Antimicrobial resistance: uncovering the challenges and key strategies for action

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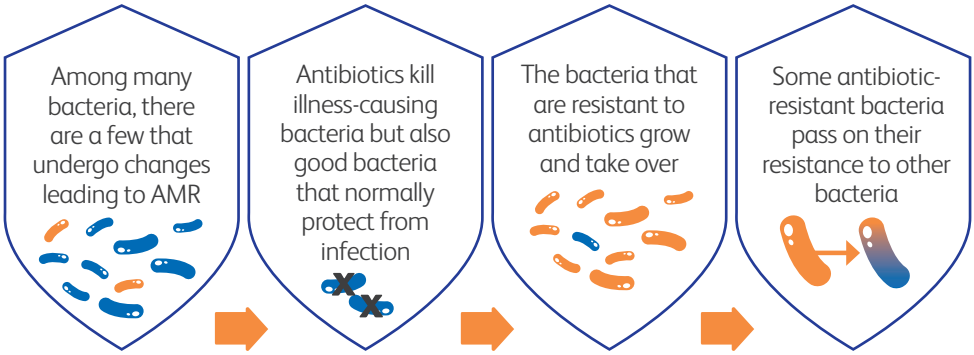
Background

How does antimicrobial resistance (AMR) develop?

Antimicrobials is the term used to describe all medicines that treat and prevent infections in humans, animals and plants.[1] They include **antibiotics, antivirals, antiparasitics, and antifungals**.[1] Over time, microorganisms undergo changes that mean they **no longer respond to antimicrobials**.[2] These treatment-resistant pathogens grow and spread, making infections difficult or impossible to treat and leading to an **increased risk of disease spread.**[2]

Figure 1: How AMR develops – example for bacteria. Similar processes occur for all types of pathogens. Adapted from National Centre for Infectious Diseases, 2024[1]



AMR in bacteria is a particular threat; there are alarming rates of resistance among prevalent bacterial pathogens, making it harder to treat common infections.[2] Antibiotic resistance therefore requires special attention.

Antibiotics play a significant role in **reducing mortality and morbidity** associated with bacterial infections.

Antibiotics can be classified as:[3]

Bactericidal
– kill bacteria

Bacteriostatic
– suppress the growth of bacteria

This classification is based on in vitro conditions, and modes of action may vary in clinical settings.[4] The effectiveness of both groups of antibiotics is comparable.[4]

Understanding resistance mechanisms helps combat the threat of AMR

Increased levels of antibiotic resistance can result in the greater use of last-resort medications.[2] **The effectiveness of these last-resort antibiotics is subsequently compromised**, increasing the risk of infections that can't be treated.[2] There is therefore a need for a greater understanding of resistance mechanisms in bacteria.

Antibiotic targets in bacteria:[5]

- Bacterial cell wall
- Protein synthesis
- RNA synthesis
- DNA synthesis
- Folic acid metabolism

Resistance to antibiotics occurs through four general mechanisms:[5]

1

Target modification

Bacteria alter the antibiotic's target site, reducing the drug's binding affinity and effectiveness

2

Efflux

Bacteria use protein pumps to expel antibiotics from their cells, lowering intracellular drug concentration

3

Immunity and bypass

Bacteria develop mechanisms to prevent antibiotics from binding to their targets or bypass the antibiotic's action

4

Enzyme-catalysed destruction

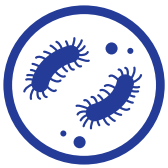
Bacteria produce enzymes that modify or degrade antibiotics, rendering them ineffective

WHO bacterial priority pathogens list

The WHO Bacterial Priority Pathogens List (BPPL) classifies antibiotic-resistant pathogens into **critical, high and medium priority categories** for research and development (R&D) and public health interventions.[6] The 2024 list covers 24 pathogens and plays a **crucial role** in the global fight against AMR.[6]

Table 1. Pathogens listed in the WHO BPPL 2024:[6]

