially with paper-based records, where patient identification numbers change with each new visit. It is essential to recognise that all data might not always be available at the laboratory, and this often requires additional visits to clinical units and pharmacies. This involves compliance with hospital protocols and obtaining the necessary approvals from local authorities.

Data collectors should be locally recruited, ideally with prior experience in healthcare settings. They must receive comprehensive training on how to use electronic data entry devices, including troubleshooting. In contrast, electronic records are more easily uploaded to the devices.

A dedicated data reviewer checks the database for completeness and accuracy after data is captured and securely uploaded to a cloud/server, either in real-time or offline (based on local constraints). The data manager then standardises entries for consistency, a critical step to reduce redundancy and errors. This process is done in compliance with a standardised glossary of terminologies, which is particularly important in large-scale studies with diverse data sources and varying quality.

c. *Data analysis.*

Once the data are standardised, it is summarized on various parameters, such as the number of cultures (total and positive), and further stratified across variables of interest. Data from positive cultures with

antimicrobial susceptibility test (AST) results are analysed to estimate the AMR rate, which is the proportion of non-susceptible isolates (intermediate or resistant) to a specific antimicrobial agent or class over a defined period. Data are generally analysed according to resistance interpretations submitted by laboratories, but results are aggregated at the antimicrobial class level wherever possible.

Duplicate AST results for the same specimen within a defined timeframe should be removed before calculating AMR rates, provided patient identifiers are available.

The AST data from all laboratories are then aggregated, and AMR rates are calculated. Results should be interpreted cautiously, as they are based on aggregated data from laboratories with varying testing capacities and service levels.

Confidence intervals (CIs) are calculated at the 95% confidence level to quantify the uncertainty in the resistance estimates. Traditionally, CIs for AST data have been constructed using the Wilson score method, a binomial calculation that assumes sample independence. However, since there may be correlations between laboratories drawing from similar populations, where applicable, the Wilson cluster robust CI method is used to account for these dependencies, with each laboratory considered a cluster.

AMR rates are not calculated when fewer than 30 isolates are tested for a given pathogen-antimicrobial combination. Beyond estimating AMR rates, additional analyses can be conducted to understand the drivers of resistance, provided relevant data on key parameters are available.

Results dissemination

Results dissemination ensures that findings reach relevant stakeholders, inform policy decisions, and contribute to broader public health efforts. The results must be compiled into a clear and comprehensive format, with visual representations such as graphs, charts, and infographics, making the findings more accessible and understandable to diverse audiences.

Creating executive summaries, detailed technical reports and concise policy briefs can help communicate the information effectively. Different stakeholders, including healthcare providers, policymakers, researchers, and community organisations, may require tailored reports that emphasise aspects of the data most relevant to their interests or responsibilities. Findings are presented at workshops, webinars, or conferences for further discussion. Facilitating direct conversations with key stakeholders helps contextualise the results and foster collaborative efforts to address AMR. Submitting findings to peer-reviewed scientific journals adds credibility and contributes to the global body of knowledge on antimicrobial resistance. This process allows for external research validation and encourages further studies in the field. Leveraging digital platforms, including social media, institutional websites, and dedicated AMR databases, can enhance the visibility of the results. These platforms can facilitate real-time sharing and broader reach, particularly among younger audiences and non-specialist stakeholders.

Establishing feedback mechanisms is important for understanding the impact of the disseminated results (i.e., how the information has influenced antimicrobial stewardship efforts, treatment protocols, or funding decisions), enhancing the effectiveness of communication strategies, and guiding future initiatives. Finally, all dissemination activities should be documented for future projects and can serve as a basis for refining dissemination strategies.

Limitations

Establishing and conducting an AMR surveillance system presents several limitations.

1. **Data retrieval challenges**. Data retrieval can be challenging when records are paper-based, illegible, or contain incomplete demographic and clinical data. The absence of hospital identifiers on laboratory records impacts demographic and clinical information collection from medical archives.
2. **Variability in laboratory practices**. The participating laboratories may demonstrate varying quality and testing practices. This inconsistency complicates the consolidation of information, making it challenging to perform robust analyses of resistance.
3. **Limited representation.** The participating laboratories may not accurately reflect resistance rates across the country, primarily if they serve only a tiny fraction of the national population or do not conduct routine testing. The failure to implement routine testing in hospitals and laboratories may lead to overestimating resistance rates, as infections that fail therapy are more likely to be tested.
4. **Insufficient clinical data.** A lack of comprehensive clinical data and information regarding antimicrobial usage can hinder the analysis of the drivers of resistance.

Conclusion

Antimicrobial resistance is a natural phenomenon that helps microbes ward off antimicrobials' effects. While the menace will only grow with time, a multisectoral and multifaceted approach can attempt to slow down its progress. The issue has gained a spotlight at most global forums, and various partnerships are aiming to fight AMR over the next few years. The Global Action Plan on AMR serves as a guidance document for countries to heighten awareness, build robust surveillance systems, improve infection prevention measures, use antibiotics responsibly, research new antimicrobials, and build collaborations. AMR surveillance is an important activity success of which rests on many factors, including uninterrupted supply chains, trained human resources, compliance to testing standards, data digitisation, continuous training of team members, and establishing a patient identifier system. AMR surveillance helps to ascertain the prevailing resistance in microbes and inform local empirical therapies across various clinical settings. Various global and regional surveillance systems aim to actively support capacity building and monitor the progress of national surveillance systems. The WHO's Global Antimicrobial Resistance and Use Surveillance System (GLASS) is widely recognized for its leadership in this area.

Competing interests

The author has no financial and non-financial competing interests to declare.

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Chapter 9

Global challenges to tackling antimicrobial resistance

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Introduction

The global public health is seriously threatened by AMR, which calls for immediate, concerted global action. Many antibiotics are now ineffective due to the emergence and spread of drug-resistant pathogens, which has raised global healthcare costs as well as morbidity and mortality rates. A thorough grasp of the intricate interactions between agriculture, the environment, animal health, and human health is necessary to address the issues raised by AMR. Because AMR is a complex problem that cuts across national and disciplinary boundaries, it calls for a One Health strategy that acknowledges the interdependence of environmental, animal, and human health. AMR is one of the most urgent global health concerns of our time, according to the World Health Organization (WHO), which highlights the necessity of coordinated efforts to counter this expanding threat. According to the Global Burden of Disease (GBD), there were an estimated 4.95 million (3.62–6.57) deaths associated with bacterial AMR in 2019, including 1.27 million (95% UI 0.911–1.71) deaths directly attributable to bacterial AMR.

In 2016, there was a rise in political interest in AMR at the highest levels. The United Nations member states promised to adopt a coordinated strategy to address the underlying causes of AMR across human health, animal health, agriculture, and environmental health at a high-level meeting (only the fourth on a health issue). However, after eight years, the situation has not improved much. Less than half of the 178 nations that have created national action plans actually have funding or are being carried out.

Antimicrobial resistance was listed by the WHO as one of the top 10 worldwide public health hazards that humanity faces. Up to 10 million deaths annually due to antibiotic-resistant infections are predicted by 2050, at a cost of approximately $100 trillion to the world economy. Since few new drugs are being developed and the number of bacteria that are resistant to treatment with all known antibiotics is growing, it is urgently necessary to develop new classes of antibiotics to prevent serious global health disasters.

The lack of public knowledge and comprehension of AMR, the slow development of new antimicrobial medications, the scarcity of funding for research, and the effects of antimicrobial use and resistance on the environment are major obstacles to solving AMR. Governments, healthcare organizations, researchers,

pharmaceutical companies, and the general public must work together to implement sustainable solutions that preserve the efficacy of currently available antibiotics while fostering the development of new treatment options in order to address these issues. This chapter will examine the global obstacles involved in combating AMR in detail, emphasizing the value of international cooperation, novel research, public outreach, and policy interventions in resolving this pressing problem. A number of factors play in the global AMR issue as summarized in **Table 1**.

Table 1. A summary of the key global challenges in tackling Antimicrobial Resistance (AMR), along with key examples and solutions.

Challenge	Key examples	Key solutions
Public awareness	Limited understanding among healthcare workers and the public of AMR	Effective global awareness campaigns and educational initiatives
New antimicrobial drugs in the pipeline	Drying pipeline for new and novel antimicrobial agents	Incentivizing pharmaceutical companies to invest in AMR research and development
Research funding	Inadequate and limited coordinated research activities	Attracting talent to the field of AMR, Increased and coordinated research efforts across disciplines and borders
Environmental factors	Waste management, and water treatment	One Health approach to integrate human, animal, and environmental health
International collaboration and governance	Insufficient global surveillance networks, laboratory capacity, and data sharing	Global coordination among agencies, governments, and stakeholders
Aligning policies and regulations	Different countries with various National Antimicrobial Resistance Action Plans	Implementation and alignment of policies across sectors and countries
Heterogeneity of stakeholders	Difficulty in aligning objectives and activities across sectors	Multisectoral approach and global action plans

One major obstacle to addressing AMR is the general public's ignorance of drug resistance, especially among young people. Youth engagement is low and there are insufficient education and awareness campaigns, which all contribute to this problem. Adopting successful global awareness campaigns and youth-focused educational initiatives is essential to addressing this challenge.

Medical officers in public healthcare facilities in Kedah, Malaysia, have moderate knowledge levels, frequently prescribe antibiotics, and need better training, according to their knowledge, attitudes, and practices regarding antibiotic prescribing. Research suggests that a considerable percentage of medical officers are comfortable prescribing antibiotics but rarely consult other medical officers, underscoring the significance of continuous education regarding the proper use of antibiotics.

Furthermore, there is a potential for misuse and concerns about microbial resistance due to the public's moderate understanding of antibiotics and ignorance of antibiotic resistance in Malaysia. In addition, medical professionals working in Penang government hospitals acknowledge the overuse of antibiotics and the

national importance of antibiotic resistance. They stress the necessity of ongoing antibiotic management programs and focused educational initiatives to improve medical professionals' expertise.
Educational programs in schools are one way to increase awareness among young people. Comprehensive AMR education can be incorporated into school curricula to give young people the information and comprehension they need to use antibiotics responsibly, comprehend the effects of AMR, and recognize the significance of infection prevention and control measures. This can enable people to use antibiotics wisely and help stop AMR.
The media is critical in influencing public perception and opinion. In an Australian study, the media reports that were examined for this study's context were insightful and of high quality. It was impossible to determine exactly what effect they had on the public's understanding of the AMR problem or in inspiring behavior changes to lessen the AMR crisis.
Reaching out to media organizations in order to provide clear and understandable information about AMR can help reach a larger audience, which includes youth. Key messaging regarding AMR, its impact, and preventive measures can be effectively communicated through the use of informative videos, social media engagement, and other digital communication channels.
Another way to engage youth and spread awareness about AMR is through community outreach programs. Workshops, seminars, and interactive sessions on AMR can be organized more easily by working with neighborhood organizations, civic leaders, and healthcare professionals. These kinds of programs can give young people the chance to learn about AMR, pose questions, and actively engage in dialogues.

Limited development of new antimicrobial drugs

The limited development of new antimicrobial drugs in recent decades poses a significant challenge in combating AMR. Several factors contribute to this issue, including the high costs and low profitability associated with AMR research and development for pharmaceutical companies.
One major obstacle in the global fight against AMR is the limited development of new antimicrobial drugs in recent decades. The complex nature of AMR, the small market for novel antibiotics, and the difficulties in recovering investment costs make pharmaceutical companies' research and development efforts costly and unprofitable. Pharmaceutical companies have been reluctant to invest in AMR research due to the current financial climate, which has left a shortage of new, effective treatments to combat resistant pathogens. Few studies estimated the time to develop a new antimicrobial molecule to be 10–20 years with the need of more than £(GBP) 1.5 billion.
Encouraging pharmaceutical companies to conduct AMR research is essential to addressing this problem. An "antibiotic investment charge" is one suggested remedy that might assist in reducing the financial risks connected with creating new antimicrobial medications. Increased investment in AMR research and development can lead to the discovery of new antibiotics and treatment approaches by offering financial incentives and lowering the financial burden on businesses. Furthermore, building public-private collaborations in the field of AMR research can be crucial to surmounting the obstacles caused by insufficient drug development. Working together, the public and private sectors can share risks, resources, and expertise, which speeds up the search for new antimicrobial drugs. Public-private partnerships can accelerate the development of critically needed antimicrobial therapies, improve innovation, and streamline research efforts by utilizing the strengths of both sectors.
Boosting funding for research and development projects aimed at preventing AMR is crucial, as is encouraging cooperative partnerships and pharmaceutical companies. In order to fill the gaps in the development of

antimicrobials, creative research projects need greater funding from governments and international organizations. More funding can spur scientific discoveries, hasten the clinical application of research results, and strengthen the international response to the escalating threat of antibiotic resistance.
The international community can work to overcome the difficulties associated with the slow development of new antimicrobial drugs and advance efforts to effectively combat antimicrobial resistance by putting strategies in place to incentivize pharmaceutical companies, fostering collaborative partnerships, and increasing funding for AMR research and development.

Insufficient research funding: a major barrier to combating AMR

A major worldwide obstacle in combating AMR is the inadequate financial support for research given by governmental and agency entities. The current state of research and development efforts to combat AMR is inadequate, as evidenced by the recent halt of antibiotic R&D by nearly all large pharmaceutical companies. The growing threat of drug resistance is being poorly understood and effectively countered due to a lack of investment from the public and private sectors. This funding gap has dire consequences. According to a study in the Journal of Infection Control and Hospital Epidemiology, AMR is the third most common cause of death worldwide, accounting for up to 162,044 deaths annually in the US alone.
This funding gap has dire consequences. According to a study that was published in the Journal of Infection Control and Hospital Epidemiology, AMR is the third largest cause of death in the United States, accounting for up to 162,044 deaths annually. An estimated 700,000 deaths worldwide are thought to be related to AMR each year, with multidrug-resistant tuberculosis (MDR-TB) being the primary cause of these deaths. Increased and coordinated research across borders and disciplines is essential to addressing this challenge. More funding must be provided by governments and international organizations to support creative research initiatives that address AMR from a variety of perspectives, such as the creation of novel antimicrobial medications, complementary and alternative therapies, diagnostic instruments, and infection prevention and control plans.
Increased and coordinated research across borders and disciplines is essential to addressing this challenge. More funding must be provided by governments and international organizations to support creative research initiatives that address AMR from a variety of perspectives, such as the creation of novel antimicrobial medications, complementary and alternative therapies, diagnostic tools, and infection prevention and control plans. Securing long-term funding for research on antimicrobial resistance is also essential to the solution. The Innovative Medicines Initiative's New Drugs 4 Bad Bugs (ND4BB) program in the EU is one example of a public-private partnership that demonstrates the potential of collaborative funding models to advance antibiotic discovery and development. To guarantee that these initiatives are suitably funded and globally coordinated, more work must be done.
Thus, one of the main obstacles to combating AMR is a lack of funding for research. Governments and agencies may contribute to the acceleration of research efforts aimed at comprehending and reducing the threat of antimicrobial resistance by boosting funding, drawing in talent, and encouraging cooperative efforts. If this issue is not resolved quickly, there is a chance that the AMR crisis will worsen and have far-reaching effects on public health around the globe.
Another important factor in advancing AMR research is attracting and keeping talent. Building a strong and long-lasting workforce requires investing in AMR research education, training, and career opportunities.

Environmental factors fueling the spread of AMR

AMR is largely caused by environmental factors, which emphasizes the necessity of a comprehensive One Health strategy that incorporates environmental, animal, and human health.

A One Health approach that recognizes the interdependence of environmental, animal, and human health is necessary in light of AMR. This interdisciplinary approach recognizes the shared reservoir of pathogens among species and the influence of human-animal interactions on disease emergence, emphasizing collaboration across sectors to address the complex dynamics of antimicrobial resistance. The One Health framework's surveillance initiatives center on tracking the use of antibiotics in people and animals, which is crucial for comprehending and preventing the emergence of resistance. The indiscriminate use of antibiotics in animal husbandry and their environmental persistence greatly contribute to the persistence and spread of resistant bacteria, underscoring the necessity of concerted national and international efforts to effectively combat AMR.

Inadequate water treatment, inappropriate waste management, and pollution are some of the major environmental issues fueling the global AMR crisis. A number of processes can lead to the release of antibiotic residues, resistant bacteria, and resistance genes into the environment. These include runoff from agricultural activities, improper disposal of pharmaceutical waste, and the discharge of untreated wastewater. By building up in the soil, water, and food chain, these pollutants can create environmental hotspots for AMR.

Problems with waste management: When waste from medical facilities, drug manufacturing facilities, and animal production facilities is not properly collected, handled, and disposed of, it can leak antibiotics, resistant bacteria, and resistance genes into the environment. Environmental AMR is largely caused by improper handling of animal manure and wastewater from livestock and aquaculture operations.

Conventional wastewater treatment facilities frequently lack the capacity to eliminate resistant bacteria and antimicrobial residues, which permits these pollutants to linger in treated effluent and find their way into drinking, recreational, and irrigation water bodies. In many regions of the world, inadequate access to sanitary facilities and safe water exacerbates the environmental pathways that lead to the spread of AMR. Adopting sustainable practices can help reduce the amount of AMR determinants released into the environment. Best management practices in agriculture include managing manure well, using antibiotics responsibly, and implementing alternate disease control techniques. It is essential to properly dispose of pharmaceutical waste and implement infection prevention and control measures in healthcare settings.

To stop resistant microbes and antimicrobials from leaking into the environment, waste collection, treatment, and disposal systems must be improved. This entails creating and putting into practice national guidelines for waste management in addition to modernizing wastewater treatment facilities to get rid of resistant bacteria and antimicrobial residues.

Educating stakeholders—policymakers, medical professionals, farmers, and the general public—about the environmental aspects of AMR and cultivating a sense of accountability among them are essential to bringing about change. Encouraging AMR research, surveillance, and monitoring in the environment can help direct interventions and provide evidence for evidence-based decision-making.

AMR is a complex problem that can be solved collaboratively by stakeholders by implementing a One Health approach that gives environmental factors priority. A comprehensive strategy to prevent the spread of AMR and safeguard the health of people, animals, and the environment must include sustainable practices, optimal waste management, and environmental stewardship.

AMR is a serious threat to global health; estimates suggest that by 2050, inadequate treatments could result in up to 10 million deaths yearly. The emergence of multidrug-resistant pathogens is largely caused by the overuse and misuse of antibiotics, which puts a burden on healthcare resources and increases hospital stays

and costs. The creation of precision antibiotic treatments that target the virulence traits of particular infections is one strategy used to combat AMR. Because pathogens are adaptive, it is difficult to predict the prevalence of AMR. Therefore, in order to identify the best interventions, ongoing model recalibration and real-world testing are necessary. In order to prevent the emergence of resistance and progress the development of novel antimicrobial drugs, multidisciplinary approaches encompassing agriculture, the environment, and healthcare are essential. To effectively address AMR, public awareness, international collaboration, and the implementation of strategies like the One Health Approach to ensure the sustainability of effective antimicrobials for human and animal health.

Different levels of effort and effectiveness in controlling antimicrobial resistance were revealed by the systematic governance analysis of 114 countries concerning the global response to antimicrobial resistance in 2020–21. Using a governance framework comprising 18 domains and 54 indicators, the study evaluated national action plans (NAPs) on antimicrobial resistance, pointing out areas that needed improvement, such as monitoring and evaluation initiatives. The World Health Organization (WHO) in 2015 approved the Global Action Plan (GAP) on antimicrobial resistance, which placed a strong emphasis on the creation of NAPs and strong governance frameworks for coordinated interventions. Furthermore, an analysis of the alignment between the GAP and the current NAPs revealed a strong vertical alignment but a weaker horizontal alignment within regions, indicating the need for enhanced global governance initiatives to reduce policy fragmentation and mimicking behavior worldwide.

The AMR concept of the 10-20-30 by 2030 target

A growing threat to global health, antimicrobial resistance (AMR) compromises the effectiveness of antibiotics, antivirals, antifungals, and antiparasitic agents, ultimately resulting in longer illness duration, higher death rates, and rising healthcare expenses. The "10-20-30 by 2030" target has been put forth as a tactical framework to successfully address AMR in response to this pressing issue. This goal is intended to rally global cooperation and resources in order to hit important benchmarks by 2030. The objective is to have at least ten novel antibacterial treatments on the market for clinical application by 2030. This covers both cutting-edge antibiotics and non-traditional treatments that can successfully cure infections caused by resistant bacteria through research and development (R&D), investment, public-private partnerships and regulatory support. The key to delaying the emergence of resistance is lowering the overuse of antibiotics. By 2030, the goal is to reduce the use of antibiotics worldwide by 20%. To guarantee that antibiotics are used appropriately and only, when necessary, healthcare settings should implement strong antimicrobial stewardship programs. A 30% reduction in the frequency of particularly resistant pathogens of epidemiologic significance. The goal is to reduce the incidence of some high-priority resistant infections by 30%, including methicillin-resistant *Staphylococcus aureus* (MRSA) and carbapenem-resistant *Enterobacteriaceae* (CRE). In order to stop the spread of resistant infections, healthcare facilities should strengthen their infection prevention and control (IPC) procedures. Improving worldwide monitoring systems to monitor the occurrence and spread of resistant pathogens so that prompt interventions can be made.

Conclusion

This chapter highlights the global challenges in tackling AMR, emphasizing the complex nature of the issue, inadequate surveillance systems, inappropriate antibiotic use, and the importance of international collaboration. Addressing these challenges requires a comprehensive, multifaceted approach involving policymakers, healthcare professionals, researchers, and communities worldwide. By working together, we can strive towards preserving the effectiveness of antimicrobial drugs and safeguarding public health for future generations.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 10

Challenges for sustainable implementation of national action plans on AMR

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Introduction

The World Health Assembly (WHA) endorsed the Global Action Plan (GAP) on antimicrobial resistance (AMR) in 2015 calling on countries to develop and implement national action plans (NAPs) on AMR. Developing a NAP was accomplished by most of the countries. However, the implementation of the plans presented several criticalities. In 2022, the first Quadripartite biennial report on the progress in the implementation of multisectoral NAPs highlighted many areas in all sectors where urgent action was needed to address AMR. According to the Tracking AMR Country Self-Assessment Survey (TrACCS), 60% of the responding countries reported the existence of a monitoring and evaluation plan for their NAP on AMR in 2023, while only 11% reported the allocation of funding to support NAP implementation. Countries reported diverse challenges i.e. limited financial and human resources, lack of technical capacity, and variable political commitment. Recently, to provide a practical, stepwise approach to the implementation of the NAPs on AMR, the World Health Organization (WHO) published some supporting documents indicating six steps for sustainable implementation of NAPs, as follows: strengthen governance, prioritize activities, cost the operational plan, mobilize resources, implement prioritized activities, monitor and evaluate. National health authorities, multi-sectoral coordination groups and technical experts, together with policymakers involved in implementing AMR activities at all levels of the health system have been working to accelerate sustainable implementation, monitoring, and evaluation of their NAPs, and to achieve the national and global targets on AMR.