Category of priority	Pathogens	Resistance
Critical group	*Acinetobacter baumannii*	Carbapenem-resistant
	Pathogens in the Enterobacterales order	Third-generation cephalosporin-resistant Enterobacterales Carbapenem-resistant Enterobacterales
	Mycobacterium tuberculosis	Multidrug resistant (MDR)[7]/ rifampicin-resistant
High group	*Salmonella Typhi*	Fluoroquinolone-resistant
	Shigella spp.	Fluoroquinolone-resistant
	Enterococcus faecium	Vancomycin-resistant
	Pseudomonas aeruginosa	Carbapenem-resistant
	Non-typhoidal *Salmonella*	Fluoroquinolone-resistant
	Neisseria gonorrhoeae	Third-generation cephalosporin, and/or fluoroquinolone-resistant
	Staphylococcus aureus	Methicillin-resistant
Medium group	Group A Streptococci	Macrolide-resistant
	Streptococcus pneumoniae	Macrolide-resistant
	Haemophilus influenzae	Ampicillin-resistant
	Group B Streptococci	Penicillin-resistant



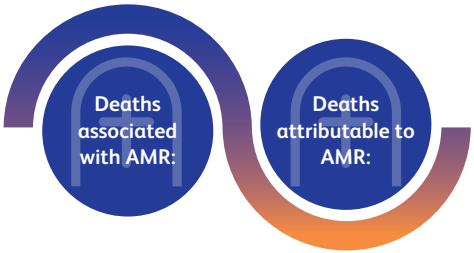
Pathogens have been listed in the critical group owing to their:

- Ability to transfer resistance genes
- Ability to cause severe infections
- Significant global burden[6]

AMR burden

AMR is among the top 10 threats to global health, putting human and animal health and welfare at risk.[8]

The burden of AMR can be defined using deaths **associated** with AMR, and deaths **attributable** to AMR:



death that occurs from a drug-resistant infection, but where resistance may not have been the direct cause.[9]

death that occurs directly as a result of treatment failure to a drug-resistant infection.[9]

There were 8.9 million deaths from bacterial infections in 2019.[9] Of these, 4.95 million were associated with AMR and 1.27 million were directly attributable to AMR (Figure 2).[9] Lower respiratory infections was the most burdensome infectious syndrome, accounting for more than 1.5 million deaths associated with AMR.[10]

Figure 2: Global burden of AMR in 2019[9,10]