Challenges for sustainable implementation of national action plans on AMR

Despite worldwide efforts, AMR continues to pose a significant threat to public health globally and decreases life expectancy. According to an analysis conducted by the Organisation for Economic Co-operation and Development (OECD) in 34 countries, nearly 4.3 million resistant infections occur every year. On average, every 7.3 seconds someone is infected by a resistant bacterium, most often in the community. Of note, around 35% of these resistant infections are acquired in healthcare settings accounting for about 62%-73% of AMR-related deaths. Around 2 in 3 AMR-related deaths occur among people above 65 years of age, while about 4% of deaths due to AMR regard people under 20 years of age, particularly newborns or young children. In terms of annual economic burden due to AMR, recently a meta-analysis study found the highest impact in China (35 billion US$ from direct costs and 42 billion US$ of indirect costs), followed by the USA (4.6 billion US$) and Japan (2 billion US$). Also, AMR concerns health inequities and universal health coverage (UHC),

together with the achievement of the 2030 Sustainable Development Goals (SDGs). UHC and SDGs, together with pandemic preparedness and response (PPR) strategies, are closely linked to AMR, showing how AMR can affect global health achievements. Often, criticalities are interdependent and resolving one aspect could impact several factors, with a concrete result in the fight against AMR.

An analysis based on 51 OECD countries revealed that around 20% only of the NAPs had advanced implementation, while gaps were reported in AMS, both in human and aquatic animal use, raising AMR awareness and understanding, and good hygiene practices in animal production as well as in food processing. Even among the Group of Seven (G7) countries, which represent some of the world's most advanced economies, wide space for improvement was recognized in the areas of IPC measures, adoption of WHO access/watch/reserve (AWaRe) classification of antibiotics and AMS, effective integration of AMR surveillance in the animal health and food safety sectors, AMR training and education, good manufacturing and hygiene practices in food processing, optimising pesticides use and environmental residues of antimicrobial drugs.

Some of these challenges are well-documented by local and international studies. In low- and middle-income countries (LMIC) where healthcare resources may be limited and the AMR burden is much higher than in the industrialized countries, this may require additional financial and technical support from the global community. High-level political engagement of nations and robust governance can ensure accountability for NAP implementation and monitoring, allocation of adequate human and financial resources, and strengthening AMR technical capacity and education. Strengthening governance, prioritizing activities, and cost the operational plan are the first three steps pointed out by the WHO to implement NAPs on AMR. However, ineffective communication across the science-policy practice interface can obstacle to an effective NAP implementation. Also, a rising prevalence of multi-drug-resistant organisms MDRO in the healthcare and community settings together with a high incidence of healthcare-associated infections (HAI) hinder the actions implemented, even in high-income countries (HIC). The post-COVID-19 scenario is even worsened among hospitalized patients. The spread of MDRO complicates treatment options and leads to poor patient outcomes. In the last years, the prevalence of colonization due to resistant microbes has increased both in the healthcare and the community setting. Notably, *K. pneumoniae* resistant to carbapenems is endemic in many areas worldwide, and extended-spectrum beta-lactamases (ESBL) are becoming increasingly common. Then, in most countries the information technology (IT) adaptation of data flows and medical instruments is not appropriate compared to the existing technologies, and often the availability of these tools varies greatly in different geographical areas in the same nation. E-health is hindered by the regional fragmentation of many national health systems and by the rare interoperability of health information systems. Although the “Bring Your Own Device" (BYOD) approach has been piloted for the last 10 years in some countries, this practice is still uncommon in most healthcare facilities globally. Moreover, some distance can exist between the investment priorities on digital technologies decided strategically by the public health authorities and the operational priorities at the healthcare facility level. The inadequate relationship between computerized workstations and the number of healthcare personnel in hospital settings can cause a slowdown in data updating or even missing data. Governments should encourage innovation related to work organisation and the use of new technologies to respond efficiently to the growing demand for care.

Both at the local and national level, the implementation of the actions indicated in the NAPs also depends on the human and financial resources dedicated to achieving the objectives. The health workforce is the fulcrum on which the health system performance of each country relies to offer affordable, accessible and high-quality health services. The demand for healthcare has also increased due to population ageing and more people living with chronic conditions. The ability of a country to meet its health commitments and goals largely depends on the number, skills, competencies and availability of health workers to deliver integrated and people-centred health services. However, in the last decades, many countries did not train enough health

workers to respond to current and future needs. The COVID-19 pandemic has even deteriorated the health staff conditions, and most countries have not yet introduced staff retention strategies to avoid worsening shortages. Shortages of doctors can be alleviated through greater task sharing with nurses, pharmacists and other paramedical professionals. Also, the emergence of categories of nurses taking on new roles such as family and community nurses in some European countries can alleviate pressures on primary care doctors (GPs) and hospitals. In 2021, the number of new medical graduates ranged widely between countries, from about 7 per 100,000 people in Israel, Japan, and Korea to over 20 per 100,000 in Latvia, Ireland, Denmark, and Lithuania. Besides, in some countries (e.g. Romania, Ireland, Bulgaria, the Slovak Republic, Czechia, and Hungary) a large number of new medical graduates are international students who will not stay in the country after graduation. The recent WHO manual on workload indicators of staffing need (WISN) can help in estimating current staffing requirements and determining optimal staffing allocations to improve task sharing and better health workforce projections. Challenges due to inadequate human resources, insufficient training on AMR, and lack of engagement from overwhelmed and underpaid healthcare professionals do not allow for adequate infection prevention and control (IPC) practices. Staffing, training, and personal motivation and performance, together with increasingly frequent drug shortages, also are linked to suboptimal antimicrobial stewardship (AMS). Some countries still register excessive rates of antibiotic consumption in Europe. Examples of inappropriate antimicrobial prescriptions were highlighted in several countries, indicating the need to improve AMS programs. In many LMICs, despite the existence of policies aimed at slowing down the spread of AMR, still there are gaps in their implementation and enforcement. Around half of the LMICs only have developed specifically targeted policies to limit the sale and use of protected or reserved antibiotics and getting antibiotics without a prescription is possible in over two-thirds of LMICs. Inappropriate prescriptions and illegal over-the-counter availability of antibiotics exacerbate AMR. This excessive use, both in human health and in veterinary settings, contributes to the development and spread of resistant microbes through the community and the environment. We also need to consider that 63 new antibiotics were approved for clinical use between 1980 and 2000, while just 15 were approved between 2000 and 2018. Limited access to novel antibiotics as well as the absence of antibiotic-related innovation also affect AMS. The global and national pharmaceutical industry has decreased the development of new antibiotics due to economic disincentives, resulting in increasing antibiotic shortages and the absence of alternative treatment options. Non-routine use of rapid diagnostic tools can limit improvements for AMS as well.

Jeopardized adherence to microbiological surveillance, limited use of genome sequencing techniques, and lack of integration between human and animal surveillance in most countries make epidemiological investigation and epidemic control difficult. Also, the protection of the patient's privacy is often an obstacle to information sharing, even if clinical decisions increasingly are the result of multidisciplinary consultation and collaborative process between professionals, sometimes distant from each other geographically.

Adequate national funding is needed to implement the NAP's actions and to empower existing R&D public-private partnerships to support and coordinate the development and provision of new antimicrobials. Particularly, support is needed for preclinical studies - in order to replenish a clinical pipeline that is unanimously considered too thin, to strengthen the health workforce, education and training, and to share adequate IT systems. Governments will need to coordinate actions in building a global capacity for independent scientific research for providing long-term forecasting of antimicrobials ensuring consistent supply and effective treatment. In 2023, 106 (60%) out of 177 countries worldwide reported the existence of a monitoring and evaluation plan for their NAP on AMR, and just 20 countries (11%) the allocation of funding to support its implementation. Besides, the design of the healthcare environment matters. An evidence-based awareness is growing of the way healthcare buildings are designed and constructed and the impact on healthcare delivery, patient and staff outcomes, and ultimately medical negligence claims.

Public knowledge regarding AMR obstacles to the efforts to control the development and spread of drug-resistant microorganisms still needs improvement. Particularly, scarce awareness of responsibility among healthcare professionals and the general public about the consequences of antibiotic misuse hampers efforts to combat resistance. Hospitals can also pose a major threat to our aquatic environment and ultimately mankind. Before discharging hospital wastewaters, which contain high levels of pharmaceutical residues, like antibiotics or bacteria and viruses, into nearby rivers, these wastewaters need to be properly treated. However, conventional wastewater treatment technologies often are unfortunately not sufficiently reliable when it comes to separating these micropollutants. Therefore, pharmaceutical pollutants, inappropriate disposal of antibiotics together with ineffective wastewater treatment from healthcare facilities and pharmaceutical enterprises contribute to the environmental development and spread of antimicrobial residuals, and drug-resistant microbes and genes. The steady rise in overall antimicrobial consumption in several medical, domestic, agricultural, industrial, and veterinary applications, involves environmental release. Antibiotic residues and antibiotic-resistance genes can contaminate terrestrial and aquatic environments directly or through urban and industrial sewages and can lead to the selection of resistant microbial strains in both human and animal populations.

With a One Health perspective, OECD identified 11 policy interventions to optimise the use of antibiotics in human health, to promote AMR awareness and understanding and to reduce the incidence of infections in healthcare settings, farms and food establishments, in order to improve population health and reduce health expenditure, while generating positive returns for the national and global economy. Policies on AMS, hand and environmental hygiene, are expected to yield the greatest health gains, producing an average of 71,000-153,000 life years (LYs) gained each year if resistant infections were eliminated across the 34 countries included in the OECD analysis. Particularly, AMS interventions are estimated to result in the greatest gains in terms of a number of averted AMR-related deaths. On average, this intervention is estimated to prevent over 10,000 deaths per year across the 34 countries if resistant infections were eliminated and more than 3,200 deaths if resistant infections were replaced by susceptible ones. Moreover, AMS interventions promise the greatest reduction in the extra days spent in hospitals, ranging from more than 3.7 million fewer days annually if resistant pathogens were eliminated and 822,000 fewer hospital days if resistant infections were replaced by susceptible infections.

Overall, these challenges highlight opportunities to facilitate sustainable delivery and operationalisation of NAPs, identifying AMR-related priorities.

Conclusion

Over 1 million years of life are lost yearly in the European Union (EU)/European Economic Area (EEA) alone due to AMR, with an expenditure of about €1.1 billion per year. These health and economic impacts are expected to worsen. Globally, many countries have implemented a NAP on AMR in the last years. However, several factors at all levels hinder the operational effectiveness of the actions indicated in these NAPs. Challenges associated with AMR are multifaceted and interconnected, stemming from the insufficient concrete commitment of policymakers, inadequate human and financial resources dedicated to combat AMR, inappropriate healthcare practices and behaviours, inadequately built environment, jeopardised socio-economic factors, and amplification of the phenomenon due to the global mobility of people, animals and goods. OECD estimated that AMS interventions should gain the greatest reduction in terms of AMR-related deaths as well as extra days spent in hospitals. AMS interventions together with policies on hand and environmental hygiene are estimated to yield the greatest health gains.

Tackling AMR demands a holistic approach that embraces the complexity of human, animal, and environmental health. By focusing on surveillance, capacity-building, sustainable and adequate human resources and financing, we can create a framework that not only addresses AMR, but also promotes health equity, food safety, environmental sustainability, and achievement of SDGs, allowing for PPR. Collaborative efforts across sectors supported by sound policies and innovative solutions will be essential to safeguarding public health and preserving the effectiveness of antimicrobials for future generations.

Competing interests

The author has no financial and non-financial competing interests to declare.

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Chapter 11

What the COVID-19 pandemic can teach about antimicrobial resistance

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Introduction

This article aims to briefly address how the COVID-19 pandemic has influenced the silent antimicrobial resistance pandemic, reviewing key data published in the literature and exploring significant insights and lessons that can be applied to combat antibiotic resistance now and in the future.

The antimicrobial resistance issue

Antimicrobial resistance (AMR) is one of the most complex and dynamic global challenges, directly responsible for an estimated 1.27 million deaths worldwide in 2019, with a total contribution of 4.95 million deaths. The World Health Organization (WHO) recognized antimicrobial resistance as one of the top 10 most urgent global health threats. The primary drivers of AMR are the misuse and overuse of antimicrobials in humans, animals, and plants, which lead to developing drug-resistant pathogens. This issue affects countries across all regions and income levels, but it is particularly severe in low- and middle-income countries, where poverty and inequality exacerbate the problem. The world is facing a crisis in the antibiotics pipeline, with an inadequate amount of research and development to combat rising resistance levels. The economic impact of AMR is equally alarming. The World Bank projects that by 2050, AMR could result in an additional US$ 1 trillion in healthcare costs, along with gross domestic product losses ranging from US$ 1 trillion to US$ 3.4 trillion per year by 2030. In 2024, WHO published the Bacterial Priority Pathogens List including *Acinetobacter baumannii* and *Enterobacterales* in the critical group, *Salmonella typhi*, *Shigella* species, *Enterococcus faecium*, *Pseudomonas aeruginosa*, non-typhoidal *Salmonella*, *Neisseria gonorrhoeae*, *Staphylococcus aureus* in the high group, and other pathogens including streptococci and *Haemophilus influenzae* in the medium group.

Some of these microorganisms were previously referred to by the Infectious Diseases Society of America as 'ESKAPE' pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa,* and *Enterobacter* spp.) and they are increasingly difficult to treat due to limited antimicrobial options. The mechanisms of AMR vary and can be summarized into four categories: restricted drug uptake, altered drug targets, drug inactivation, and efflux pumps. Many bacteria are naturally resistant to antimicrobials; however, others can develop resistance through gene mutations and horizontal gene transfer via conjugation, transformation, or transduction by temperate phages.

To address the rise of AMR, the WHO introduced the AWaRe (Access, Watch, Reserve) classification system to guide the appropriate use of antibiotics. The Access group includes first or second-line treatments for common infections, such as amoxicillin, doxycycline, and metronidazole. The Watch group includes antibiotics for specific, limited indications due to their higher potential for resistance development, such as ciprofloxacin, ceftriaxone, and azithromycin. The Reserve group includes last-resort antibiotics reserved for treating confirmed or suspected multi-drug resistant (MDR) infections, such as linezolid, ceftobiprole, and meropenem/vaborbactam. However, recent analyses have labeled AMR as a "silent pandemic," estimating that by 2050, AMR could be responsible for 10 million deaths annually and could cost as much as US$100 trillion. In the United States, it is estimated that each year at least 2.8 million people develop an antibiotic-resistant infection, with over 35,000 deaths resulting from these infections.

The European CDC (ECDC) estimated 35,813 deaths due to antibiotic-resistant bacteria in Europe in 2020. They observed reduced total consumption of antibacterials for systemic use in the community during the first two years of the COVID-19 pandemic. Still, they noted an increased hospital consumption of last-line antibiotics, particularly carbapenems. Despite the growing threat of AMR, there has been a decline in the availability of newly developed antimicrobial agents. The emergence of the COVID-19 pandemic has further complicated the issue, highlighting vulnerabilities in global health systems and significantly impacting public health, economies, societies, and healthcare policies worldwide. During the initial wave of the COVID-19 pandemic, antibiotic consumption surged due to the lack of proper antiviral therapies and guidelines. Fungal and bacterial coinfections in SARS-CoV-2 patients have posed additional challenges to healthcare systems. The evolution of antimicrobial resistance in a population is usually shaped by three primary factors: emergence, transmission, and the overall infection burden within the population. Antimicrobial resistance can develop due to selective pressures on microbial populations in humans, animals, or the environment. Once resistant organisms emerge, environmental conditions and human behaviors can promote or hinder their spread. The COVID-19 pandemic has directly or indirectly influenced all three of these factors, particularly regarding antibiotic use and the working conditions during the first wave of SARS-CoV-2. Conflicting data about the effects of COVID-19 on AMR have been reported in the literature. For instance, during the COVID-19 pandemic, reports on bacteremia have highlighted MDR isolates, especially *Enterococcus* species, *Pseudomonas aeruginosa*, *Enterobacterales*, and *Acinetobacter baumannii*, but other studies show no differences or even a reduction in some of these pathogens.

Inappropriate use of antimicrobials during COVID-19 pandemic

During the pandemic, there was a surge in the use of antibiotics, particularly in the early stages when there was uncertainty about effective treatments for COVID-19. Many patients, even those without bacterial coinfections, were prescribed antibiotics as a precautionary measure, likely contributing to the acceleration of AMR Even before COVID-19, 50% of antibiotic prescriptions were deemed inappropriate, and the spread of false myths regarding the use of molecules such as azithromycin or hydroxychloroquine to treat COVID-19

has contributed to the phenomenon of antibiotic resistance. Another significant factor contributing to the spread of antibiotic resistance during the pandemic is the widespread misunderstanding of the viral nature of COVID-19 among the general public and, in some cases, even among healthcare professionals. For instance, a population survey in Australia revealed that 44% of respondents mistakenly believed that antibiotics could be used to treat COVID-19. The trend towards self-medication with various types of antimicrobials has advanced not only in developed countries but also in developing ones. The significant uncertainty surrounding the virus and its treatment at the onset of the COVID-19 pandemic contributed to a marked increase in the misuse of antibiotics, as the overlapping symptoms of viral and bacterial infections complicated diagnosis. As a result, antibiotics were frequently prescribed without clear evidence of a bacterial infection. First works published in 2021 estimated that 75% of adults with COVID-19 and comorbidities received antibiotic prescriptions, and it was inappropriate in more than one-third of cases. Irrational antimicrobial use was also reported in the pediatric population. Furthermore, the COVID-19 pandemic has revealed global health systems and infrastructure weaknesses. Since the emergence of COVID-19, collected data have shown an increase in exposure to healthcare settings and invasive procedures that favored the emergence of resistant pathogens. The less opportunity for isolation of patients colonized with MDR pathogens and the overcrowding associated with overloading of healthcare systems, and the overcrowding associated with overloading of healthcare systems were hypothesized to be responsible for the increased transmission of MDR microorganisms. Hospital admissions increase the in-hospital demand for antimicrobial agents, the risk of healthcare-associated infections, and the transmission of MDR pathogens. Then, important drivers of increased antimicrobial resistance during the COVID-19 pandemic in the hospital were the horizontal spread of resistant strains and the use of broad-spectrum antimicrobials due to the wide prescription for the difficulty in differentiating between pulmonary bacterial coinfection and viral infection alone.

Secondary infections in COVID-19 patients

Several mechanisms contribute to an increased risk of secondary bacterial infections during viral respiratory infections, though they are not yet fully understood. These mechanisms include immune system dysregulation, virus-mediated immunosuppression, alterations in immune responses directed towards the virus, and increased susceptibility of mammalian cells to bacterial attachment when infected by viruses. Elevated levels of pro-inflammatory cytokines may also play a role, as these changes in the inflammatory response can contribute to lung damage, making patients more susceptible to superinfections. Among the pathogens responsible for secondary infections, the most frequently observed bacterial pathogens included pandrug-resistant *Acinetobacter baumannii*, carbapenemase- and ESBL-producing *Klebsiella pneumoniae*, ESBL-producing *Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Serratia marcescens*, *Mycoplasma* species, and *Haemophilus influenzae*. The most common fungal pathogens reported were *Aspergillus fumigatus*, *Aspergillus flavus*, *Candida albicans*, *Candida glabrata*, and *Candida auris*. However, evidence accumulated that the prevalence of true bacterial co-infections and secondary infections among COVID-19 patients is low compared to the excessive use of antibiotics, and mainly interests critically ill patients. First data from 2020 showed that secondary infections have been reported in about 10% of COVID-19 patients included in published series from hospitals in China, Europe and the USA, with higher incidence in intensive care units. The most used agents have been fluoroquinolones, cephalosporins, carbapenems, azithromycin, vancomycin, and linezolid, and the most common type of infection was pneumonia, followed by bloodstream and urinary tract infections. Hospital-acquired and ventilator-associated pneumonia became significant concerns, largely driven by nosocomial pathogens that were often MDR, reflecting the local institutional ecology and

antimicrobial resistance patterns. A Chinese retrospective study conducted at Wuhan Union Hospital between January 27 and March 17, 2020, evaluated secondary bacterial infections in a cohort of 1,495 COVID-19 patients, revealing a prevalence of 6.8%. This study highlighted the role of carbapenem-resistant *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Stenotrophomonas maltophilia*. Staphylococci methicillin-resistant and extended-spectrum beta-lactamase *Escherichia coli* were also isolated. In a meta-analysis published by Langford *et al.* in July 2020, the prevalence of acute bacterial infections in COVID-19 patients was analyzed, including bacteria detected from respiratory tract and bloodstream sources. The study evaluated 3,338 patients and found that bacterial co-infection was present in 3.5% at the time of admission, while secondary bacterial infections occurred in 14.3% of cases. Despite these findings, most patients (71.9%) received antibiotics. Similar data were reported in a prospective cohort study conducted in February 2021 at a tertiary hospital in Mexico City. In this study, empirical antibiotic treatment was initiated in 92% of patients admitted with severe COVID-19, and 11.3% developed hospital-acquired infections, predominantly ventilator-associated pneumonia and bloodstream infections. The prescribed antibiotics included ceftriaxone, amoxicillin-clavulanate, and macrolides. The most common pathogens responsible for ventilator-associated pneumonia were *Enterobacteriaceae* and non-fermenter Gram-negative bacilli, while coagulase-negative staphylococci and *Enterobacter complex* for bloodstream infection. The main mechanism of antimicrobial resistance reported was AmpC production (29.1%). Higher mortality was associated with hospital-acquired infection. It is known that the use of beta-lactam antibiotics, such as third-generation cephalosporins, can favor the induction of Amp-C production.