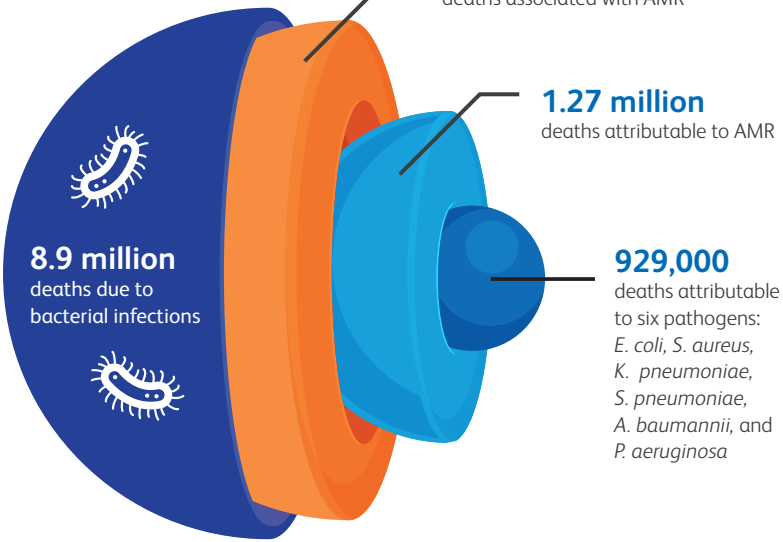
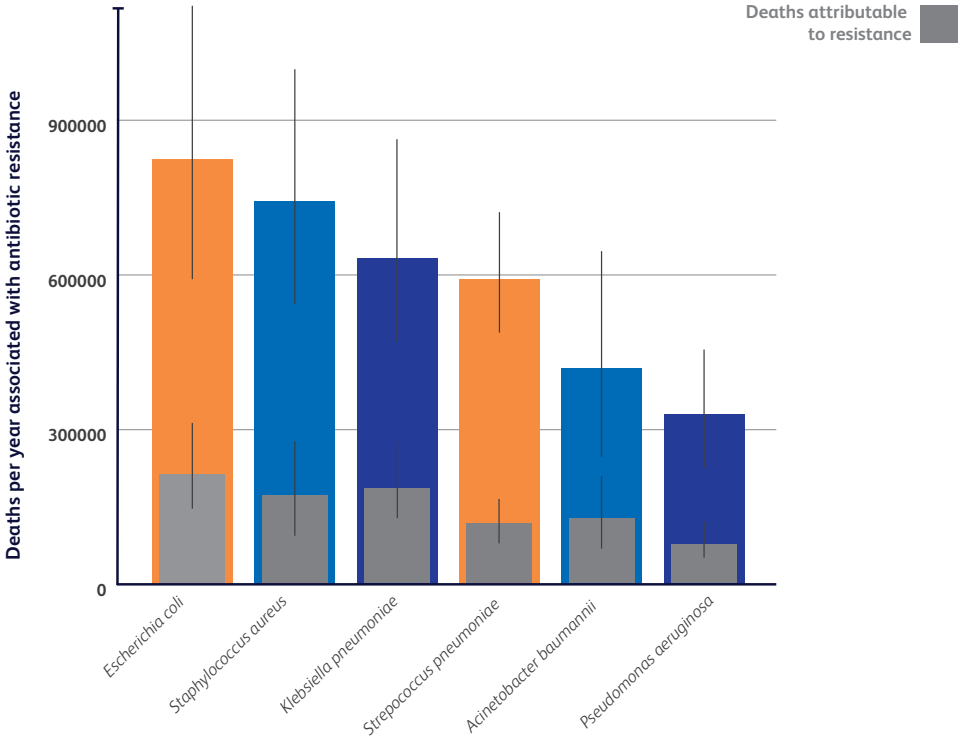
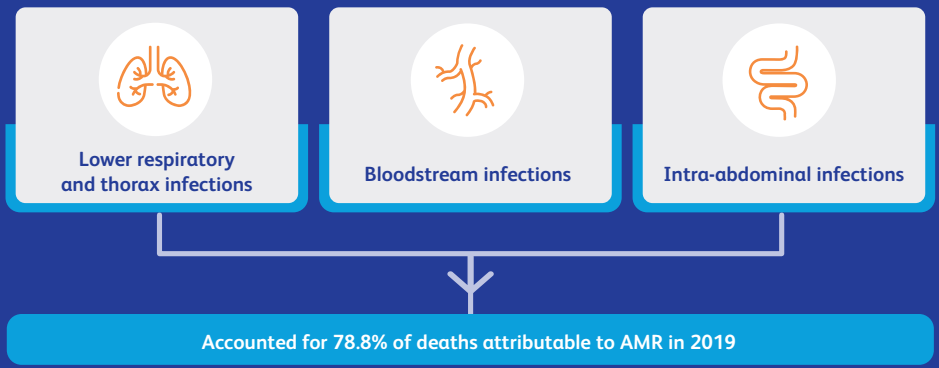


Figure 3: Number of deaths attributable to the top 6 pathogens[10]



Box 1: Infectious syndromes dominating the global burden attributable to AMR in 2019[10]



While there has been a general increase in the global burden of AMR between 1990 and 2021, there has been a notable divergence in trends across age groups (Figure 4). There was a > 80% increase in both attributable and associated AMR deaths in adults aged 70 years and over.[9] However, there was a > 50% reduction in both attributable and associated AMR deaths in children < 5 years between 1990 and 2021.[9] This decline in AMR mortality in children younger than 5 years is due to:

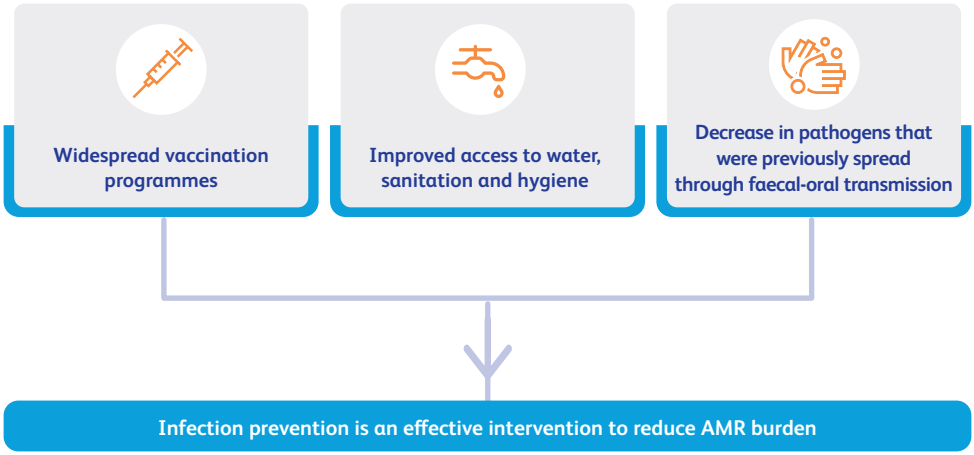
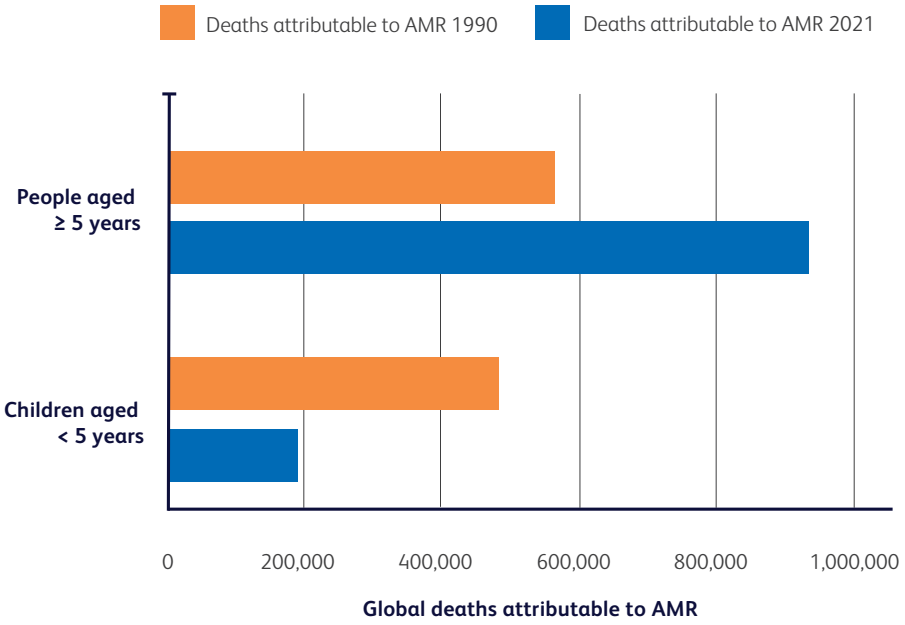
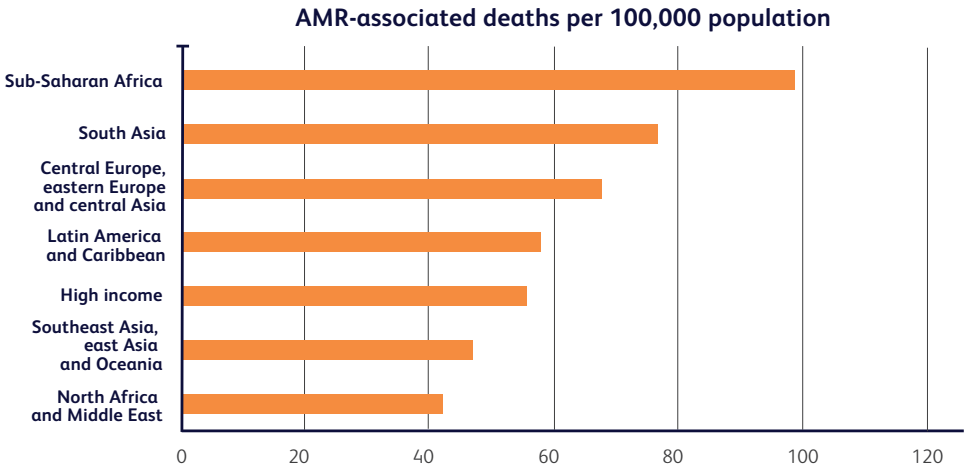


Figure 4: Deaths attributable to AMR in 1990 and 2021 in people aged ≥ and < 5 years old[9]



As well as divergence in trends across age groups, there are regional variations in deaths attributable to and associated with AMR. **The impact of AMR is heaviest in low- and middle-income countries** (LMICs), with the highest rates of death in sub-Saharan Africa and South Asia.[10] (Figure 5).