Increase in MDR isolates in the pandemic period

These data demonstrate that the combination of inappropriate antibiotic use in both outpatient and hospitalized COVID-19 patients, true co-infections, secondary hospital-acquired infections, the disruption of antimicrobial stewardship programs, overcrowded healthcare facilities, and inadequate responses to the pandemic have likely accelerated the development of antibiotic resistance. In fact, numerous reports have shown a significant increase in the prevalence of MDR pathogens between the pre-pandemic and post-pandemic periods. A review published by Lai *et al.* in March 2021 summarized data on antimicrobial resistance during the first year of the pandemic. The review observed a rapid increase in MDR organisms, including extended-spectrum β-lactamase-producing *Klebsiella pneumoniae*, carbapenem-resistant New Delhi metallo-β-lactamase-producing *Enterobacterales*, *Acinetobacter baumannii*, methicillin-resistant *Staphylococcus aureus*, pan-echinocandin-resistant *Candida glabrata*, and multi-triazole-resistant *Aspergillus fumigatus* in intensive care units across China, France, India, the United States, Taiwan, and other regions. In Mexico, a multicentric study involving 46 centers revealed an increase in oxacillin-resistant *Staphylococcus aureus*, ampicillin-resistant *Enterococcus faecium*, carbapenems resistant *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa* across various sample types (blood, urine, respiratory tract), when comparing data from the second half of 2019 (pre-pandemic) to the second half of 2020 (pandemic). Similar findings were reported in South Korea, where increased antimicrobial use was associated with a significant rise in MDR ESKAPE pathogens. An Italian monocentric study revealed a higher prevalence of ESKAPE isolates in COVID-19 patients than non-COVID-19 patients, with *Acinetobacter baumannii* being the predominant pathogen in COVID-19 patients (58.7%). This pathogen was the most frequent cause of bloodstream infections and was associated with the highest mortality rate (68.7%) in these patients. However, the increase in MDR appeared to be particularly associated with COVID-19 in the ICU setting. Additionally, Karataş *et al*. highlighted the role of *Acinetobacter baumannii* in respiratory infections in COVID-19 patients, although they observed lower levels of

ESBL-producing *Enterobacterales. Acinetobacter baumannii* is a significant challenge for clinicians due to its ability to develop resistance to nearly all available antibiotics, leaving only a few therapeutic options, such as cefiderocol and high-dose sulbactam. Alarmingly, strains resistant to cefiderocol, currently the most effective therapeutic option, have already emerged. The combination of durlobactam and sulbactam offers a promising alternative, although it remains unavailable in many countries. The primary challenge, however, lies in distinguishing between colonization and true pathogenicity in respiratory samples. Another pathogen of concern, highlighted by data on secondary infections during the pandemic, is *Enterococcus faecium*. *Enterococcus* species, particularly vancomycin-resistant *Enterococcus faecium* (VRE), present a significant challenge due to severely limited therapeutic options. Sometimes, the only available treatments are linezolid, daptomycin, and fifth-generation cephalosporins, which have limitations in managing difficult VRE infections. Studies from Romania reported a high prevalence of van An *Enterococcus faecium* colonization and multidrug-resistant organisms among COVID-19 patients during the pandemic, with several instances of vancomycin-resistant *Enterococcus* species being isolated. An increase in *Enterococcus* species isolated from blood samples in critically ill COVID-19 patients was also observed in an Italian study. Additionally, a multicentric study from Greece indicated a rising frequency of *Enterococcus faecium* bloodstream infections during COVID-19, accompanied by an increasing trend in glycopeptide resistance. The use of antibiotics has further contributed to alterations in the gut microbiota, potentially promoting the selection of resistant *Enterococci*. Numerous studies worldwide have highlighted increased incidence of MDR infections, including carbapenem-resistant Gram-negative pathogens, particularly in intensive care units, compared to the pre-pandemic period. A Greek study reported increased macrolide resistance among *Mycoplasma* and *Ureaplasma* species, likely related to the overuse of azithromycin during the pandemic. Although this study did not provide data on *Mycoplasma genitalium*, it is worth noting that this microorganism is an emerging pathogen in sexually transmitted infections, with limited therapeutic options available for macrolide-resistant strains. The pandemic and the excessive use of macrolides have likely exacerbated an already critical situation.

Fungal infections in COVID-19 patients

Fungal infections have also been a significant concern during the COVID-19 pandemic. The use of steroids and immunosuppressive therapies to treat cytokine storms in severely ill patients, along with immune system alterations caused by SARS-CoV-2 infection, have favored the development of fungal infections. Early co-infections in COVID-19 patients were predominantly bacterial, whereas secondary infections were both bacterial and fungal. A recent meta-analysis reported pooled fungal co-infection rates of 5.01% in ICU and critically ill COVID-19 patients, compared to 2.09% in non-ICU patients. Several reports have noted an increase in *Candida* infections, often multidrug-resistant, even in developing countries. Italian researchers reported a nosocomial outbreak of *Candida auris* in ICUs at a hospital dedicated to COVID-19 care. Of particular interest is the new clinicopathological entity known as COVID-19-associated pulmonary aspergillosis (CAPA), identified as a significant complication among ventilated patients. Although the exact pathophysiology remains unclear, predisposing factors include prolonged mechanical ventilation, severe COVID-19 pneumonitis, and immunosuppression. Diagnosis is challenging, as the mere isolation of *Aspergillus* species in respiratory samples does not confirm infection but may indicate colonization or contamination. Patients were stratified by clinical and radiological features into different risk groups, requiring intensive screening that includes serum galactomannan, 1-3-β-D-glucan, and deep respiratory sample testing. However, a positive serum galactomannan test indicates angio-invasive infection, and early diagnosis involves its detection in bronchoalveolar lavage fluid.

Diagnostic tools

The challenge of distinguishing between bacterial, fungal, and viral infections during the COVID-19 pandemic has exposed the limitations of existing diagnostic tools. Standard methods, which often require several hours or even days, were too slow for urgent care settings, leading to empirical treatment decisions. The urgency of the pandemic has driven rapid advancements in diagnostic technologies. Innovations such as polymerase chain reaction (PCR) tests and rapid antigen tests, initially developed for detecting SARS-CoV-2, now hold promise for identifying bacterial infections and resistance patterns even before phenotypic results are available. These advancements have the potential to improve significantly our ability to diagnose and manage infections with speed and precision. For example, the COVID-19 pandemic has significantly accelerated the adoption of advanced microbiological techniques, such as molecular methods and Matrix-Assisted Laser Desorption Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF-MS). These tools are now widely used to quickly identify infectious agents and detect antibiotic resistance, such as beta-lactamase and carbapenemase production, often within less than an hour.

Antimicrobial soap and disinfectant cleaners

The COVID-19 pandemic has also brought about a significant shift in societal behavior, with a heightened focus on hygiene practices, including the widespread use of antimicrobial soaps and disinfectant cleaners to prevent the spread of the virus. This increased vigilance around hygiene, including avoiding direct contact with potentially contaminated surfaces, droplets, and aerosols, along with additional sterilization procedures and reductions in travel, may limit the spread of antimicrobial-resistant bacteria. However, the widespread use of antimicrobials, soaps, and disinfectant cleaners poses environmental concerns, as these substances could contaminate the environment in their active forms and exert selective pressure for resistant bacteria. Research has shown that subinhibitory concentrations of certain quaternary ammonium compounds can select bacteria resistant to medically important antibiotics such as ampicillin, cephalosporins, fluoroquinolones, and colistin. Additionally, studies have highlighted the synergistic effect of quaternary ammonium compounds and trihalomethanes in exacerbating environmental antimicrobial resistance (AMR), underscoring the need for rational usage of disinfectants and greater attention to environmental microbes. Many homemade and commercial cleaning and hand-sanitizing products contain chemicals, such as phenol and hydrogen peroxide, which can cause DNA damage in microbes. In response to this DNA damage, bacteria may activate translesion synthesis polymerases, enzymes that allow bacteria to bypass or tolerate unrepaired DNA lesions, leading to mutations that could contribute to the development of antimicrobial resistance. When exposed to disinfectants containing antibiotics, bacteria can form a subpopulation of cells highly tolerant to antimicrobials. While proper handwashing in appropriate contexts is associated with reducing infections and AMR, the excessive and inappropriate use of disinfectants outside the hospital environment could foster the development of antibiotic resistance.

One Health perspective

The COVID-19 pandemic has highlighted the importance of adopting a "One Health" perspective, which recognizes the interconnectedness of human, environmental, and animal health in the context of AMR

development and prevention. This holistic strategy addresses AMR by promoting coordinated efforts across multiple sectors, including healthcare, veterinary medicine, agriculture, and environmental management. The pandemic has significantly raised public and political awareness of the threat of infectious diseases, including antibiotic-resistant infections. It has demonstrated how rapidly infectious diseases can spread and the severe consequences they can have on healthcare systems and economies. As a result, governments and international organizations may now be more motivated to invest in research, implement stewardship programs, and support the development of new antimicrobial agents, health infrastructures, and rapid diagnostic tools. Monitoring antimicrobial use and resistance patterns in healthcare settings, tracking antibiotic usage and resistance in livestock, pets, and wildlife, and assessing the presence of antimicrobials and resistant bacteria in the environment, including water, soil, and wastewater, are essential measures. Antimicrobial stewardship programs and education for healthcare professionals, veterinarians, farmers, and the public about the risks of AMR are crucial for promoting the responsible use of antibiotics. Increasing public awareness of the connection between infectious diseases and the long-term AMR pandemic can significantly impact the adoption of best practices for controlling AMR. However, during the COVID-19 pandemic, research on AMR has faced significant disruptions, with surveillance and antimicrobial stewardship programs being deprioritized, delayed, or even halted. Vaccination is one of the primary strategies for controlling the spread of infectious diseases, including SARS-CoV-2. The rapid development and approval of COVID-19 vaccines have demonstrated the potential of coordinated global efforts and substantial investment. Expanding research and utilizing mRNA technology for bacterial infections could reduce the costs and time required for vaccine development. Similar strategies can be applied to developing new antibiotics and alternative treatments, such as bacteriophages and immunotherapies.

Conclusion

COVID-19 has accelerated a process already in progress, presenting one of the century's greatest challenges: antimicrobial resistance. This pandemic has underscored the problem of antibiotic resistance linked to the overuse of antibiotics. Lessons from COVID-19 include:

- The excessive use of antibiotics in both community and hospital settings promotes the emergence of MDR pathogens. Numerous reports from different regions worldwide have documented an increase in microorganisms with limited therapeutic options, such as *Acinetobacter baumannii* and *Enterococcus faecium.*
- The pandemic has highlighted the urgent need for investment in research. This includes developing faster diagnostic tools to quickly differentiate when antibiotics are necessary, particularly in cases where viral and bacterial infections present with similar symptoms, as well as the development of new vaccines and antimicrobials.
- The pandemic has demonstrated the importance of adopting a One Health approach, which involves a multidisciplinary team to combat antimicrobial resistance. This approach should include educational programs on antibiotic use that target healthcare professionals across all fields and the broader community, the environment, and animals.
- There is a critical need to invest in and implement robust antimicrobial stewardship programs supported by international collaboration.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 12

Impact of antimicrobial resistance on healthcare

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Introduction

Antimicrobial resistance (AMR) has emerged as one of the most significant threats to global public health in the 21st century. The rapid evolution of resistant pathogens has outpaced the development of new antibiotics, leading to a situation where common infections are becoming increasingly difficult, and sometimes impossible, to treat. AMR not only jeopardizes the efficacy of essential medicines but also undermines advances in healthcare, particularly in surgery, chemotherapy, and the management of chronic diseases.

The World Health Organization (WHO) has identified AMR as a priority health issue, stressing that without urgent action, the world is heading towards a post-antibiotic era, where minor infections and injuries could once again become fatal. In 2019 alone, AMR was directly responsible for an estimated 1,27 million deaths globally, and this number is expected to rise dramatically in the coming decades if effective interventions are not implemented.

The impact of AMR is particularly severe in healthcare settings, where it complicates the treatment of infections and increases the risk of healthcare-associated infections (HAIs). These resistant infections lead to longer hospital stays, higher medical costs, and an increased risk of death. For instance, the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infections requires more expensive and toxic alternatives, resulting in significant economic and health burdens.

Furthermore, the global nature of AMR means that resistant bacteria can easily spread across borders, exacerbating the challenge for healthcare systems worldwide. The interconnectedness of modern healthcare, travel, and trade amplifies the spread of resistance, making international collaboration and coordinated efforts essential to combating this threat.

As AMR continues to rise, healthcare systems must strengthen their antimicrobial stewardship programs, improve infection prevention and control measures, and foster innovation in the development of new antibiotics and diagnostics. This introduction aims to underscore the critical need for a comprehensive approach to tackle AMR, emphasizing its impact on healthcare and the urgent actions required to mitigate its consequences.

The growing burden of AMR in healthcare

AMR poses a significant and escalating threat to global health, with profound implications for healthcare systems worldwide. The growing burden of AMR is driven by the widespread misuse and overuse of antibiotics, the lack of new antimicrobial development, and the increasing prevalence of drug-resistant infections. This burden is not only a medical challenge but also a social and economic one, with far-reaching consequences.

The scale of the problem

AMR has reached alarming levels globally, with resistant infections causing an estimated 1.27 million deaths in 2019 alone, and nearly 5 million deaths associated with bacterial AMR. By 2050, it is projected that AMR could lead to 10 million deaths annually, surpassing current mortality rates for cancer and other leading causes of death. This crisis is particularly acute in low- and middle-income countries (LMICs), where healthcare systems are often under-resourced and ill-equipped to handle the growing number of drug-resistant infections.

Healthcare-associated infections (HAIs) and AMR

HAIs are a significant contributor to the AMR burden in healthcare settings. These infections are often caused by multi-drug-resistant organisms (MDROs), which are difficult to treat and lead to higher mortality rates. Common HAIs, such as those caused by MRSA, carbapenem-resistant *Enterobacteriaceae* (CRE), and *Clostridioides difficile*, are becoming increasingly prevalent, further complicating patient care and increasing the burden on healthcare systems.

The global response to AMR

The global response to AMR has been multifaceted, involving efforts from international organizations, governments, and healthcare providers. The One Health approach, which recognizes the interconnectedness of human, animal, and environmental health, has been pivotal in addressing AMR on a global scale. This approach emphasizes the need for coordinated action across sectors to reduce the spread of resistance, promote the responsible use of antibiotics, and enhance surveillance and research.

Despite these efforts, significant gaps remain. Many countries lack comprehensive national action plans to combat AMR, and even where such plans exist, implementation is often inconsistent and underfunded. Moreover, the development of new antibiotics has not kept pace with the emergence of resistant strains, leaving healthcare providers with limited options to treat infections.

The growing burden of AMR in healthcare is a clear and present danger that requires urgent and sustained action. Without coordinated global efforts to curb the misuse of antimicrobials, strengthen healthcare systems, and invest in new treatments, the impact of AMR will continue to escalate, leading to higher mortality rates, economic losses, and a profound impact on global health security.

Factors contributing to AMR in healthcare settings

The rise of AMR in healthcare settings is a multifaceted issue driven by various factors. These factors are interlinked, creating a complex environment where resistant pathogens can thrive and spread. Understanding these contributing elements is crucial for developing effective strategies to combat AMR in healthcare.

Overuse and misuse of antibiotics

One of the most significant contributors to AMR in healthcare settings is the overuse and misuse of antibiotics. Antibiotics are often prescribed unnecessarily or inappropriately, such as for viral infections where they have no effect. This misuse promotes the selection of resistant bacteria, which can spread within healthcare facilities and beyond. The inappropriate use of broad-spectrum antibiotics, instead of targeted therapy, also exacerbates the problem by promoting resistance in a wide range of bacterial species.

Inadequate infection prevention and control (IPC)

IPC practices in healthcare settings significantly contribute to the spread of AMR. Poor hand hygiene, insufficient sterilization of medical equipment, and inadequate isolation procedures for patients with resistant infections allow resistant bacteria to spread more easily. HAIs caused by MDROs are particularly problematic in settings where IPC measures are weak.

Environmental factors

Environmental factors play a crucial role in the development and spread of AMR within healthcare settings. The release of antibiotics and other antimicrobials into the environment through wastewater, coupled with the presence of resistant bacteria in hospital settings, creates a breeding ground for AMR. Contaminated surfaces, medical waste, and improper disposal of unused antibiotics further contribute to the persistence and spread of resistant organisms.

Patient factors

Patient-related factors, including prolonged hospital stays, invasive procedures, and the use of medical devices such as catheters and ventilators, increase the risk of developing infections with resistant bacteria. Patients with weakened immune systems, such as those undergoing chemotherapy or organ transplants, are particularly vulnerable to AMR. Additionally, the overuse of antibiotics in these vulnerable populations can lead to the development and spread of resistance.

Globalization and travel

Globalization and increased travel contribute to the spread of AMR by allowing resistant bacteria to move across borders rapidly. Healthcare settings, particularly those in regions with high levels of antibiotic use or poor IPC practices, can become hubs for the transmission of resistant organisms. Medical tourism and the global exchange of healthcare workers also facilitate the spread of AMR between countries and healthcare facilities.

COVID-19 pandemic and AMR

The COVID-19 pandemic has exacerbated the AMR crisis in healthcare settings. The increased use of antibiotics to treat secondary bacterial infections in COVID-19 patients, often without proper diagnostic confirmation, has led to a surge in antibiotic resistance. Furthermore, the strain on healthcare systems during the pandemic has led to lapses in IPC measures, further contributing to the spread of AMR.

The economic impact of AMR on healthcare systems

The economic impact of AMR on healthcare systems is both extensive and profound, encompassing direct costs related to medical care and broader economic consequences that affect global economies. AMR increases the financial burden on healthcare systems due to longer hospital stays, the need for more expensive treatments, and higher mortality rates, all of which drive up healthcare expenditures significantly.
The World Bank estimates that, if left unchecked, AMR could cause a global economic loss of up to $3.4 trillion annually by 2050 and push 24 million more people into extreme poverty. In the European Union alone, AMR is responsible for €1.5 billion in extra healthcare costs and productivity losses each year. The financial burden is compounded by the increased need for more expensive and prolonged treatments, longer hospital stays, and the necessity for more intensive care, all of which strain healthcare budgets and resources.

Direct healthcare costs

The direct costs of AMR are substantial, with healthcare systems bearing the brunt of increased spending due to the need for more intensive care, extended hospital stays, and the use of more expensive antibiotics. According to the KPMG report on the global economic impact of AMR, the cost of treating resistant infections can be significantly higher than treating non-resistant infections. For example, in the United States, the treatment of MRSA infections can be up to 50% more expensive than treating infections caused by methicillin-susceptible strains. The estimated additional cost per patient for treating a resistant infection can range from $18,000 to $29,000, depending on the severity and type of infection.
In Europe, the annual healthcare costs associated with AMR are estimated to exceed €1.5 billion. This figure includes costs related to additional hospital stays, diagnostic tests, and the use of last-resort antibiotics, which are often more expensive and less effective. A significant portion of these costs are attributed to the need for advanced laboratory testing and specialized care for patients with resistant infections.

Impact on length of hospital stay

AMR infections considerably increase the length of hospital stays, thereby compounding the economic burden on healthcare systems. According to data from the Global Antimicrobial Resistance Surveillance System (GLASS) 2022 report, patients with drug-resistant infections experience significantly longer hospital stays than those with non-resistant infections. For example, patients with bloodstream infections caused by extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* had an average hospital stay that was 21 days longer than those with susceptible strains.
This extended hospitalization results in higher healthcare costs due to the increased need for medical resources, including more frequent monitoring, additional medications, and prolonged use of hospital facilities. These prolonged hospital stays contribute to the overall increase in healthcare costs associated with AMR, as hospitals must allocate more resources to care for these patients.

Broader economic consequences

Beyond the direct impact on healthcare systems, AMR also has far-reaching economic consequences that extend to the broader economy. The KPMG report projects that by 2050, AMR could lead to a global GDP loss of up to $100 trillion if no effective measures are taken to combat its spread. This economic burden stems from reduced productivity, higher mortality rates, and the increased cost of healthcare.
AMR also affects sectors beyond healthcare, including agriculture and trade. The widespread use of antibiotics in livestock has contributed to the rise of resistant bacteria in the food supply, leading to trade restrictions and loss of revenue in the agricultural sector. The economic impact is particularly severe in LMICs,

where the loss of productivity and increased healthcare costs can exacerbate poverty and hinder economic development.

Impact on mortality and productivity

AMR significantly impacts mortality rates and overall productivity. The KPMG report highlights that by 2050, AMR could cause an additional 10 million deaths per year globally, surpassing the mortality rates of cancer and other major diseases. This loss of life has a direct impact on labor markets, as the premature deaths of working-age individuals lead to reduced productivity and economic output.

The economic burden of AMR is further compounded by the loss of productivity due to prolonged illness and disability associated with resistant infections. The World Bank estimates that the global economic loss due to AMR-related reductions in labor supply could reach $6.1 trillion by 2050. This figure includes lost income due to extended time away from work, the costs associated with long-term disability, and the economic impact of premature death.

The economic impact of AMR on healthcare systems is vast and complex, involving both direct healthcare costs and broader economic disruptions. Addressing AMR requires a coordinated global effort to improve antimicrobial stewardship, invest in the development of new antibiotics, and enhance international cooperation to mitigate its far-reaching economic consequences.

AMR's impact on surgical outcomes

AMR has emerged as a significant threat to surgical outcomes, compromising the effectiveness of prophylactic and therapeutic antibiotics that are essential in preventing and treating infections during and after surgery. The rise of resistant pathogens in surgical settings has led to an increase in surgical site infections (SSIs), longer hospital stays, higher treatment costs, and increased mortality rates. This section explores the various ways in which AMR impacts surgical care, emphasizing the need for robust antimicrobial stewardship and infection control measures.

Increase in surgical site infections (SSIs)

SSIs are one of the most common complications following surgery, and AMR has significantly exacerbated this problem. The global incidence of SSIs varies widely, with estimates ranging from 3% to 50%, depending on the type of surgery and the region. The situation is particularly dire in LMICs, where SSIs are the most frequently reported HAI. AMR has made SSIs more difficult to treat, as many of the pathogens responsible for these infections, such as *Escherichia coli* and *Staphylococcus aureus*, have developed resistance to commonly used antibiotics.

In the United States, it is estimated that 39% to 51% of bacteria causing SSIs are resistant to standard prophylactic antibiotics. A reduction in the efficacy of these antibiotics by just 30% could result in an additional 120,000 SSIs and 6,300 infection-related deaths each year. The increase in resistant infections leads to prolonged hospital stays and more intensive care, driving up healthcare costs and adversely affecting patient outcomes.

Impact on mortality and morbidity

The impact of AMR on surgical outcomes is not limited to the increased incidence of SSIs; it also includes a significant rise in mortality and morbidity. Patients with SSIs caused by resistant organisms face higher risks

of complications and death. For example, infections caused by MRSA have been associated with higher mortality rates compared to those caused by methicillin-susceptible strains.
In addition to SSIs, other postoperative infections, such as pneumonia, urinary tract infections, and bloodstream infections, are also becoming more challenging to treat due to AMR. In regions with high levels of AMR, these infections contribute to a substantial burden on surgical patients, leading to longer recovery times and an increased likelihood of surgical revisions or reoperations.

Challenges in antimicrobial stewardship

Antimicrobial stewardship (AMS) in surgical departments is critical in combating AMR, yet it faces significant challenges. Surgical teams have historically been more difficult to engage in AMS programs, often due to a lack of awareness or reluctance to change established practices. Inadequate compliance with surgical antibiotic prophylaxis (SAP) guidelines is a major issue, with studies showing that compliance rates vary widely, often falling below recommended levels.
The overuse and inappropriate use of antibiotics in surgical settings, such as extending prophylaxis beyond the recommended duration or using broad-spectrum antibiotics unnecessarily, contribute to the development of resistance. Effective AMS in surgery requires a multidisciplinary approach, involving surgeons, anesthesiologists, pharmacists, and infection control specialists, to ensure the optimal use of antibiotics and reduce the selective pressure that drives resistance.

Future directions and recommendations

To mitigate the impact of AMR on surgical outcomes, several key strategies should be implemented. First, there must be a stronger emphasis on adherence to evidence-based guidelines for surgical antibiotic prophylaxis. Hospitals should regularly review and update their SAP protocols to reflect the latest evidence and local resistance patterns. Second, AMS programs must be expanded and strengthened in surgical departments, with a focus on education, monitoring, and feedback to ensure appropriate antibiotic use.
Investing in new diagnostic technologies, such as rapid testing for resistant pathogens, can also help guide more targeted antibiotic therapy, reducing the unnecessary use of broad-spectrum antibiotics. Additionally, the development of alternative approaches, such as vaccines or bacteriophage therapy, may offer new avenues for preventing and treating infections in surgical patients.

Strategies for combating AMR in healthcare

Addressing AMR in healthcare settings requires a comprehensive, multifaceted approach that integrates antimicrobial stewardship, infection prevention and control, enhanced surveillance, research and development, and global collaboration. The following strategies outline the key components necessary to combat AMR effectively.

Antimicrobial stewardship programs (ASPs)

ASPs are crucial in optimizing the use of antibiotics to effectively combat AMR in healthcare settings. These programs focus on implementing coordinated strategies that promote the appropriate use of antimicrobials, ensuring that patients receive the right antibiotic, at the correct dose, and for the appropriate duration. By doing so, ASPs play a vital role in reducing the emergence of resistant bacteria and improving overall patient outcomes.

A central aspect of ASPs is the development and implementation of evidence-based guidelines for antimicrobial use. These guidelines are carefully tailored to local resistance patterns and are regularly updated to incorporate the latest evidence. This approach ensures that the use of antibiotics is both effective and appropriate, reducing the likelihood of resistance developing.
In addition to guideline implementation, education and training are integral components of ASPs. Continuous education for healthcare providers is essential, focusing on the principles of antimicrobial stewardship, the risks associated with inappropriate antibiotic use, and the latest best practices. This ongoing education empowers healthcare professionals to make informed decisions that align with the goals of antimicrobial stewardship.
Another critical element of ASPs is the regular monitoring of antibiotic prescribing patterns. This monitoring process is complemented by feedback provided to prescribers, which helps ensure adherence to established guidelines. By offering constructive feedback, healthcare providers are encouraged to continuously improve their prescribing practices, further contributing to the effectiveness of ASPs in combating AMR.

Infection prevention and control (IPC)
IPC measures are fundamental in reducing the transmission of resistant pathogens within healthcare settings. Effective IPC programs are essential for significantly lowering the incidence of HAIs, many of which are caused by resistant organisms.
One of the most effective strategies within IPC programs is promoting strict adherence to hand hygiene protocols among healthcare workers. Proper hand hygiene is a simple yet powerful tool that plays a crucial role in preventing the spread of infections. Ensuring that healthcare professionals consistently practice effective hand hygiene can dramatically reduce the transmission of harmful pathogens.
Another vital component of IPC is maintaining rigorous standards for environmental cleaning and disinfection. Regular and thorough cleaning of healthcare environments is critical to minimizing the risk of pathogen transmission. By ensuring that all areas, especially high-touch surfaces, are disinfected regularly, healthcare facilities can create a safer environment for both patients and staff.
Additionally, implementing isolation procedures for patients who are infected or colonized with resistant organisms is essential in preventing the spread of these pathogens to other patients. Isolation protocols help contain the infection within a controlled area, reducing the risk of cross-contamination and further transmission within the healthcare setting.
By integrating these strategies into a comprehensive IPC program, healthcare facilities can effectively combat the spread of resistant pathogens, protecting patients and reducing the overall burden of HAIs.

Enhanced surveillance
Surveillance is a critical component in the fight against AMR, as it provides the necessary data to monitor trends, detect outbreaks, and guide public health interventions. Effective surveillance systems are indispensable for tracking the prevalence of resistant organisms, monitoring antibiotic usage, and evaluating the success of various interventions.
Participation in both national and global surveillance networks is essential for accurately tracking resistance patterns and facilitating the sharing of critical data across different regions. Networks such as the GLASS enable countries to collaborate, ensuring a more comprehensive understanding of AMR trends worldwide and enhancing the global response to this growing threat.
Integrating data from various sources, including laboratories and hospitals, is another vital aspect of effective surveillance. By combining data from these different points, healthcare systems can conduct comprehensive analyses that provide a more complete picture of resistance patterns. This integration allows for timely

responses to emerging trends, ensuring that public health interventions are based on the most accurate and up-to-date information.

Furthermore, the success of surveillance efforts is greatly enhanced by the timely reporting of findings to healthcare providers and policymakers. Providing regular feedback based on surveillance data supports the implementation of targeted interventions and informs necessary policy adjustments. This approach ensures that healthcare strategies remain dynamic and responsive to the evolving challenge of AMR, ultimately improving outcomes and reducing the spread of resistant organisms.

Research and development (R&D)

Research and development (R&D) play a pivotal role in overcoming the challenges posed by AMR. The continuous evolution of resistant pathogens demands the development of new antibiotics, rapid diagnostic tools, and alternative therapies to effectively counteract this growing threat.

Investing in the research and development of new antibiotics is essential, particularly those that target multi-drug-resistant organisms. As the arsenal of effective antibiotics diminishes, it is critical to replenish it with new, potent drugs that can combat the most resistant strains. This investment not only addresses current gaps but also prepares healthcare systems for future challenges posed by emerging resistant pathogens.

The development of rapid diagnostic tools is equally crucial in the fight against AMR. These tools enable healthcare providers to quickly and accurately identify pathogens and their resistance profiles, facilitating more targeted and effective treatment. By ensuring that the correct antibiotic is used from the outset, rapid diagnostics help reduce the misuse of broad-spectrum antibiotics, thereby minimizing the selective pressure that drives the development of resistance.

In addition to new antibiotics and diagnostics, exploring alternative therapies is an important strategy in addressing AMR. Research into therapies such as bacteriophages, vaccines, and other innovative approaches offers promising avenues for reducing reliance on traditional antibiotics. These alternatives can provide effective treatment options for resistant infections and contribute to a more sustainable approach to managing AMR.

Through dedicated research and development efforts, the healthcare community can stay ahead of the evolving threat of AMR, ensuring that both current and future challenges are met with effective solutions.

Global collaboration and policy development

AMR is a global challenge that demands coordinated international action. The transnational nature of AMR means that no single country can effectively combat it alone; thus, collaboration across nations and sectors is crucial for ensuring a unified and effective response.

Strengthening international partnerships is vital in fostering cooperation and resource sharing among countries. Initiatives such as the Global Action Plan on Antimicrobial Resistance, led by the WHO, play a critical role in aligning efforts worldwide. By working together, countries can pool their knowledge, expertise, and resources to tackle AMR more efficiently and effectively.

The development and enforcement of harmonized policies and regulations on antibiotic use are also essential in combating AMR. These regulations must span healthcare, agriculture, and the environment to limit the spread of resistance across borders. Harmonized policies ensure that all countries adhere to best practices in antibiotic use, reducing the risk of resistant pathogens emerging and spreading globally.

Additionally, capacity building in LMICs is crucial for a comprehensive global response to AMR. Providing technical and financial support to these countries helps them develop and implement robust systems for AMR surveillance, IPC, and antimicrobial stewardship. By empowering LMICs with the necessary tools and knowledge, the global community can enhance its collective ability to address AMR effectively.

Through coordinated international collaboration and the development of unified policies, the global fight against AMR can become more cohesive and impactful, ensuring a stronger and more resilient response to this critical threat.

Conclusion

AMR represents a critical challenge to global health, with far-reaching implications for patient outcomes, healthcare costs, and the efficacy of medical interventions. The rise of resistant pathogens has already led to increased morbidity and mortality, extended hospital stays, and significant economic burdens on healthcare systems. Addressing this complexity requires a comprehensive, coordinated response that integrates AMR strategies into broader healthcare policies.

The urgent need for global action against AMR cannot be overstated. Without immediate and sustained efforts, the world faces the risk of entering a post-antibiotic era where common infections and minor injuries could once again become fatal. It is crucial to develop and implement robust ASPs to optimize antibiotic use and curb the spread of resistance. In parallel, strengthening IPC measures is vital to reduce the incidence of healthcare-associated infections, particularly those caused by multidrug-resistant organisms.

To effectively combat AMR, these strategies must be integrated into wider healthcare policies. This integration should involve developing and enforcing guidelines for appropriate antibiotic use, enhancing surveillance systems to monitor resistance trends, and investing in research and development for new antibiotics and alternative therapies. Policymakers must prioritize AMR as a critical public health issue, ensuring that resources are allocated to support necessary interventions and that regulations governing antibiotic use are rigorously enforced.

Healthcare professionals have a pivotal role in the fight against AMR. Their responsibilities extend beyond individual patient care to the broader community, as their prescribing practices directly influence the development of resistance. Equipping healthcare workers with the knowledge and tools to implement best practices in antibiotic use, infection control, and patient education is imperative.

Continuous professional development and adherence to evidence-based guidelines are essential to ensure that healthcare professionals lead efforts to combat AMR effectively.

In conclusion, combating AMR requires a global, multi-sectoral response, with coordinated efforts from governments, healthcare providers, and the public. By integrating AMR strategies into healthcare policies and empowering healthcare professionals to take a leading role, the impact of AMR can be mitigated, preserving the effectiveness of life-saving antibiotics for future generations. The time to act is now before the consequences of inaction become irreversible.

Competing interests

The author has no financial and non-financial competing interests to declare.

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Chapter 13

Antimicrobial resistance: challenges and prospects in low-and middle-income countries

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Introduction

Antimicrobial resistance is becoming a serious public health threat, if unchecked, AMR is projected to claim approximately 10 million lives annually by 2050, surpassing cancer-related deaths. AMR has dire consequences, especially for Low- and Middle-Income Countries (LMICS). AMR will continue to devastate global health security, increase mortality rates, prolong illnesses, and overwhelm healthcare systems. LMICs face unique challenges in terms of insufficient political commitment, limited resources, poor regulatory frameworks, lack of awareness of one health, insufficient workforce capacities, and poor IPC, WASH and vaccine coverage. This chapter provides an in-depth examination of the drivers of AMR in resource-limited settings/ LMICs, highlighting the unique challenges faced by these regions. Subsequently, the chapter explores potential approaches and interventions tailored to address AMR in LMICs, taking into account their specific constraints and limitations. By addressing these challenges and implementing effective strategies, LMICs can make significant progress in combating AMR and protecting global health security.

Global burden of antimicrobial resistance

Antimicrobial resistance (AMR) poses a grave threat to global public health, necessitating urgent attention. The alarming rise of resistant pathogens imperils human well-being, constituting a silent pandemic. Addressing this multifaceted issue demands collective engagement from diverse stakeholders. To combat AMR effectively, we must adopt an integrated holistic approach that involves the interconnectedness of human, animal, and environmental health. A 2019 study revealed alarming statistics on the global impact of AMR: approximately 1.27 million deaths annually are directly attributed to AMR, with an additional 4.95 million deaths linked to AMR. In another study from 1990-2021, the burden was estimated as 1.91 million (1.56–2.26) deaths attributable to AMR and 8.22 million (6.85–9.65) deaths associated with AMR could occur globally in 2050. The study highlighted that the major burden with the highest mortalities will be in South Asia, Latin America and the Caribbean.

Antimicrobial resistance and resource-limited settings

AMR situation is a serious concern in LMICs. The challenges in LMICs are aggravated by many factors. Already LMICs face high burden of infectious diseases including tuberculosis, HIV/AIDS, malaria, pneumonia, diarrhea, measles, and influenza. The added challenge of drug resistance to treat these infections is alarming. LMICs have inadequate access to healthcare, poor sanitation and hygiene, malnutrition, conflict and displacement, climate change, and socioeconomic challenges such as poverty, limited education, overcrowding and weak health systems. The limited availability of essential medicines, poor supply chain management, and inadequate healthcare workforce further compound the issue. Moreover, the overuse and misuse of antibiotics in LMICs have accelerated the emergence of antimicrobial resistance, making infections harder to treat. As a result, LMICs account for a significant proportion of global infectious disease-related morbidity and mortality, with vulnerable populations such as children, pregnant women, and those living with chronic conditions being disproportionately affected.

LMICs face significant challenges in accessing vaccines and immunization programs, leaving millions vulnerable to preventable infectious diseases. Limited financial resources, inadequate healthcare infrastructure, and logistics constraints (cold chain systems, storage of vaccines) hinder the availability and distribution of vaccines. As a result, LMICs often struggle to achieve high vaccination coverage. This vaccination gap leads to grave consequences in terms of morbidity and mortality. Conflict and displacement lead to the destruction of healthcare infrastructure, displacement of healthcare workers, and disruption of medical supply chains limiting access to essential medicines, including antibiotics. Overcrowding in refugee camps and poor living conditions facilitate the spread of infectious diseases. The displaced populations often carry resistant infections across borders, posing a global health security risk. There is a lack of regulation on the misuse of antimicrobials. Over-the-counter availability of antimicrobials is a serious concern. Injudicious use of antimicrobials is largely seen in clinical treatment, agricultural practices, animal healthcare, and the food system.

Drivers of AMR in resource-limited settings

Resource-limited settings face many challenges that fuel the rise of AMR. Inadequate facilities, poor sanitation, and insufficient regulations exacerbate the issue. Understanding this complex interplay is critical to developing effective AMR strategies. Key drivers related to AMR in resource-limited settings/ LMICs are presented below (**Figure 1**).

Insufficient political commitment

The insufficient political commitment to address AMR in LMICs poses a significant barrier to effective control and mitigation. LMIC governments have yet to prioritize AMR action. Generating the resources and building multisector collaborations is a challenge. The engagement of external stakeholders needs to be channeled. The poor regulatory frameworks for diagnostics, antimicrobials, and treatment are some examples that show the lack of political will and commitment. National Action Plans on AMR have been developed, but the cost of the plans is often neglected using standardized tools.

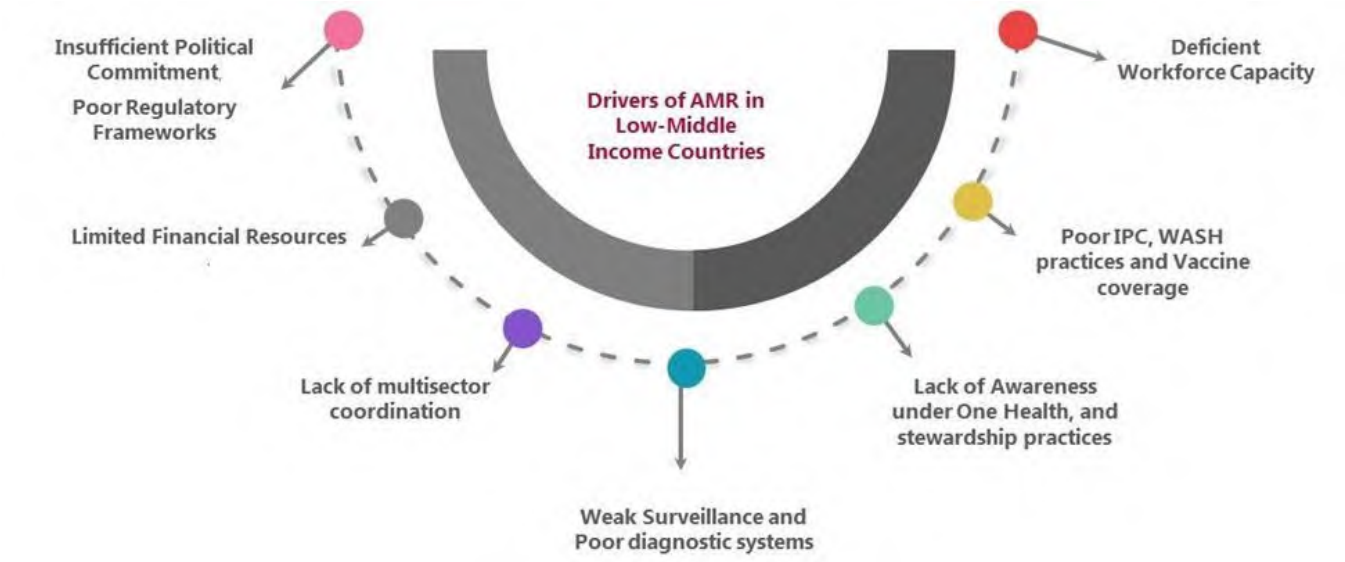

Figure 1. Key drivers related to AMR in resource-limited settings/ LMICs.

Limited financial resources

Controlling AMR requires significant financial investments to address the complex and multifaceted nature of this global health threat. Funds are essential to support research and development of new antimicrobials, diagnostics, and vaccines, as well as to strengthen healthcare systems and improve infection prevention and control practices. Moreover, effective AMR surveillance, monitoring, and reporting require substantial resources to establish and maintain robust data collection and analysis systems. Adequate funding also enables the development of evidence-based policies, guidelines, and training programs for healthcare professionals. Implementing comprehensive National Action Plans to tackle AMR demands substantial financial investments and multidisciplinary expertise. Regrettably, numerous LMICs struggle to allocate sufficient funds, severely impeding their capacity to execute these critical plans and address the burgeoning AMR threat.

Poor regulatory frameworks

In LMICs regulations and policies regarding antimicrobial use exist, but the real challenge lies in their ineffective implementation. The lack of monitoring and evaluation frameworks allows these policies to be easily disregarded, ultimately undermining the entire system. For instance, regulatory authorities in some countries require antimicrobials to be dispensed only with a prescription from a qualified healthcare professional. However, in reality, people can still access these medications over the counter without a prescription. This disregard for policy goes unchecked, exacerbating the issue. Furthermore, LMICs often lack policies regulating the manufacture, importation, and distribution of substandard or falsified medicines. This legislative gap enables the circulation of harmful or ineffective medications, contributing to the rise of antimicrobial resistance. Effective policy implementation and outcome evaluation are crucial to address these challenges. It can be achieved through robust monitoring systems, regular assessments, and collaboration between advocacy organizations, researchers, and policymakers. By strengthening regulatory frameworks and ensuring their enforcement, LMICs can combat antimicrobial resistance and promote responsible antibiotic use. The escalating AMR crisis is further complicated by a declining interest in developing new antibiotics, posing a significant threat to global health. Even when new antibiotics are discovered, numerous barriers hinder their timely availability in LMICs. Regulatory hurdles, fragile health systems, and unreliable supply chains delay market entry, limiting access to these life-saving medications. In many countries, antibiotics are used for treatment,

disease prevention, or growth promotion in livestock and crops. The inappropriate use of antibiotics in agriculture leads to the emergence of antibiotic-resistant bacteria and resistance genes that can be passed on to humans via the food chain or by direct contact with animals. The weak regulation in the animal, environmental and agriculture sectors further complicate the AMR issue.

Lack of multi-sectoral coordination

The implementation of National Action Plans to combat AMR requires a multifaceted approach and multisectoral coordination. All resource-limited settings face the challenge of insufficient collaboration between human and animal health, agriculture, environment, education, and research sectors. There is a lack of comprehensive policies and frameworks to guide multisector coordination. Various sectors have weaknesses in terms of limited capacity and resources for effective implementation.

Lack of awareness under One Health and poor stewardship practices

In LMICs, a significant obstacle in combating AMR is the pervasive lack of awareness among healthcare professionals, patients, and the general public. Limited understanding of AMR's causes, consequences, and prevention strategies hinders effective management and control. Healthcare providers often lack training on proper antibiotic prescribing practices, while patients and communities are unaware of the risks associated with the misuse and overuse of antibiotics. This knowledge gap perpetuates harmful practices, such as self-medication and inappropriate antibiotic use, exacerbating the AMR threat.

AMS programs, which promote responsible antibiotic use, are often lacking or ineffective, leading to unchecked prescribing and dispensing practices. Healthcare providers frequently prescribe antibiotics unnecessarily or inappropriately, while patients and caregivers often demand antibiotics for viral infections. Furthermore, inadequate regulation and oversight of pharmaceutical sales facilitate over-the-counter antibiotic access, exacerbating misuse.

Weak surveillance systems

In LMICs, the development of surveillance systems is still underway, hindering the timely generation of critical evidence on AMR trends and patterns. This lack of data significantly impacts policy development and implementation, as evidence-based decision-making is compromised. Effective surveillance is crucial for tracking local antibiotic consumption and hospital-acquired infections, but these systems are yet to be implemented in many LMICs. As a result, vital information is not readily available to guide antibiotic therapy at institutional levels or inform policy formulation at national levels. To combat AMR effectively, LMICs must prioritize developing and strengthening surveillance systems, enhancing data collection and analysis capacities, and improving reporting and feedback mechanisms. By addressing these gaps, LMICs can generate quality evidence to inform policy, optimize antibiotic use, and ultimately mitigate the AMR threat.

Poor IPC, WASH practices and vaccination coverage

Many countries have inadequate IPC practices that significantly contribute to the spread of resistant pathogens. Weak IPC measures, such as insufficient hand hygiene, inadequate sterilization, and poor waste management, facilitate the transmission of resistant pathogens. Overcrowded and poorly ventilated healthcare facilities, lack of personal protective equipment, and insufficient training for healthcare workers further exacerbate the issue. These IPC deficiencies lead to increased hospital-acquired infections, higher morbidity and mortality rates, prolonged hospital stays and increased healthcare costs.

In many LMICs, lack of access to WASH facilities results in a vicious cycle of high burdens of communicable diseases, increased antibiotic consumption and the emergence of AMR. Vaccination has a positive impact on

population health, productivity and education and adds value by reducing disease burden on individuals, families and communities. By preventing the occurrence or spread of bacterial infections, vaccination reduces antibiotic consumption and the emergence of AMR. Factors responsible for low vaccine coverage include distrust of parents and caregivers in vaccination, considerable distance between the home and the vaccination center, language barriers and inadequate infrastructures to maintain the cold chain and adequate supply of vaccines.

Insufficient workforce capacity

There are significant workforce capacity gaps, hindering effective management at many levels. Insufficient training in antimicrobial stewardship, diagnostic practices, and other essential skills leaves healthcare personnel ill-equipped to address AMR. This shortage affects various levels, from community health workers to laboratory professionals and clinicians. Key workforce capacity gaps include limited expertise in antimicrobial stewardship and prescribing practice, inadequate training in diagnostic techniques and interpretation, insufficient knowledge of IPC, lack of epidemiology and surveillance skills, and inadequate laboratory capacity and quality assurance.

Consequences of these gaps are misdiagnosis and inappropriate treatment, overuse and misuse of antibiotics, delayed detection and response to AMR outbreaks, and compromised patient safety and outcomes. To bridge these gaps, LMICs should invest in healthcare workforce development and training programs, strengthen education and professional development opportunities, and enhance laboratory capacity and quality assurance.

Lack of access to quality laboratory services

Diagnostic systems for detecting AMR are often scarce and unevenly distributed, creating significant challenges in identifying and tracking resistant pathogens in LMICs. The shortage of quality laboratory services presents a dual challenge: inadequate access and inequitable access. From the perspective of inadequate access, many LMICs face significant shortages in laboratory infrastructure, trained personnel, and essential equipment. This results in limited capacity for accurate diagnosis, surveillance, and monitoring of diseases, including AMR. Consequently, healthcare providers often rely on symptomatic diagnosis, leading to misdiagnosis and inappropriate treatment. From the perspective of inequitable access, even where laboratory services exist, they are often concentrated in urban areas, leaving rural and marginalized populations without access to these essential services. This disparity exacerbates health inequalities, as vulnerable populations are forced to rely on makeshift or private facilities, which may provide substandard care. Furthermore, inequitable access disproportionately affects disadvantaged groups, including women, children, and the poor, who are already more susceptible to health risks.