Figure 5: AMR-associated deaths per 100,000 population according to region[10]



LMICs face a number of challenges in tackling the high AMR mortality rate, including: [9]

- Limited access to antibiotics
- Fragmented health systems
- Overcrowded and inadequate intensive care units (ICUs)
- Limited staff numbers
- Few staff trained in infection control and prevention

Box 2: Economic impact of AMR

AMR is associated with substantial increases in healthcare costs (e.g., from prolonged hospital admissions and additional investigations) – in 2017 the cost in the USA was US$4.6 billion[11]

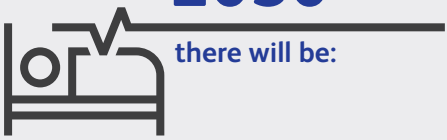
Estimates project that globally, AMR may result in:[12]

- US$1 trillion in **additional healthcare costs** by 2050
- US$1 trillion to US$3.4 trillion **gross GDP losses/year** by 2030

LMICs are therefore potential hotspots for emergence of resistant organisms. By 2050, LMICs are projected to lose > 5% of gross domestic product (GDP) if AMR remains unaddressed.[11] The global GDP will decline by 3.8%, with a resulting **global loss of US$100 trillion by 2050 if action against AMR is not taken.**[11]

Burden forecasts

By **2030** the forecast is that there will be **1.28** million deaths attributable to AMR, an increase of **13.4%** from 2022.[9]



1.91 million annual deaths attributable to AMR globally

8.22 million annual deaths associated with AMR[9]

Causes of AMR

Inappropriate antibiotic use is a major cause of AMR

Patients and carers often ask for antibiotics even when they are deemed unnecessary.[13] Physicians may relent and prescribe when pressured by patients,[14] leading to unnecessary treatment and increasing the risk of AMR.

Both the indication and adherence to antibiotics are particularly important for ensuring appropriate use.[13] The unnecessary use of antibiotics (such as for viral infections) and failure to complete the full course both contribute to inappropriate antibiotic use, which raises the risk of AMR.

As a result, the global 10-20-30 targets for 2030 include: a 10% reduction in mortality from AMR, a 20% reduction in inappropriate use of antibiotics in humans, and a 30% reduction in inappropriate animal antibiotic use.[15]

Table 2: Reasons for reducing inappropriate antibiotic use in animals[16,17]

Preservation of antibiotic efficacy	Public health	Food safety	Sustainability
Overuse can lead to resistance developing - making antibiotics less effective for both animals and humans	Resistant bacteria can transfer from animals to humans increasing the risk of hard-to-treat infections in humans	Overuse of antibiotics increases the risk of resistant bacteria in the food chain	Improving hygiene, using vaccines and other sustainable farming practices can reduce the need for antibiotics and contribute to a safer and healthier food system

Reducing inappropriate antibiotic use in animals is crucial for the One Health approach against AMR: an **integrated, unifying approach** that recognises the link between the health of humans, animals and the wider environment.[16] This approach is important for AMR: resistant organisms can quickly spread through the environment (soil and water), animals, food and healthcare facilities. The One Health model therefore provides a **holistic approach** to tackling AMR, involving collaboration between human, animal and environmental health sectors.[16]

Figure 6: The One Health approach against AMR[16]

Suboptimal diagnostic testing can result in excessive antimicrobial prescribing

Suboptimal diagnostic testing can result from lack of access to safe, affordable, and quality-assured diagnostic tests.[18]

Access to health and diagnostics may be more challenging in resource-limited settings, often leading to the use of diagnostic tests after treatment failure, which can lead to exacerbation of AMR.[14]

Optimising diagnostic testing is pivotal to the success of any programme aiming to contain AMR.