Outcomes of AMR in case of inaction

It is estimated that by the year 2050, there might be approximately 10 million deaths annually attributed to drug-resistant infections. The burden on the economy due to AMR will reach USD 100 trillion by 2050. Uncomplicated infections and minor injuries could once again become life-threatening, while major procedures like organ transplants, chemotherapy, or hip replacements may become extremely risky. Low- and middle-income countries are expected to face more burdens due to weak health systems and multiple challenges. The impact will be seen across One Health including healthcare, animals, food systems, agriculture, aquaculture, and the environment.

The global health security implications of AMR are far-reaching and alarming. AMR can spread rapidly across borders through international travel and trade, making it a pressing concern for global health security. It can hamper the achievement of Sustainable Development Goals, particularly those related to health, well-being, and economic growth.

Recommendations to combat AMR in resource-limited settings

Enhance political commitment

The first major requirement is to develop strategies to enhance political will and commitment for AMR. There should be increased advocacy on AMR. There is a need to build collaborations between key policymakers, influencers and major stakeholders. There is a need to enhance writing and develop policy briefs and position papers. The political approach can be improved by working on an economic analysis of AMR. The studies on cost-benefit analyses of AMR interventions can highlight the role of interventions. The work towards estimation of the economic impacts of AMR on healthcare systems should be carried out. Leadership should play a key role in creating an enabling environment for stakeholders and interventions. The relevant task forces or committees should develop AMR action plans and strategies and review the measures periodically. Monitoring and Evaluation help to track progress on AMR policy implementation. It can help to evaluate the effectiveness of AMR interventions. Key Performance Indicators should be defined as related to AMR policy development and implementation, antibiotic use and prescribing practices, AMR surveillance and reporting and research and development investments.

Strengthen healthcare systems

Improvement is required in healthcare infrastructure, diagnostics, and human resources at hospitals. Outdated hospital facilities, inadequate equipment, and insufficient infection control measures hinder effective patient care and exacerbate the spread of resistant pathogens. Limited access to accurate and timely diagnostics further complicates treatment decisions, while shortages of skilled healthcare professionals compromise care quality. To address these challenges, hospitals require upgraded infrastructure, advanced diagnostic tools, and robust human resource development programs. Investing in modern facilities, laboratory enhancements, and staff training will enhance patient outcomes, reduce AMR transmission, and strengthen healthcare systems. Moreover, integrating technology, such as electronic health records and data analytics, will improve efficiency and inform evidence-based decision-making.

Increase advocacy on AMR

Major step to control AMR in this crucial time is creating awareness on the issue at all levels. Awareness campaigns can educate healthcare professionals, patients, and the general public on the risks of antibiotic overuse and misuse, proper hand hygiene, and infection control practices. By understanding the consequences of AMR, individuals can adopt responsible behaviors, such as completing prescribed antibiotic treatments and avoiding self-medication. Furthermore, awareness initiatives can promote policy changes, encourage research and development of new antimicrobials, and foster intersectoral collaboration among healthcare, agriculture, and veterinary medicine.

Enhance surveillance

Enhanced surveillance is critical for combating AMR, protecting public health, and ensuring global health security. By strengthening surveillance systems, we can monitor AMR trends and patterns, identify knowledge gaps and research priorities, evaluate the effectiveness of interventions, and most importantly generate evidence for policy development. Effective surveillance involves laboratory-based surveillance for antibiotic resistance, hospital-based surveillance for healthcare-associated infections, community-based surveillance for antibiotic use and resistance, and data sharing and analysis through global networks.

Promote rational antibiotic use

There should be advocacy towards rational use of antimicrobials. It can be achieved by implementing prescription guidelines, public awareness campaigns, and antibiotic stewardship programs. Standardized guidelines ensure healthcare professionals prescribe antibiotics judiciously, while public awareness campaigns educate patients on the risks of misuse and overuse. Antibiotic stewardship programs monitor and optimize antibiotic use in healthcare settings, minimizing unnecessary prescriptions.

Infection prevention and control, WASH and vaccine

Improving IPC practices, such as proper hand hygiene, sterilization, and isolation, prevents the spread of resistant pathogens. Adequate WASH infrastructure ensures a clean environment, reducing the risk of healthcare-associated infections. Vaccination plays a vital role in preventing infections, thereby reducing antibiotic use and subsequent resistance.

Research and development

There is a need to promote and encourage innovation in antibiotic development and alternative treatments. The dwindling pipeline of new antibiotics necessitates urgent investment in R&D to develop novel antimicrobials, vaccines, and diagnostic tools. Some innovation in antibiotic development involves identifying new targets and mechanisms of action, exploring alternative approaches, such as bacteriophage therapy and antimicrobial peptides, developing broad-spectrum antibiotics effective against multiple resistant pathogens, immunotherapies, and gene editing technologies. There must be more collaborations to provide funding and incentives for R&D, streamline regulatory processes, and promote public-private partnerships.

Conclusion

The global burden of AMR is escalating, with devastating consequences, particularly for resource-limited settings. If left unchecked, AMR poses a monumental threat to global health security, exacerbating mortality rates, prolonging illness, and crippling healthcare systems. LMICs face unique challenges, including limited resources, inadequate infrastructure, and insufficient access to quality healthcare, making them disproportionately vulnerable to AMR's impacts. However, concerted efforts and strategic approaches can effectively mitigate and combat AMR in these regions. The global community must prioritize AMR mitigation in LMICs, ensuring equitable access to effective antimicrobials, diagnostics, and treatments.

Competing interests

The author has no financial and non-financial competing interests to declare.

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Chapter 14

Barriers to combat antimicrobial resistance in European countries

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Introduction

Antimicrobial resistance (AMR) has become one of the three main global health problems worldwide. The emergence and spread of antimicrobial-resistant microorganisms (bacteria, fungi, parasites and viruses) have led to this situation named "the silent pandemic". A study published in 2016 estimated that, if measures were not taken, more than 10 million people could die from infections caused by AMR microorganisms, 2 million more than by cancer. The same year, AMR was the focus of a high-level United Nations (UN) general assembly, leading to the inclusion of an AMR-specific indicator as a Sustainable Development Goal. More recently, it was estimated the burden of bacterial AMR in 2019, finding that 1.27 million deaths were attributable to AMR and 4.95 million deaths were associated with AMR. A recent study reviewing the AMR-attributable and associated deaths since 1990 forecast that the target established by the UN for 2030 according to the global burden of AMR will not be accomplished if no added efforts on drug development, infection prevention, better treatment of severe infections, and better access to currently available antibiotics are taken.
AMR is not only a human problem but also for animals and for the environment where they live, being human and animal health interdependent and closely linked to the ecosystems in which they coexist. Thus, to combat AMR it is necessary a One Health vision taking into account that human and animal health are interconnected with the surrounding environment.

Actions taken and general barriers

To tackle AMR many European countries have launched National Action Plans (NAPs) against AMR. NAPs are implemented or are in progress to be implemented/updated in 28 of the 29 European countries. Although most of them follow a One Health approach, some continue focusing on the human and animal health sectors and tend to not cover the environmental dimension.
However, in a recent study, several barriers have been identified in the implementation of these NAPs being different for each country.

In general, the most common barriers affecting the implementation of NAPs are those related to government institutions and policy, including the lack of coordination between the different sectors and ministries involved in this issue. Another general barrier found in many European countries is the lack or insufficient funds dedicated to the implementation of these programmes. At the sector level, there is no homogeneity in the collection of data for systematic monitoring and surveillance of AMR, even in antibiotic consumption data.

Human health

In order to identify the effectiveness of the measures taken to reduce AMR, three main interventions must be tackled: Infection Prevention and Control (IPC), Antimicrobial Stewardship (AMS), and AMR Awareness.

Infection and prevention control (IPC).

IPC guidelines and legislation have been developed in most European countries, and are the base of the IPC programmes implemented by the healthcare institutions. However, due to this "freedom" in the development and implementation of IPC programmes in each hospital, the monitoring of compliance with IPC programmes and the reporting indicators, such as cases of infections caused by multidrug-resistant bacteria, are very diverse. These facts lead to a lack of harmonized indicators for monitoring and evaluating IPC measures, as well as limitations in the methodologies to collect, process and use surveillance data, at both national and regional levels.

Other barriers that affect the development and implementation of IPC measures, especially in hospitals, are the lack of continuity of the staff, limited awareness and education in terms of IPC and AMR, and, as commented previously, insufficient funds dedicated to IPC implementation. In the case of long-term care facilities, this situation is even more heterogeneous. Some of the measures that should be addressed in the NAPs regarding the IPC interventions should be:

- Implementation of training sessions for healthcare professionals and awareness campaigns to improve compliance with the IPC strategies.
- Improving and homogenizing protocols for the identification of high-risk individuals to prevent infectious diseases.
- Improving and homogenizing protocols regarding the sanitation and sterilization of health facilities and periodically monitoring the aseptic conditions of surfaces and air of these resources.
- Engaging the community to raise awareness, involving them in decision-making regarding AMR, thus promoting a sustainable behaviour change.

Antimicrobial stewardship (AMS)

Most European NAPs consider AMS as an important part of combating AMR. However, in many cases, AMS teams in hospitals are formed by professionals who accept to form part of these teams in a voluntary manner because they consider this area a priority. In addition to this, AMS is not considered a priority at the political level leading to insufficient funds dedicated to these programmes, and a lack of harmonized AMS strategies within and between hospitals.

As in the case of IPC, there is also a lack of an integrated system for collecting the data on AMs in a harmonized way at the national and regional levels, and not enough education and awareness among the clinical staff. There are some European countries where prescriptions are not automatised and, therefore, their control in these countries and/or regions is impossible. In recent years, supply shortages and limited availability of narrow-spectrum antimicrobials are suffering.

Finally, an important behavioural barrier is the pressure from patients on medical doctors to prescribe antibiotics. In order to achieve a behavioural change in this sense, some European projects are being developed to improve patient engagement in the treatment of infectious diseases (7).
Regarding the AMS interventions, some of the proposed measures that should be taken into account in the NAPs are:

- Create a homogenous European repository of the AMR stewardship of infectious diseases in the different health facilities.
- Create a European level Committee to monitor and periodically report and update the treatment protocol of bacterial infections according to the resistance prevalence rates of each microorganism to each antimicrobial family.
- Design of awareness campaigns on the importance of AMS and good practices focused on healthcare professionals.
- Ensure regular supply and availability of narrow-spectrum antimicrobial agents.

AMR awareness

This is an important area to combat AMR and must be directed to both health professionals and the general public. In terms of healthcare professionals, there is a lack of AMR awareness and education during their respective formation. This lack of awareness is most notable among primary care physicians who, in addition, are submitted to the patient pressure for prescribing antibiotics. In terms of the general public, there is a lack of knowledge on AMR, its importance, when and how they have to take antibiotics, why it is important to do all the treatment with the correct dosages, etc. As a means to offset this gap, it would be necessary that NAPs include training programmes for the general public addressed to different levels of understanding or even by age ranges.
Some of the measures that should be addressed in the NAPs regarding AMR awareness interventions should be:

- Develop European guidelines for the diagnostic of bacterial infections according to the ones more prevalent in each country and to the resistance prevalence rates of each antimicrobial family in different settings.
- Design of awareness campaigns on the importance of AMR awareness and good practices addressed to healthcare professionals and the community.

Animal and environmental health

As we previously commented, in order to combat the AMR problem, it is necessary to act under the One Health vision, involving animal and environmental health.
The European Union (EU) has been the main driver promoting anti-AMR practices in Europe. This has been achieved through the firm adoption of the One Health approach, by raising awareness and increasing understanding of AMR, and by improving cooperation and coordination between Member States in the fight against AMR. In 2017, The European Commission (EC) approved an AMR action plan entitled A European One Health Action Plan against Antimicrobial Resistance). The principal objectives of this plan were as follows: to strengthen the surveillance, control and prevention of AMR; to raise awareness about the problem; to promote a better understanding of the role of the environment; to enhance coordination among EU member countries; and to improve compliance with EU rules aimed at combating AMR. With the approval of the

Council Recommendation on stepping up EU actions to combat antimicrobial resistance in a One Health approach by the EC in April 2023, the EU committed to expanding the 2017 One Health plan and taking additional action, maximizing synergies and fostering joint action. The EU initiatives with the greatest impact come under the Common Agricultural Policy (CAP), which includes a set of agricultural and environmental practices that professionals can apply voluntarily on their farms to contribute to biodiversity, natural resources and the protection of the environment. These practices are summarized in a set of nine standards called the Good Agricultural and Environmental Conditions (GAEC). Professionals who comply with CAP requirements can access certain subsidies and direct payments. There are also many European regulations and directives governing all stages of animal food production and limiting drug residues in both water and soil.

However, some points should be improved: the high consumption of antibiotics in animals for treatment as prophylaxis; the lack of implementation of new IPC measures in livestock, such as vaccination and isolation of infected animals; the insufficient involvement of food safety and health authorities in the implementation of more strict measures along the food processing chains. Nevertheless, all these measures imply the investment of new funds that are not always available. As in the case of human health, there is a lack of an integrated data collection system for surveillance at the European, national, and regional levels. Finally, there is a lack of monitoring and surveillance protocols for AMR in the case of wastewater treatment plans. Thus, there is a lack of clear standards that set maximum values for antibiotic-resistance genes (ARG) and antibiotic-resistant bacteria (ARB) in raw sewage and wastewater effluents.

Conclusion

The implementation of well-designed NAPs involving the One Health vision is one of the main measures to combat AMR. This includes the enforcement of a systematic monitoring and surveillance system in all European countries at both national and regional levels in the three levels of intervention in a One Health approach, as well as the homogenization of IPC and AMS measures among all the health centers. To have success, the involvement of professionals from the different sectors (human health, animal health and environmental health) and more efforts in awareness directed to both professionals and the general public should be a priority. All these measures should be accompanied by greater public funds as well as stricter regulations to ensure compliance.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 15

The challenges posed by antimicrobial resistance in Africa

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Introduction

Antimicrobial resistance (AMR) is recognized as one of the top ten public health threats facing humanity, making it a global health challenge in the 21st Century. AMR occurs when microorganisms such as bacteria, viruses, fungi, and parasites no longer respond to antimicrobial drugs that were once effective. The resulting drug resistance leads to the ineffectiveness of antibiotics and other antimicrobial medicines, challenging treatment efficacy and escalating the risk of disease spread, severe sickness, disability, and mortality.
Africa bears a significant burden of infectious diseases, accounting for approximately 95% of malaria deaths, 70% of people living with HIV, and 25% of TB deaths globally.
Major drivers of AMR in the region include the overuse and misuse of antimicrobials in human, health, animal health and food systems, migration, suboptimal vaccination rates, and environmental contamination from hospital and pharmaceutical effluents. Additionally, there is a lack of access to quality-assured antimicrobials and diagnostics, compounded by inadequate knowledge about AMR. Unlike high-income countries, where indiscriminate antimicrobial use is the primary factor driving AMR, African countries face additional challenges, including a lack of access to clean and safe water, poor Water, Sanitation, and Hygiene (WASH) programs, inadequate infection prevention measures, and suboptimal vaccinations for preventable diseases. One in three hospitals in the region lacks clean, safe running water, and one in eight people defecate openly due to inadequate sanitation.

Burden and impact of AMR in Africa

The impacts of AMR are far-reaching, posing threats to the achievement of the Sustainable Development Goals (SDGs) and Universal Health Coverage (UHC), representing a significant public health challenge in Sub-Saharan Africa. In 2021 the Global Research on Antimicrobial Resistance (GRAM) study identified the highest burden in low-resource settings, which face the greatest burden of infectious diseases and have weaker health systems.

The study indicated that globally, between 1.14 million and 4.71 million people died because of bacterial antimicrobial resistance. 21.36 million sepsis-related deaths were recorded of these 5.17 million (25% of total deaths) people died in Sub-Saharan Africa due to sepsis, between 209,245 and 923,373 people died because of bacterial antimicrobial resistance.

In addition to death and disability, AMR carries substantial economic implications at personal, national, and global levels. If left unchecked, the AMR crisis will push an additional 28 million people into poverty, disproportionately affecting the world's poorest communities in low- and middle-income countries.

In response to the serious implications of AMR for global public health, The World Health Assembly adopted the Global Action Plan on AMR, providing a blueprint to guide countries in developing and implementing national action plans (NAPs) on AMR. The GAP outlines strategic five objectives: (i) to improve awareness and understanding of AMR; through effective communication, education and training; (ii) to strengthen the knowledge and evidence base through surveillance and research; (iii) to reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures; (iv) to optimize the use of antimicrobial medicines in human and animal health; (v) and to develop the economic case for sustainable investment for the needs of all countries and to increase investment in new medicines, diagnostic tools, vaccines and other interventions However, the adoption and implementation of AMR interventions in Africa have been limited due to misalignment of priorities, lack of resources, and inadequate coordination. From self-assessment reports of the 41 countries that responded to the 2021 TrACSS, 35 (85%) developed NAPs. Fifteen 15 (37%) had functional AMR multisector working groups. 55% (21/41) of countries were generating data nationally on AMR surveillance. In addition, 83% of countries reported having laws and regulations on the prescription and sale of antimicrobials, however only 32% (13/41) reported having national systems for monitoring antimicrobial use. On prevention and control of infections, only twenty-three (58%, 23/41) reported having Infection Prevention and Control (IPC) programs implemented at select health facilities.

Despite the challenges and resource constraints, countries in Africa have made significant strides in implementing specific objectives within NAPS developed such as antimicrobial stewardship and surveillance, with 57% of African countries self-reporting having adopted the AWaRE (Access, Watch, Reserve) classification of antibiotics for the National Essential Medicine Lists (NEMLs), surpassing the global average of 47%. These improvements highlight the continent's potential and ongoing efforts to combat AMR through comprehensive and coordinated strategies.

The implementation of AMR One Health National Action Plans (NAPs) presents a significant challenge in Africa. From the reports, progress has been mixed, with some countries initiating activities across various pillars, while others have not started implementing their plans. Implementation has been significantly hindered due to the lack of funding, where the financial requirements for an effective AMR response in Africa are estimated to be between USD 2-6 billion per year compared to an estimated annual budget for AMR NAPs of around USD 100 million, indicating a substantial funding gap that requires support from governments and the international community.

Challenges of AMR in Africa

Inadequate surveillance systems and data gaps for antimicrobial surveillance use and consumption

Limited AMR data. One of the most critical challenges in addressing AMR in Africa is the lack of robust surveillance systems to track and monitor antibiotic use and resistance patterns. Without reliable data, governments and healthcare providers cannot accurately assess the extent of the problem or develop targeted interventions. Few countries have national AMR surveillance programs, and the infrastructure to support microbiology testing is limited. For countries in Africa, robust surveillance systems would require enhancing coverage of the population, access to uninterrupted quality assured laboratory services, implementation of adequate diagnostic stewardship to ensure uptake of laboratory services and strong reporting systems with reliable feedback mechanisms. Data from the WHO Global Antimicrobial Resistance Surveillance System (GLASS) indicate that while as many high-income countries meet these requirements through systematic continuous data collection and analysis from routine clinical practice, most LMICs are not yet able to generate quality representative data to inform national policy development, influence practice and behaviour change and evaluate trends of resistance, consumption and use. This lack of quality representative data ultimately presents an obstacle to detection and response to emerging resistant strains, implementation of targeted interventions and the effectiveness of development treatment guidelines. Some of the gaps in laboratory capacity include the absence of adequate laboratory infrastructure and expertise to detect pathogens, diagnose infections and perform susceptibility testing. Inadequate microbiology laboratory Capacity to support AMR surveillance across the sectors, lack of integrated surveillance systems and Inadequate infrastructure to support surveillance systems for AMR, AMU and AMC across human, animal and environmental sectors has been demonstrated through the Mapping Antimicrobial where only 1.3% of the 50,000 medical laboratories forming the laboratory networks of the 14 participating Member States in Africa conduct bacteriology testing, and only a fraction could handle the scientific processes needed to evaluate AMR. In eight of these countries, more than half of the population is out of reach of any bacteriology laboratory. In addition, clinical and treatment data are not being linked to laboratory results, making it hard to triangulate the drivers of AMR.

Overuse and misuse of antimicrobials

Despite a legal framework existing in many countries through the National Regulatory Authorities in African countries that prohibit the dispensing of antibiotics without a valid medical prescription, over-the-counter (OTC) sales of antibiotics are very common. Pointing towards challenges in the enforcement of regulations and the capacity of health systems to meet the population's needs appropriately. The misuse and overuse of antibiotics are prevalent in both human and animal health sectors. In healthcare, antibiotics are often prescribed without adequate diagnosis, with patients demanding antibiotics even for viral infections where they are ineffective. Even where policies exist, the enforcement is often weak, leading to non-compliance with antimicrobial stewardship programs.

Additionally, the widespread practice of self-medication and over-the-counter antibiotic sales further compounds the problem. Purchasing of antibiotics without a prescription across Africa varies considerably both within and across countries but is still considerably high with some African countries reporting that 100% of community pharmacies dispense antibiotics without a prescription. This has been attributed to aspects such as affordability of healthcare services as determined by cost of medicines and physician costs as well as travel costs to facilities and possible loss of earnings due to long waiting times to see a healthcare provider in healthcare facilities. Other challenges that compound overuse and misuse of antimicrobial agents include the availability of substandard or falsified antibiotics in the market. This is compounded by weak regulatory

systems, limited local manufacturing capacity, and inadequate quality assurance testing and lack of post-market surveillance of antimicrobials.

In agriculture, antibiotics are used indiscriminately to promote growth in livestock, contributing to the development of resistant bacteria that can be transmitted to humans through the food chain. Within most LMICs, the combined realities of underfunded veterinary healthcare systems and limited regulatory capacities constrain efforts to promote prudent antimicrobial use and control AMR in the agricultural sector. Available studies generally find that farmers administer antimicrobials themselves, and mostly without prescriptions or using input from animal health professionals, as well as engaging in other non-prudent practices, such as violating antimicrobial withdrawal periods. Frequent and unregulated use of antimicrobials (AM) in livestock could be a factor contributing to inappropriate use of antimicrobials in animals. Antimicrobials are important tools for herd management, but how they are used varies with species, local conditions, and cultural practices. The large herds typical of pastoralist groups graze across considerable distances and may experience more exposure to pathogens resulting in greater motivation for AM use, thereby promoting the emergence and selection of AMR. When these herds are found in remote locations, professional veterinary care is probably limited.

Limited access to essential medicines

Even with appropriate use of existing antibiotics, new drugs are needed as this is made possible, however, in many countries, even existing antibiotics are not available or accessible to patients who need them due to cost implications, regulatory challenges, frequent stockouts and counterfeit and sub-standard drugs. Some countries face intermittent supply of quality antibiotics, while counterfeit medications contribute to ineffective treatment and resistance. Addressing a wide range of factors affecting the availability, safety, quality, affordability, and pricing of critical medicines such as antimicrobials is necessary to increase access to them in healthcare institutions. From the MAAP report, newer more effective medicines to treat more resistant infections were not available, suggesting limited access to some groups of antibiotics in Africa.

Diagnostic, prescribing medicine, dispensing and responsible use

One of the critical elements for improving antimicrobial stewardship to enhance appropriate use and drug development is the rapid and accurate identification of pathogens, as well as rapid and accurate antimicrobial susceptibility testing. Effective antimicrobial stewardship is closely linked with the ability to make correct diagnoses. Incorrect diagnoses can lead not only to overuse or misuse of antibiotics, particularly the critical broad-spectrum antibiotics but also to poor outcomes for patients resulting from failure to treat the actual disease present. A poor supply chain to guarantee the availability of recommended antimicrobials is critical for appropriate use. Inadequate staffing, insufficient training in microbiology skills and supervision of health personnel, and lack of access to rapid diagnostic facilities to support treatment decisions. There is a need for continuous interaction between the laboratory, clinicians and patients on the availability of diagnostic tests and the establishment of facility-level structures like Medicines and Therapeutics Committees (MTC) stewardship committees to guide diagnostic and prescribing patterns and requirements. In addition to build a robust supply chain challenges exist within the regulation and manufacturing aspects in Africa with weak enforcement of regulations or practices, stringent regulations and guidelines impending availability of new drugs from the manufacturing standpoint and weak enforcement of policies and guidelines for Good Manufacturing Practices (GMP).

Poor infection prevention and control (IPC) and biosecurity measures

Despite infection prevention and control (IPC) evidence-based practices (EBP) to minimize the transmission of HAIs, many healthcare systems in SSA are challenged to implement them as recommended in the AMR Global Action Plan (GAP) in 2015.

IPC programmes are mostly not enabled to function effectively in Low-Income Countries, since IPC expertise and staffing, as well as financial support, are essential to drive and sustain action. Compared to over 80% of facilities in HICs, at all care levels, which met all but one of the built environment minimum requirements fewer healthcare facilities in LICs reported that they had functioning hand hygiene stations at all points of care (24%), functioning toilets or latrines (53.6%), an energy/power supply (55.2%), continuously available water services (67.71%) and PPE (53.8%). For the WHO African Region, according to the country self-assessments through TrACCS (World Health Organization, 2022), in 2020–2021 (69), 42.5% (17/40) of countries in the WHO African Region either did not have an IPC programme or plan, or they had one but had not fully implemented it. Only 17.5% (7/40) of countries had an IPC programme supported by plans and guidelines implemented nationwide. From the report countries in the African Region lack effective IPC programs with many facilities having inadequate infection control practices, increasing the risk of the spread of resistant infections. Bottlenecks that have hindered the effective implementation of prevention and control interventions in Africa to reduce antimicrobial resistance include competing priorities for investment resulting in the lack of financial investments in IPC weak legal frameworks to support compliance to IPC standards, weak infrastructure and supplies including those supporting water sanitation and hygiene to support optimal implementation of IPC programs, limited integration of IPC into other public health programs, inadequate IPC education and training for all levels, inadequate IPC experts and mentors and weak monitoring and evaluation of IPC programs including feedback and data use of action.

Inconsistent hygiene and sanitation. Water hygiene and sanitation are a prerequisite for infection prevention and control and preventing the spread of antimicrobial-resistant pathogens in the community and health care settings. The limited availability of clean water, proper sanitation, and hygiene facilities in healthcare settings and communities further complicates the fight against AMR.

Lack of awareness and education among healthcare workers and the public

Evidence has demonstrated that the overuse and misuse of antimicrobials are major contributing factors to AMR in humans and the lack of knowledge and awareness of AMU, AMR and AMS among healthcare workers could contribute to the development of antimicrobial-resistant infections as lack of knowledge may result in inappropriately prescribing, dispensing and administering antimicrobials. This is further complicated by inadequate diagnostic capacity, access to antimicrobials without prescriptions, medicine stockouts, shortage of qualified health workers, inappropriate use of antibiotics in animals and agriculture, poor hygiene and sanitation and infection prevention and control measures, weak regulatory systems and lack of robust AMR surveillance programs to generate data for decision making.

Public understanding of the dangers of AMR is low, leading to the misuse of antibiotics both in humans and animals. For the general public inadequate awareness and education is a challenge in addressing AMR in Africa as demonstrated by responses from eighty-nine clients buying antibiotics in one study, slightly over half of the respondents 58.6%, responded that they should stop antibiotics after finishing the dose as directed and a further 50.7% thought that it was acceptable to share antibiotics with other individuals 65.1% thought that they should request the same antibiotics if they had used them to treat a similar illness in the past. The study indicated that only 25% had adequate knowledge about the use of antibiotics. These findings indicate a major challenge in the fight against AMR in the African region where the enforcement of regulations is weak towards the rational use of antimicrobial agents.

Agricultural use of antimicrobials

An increase in demand for food from agricultural and animal products has been noted due to an increasing growth in the world's population is expected to continue growing over the coming fifty or sixty years, reaching a peak of around 10.3 billion people in the mid-2080s, up from 8.2 billion in 2024. In 2017, Africa had a projected population rise of 1.3 billion by 2050. The increase in population is in tandem with the demand for food products meaning that more agricultural and livestock products need to be produced to cater for economic, social and dietary demands. Due to the increased demand, intensive agriculture and food production systems, antimicrobial use (AMU), to maintain animal health and productivity, is inevitable. With the weak surveillance systems data on use and consumption in animal health and crops is scarce.

Challenges in human-animal health and the environment integration: the One Health approach

In recent years, there has been increased global advocacy for the use of a collaborative, multisectoral, and transdisciplinary approach. The One Health approach, which integrates human, animal, and environmental health, faces challenges occasioned by weak collaboration within and between sectors and resource constraints. The OH implementation and practice although hailed as a key strategy and a model for other countries in the region, it still faces significant challenges including concerns over its sustainability, insufficient funding and competing priorities. Complex political, socio-economic and cultural attributes configure multispecies interactions, the health outcomes of these interactions, and health interventions. resource barriers" namely, non-availability of government budget to implement NAPs, insufficient specialized human resources, and lack of an integrated surveillance system. countries did not have a dedicated government budget in place to implement their NAPs. Data analysis revealed a lack of integrated surveillance systems in place to monitor AMR patterns and antimicrobial use using OH approach data analysis revealed lack of integrated surveillance systems in place to monitor AMR patterns and antimicrobial use using OH approach. This points towards the need to define and finance a context-specific research agenda for AMR in Africa to enable effective linkage of research findings policy decisions and practice.

Conclusion

With nearly ten years since the WHA adopted the GAP in 2015, countries in Africa have just started implementing their National Action Plans. In Africa, several barriers to the implementation of NAPs have been identified by the authors. A systems approach is best placed to overcome the challenges of AM. Tackling these barriers is further compounded as the themes are highly interrelated and interconnected hence action has to be driven across the board. The barriers to effective implementation of NAPs in Africa are many. Focusing on leadership, governance, accountability, sustainable financing, public health systems, robust supply chains and regulation and enforcement, building professional capacity and capability, improving infrastructure to support preventive, diagnostic and treatment efforts and strengthening cross-sectorial collaborations remains critical. It is a pivotal document and better understand AMR and its determinants, delving into health inequities and identifying politics and policies that impact multisectoral decisions is important.

To tackle AMR, a wholesome move towards systems strengthening is necessary. Inclusivity in policy analysis, development and implementation process by all is pivotal for ownership of the shared vision and sustained implementation of interventions that are context-specific (**Figure 1**).

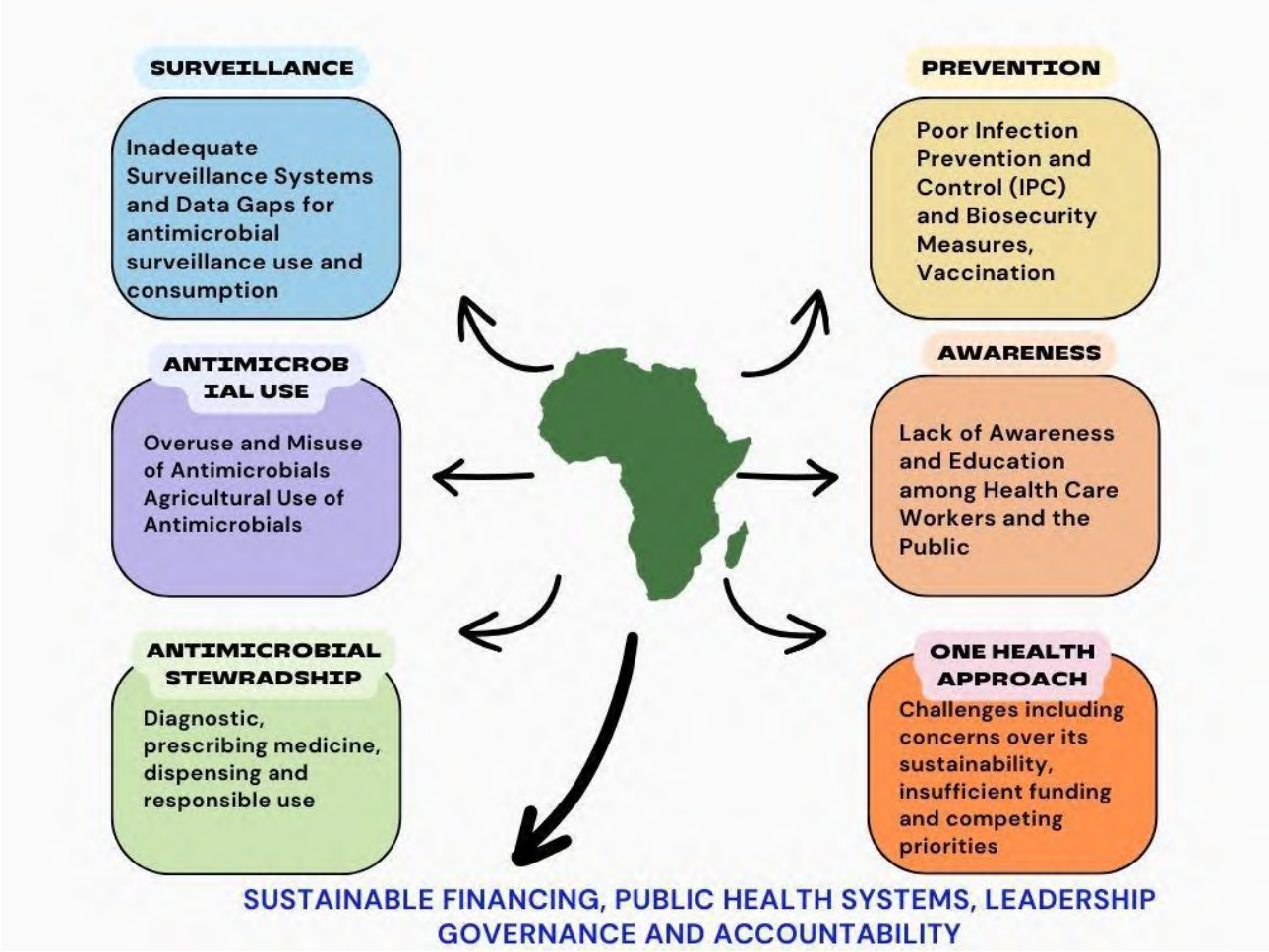

Figure 1. The ecosystem of AMR challenges in Africa.

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 16

Antimicrobial resistance: the most critical bacteria

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Introduction

Antimicrobials are vital and life-saving medications, and their effective utilization is an essential component of universal healthcare. Unfortunately, the major drivers for the development and spread of antimicrobial-resistant bacteria, which render drug treatment ineffective, are overuse and misuse of antimicrobials in humans, animals and plants as well as social and economic determinants, and ineffective infection prevention and control (IPC) practices. Since the 1928 discovery of penicillin by Sir Alexander Fleming, the existence of bacterial resistance to antibiotics has been known for more than 50 years. The WARNING (Worldwide Antimicrobial Resistance National/international Network Group) taskforce develops 10 golden rules for raising awareness, good IPC measures and appropriate use of antibiotics by clinicians in their clinical practices. AMR is connected to the four components of One Health due to the irresponsible and excessive use of antimicrobials across different sectors including human, animal, plant and the environment. One Health approach is a collaborative strategy that links multi-disciplines to address and find intervention solutions for human, animal and environmental health.

The 21st century presents a significant challenge to global health due to antimicrobial resistance (AMR). According to 2022 projections, bacterial AMR directly caused 4.95 million deaths, including 1.27 million global deaths attributable to bacterial AMR in 2019. Current estimates published in 2024 revealed that an estimated 1.91 million deaths attributable to AMR and 8.22 million deaths associated with AMR could occur globally in 2050. Bacterial infections resistant to antibiotics might claim the lives of approximately 39 million people worldwide in the next 25 years. In order to mitigate the spread and development of AMR over the coming decades, estimating the burden of AMR suggests new implications for practical and successful intervention measures.

Up until 1960, AMR was not a major concern since resistance could be readily addressed by the development of new antimicrobials. Unfortunately, bacteria have evolved a wide range of antibiotic resistance mechanisms that have protected them from the effects of the newly discovered drugs, leading to an increase in AMR. Gram-negative bacteria are naturally able to develop novel defense mechanisms against antibiotics, and they may genetic material to other bacteria that makes them resistant to drugs. In 2024, the World Health Organization (WHO) published a list of 15 families of bacteria that pose the greatest threat to human health. According to the severity of the need to create new medicines and vaccines to battle these infections, the WHO list categorizes bacteria into three priority categories: critical, high and medium priority. Critical priority pathogens pose a significant global health threat because of their high burden, ability to resist drugs,

and spread resistance, and potential to harm hospitalized patients, nursing home residents, immuno-compromised patients, and patients whose conditions require medical devices or procedures. Examples of these pathogens include Gram-negative bacteria resistant to last-resort antibiotics such as carbapenem-resistant *Acinetobacter baumannii*, carbapenem and/or third-generation cephalosporin-resistant *Enterobacterales*, and *Mycobacterium tuberculosis* strains resistant to rifampicin. High-priority pathogens include fluoroquinolone-resistant *Salmonella*, non-typhoidal *Salmonella* and *Shigella* species, carbapenem-resistant *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus*, third-generation cephalosporin and/or fluoroquinolone-resistant *Neisseria gonorrhoeae* and vancomycin-resistant *Enterococcus faecium*. Particularly in resource-limited countries, these pathogens can cause serious and often fatal infectious diseases such as nosocomial infections, bloodstream infections, pneumonia and tuberculosis. *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacterales* species are among the pathogens referred to as "ESKAPE", a term that describes their capacity to evade the bactericidal effect of antibiotics. ESKAPE has been used to categorize the most prevalent MDR pathogens. *A. baumannii* is one of the most dangerous ESKAPE organisms that successfully evade the effect of antimicrobial medications, according to the WHO report.

The hardest-to-treat antibiotic-resistant bacteria

The rise of AMR in key bacterial pathogens is recognized as a significant public health challenge impacting humans, animals and the environment globally. Multidrug-resistant organisms are now emerging not only in the hospital environment but also in the community settings, suggesting that antibiotic-resistant bacteria have reservoirs outside the hospital environment. Although the hardest-to-treat antibiotic-resistant bacteria are genetically diverse, they share common resistance strategies, such as reduced drug uptake, drug target alterations, drug inactivation and activation of drug efflux pumps. Bacteria deploy various resistance mechanisms, some of which are intrinsic, utilizing existing genes to endure antibiotic exposure, while others are acquired, involving the introduction of new genetic material that enhances survival capabilities.

Mycobacterium tuberculosis

Tuberculosis (TB), caused by *M. tuberculosis*, is one of the deadliest infectious diseases and a significant global public health issue. It is estimated that drug-resistant TB accounts for 13% of deaths worldwide. The situation is worsened by the existence of rifampicin-resistant (RR) and multidrug-resistant (MDR) strains of *Mycobacterium tuberculosis*. Mono-resistance to rifampicin is quite uncommon, as nearly all RR strains also develop resistance to other anti-TB drugs, particularly isoniazid. Consequently, RR is considered a critical pathogen and serves as a surrogate marker for MDR-TB. Rifampicin, the key anti-TB drug that has enabled shorter treatment regimens, acts as both a bactericidal and sterilizing agent. MDR-TB is defined as strains of *M. tuberculosis* that are resistant to rifampicin and isoniazid. Pre-extensively drug-resistant TB (pre-XDR-TB) is defined as RR or MDR strains of *M. tuberculosis* that are also resistant to any fluoroquinolone, such as levofloxacin or moxifloxacin. Extensively drug-resistant TB (XDR-TB) is characterized by RR or MDR strains of *M. tuberculosis* that are also resistant to any fluoroquinolone and at least one other Group A drug, including bedaquiline and linezolid. The emergence of these drug-resistant *M. tuberculosis* strains is driven by ongoing resistance development and person-to-person transmission. *M. tuberculosis* has varying degrees of intrinsic resistance to multiple classes of antibiotics due to diverse mechanisms such as drug target modification, drug efflux, enzymatic drug inactivation, and structural features like a hydrophobic waxy cell envelope, limited porin channels and low lipid fluidity of the cell membrane. However, the idea that horizontal gene transfer

plays a role in *Mycobacterium tuberculosis* medication resistance hasn't been proven to be true or false with any degree of certainty.

Acinetobacter baumannii

Acinetobacter baumannii is a non-motile, non-fastidious, catalase-positive, oxidase-negative, an aerobic Gram-negative multidrug-resistant bacillus that belongs to the group of "ESKAPE" pathogens. This highly invasive pathogen is responsible for various nosocomial infections and can lead to a variety of infections such as pneumonia, septicemia, meningitis, urinary tract and wound infections, often associated with high mortality rate. Resistance mechanisms in *A. baumannii* includes enzymatic degradation of drugs, target modifications, multidrug efflux pumps, and permeability defects.

The pathogen's multiple virulence factors such as biofilm production, porins, capsules, and lipopolysaccharide in the cell wall, enzymes, and iron-acquisition systems, enhance its ability to cause diverse infections and exhibit various resistance mechanisms. A significant factor in the success of *A. baumannii* is its adaptable genome, which can rapidly mutate in response to stress. Carbapenem-resistant *Acinetobacter baumannii* predominantly colonizes and infects hospitalized patients. Multidrug resistance poses one of the biggest challenges in modern medical care, and *A. baumannii* is recognized as one of the most difficult Gram-negative bacteria to control.

This pathogen not only exhibits resistance mechanisms but also possesses strategies for survival in a wide range of environments, including biofilm production, facilitating its spread within healthcare settings. It is the unique ability to maintain a multidrug-resistant phenotype is attributed to a range of antibiotic-hydrolyzing enzymes, efflux pump systems, impermeability defects, and mutations in antibiotic targets, which further complicate treatment options. Although carbapenems were previously the treatment choice for multidrug-resistant *A. baumannii* infections, their overuse has led to an increase in carbapenem resistance. In 2024, the WHO ranked carbapenem-resistant *A. baumannii* (CRAB) as a top priority for antibiotic research and development, because carbapenem resistance is often associated with co-resistance to multiple antibiotic classes.

The main mechanism of carbapenem resistance in *A. baumannii* is the overexpression of carbapenem-hydrolyzing class-D beta-lactamases (CHDL), and ArmA RNA 16S ribosomal methyltransferase. All four classes of beta-lactamase enzymes have been identified in *A. baumannii*, with common genes including blaOXA-23, blaOXA-24, bla OXA-51, blaOXA-58 and blaOXA-143. The blaOXA-51-like group, which consists of chromosomally encoded enzymes intrinsic in *A. baumannii*, is particularly significant. Many strains that are extremely multidrug-resistant and produce carbapenemase contain the bla OXA-23 gene cluster, often acquired through plasmids, contributing to global carbapenemase resistance. Other plasmid-mediated gene clusters, such as blaOXA-24, blaOXA-58 and blaOXA-143 are also dominant.

Enterobacterales

Enterobacterales is an order of Gram-negative, facultative anaerobe and non-spore-forming bacilli that typically inhabit the gastrointestinal tract of humans and animals. *Enterobacterales* are responsible for a wide variety of both nosocomial and community-acquired infections. The burden of multi-drug resistant *Enterobacterales*, particularly those producing extended-spectrum beta-lactamases (ESBLs) and carbapenemase-resistant *Enterobacterales* (CRE) is rising globally, posing significant public health, especially in resource-limited countries. CRE is characterized by the presence of a carbapenemase or resistance to at least one carbapenem. Antibiotic resistance among Gram-negative bacteria has escalated dramatically over the past three decades, with a particular concern surrounding the emergence of *Enterobacterales* resistant to third-generation cephalosporins and aztreonam. This resistance is primarily associated with the production of ESBLs, a

group of enzymes first identified in the mid-1980s that confer resistance to nearly all beta-lactam antibiotics except carbapenems and cephamycins.

Third-generation cephalosporin-resistant (3GC-R) *Enterobacterales* represent a significant health threat due to their ability to rapidly spread AMR determinants among bacterial populations. Both infections and colonizations by these globally disseminated organisms are associated with poor clinical outcomes and increased mortality. Resistance to 3GC in *Enterobacterales* is mainly due to the production of ESBLs, with resistance generally conferred by the presence of ESBLs or the overexpression of a chromosomal or plasmid-encoded AmpC beta-lactamase gene.

Conclusion

The rise of the most critical drug-resistant bacteria such as M. tuberculosis resistant to rifampicin, carbapenem-resistant *A. baumannii*, and ESBLs and carbapenemase-resistant *Enterobacterales*, poses a significant global health threat. These highlight an urgent need for interventions that include raising awareness, effective surveillance, use of molecular-based diagnostics for early detection, innovative treatment strategies, minimizing inappropriate antibiotic use in the One Health approach, vaccinations, improving infection prevention and control practices, implementing antibiotic stewardship programs, and research into new antimicrobials.

Competing interests

The author has no financial and non-financial competing interests to declare.

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Chapter 17

The challenge of antimicrobial resistance in carbapenem-resistant Gram-negative bacteria

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Introduction

Carbapenem-resistant organisms (CRO) are Gram-negative bacteria that are resistant to one or more carbapenems which include *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Escherichia coli*, *Klebsiella pneumoniae* and other *Enterobacterales*. The mortality rate ranges between 48% to 57.4% for CRE, 52.7% for CRAB, and 8% to 18.4% for CRPA. According to the CDC, AMR leads to probably 10 million deaths each year by 2050 and arises healthcare burdens. Carbapenemase enzymes classified based on Ambler into three molecular classes: class A (e.g., *Klebsiella pneumoniae* carbapenemase (KPC) enzymes or Guiana extended spectrum β-lactamases (GES) enzymes), class B (metallo-β-lactamases (MBLs) New Delhi MBLs (NDM), Verona integron-encoded MBLs (VIM), or imipenemase (IMP), and class D carbapenem-hydrolyzing oxacillinase (OXA), e.g., OXA-48-like enzymes. Non-fermenters exhibit higher carbapenem resistance rates (>60%) compared to fermenters (<10%) due to their lower outer membrane permeability and effective efflux pumps. The prevalence of carbapenemase-encoding genes ranges between 4 to 32% for CRPA, with a predominance of bla_{VIM}, bla_{IMP} and bla_{GES}, between 45 to 90% for CRE, with a predominance of bla_{KPC} and bla_{NDM} and up to 80 to 100% for CRAB, with a predominance of $bla_{OXA.}$ The GAP-AMR and NAP-AMR initiatives will combat antimicrobial resistance and reduce the AMR burden by preventing its emergence and spread. This provides a framework for stakeholders and improves governance systems. In India, NARS-Net offers a countrywide database for access to the antimicrobial resistance trends of all high-priority pathogens. Healthy individuals are not prone to CRE. However, those with indwelling catheters, mechanical ventilation support, and multiple antibiotic exposure are more vulnerable to CRE infections. The detection of carbapenemase-producing microorganisms involves phenotypic and genotypic methods. Phenotypic methods are non-molecular assays

that detect the carbapenemase enzyme's structure in Gram-negative isolates. Genotypic methods aim at detecting resistance genes which is accurate and expensive. The CRE treatment recommendations are limited and optimized based on the antimicrobial susceptibility pattern, which can be either monotherapy or combination therapy. Overuse of antibiotics and poor infection prevention control surveillance in hospitals facilitate the increase in CR-GNB. The core strategies to combat the transmission of CRE infections in healthcare settings are diagnostic stewardship, antimicrobial stewardship and infection prevention control standards.

Aim

This chapter explores the accelerating threat of antimicrobial resistance and the challenge in diagnosing methods and treatment of carbapenem-resistant Gram-negative bacteria and discusses its current and future treatment and prevention strategies to combat this critical public health challenge.

Carbapenem-resistant *Acinetobacter baumannii* (CRAB)

Acinetobacter baumannii is an aerobic, non-fermenting, Gram-negative bacteria found in water and soil, and in people, it may colonize numerous places including the skin, respiratory, and gastrointestinal systems. NFGNB is the major cause of HAI such as hospital-acquired pneumonia, urinary tract infections and septicemia, especially in ICU. According to WHO, around 30% of ICU patients in high-income nations have at least one HAI; however, the prevalence is at least two to three times greater in middle- and low-income countries. According to the NARS-Net 2022 report from India, the total number of isolates collected was 1,19,686, *A. baumannii* accounts for 11,782 (10%) distinct patient isolates. In all, 2447 isolates (19%) were obtained from the ICU itself. *Acinetobacter* infections have a significant death rate, which can range between 45 to 70%. Carbapenem-Resistant *Acinetobacter baumannii* is resistant to at least one carbapenem antibiotic, such as imipenem, meropenem or doripenem. CRAB consist of carbapenemase genes. In US between 2017-2022, out of 17,964 CRAB isolates, 441carbapenemase gene-positive (CP-CRAB) isolates were identified by AR Lab Network of which 325 isolates (73.7%) with the NDM gene, 101 isolates (22.9%) with the KPC gene, 15 isolates (3.4%) with the OXA-48 gene, and no isolates with the VIM or IMP genes were found. Antibiotic resistance is a big concern in hospitals across the world since *A. baumannii* develops resistance mechanisms as a result of antibiotic overuse and abuse. This causes degradative enzymes, reduced bacterial membrane permeability, changed antibiotic targets, efflux pumps, metabolic alterations, and biofilm development. *A. baumannii*'s genetic plasticity permits it to form multidrug-resistant, extensively drug-resistant, and pan-drug-resistant strains, providing considerable therapeutic problems. To treat CRAB infections, an antibiotic therapy with sulbactam is recommended. The available treatment option is sulbactam-durlobactam combined with a carbapenem such as meropenem or imipenem-cilastatin. If sulbactam-durlobactam is unavailable, an alternate therapy is high-dose ampicillin-sulbactam, a total daily dosage of 9 grams of sulbactam component combined with at least one other drug such as polymyxin B, minocycline, tigecycline, or cefiderocol. Durlobactam especially inhibits class A (TEM-1), class C (ADC) and class D (OXA-24/40, OXA-23) but it does not inhibit Class B MBL (NDM).

Carbapenem Resistant *Pseudomonas aeruginosa* (CRPA)

Pseudomonas aeruginosa is a motile, non-fermenting, Gram-negative bacilli causing infections in the gastrointestinal, otitis externa and skin and soft tissue and develops HAIs such as sepsis, pneumonia, bones and joints, urinary tract infection and mainly affects immunocompromised patients. The MDR *P. aeruginosa* caused around 32,600 infections and 2,700 deaths in the US among hospitalized patients in 2017. Reduced outer membrane porins expression, increased amino acid substitution production in *Pseudomonas*-derived cephalosporinase enzymes, efflux pumps upregulation, alterations in PBP targets, and the existence of ESBL are the resistance mechanisms. Among the NFGNB data collected from Jan to Dec 2022 in India, NARS-Net found that *Pseudomonas* species with 14,684 isolates were most frequently isolated, predominantly from inpatients with 12%. The AR Lab Network in the US tested 1,20,338 total isolated CRE and CRPA out of which were 24,364 CP- CROs in the year from 2018- 2021. A total of 414 multi-CP gene CRE and 26 multi-CP gene CRPA were detected from 440 multi-CP gene CRE or CRPA. In this, NDM and OXA-48 combination genes were 44% among CRE isolates and KPC and VIM combination genes were 35% among CRPA isolates. In the 2017-2022 CDC report, 68,712 CRPA isolates were tested. Among them, 1530 (2.23%) isolated CRPA with at least one targeted carbapenemase gene has been detected. The most common carbapenemase gene detected was CRPA with VIM which was about 892 (58.3%). In 2018, EARS-Net of the ECDC reported that 32.1% of *P. aeruginosa* isolates in the EU were resistant to at least one of the antimicrobial groups and 19.2% of isolates were resistant to two or more groups of antimicrobial agents. Several healthcare-associated VIM-CRPA outbreaks were reported in European countries. The term “difficult-to-treat” resistance was proposed in 2018. DTR is described as *P. aeruginosa* which reveals non-susceptibility to all classes of antibiotics. Ceftazidime-avibactam, Ceftolozane-tazobactam, imipenem-cilastatin-relebactam and cefiderocol are treatment options for pyelonephritis, uncomplicated cystitis, complicated UTI and non-urinary tract infection caused by DTR *P. aeruginosa*. Tobramycin or amikacin are alternative regimens. Cefiderocol is used to treat MBL-producing DTR *P. aeruginosa*. Ceftazidime-avibactam remains effective against GES-producing *P. aeruginosa*. Colistin is an alternate option for DTR *P. aeruginosa* cystitis. ceftazidime-avibactam and aztreonam combination for MBL-producing *P. aeruginosa* infections had found clinical success.

Klebsiella pneumoniae

Klebsiella pneumoniae is a non-motile, Gram-negative, encapsulated, environmental bacterium, typically inhabitant in the oropharyngeal and gastrointestinal (GI) tract and it causes urinary tract infection, pneumonia, meningitis, surgical site infections and bloodstream infections. *K. pneumoniae* produces lactamases or aminoglycoside-modifying enzymes and decreases cell permeability through the loss of OMPs. The KpnGH efflux pumps and antimicrobial binding site modification are the cause of antimicrobial resistance in *K. pneumoniae*. The latest figures available from the Indian NARS - Net (2022) show approximately 47% of CRE *Klebsiella* species, out of which 24,377 isolates were resistant to at least one of the carbapenems, a figure similar to 50% reported in the previous year's surveillance (2021). From 2014 to 2018, an Indian meta-analysis on multi-drug resistant *Klebsiella pneumoniae* shows a prevalence of 34.37% and a pooled prevalence of 2% in hospital-acquired *K. pneumoniae*’s data. It can be regarded as a moderate level, and analysis of their antibiotic resistance patterns revealed a high resistance of 86% to β-lactamase inhibitors. *K. pneumoniae* causes a 50% mortality rate in patients affected by Pneumonia. The strains of OMP deficiency in *K. pneumoniae* are responsible for a lower resistance rate. OmpA, OmpK35, OmpK36, and OmpK37 are well-known globally.

Over 4928 samples were positive for *Enterobacteriaceae* among them, 1433 samples became positive for CRE, in which 788 (55%) positive cultures were reported from ICU, emergency, and trauma care. The treatment options preferred for NDM and other MBL-producing *Enterobacterales* are Ceftazidime-avibactam in combination with aztreonam, or cefiderocol as monotherapy, and for KPC-producing Meropenem-vaborbactam, ceftazidime-avibactam, and imipenem-cilastatin- relebactam. Cefiderocol is an alternative option. If OXA-48-like enzymes are produced by an *Enterobacterales* clinical isolate, ceftazidime-avibactam is preferred and an alternate regimen is cefiderocol. The infections caused by CRE don't require colistin and polymyxin B as a treatment whereas the second-line treatment option for uncomplicated CRE cystitis is colistin.

Escherichia coli

Escherichia coli is a rod-shaped non-motile Gram-negative bacillus and the bacteria colonizes the intestine of humans and causes a range of illnesses, including diarrhoea, pneumonia, bacteraemia, septicaemia, uncomplicated cystitis, renal failure, and bacterial peritonitis. The Indian NARS-Net 2022 report states that out of 39,620 *E. coli*-positive isolates, 35% of CRE, *E. coli* were resistant to the carbapenem class of drugs. *Escherichia coli* Carbapenems resistance was caused by the genes of KPC, VIM, NDM, and IMP. Among them, OXA-48 genes are frequently reported. The main mechanisms behind this resistance are caused by multi-drug efflux pump and porin loss, which contribute to the CRE. The global study, which evaluated 11,091 CRE isolates from the NCBI database and 7918 isolates with needed details evaluated the prevalence of carbapenem-resistant genes of *E. coli*., 75 countries and five continents catch three sequences (ST131, ST410, and ST167) and 497 unique sequences. The NDM genes were dominated in North America, China, France, Asia, and the United States, KPC genes were reported in South America and OXA-48 genes were highly identified in Europe. Ceftazidime-avibactam resistance on KPC genes was caused by rapid hydrolysis of ceftazidime, gene mutations, and amino acid changes in the bla_{KPC} carbapenemase. The resistance increased for imipenem-cilastatin-relebactam and meropenem-vaborbactam was facilitated by efflux systems, modification in bacterial membrane permeability, and increase in bla_{KPC} copy numbers. The increased NDM expression, amino acid changes in AmpC B-lactamases, and mutations of the TonB-dependent iron transport are mechanisms catalysing drivers of cefiderocol resistance *Enterobacterales* CRE infection. The resistance has increased since the insertion of amino acid in PBP3 and the active binding site of aztreonam and cefiderocol and due to this action, there is no beta-lactam left to treat NDM-producing *E. coli*. The *Enterobacterales* isolates show a lofty resistance percentage in Cefiderocol (83%), and ceftazidime-avibactam (7%). The increased use of ceftazidime-avibactam (10–20%) and meropenem-vaborbactam (<5%) unfolded the resistance of these antibiotics. The CRE *E. coli* has left deficient treatment options and needs precise decision-making in a short time, according to the resistance gene identified with the aid of advanced diagnostic stewardship to optimize the rational selection. Non-CP and KPC producing CRE isolates can be treated by imipenem-cilastatin-sulbactam, meropenem-vaborbactam, and ceftazidime-avibactam. The treatment options for NDM and other MBL-producing *Enterobacterales* infections are ceftazidime-avibactam in combination with aztreonam, or cefiderocol as monotherapy. The treatment option for OXA-48-producing *Enterobacterales* is ceftazidime-avibactam and second-line treatment option is cefiderocol is also used as an alternate option for KPC-producing organisms. The low-level serum and urine concentrations are the major reasons for not using tigecycline and eravacycline in the bloodstream and urinary tract infections.

Role of diagnostic stewardship

"Diagnostics are the single biggest potential game changer in the fight against AMR"

Diagnostic stewardship is stated in the GLASS Manual as "coordinated guidelines and interventions to enhance the appropriate use of microbiological diagnostics to support therapeutic decisions." It includes diagnostic testing, sampling, pathogen identification, and timely reporting of results". The delay in appropriate proper antibiotic treatment and quality of care can be crucial for patient survival in serious infections such as meningitis, sepsis and pneumonia. This situation is made even more challenging by the increasing number of patients suffering from MDR bacterial infections, which have very limited treatment options. Thus, Microbiology laboratories are crucial in detecting infectious agents and determining potential antibiotic resistance, allowing clinicians to quickly prescribe the most appropriate treatment. The goal of testing is to enhance patient care and minimize uncertainty in the medical field. However, the improper application of diagnostic tests can result in unnecessary treatments, higher costs, and possible negative effects. Diagnostic stewardship seeks to mitigate these risks by guiding clinical choices and educating healthcare providers. The use of laboratory tests for diagnosing conditions significantly influences:

- Accurate diagnosis, leading to appropriate treatment.
- Healthcare costs and expenses to undiagnosed conditions.
- The consequences of incorrect diagnoses in clinical settings.

The hospital system and clinical faculty require a well-organized and supervised method for using tests related to infectious diseases, where microbiologists are suitable experts.

Antimicrobial stewardship (AMS)

Coordinated antimicrobial stewardship interventions focus on improving and monitoring the proper use of antimicrobial agents by encouraging the best choice of drug regimens, including accurate dosing, therapy duration, and methods of administration. The purpose of AMS is to improve patient care while both reducing antibiotic use and providing cost-effective to healthcare. The primary goal is to ensure safe and appropriate antibiotic use to improve clinical outcomes and minimize adverse effects. The secondary goals include reducing healthcare costs without compromising patient care quality and decreasing the incidence of antibiotic-induced collateral damage. ICMR's strategic approaches and recommended guidelines to achieve AMSP goals:

- Developing institutional antibiograms and implementing antibiotic policies and standard treatment guidelines.
- Conducting prospective audits, providing feedback, and timely interventions to streamline antibiotic prescriptions.
- Pre-authorization with formulary restrictions for certain antimicrobials.
- Conduct a point prevalence study on culture samples.
- Track the rate of antibiotic usage (DDD/DOT).
- Enhancing antimicrobial prescribing through educational and administrative measures for health care workers.

- AMS interventions involve optimizing antimicrobial selection, antibiotic time out, de-escalation of antibiotics when needed, conversion of IV to oral and appropriate antibiotic duration for surgical prophylaxis, and empirical and definitive treatment.

Antibiotic overuse and antimicrobial resistance

Overuse of antibiotics refers to when the antibiotics are prescribed to the patients unwantedly as prolonged use of post-surgical prophylaxis, definitive treatment even though the recommended duration is completed. Irresponsible use (treating the dengue patient with doxycycline or ceftriaxone and inappropriate use of antibiotics for viral illness etc.). One Health is a way of working that improves health and to control the disease of people, animals and ecosystems and also gives collective information to detect, manage and prevent disease at different levels from global, national, regional and community. It requires strong governance, effective communication, collaboration and coordination, having the One Health approach helps people understand the risks, benefits, advanced opportunities and comprehensive solutions. The DDD and DOT are the methods that will be useful to monitor and interpret the hospital's drug usage regularly. Misuse of over-the-counter availability of antimicrobial agents also leads to increase in the resistance pattern of antibiotics. Antibiotic resistance is escalating rapidly, necessitating immediate and appropriate actions to limit its spread and severity. While complete eradication isn't feasible, strategies have been implemented at various levels to combat resistance. At the sub-national level in India, some specific plans include KARSAP, MP-SAPCAR, and SAP-CARD. Promoting awareness of the appropriate use of antibiotics to healthcare professionals and the public helps to minimize the irrational use of antibiotics and combat the skyrocketing AMR.

Rational use of beta-lactam inhibitor combinations

Beta-lactamase inhibitors are used in combination with beta-lactam antibiotics to prevent resistance by blocking serine beta-lactamase enzymes that deactivate the beta-lactam ring of these antibiotics. These inhibitors are prescribed for infections caused by Gram-negative bacteria that produce the enzyme. The *Enterobacteriaceae* are the common bacteria treated with beta-lactamase inhibitors. Irrational use of beta-lactamase inhibitors should be avoided, as they are used widely in modern medicine for their ability to combat bacterial resistance. The antibiotic combinations including cefoperazone-tazobactam, cefepime-tazobactam, ceftazidime-tazobactam, cefotaxime-sulbactam, cefepime-sulbactam, meropenem-sulbactam, ceftriaxone-tazobactam, ceftriaxone-sulbactam and its EDTA. The FDA does not approve the above-listed antibiotic combinations. The CLSI and EUCAST are the regulatory bodies which provides clinical breakpoints for antimicrobials but the above-mentioned antibiotics have no clinical breakpoints. As previously mentioned, antibiotic combinations were not listed in the WHO's AWaRe classification (Access, Watch, Reserve) and they were listed in the not recommended category. The WHO's DDD indexed/ATC codes were not mentioned specifically same as antibiotic's generic name, except cefepime-tazobactam, ceftazidime-tazobactam, cefotaxime-sulbactam, ceftriaxone-tazobactam, ceftriaxone-sulbactam, cefepime-sulbactam stated like cephalosporins plus beta-lactamase inhibitor and ceftriaxone sulbactam plus EDTA mentioned as ceftriaxone combinations. The aforesaid of antibiotic combinations were not recommended for the treatment of Gram-negative resistant infections by the latest IDSA guidelines. The overuse of broad-spectrum, irrational fixed-dose antibiotic combinations drives antimicrobial resistance (AMR). However, these drugs are often not properly

monitored globally because the DDD index lacks coverage for many of these combinations. Hence it makes one health approach more challenging. The above combinations are of lacking evidence and are not approved by standard international treatment guidelines. Therefore, these combinations should be more standardized by conducting further research studies in order to be preserved for future treatment.

Novel antibiotics

The combination of existing antimicrobials with novel beta-lactamase inhibitors is designed to combat multidrug-resistant Gram-negative bacteria, including pathogens that produce carbapenemase.

Aztreonam /avibactam. It belongs to the class of Monobactam/β-lactamase inhibitor and its spectrum of activity includes GNB; less effective against MBL-producing *P. aeruginosa.* It is active against KPC, MBL, Amp C, OXA and ESBL enzymes.

Cefepime/zidebactam. It is a β-lactam/novel extended-spectrum β-lactamase inhibitor and its spectrum of activity includes GPB (except *MRSA*); GNB (except *A. baumannii*). It is active against KPC, MBL, Amp C, OXA and ESBL enzymes.

Cefepime/Taniborbactam. It is a β-lactam /novel, boronate derivative, β -lactamase inhibitor and its spectrum of activity includes GPB (except *MRSA*); GNB (except *A. baumannii*). It is active against KPC, MBL, Amp C, OXA and ESBL enzymes.

It is imperative that the Government implement policies that incentivize pharmaceutical companies to invest financially in the research and development of antimicrobials. This investment is vital for maintaining the efficacy of antimicrobial agents in order to guide the appropriate treatment.

Probiotics

In this period of emerging bacterial resistance, it is crucial to develop therapies that can serve as alternatives to antibiotics and are safe for humans. Probiotic supplementation can help to lower the risk of infectious diseases and reduce antibiotic use, thereby contributing to the prevention or delay of multidrug-resistant bacteria. The mechanisms by which probiotics protect the host from infections include strengthening the epithelial barrier, enhancing adhesion to the intestinal mucosa, preventing pathogen adhesion, stimulating both non-specific and specific immune responses, outcompeting harmful microbiota, producing antibacterial substances, and modifying toxins or their receptors. Antimicrobial peptides produced by probiotics, known as bacteriocins, have the potential to replace antibiotics or decrease the emergence of multidrug-resistant strains.

Infection prevention and control (IPC)

The cornerstone of controlling AMR and the spread of MDRO is effective IPC. It is of utmost importance that infection control and prevention measures be implemented with a focus on all strains of *K. pneumoniae, E. coli, A. baumannii* and *P. aeruginosa*, irrespective of the underlying resistance mechanism. In both outbreak and endemic settings, appropriate IPC measures are essential. The International Health Regulations (IHR) have identified effective IPC as a key strategy in the management of resistant pathogens. The United Nations

Sustainable Development Goals recently marked the importance of IPC's in contributing to safe, effective and quality health services, particularly water, sanitation and hygiene (WASH) and quality universal health coverage. Effective IPC measures should be introduced in the healthcare setting to reduce the transmission, colonisation and infection of pathogens in healthcare settings. IPC programmes are effective in control of many HAIs, including CRE, CRAB and CRPA. The multimodal IPC strategies for the prevention and control of CRO are effective hand hygiene compliance, active patient surveillance, environmental cleaning, contact precautions and patient isolation. The other measured parameters are enhanced staff education, use of chlorhexidine gluconate baths, environmental surveillance cultures for CRO colonization or contamination, carbapenem prescribing restriction, Proper sterilization of medical equipment, enhancing antibiotic stewardship, monitoring, auditing and feedback of IPC, ward closure, pre-emptive isolation for suspected infected patients, and limiting public access**.**

Conclusion

The increasing prevalence of carbapenem-resistant Gram-negative bacteria including *Acinetobacter baumannii, Pseudomonas aeruginosa*, and various *Enterobacterales* such as *Klebsiella pneumoniae* and *Escherichia coli*, poses a significant global health challenge. These pathogens exhibit high resistance rates due to their robust mechanisms, including carbapenemase production, efflux pumps, biofilm formation and altered membrane permeability. The mortality rates associated with infections are alarmingly high, underscoring the need for effective treatment strategies and infection control measures. Collaborative Global initiatives such as GAP-AMR, NAP-AMR, and NARS-Net in India provide essential frameworks for monitoring, preventing, and controlling antimicrobial resistance. The approving authority of antimicrobials for clinical practices (FDA, WHO's AWaRe classification) and international regulatory bodies provide clinical breakpoints (CLSI, EUCAST) and the standard GNB guidelines (IDSA) were not recommending clinical use of an earlier mentioned fixed irrational combination of antibiotics after seeing its lack of evidence. One Health improves the health of people, animals, and ecosystems by enhancing disease control and prevention at all levels. DDD and DOT are comprehensive methods to control the misuse of OTC, overuse and irrational use of antibiotics. Novel antibiotics should be used with concern to avoid its accelerated resistance pattern in future days. The adoption of probiotics and rational use of beta-lactam inhibitors are additional strategies that can help mitigate the spread of resistant bacteria. To curb the spread of CR-GNB, healthcare settings must implement stringent IPC protocols, rational use of antibiotics, promote hand hygiene, and enhance environmental cleaning. Ultimately, a multifaceted approach involving innovation in diagnostics, treatment, and prevention is vital to addressing the formidable challenge of antibiotic resistance in carbapenem-resistant Gram-negative bacteria. It is imperative that governments implement policies that incentivize pharmaceutical companies to invest financially in the research and development of antimicrobials. Diagnostic stewardship plays a crucial role in guiding appropriate therapeutic decisions and enhancing patient outcomes. Promoting awareness of appropriate use of antibiotics to the public is essential to combat this skyrocketing AMR

Competing interests

The authors have no financial and non-financial competing interests to declare.

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Chapter 18

The challenge of AMR in Gram-positive bacteria

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Introduction

Antimicrobial resistance (AMR) in Gram-positive bacteria is a significant challenge because this group of bacteria is prevalent worldwide in community and hospital-related infections and has a high capability to develop and acquire resistance to antibiotics. Although recent literature is vast in the growing problem of resistance in Gram-negative bacteria, resistance in Gram-positive pathogens is still a matter of concern and poses challenges in clinical treatment and prevention.

The World Health Organization (WHO) published in 2024, an updated global bacterial priority pathogens list and categorized them as critical, high, and medium antibiotic-resistant bacteria that urgently need research and development of new treatments. Among Gram-positive bacteria, vancomycin-resistant *Enterococcus faecium* (VRE) and methicillin-resistant *Staphylococcus aureus* (MRSA) were considered high-priority groups; and macrolide-resistant *Streptococcus pneumoniae* and Streptococci A, penicillin-resistant Streptococci B were considered medium priority group.

In this chapter, we review relevant aspects of resistance of three highly important groups of Gram-positive pathogens causing human infection (*Enterococcus* spp., *Staphylococcus aureus*, *Streptococcus pneumoniae*) and methods for optimizing therapy for resistant Gram-positive infections.

Enterococcus species

The genus *Enterococcus* consists of facultative Gram-positive cocci that have been isolated from a variety of animals, plants, and environmental sources since ancient years. Although 58 species have been described to date, *Enterococcus faecalis* and *Enterococcus faecium* are responsible for most of human infections. To survive in this new environment, enterococci developed a rugged adaptability, including a tolerance to elevated temperatures and high salt concentrations, and a resistance to killing by a variety of chemical disinfectants.

These same traits have enabled enterococci to colonize the human gastrointestinal (GI) tract and survive in the modern hospital environment.
Enterococcus species frequently cause urinary tract, gastro-intestinal, surgical site infections, and endocarditis. Furthermore, enterococci may colonize medical devices, causing catheter-related infections. Regarding the virulence spectrum, *Enterococcus* species produces cytolysins, gelatinases, pore-forming toxins, and aggregation substances, which promote tissue invasion, immune evasion, and/or cellular damage.

Resistance in *Enterococcus* species

Recently, the beginning of the antibiotic era and the widespread use of antibiotics in human clinical practice, animal husbandry, and agriculture have shaped the evolutionary trajectory of enterococci, particularly in relation to drug resistance. These factors have driven both the sequential emergence of *E. faecalis* in the 1970s and then vancomycin-resistant *E. faecium* in the late 1980s. Additionally, the selective antibiotic pressure has driven the continued evolution of resistance to newer antimicrobials. Although beta-lactam antibiotics have long been the backbone of therapy for serious enterococcal infections, it was observed that the minimum inhibitory concentrations (MICs) for these agents were at least an order of magnitude higher than those for streptococci, and combination therapy with aminoglycosides was needed to achieve a reliable bactericidal effect. All cephalosporins, except the latest generation (ceftaroline, active against *E. faecalis*) have no activity against *Enterecococcus* spp. as single agents even in ampicillin-susceptible strains and when used for synergy, they have no efficacy on their own. Around 30% of 2017 enterococci isolates from European countries expressed high-level resistance to aminoglycosides (HLAR), mediated by ribosomal target modification or production of aminoglycoside-modifying enzymes (AMEs).

Vancomycin-resistant *Enterococcus* (VRE)

The first vancomycin resistance in clinical *Enterococcus* spp. isolates was observed in 1988 in London, United Kingdom. VRE is defined as having a MIC to vancomycin of greater than or equal to 32 mg/mL based on the Clinical and Laboratory Standard Institute (CLSI) guidelines. Vancomycin acts by binding to the D-alanyl-D-alanine (D-Ala-D-Ala) terminus and inhibits cell wall synthesis. Vancomycin-resistance gene clusters (van A, B, D, and M) are responsible for the replacement of D-Ala-D-Ala with D-alanyl-D-lactate termini which results in low binding affinity of vancomycin. Van A gene is the most common type.
VRE has spread and has been detected in healthcare facilities across the world. A rise of vancomycin resistance has been observed in clinical *Enterococcus* spp. isolates (especially in *E. faecium*) in many European countries in the last decade. VRE currently represents an important healthcare concern due to an increased mortality rate, especially among intensive care unit (ICU) patients.

Vancomycin-resistant Enterococcus (VRE) – Transmission, infection, prevention and control

VRE colonization, contact with healthcare professionals, and environmental contamination are all associated with the transmission of VRE. Little is known about the dynamics of VRE transfer in hospitals. ICU patients, a common reservoir for VRE, showed rates of colonization via rectal swabs ranging from 9.7% to 51.9%. Recent studies have shown there may be a causal relationship between patient VRE colonization and time-dependent environmental contamination within the hospital.
Common VRE infections include catheter-related urinary and bloodstream infections, endocarditis, and wound and intra-abdominal infections. *Enterococci* are remarkable in their ability to develop rapid antimicrobial resistance. High-dose daptomycin and linezolid are options for the treatment of VRE infections; however, emerging antibiotic resistance to these agents may limit appropriate antibiotic therapy Vancomycin-resistant strains of enterococci have been endemic in large hospital settings with epidemics also reported.

Obtaining source control, ensuring prompt susceptibility testing and appropriate choice of antimicrobial therapy alongside prudent use and duration of vancomycin, third-generation cephalosporins, and anaerobic antimicrobial therapy are key components in the management and prevention of VRE.
Environmental care is of higher importance. Cleaning and disinfecting surfaces with licensed disinfectants and additional technologies like UV-C can reduce environmental VRE contamination, reducing cross-transmission among patients.
Hand hygiene is a key element in decreasing the risk of VRE transmission. Surveillance programs including VRE rectal swab protocols to identify colonized patients and implement contact precautions are also strategies to prevent dissemination in healthcare settings. Chlorhexidine bathing can be an additional approach in selected situations, to reduce the burden of colonization in patients.

Staphylococcus aureus

Staphylococcus aureus is a Gram-positive, coagulase-positive pathogen belonging to the family *Staphylococcaceae*. *S. aureus* is a commensal agent that frequently colonizes parts of the human body such as skin and mucous membranes, including the noses of healthy individuals. About 20% of individuals are persistent nasal carriers of *S. aureus* and around 30% are intermittent carriers. The colonization increases the chances of developing infections by this agent.
When causing disease, *S. aureus* is a major human pathogen associated with high infection and mortality rates and is one of the leading causes of respiratory tract, skin, and soft tissue, device-related infections, and infective endocarditis; and ranging from minor to life-threatening spectrum of manifestations.

***Staphylococcus aureus* – methicillin-resistant (MRSA)**
Among *S. aureus*, the most striking resistance profile is resistance to beta-lactam antibiotics. Penicillin-resistant *S. aureus* is well known, emerged in 1942, shortly after penicillin was introduced in clinical practice and less than 2 decades later, about 80% had become resistant to penicillin through the acquisition of the blaZ gene encoding a beta-lactamase enzyme, that hydrolyzes the beta-lactam ring. Today as many as 99% of clinical *S. aureus* strains are resistant to penicillin.
After the worldwide spread of penicillin-resistant *S. aureus*, semisynthetic penicillinase-resistant beta-lactams (like methicillin and oxacillin) were developed for clinical use. In the same year methicillin was approved, the first clinical methicillin-resistant *S. aureus* (MRSA) isolates were identified. methicillin resistance occurs through the acquisition of the mecA gene encoding PBP2a, a transpeptidase with low affinity for most beta-lactam antibiotics, that confers cross-resistance to almost all members of the beta-lactam class, except cefatroline. Some evidence suggests that SCCmec evolution occurred in the *Staphylococcus sciuri* group, a primitive group of *Staphylococcus* species that frequently colonizes domestic animals and occurred previously to methicillin clinical use.
The mecA gene is present in a family of structurally complex genetic elements designated SCCmec that often carry additional genes that encode resistance to other antibiotics. Another genetic determinant, mecC, encoding a transpeptidase enzyme with only 63% identity to mecA-encoded PBP2a, was recently described. MecC, like mecA, seems to have evolved in animal-adapted lineages of *S. aureus*, emphasizing the importance of the animal staphylococci as a reservoir of resistance genes that can potentially contribute to the evolution of antibiotic-resistant human pathogens.
MRSA was previously associated with colonization and infection only in healthcare settings. However, it has also emerged as a major cause of community-associated infections since the 1980s. The epidemiology of

MRSA has changed with the global emergence of community-acquired (CA-MRSA) strains. These strains were traditionally limited to populations outside healthcare settings and mainly caused skin, and soft tissue infections (SSTIs) and occasionally pneumonia. CA-MRSA is genetically distinct from hospital-associated MRSA (HA-MRSA), exhibiting resistance to fewer non-beta-lactam antibiotics, carrying a smaller version of SCCmec, and often producing a cytotoxin called Panton-Valentine leukocidin (PVL). These differences were previously the basis to differentiate CA-MRSA from HA-MRSA, but recently the prevalence of CA-MRSA strains has increased and the epidemiological and molecular distinction between these two types of strains has become less well defined, with numerous reports of CA-MRSA invading healthcare settings and causing nosocomial cases and outbreaks.

Hospital-acquired infections (HAIs) caused by MRSA are common in acute-care facilities, with an estimated 15% of intensive care unit (ICU) infections worldwide caused by *Staphylococcus aureus*, and nearly one-third of those being due to MRSA. In North America, an estimated 23% of ICU infections are caused by *S. aureus*, and nearly half of those are due to MRSA. Even outside the ICU setting, MRSA remains one of the most common pathogens associated with HAIs, causing device-associated, surgical-site, and hospital-onset bloodstream infections worldwide.

Infections due to MRSA are associated with higher mortality rates than infections caused by methicillin-susceptible strains (MSSA). In addition, they result in increased length of hospital stays and associated healthcare costs.

Besides challenges in treatment, MRSA infection and transmission in hospitals are matters of additional concern, and there are guidelines tailored to address specifically this issue.

Additionally, MSSA and MRSA detection and decolonization before orthopedic and cardiothoracic procedures can lead to decreased surgical site infection rates in colonized patients and this is another point of attention in the clinical care of surgical patients.

***Staphylococcus aureus* – vancomycin-intermediate and resistant**

Vancomycin-intermediate *S. aureus* (VISA) is defined as an isolate with *in vitro* Vancomycin MIC of 4-8 µg/mL and Vancomycin-resistant *S. aureus* (VRSA) refers to an isolate with Vancomycin MIC > 8 µg/mL. VISA and VRSA have emerged from MRSA; however, VRSA does not progress from VISA, they have different mechanisms of resistance. VISA was first reported in Japan in 1996 and was associated with the presence of a thickened cell wall that is rich in peptidoglycan chains that are not cross-linked and offer the terminal dipeptide D-Ala-D-Ala which is the target of vancomycin. VRSA acquired the complete genetic resistance from vancomycin-resistant enterococci (VRE), the vanA gene. Fortunately, resistance to vancomycin in *S. aureus* is rare.

Streptococcus pneumoniae

Streptococcus pneumoniae, is the most common Gram-positive bacteria causing upper and lower respiratory tract infections. It spreads through direct person-to-person contact with droplets generated when infected people cough or sneeze. Patients can be asymptomatic nasal carriers; this colonization state can vary from 5 to more than 50% depending on the studied population.

The population at higher risk for infection includes children younger than 5 years old, the elderly and individuals suffering from medical conditions like chronic heart, kidney, liver, or lung diseases, diabetes mellitus, immunosuppressive diseases, alcoholism, smoking, liquor fistula, cochlear implant with increased risk of meningitis. Besides, close contact and closed environments or crowds facilitate the spread of this agent.

Beyond upper respiratory tract infection and pneumonia, *S. pneumoniae* can cause invasive diseases such as meningitis, arthritis, bloodstream infection, and endocarditis; these are usually serious infections, that can lead to hospitalization or even death.

***Streptococcus pneumoniae* – penicillin-non-susceptible**

The sensitivity of pneumococci was maintained for all classes of antibiotics until the 1970s when penicillin-resistant strains were first reported in South Africa in 1977-78. Penicillin resistance occurs due to alternations in one or more of the six PBPs found in the *S. pneumoniae* cell membrane and can be due to chromosomal mutation or acquired. Risk factors for penicillin-resistant pneumococcal infections are previous antibiotic use, previous time in daycare (for children) or in an institutional setting (nursing home, long-term care facility), or a shelter (homeless people).

Criteria for penicillin resistance vary depending on whether the *in vivo* target is cerebrospinal fluid (CSF) or non-CSF infection. According to CLSI, for central nervous system (CNS) infections, the breakpoints are as follows:

- susceptible –MIC ≤0.06 mcg/mL;
- resistant – MIC >0.06 mcg/mL.

For non-CNS infections and treatment with parenteral drugs:

- susceptible – MIC ≤2 μg/mL;
- intermediate – MIC >2 and ≤4 μg/mL;
- resistant – MIC >4 μg/mL.

When oral penicillin is being used, the following definitions apply:

- susceptible – MIC ≤0.06 μg/mL;
- intermediate – MIC >0.06 and ≤1 μg/mL;
- resistant – MIC >1 μg/mL.

Penicillin resistance rates vary according to the region of the globe and temporal trends. In the early 2000s, using older definitions of resistance, approximately 20 percent of pneumococci isolated in the United States were classified as resistant. Using current definitions, rates of resistance are much lower.

Higher rates of penicillin resistance have been described in some countries. For example, recently published data from South Korea analyzing 1460 *S. pneumoniae* isolates obtained from non-CNS infections, showed overall antimicrobial resistance rates of *S. pneumoniae* to penicillin, erythromycin, ceftriaxone, levofloxacin, and vancomycin of 16.2%, 84.7%, 25.9%, 3.3%, and 0.0%, respectively, and the MDR rate was 6.7%.

***Streptococcus pneumoniae* – resistance to other antibiotics**

In addition to penicillin resistance, currently, the problem of resistance is global and involves several classes of antibiotics such as other beta-lactams, fluoroquinolones, macrolides, lincosamines, tetracyclines and folate synthesis inhibitors (trimethoprim-sulfamethoxazole, TMP-SMX). Resistance to three or more classes of antimicrobials is referred to as MDR pneumococci.

Macrolide–lincosamide–streptogramin B resistance may be mediated by erm(B) gene that encodes a methylase, or by mef(A) gene that encodes an antibiotic efflux pump. Other resistance mechanisms include ribosomal RNA (23S rRNA), ribosomal proteins L4 and L22 mutations.

Before the 2000s, only 18% of pneumococcal isolates were resistant to macrolides. After that, there was an increase in the rate of resistance. In 2011, 25 to 45% of pneumococci in the USA were resistant to macrolides. By 2019, resistance rates were about 40% in the same country.
A higher proportion of pneumococci in Europe are macrolide-resistant and, in most resistant isolates, ermB is the responsible mechanism. Some risk factors described for the acquisition of macrolide-resistant pneumococcal strains are previous use of azithromycin, clarithromycin, penicillin, and trimethoprim-sulfamethoxazole.

***Streptococcus pneumoniae* – prevention and treatment**

Vaccination effectively prevents pneumococcal disease. Indications and availability of different pneumococcal vaccines vary according to the country. The implementation of conjugated anti-pneumococcal vaccination in children played a crucial role in reducing cases attributed to the serotypes present in the composition.
As a result of widespread vaccination of target population with conjugate vaccine, most vaccine strains have largely disappeared, and new strains have emerged (the so-called 'replacement strains'). Some of the replacement strains have been reported to be resistant to penicillin and other antibiotics. Serotype 19A emerged after the introduction of the 7-valent pneumococcal vaccine and was included in the 13-valent vaccine (PCV13). Similarly, after the introduction of PCV13, other emerging serotypes that are not contained in PCV13 or in pneumococcal polysaccharide vaccine (PPSV23) and that exhibit substantial rates of antibiotic resistance have been reported. PCV15 and PCV20 are now available in some countries, and despite the relevant results in reducing pneumococcal disease, new serotypes will continue to emerge and escape immunization.
Despite the described rates of non-susceptibility, resistance of pneumococci to beta-lactam antibiotics is relative and, in the treatment of pneumonia and other non-CNS infections, can generally be overcome by the doses currently in use; and approximately 95% of pneumococcal infections will respond to treatment with standard-doses of beta-lactam antibiotics. On the other hand, when treating meningitis, special attention needs to be directed to the susceptibility profile of the infecting organism and even empiric therapy must be guided by local rates of beta-lactam antibiotic resistance.

Optimizing therapy for resistant Gram-positive infections: therapeutic options and evidence in pharmacokinetic and pharmacodynamic (PK/PD)

Given the therapeutic limitations for treating infections caused by resistant Gram-positive bacteria, it becomes important to use PK/PD strategies to optimize the efficacy of available antibiotics. Furthermore, considering the variations in resistance profiles, it is important to consider the following variables when choosing treatment: *in vitro* susceptibility, site of infection, and severity of infection.
For VRE the treatment options include daptomycin, which can be combined with ampicillin or ceftaroline for systemic infections, bacteremia, and linezolid.
Among the therapeutic options of choice for MRSA with vancomycin MIC < 4 µg/mL are vancomycin, daptomycin, linezolid, and teicoplanin (in areas where this drug is available). As alternative drugs, we can mention: ceftaroline, telavancin, and ceftobiprole. For MRSA and VISA or VRSA profiles, linezolid, daptomycin, telavancin, and ceftaroline are active options in general. Depending on the site of infection, rifampin can be combined with another active drug.

Regarding *Streptococcus pneumoniae*, the treatment options for macrolide-resistant and penicillin-resistant are ceftriaxone, moxifloxacin, levofloxacin, vancomycin, linezolid and ceftaroline for non-meningeal infections. For CNS infections, ceftriaxone or cefotaxime (according to susceptibility profile), besides vancomycin are treatment options.

Below are summarized some recommendations regarding these antibiotic's use in clinical practice. Additional characteristics of the drugs are summarized in **Table 1**.

Table 1. Pharmacological characteristics of antibiotics commonly used for the treatment of resistant Gram-positive bacterial infections (Adapted from Sanford Guide, 2024).

Drug	Pharmacologic category	PK/PD index	Protein binding	Vd	Average serum $T_{1/2}$	Elimination	CSF*/ blood	Therapeutic levels in CSF
Vancomycin	Glycopeptide	24-hr AUC/MIC	55%	0.7 L/kg	4-6 hours	Renal	7-14%	High doses required
Teicoplanin	Glycopeptide	24-hr AUC/MIC	90 – 95%	0.9-1.6 L/kg (Vss**)	8-9 hours	Renal	0-8%	No data
Linezolid	Oxazolidinone	24-hr AUC/MIC	31%	40-50 L (Vss)	5 hours	Renal	60-70%	Yes
Ceftaroline	Cephalosporin (fifth generation)	T > MIC	20%	20.3 L (Vss)	2.7 hours	Renal	< 10%	Maybe at high doses
Ceftobiprole	Cephalosporin (fifth generation)	T > MIC	16%	18 L	3.3 hours	Renal	12%	Possibly

* Concentration with inflammation; **Vss = Vd at steady state.

Abbreviations. AUC/MIC: ratio of the antibiotic area under the curve to the time above the minimum inhibitory concentration needed to inhibit microorganisms. CSF: cerebrospinal fluid. PK/PD: pharmacokinetic/pharmacodynamic. Vd: volume of distribution.

Vancomycin

It is an antibiotic belonging to the glycopeptide class, frequently administered for either empiric or targeted treatment of infections caused by MRSA.

For therapeutic-drug monitoring (TDM) in patients with serious MRSA infections, such as bacteremia, endocarditis, and invasive infections, the main American organizations in the field of infectious diseases recommend calculating the AUC24. The suggested PK/PD index is AUC/MICBMD, meaning the area under the concentration curve over 24 hours divided by the minimum inhibitory concentration (AUC 0–24/ MIC), assuming a vancomycin MICBMD of 1 mg/L.

The calculation of AUC24 can be performed using different methods, such as trapezoidal equations or Bayesian methods, with the ideal range considered to be between 400 and 600 mg*hour/L. If monitored only by the trough, the ideal range is 15-20 µg/mL for serious infections.

When discussing critically ill patients, a loading dose should be administered to avoid subtherapeutic levels at the beginning of treatment, with a recommended loading dose of 20 to 35 mg/kg to achieve the target AUC within 24 to 48 hours, based on actual body weight and not exceeding 3,000 mg.

Continuous infusion (CI) has also been an alternative to consider when the target AUC is not achieved and has shown potential benefits. Studies have demonstrated that patients on CI reached the required plasma concentration more quickly, with less variability, reduced need for dose adjustments, and no interference with the rate of nephrotoxicity. For the dosing regimen of CI, a loading dose of 15 to 20 mg/kg is recommended, followed by a daily maintenance CI of 30 to 40 mg/kg.

Teicoplanin

Is another parenteral antibiotic of the glycopeptide class, like vancomycin, available only in some countries of the following continents: Europe, Asia-Pacific, Africa, and South America.
The ideal PK/PD index for teicoplanin is AUC/MIC and the range considered therapeutic is between 500-600 µg*hr/mL. Values around 610 were effective for MRSA strain with a MIC value of 0.5mg/L and some studies suggest a value of 700-800 for successful treatment.
The trough concentration monitoring has been used since software for AUC estimation is not available at many institutions, the recommended target for the treatment of uncomplicated MRSA infections in patients with normal and compromised renal function is 15-30 mg/L. For serious and/or complicated MRSA infections, such as endocarditis and osteomyelitis, the suggested target is 20-40 mg/L.

Daptomycin

Is a lipopeptide antibiotic effective in the treatment of Gram-positive organisms, including MRSA, VRE, *S. aureus* glycopeptide-resistant or intermediate and coagulase-negative staphylococci.
In clinical practice, daptomycin monitoring is not yet a reality, there isn't much data in the literature on optimization based on these concepts. Some studies suggest the ideal range of AUC/MIC24 is between 494-1277 when using doses between 4-12mg/kg q24h. These studies are based on *in vitro* PK/PD modeling using time-kill curves for MRSA in combination with Monte Carlo simulations suggesting that doses between 6mg to 10 mg/kg/day should be used in the treatment of bacteremia complicated by this strain.

Linezolid

Is an oxazolidinone antibiotic with *in vitro* activity against MRSA, VRE and *Streptococcus pneumoniae.*
There is little data on PK/PD because serum levels of linezolid are not routinely available. Some observational studies have shown significant variability in serum peak and trough levels after standard doses. The antibacterial activity is time-dependent, and the target is an AUC/MIC ratio of 80 to 120. It is recommended to maintain the minimum concentration between 2 to 7 mg/L to ensure optimal exposure and minimize hematological toxicity.
The potential of this drug lies in its excellent oral bioavailability, making it an option for oral step-down therapy following initial therapy with a parenteral anti-staphylococcal agent in selected patients with uncomplicated infections, controlled source, and improving infectious parameters.