Healthcare providers often face challenges due to:

- Difficulties implementing guidelines
- Difficulty in training staff due to turn over and shortages
- Difficulties accessing high quality clinical microbiological diagnostic tests[14]

There is a need to improve diagnostic capacity to ensure patients receive targeted therapy, helping to:[19]

- Reduce antibiotic pressure, decreasing the selection for increasingly resistant species
- Reduce cost
- Minimise microbiome disturbances
- Lessen toxicity

Cross-functional teams involving all stakeholders in the patient care pathway are key to successful Antimicrobial Stewardship (AMS) programmes and, more broadly, to successful diagnostic stewardship programmes.[14] By fostering **collaboration among healthcare professionals**, diagnostic accuracy and appropriate therapy can be enhanced, ultimately enabling improved patient outcomes and containing the spread of antimicrobial resistance.

Challenges addressing AMR

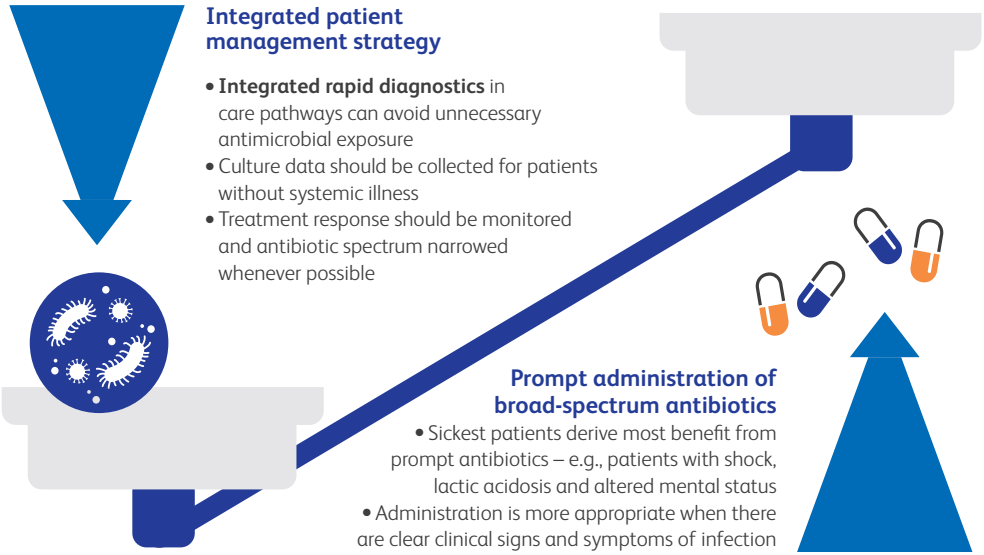
Sepsis guidelines, rapid diagnostics and antimicrobial stewardship: the path to optimal care

The Surviving Sepsis Campaign (SSC) recommends the implementation of the one-hour bundle protocol to decrease mortality rates in patients with sepsis and septic shock. This protocol requires the administration of antibiotics within the first hour for patients suspected of septic shock or with a high likelihood of sepsis.[20] Surveillance programmes can help to inform treatment decisions[21] and ensure that the empirical antibiotic therapy chosen at this stage is the most appropriate option.

While initiating therapy as soon as sepsis is suspected is vital to reduce mortality, it is equally important to **promptly follow up with diagnostic testing**.[14] This approach ensures that the empirical treatment can be **confirmed or adjusted** as needed.

The urgency of early antibiotic administration and the risk of inappropriate treatment underscores the necessity for an **integrated patient management strategy**[22] that combines clinical and diagnostic need, achieving the best patient outcomes.

Figure 7: The importance of an integrated patient management strategy combining clinical and diagnostic needs[14,22]



AMR surveillance data: limited but vital

Comprehensive AMR surveillance data, especially in resource-limited settings, are lacking, with heterogeneity in data gathered between countries also impacting comparisons.[11]

The World Health Organization (WHO) launched the WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS) in 2015.[23] This was the first global initiative aimed at standardising AMR surveillance.[11]

High-quality surveillance data are key to assess and monitor trends in AMR; however, there are a number of barriers for effective surveillance of AMR, especially in resource limited settings, including:[24]

Healthcare-associated infections (HAIs) – the greatest infectious disease burden in Europe[25]

Worldwide, 1 in 10 patients is affected by a HAI[25]

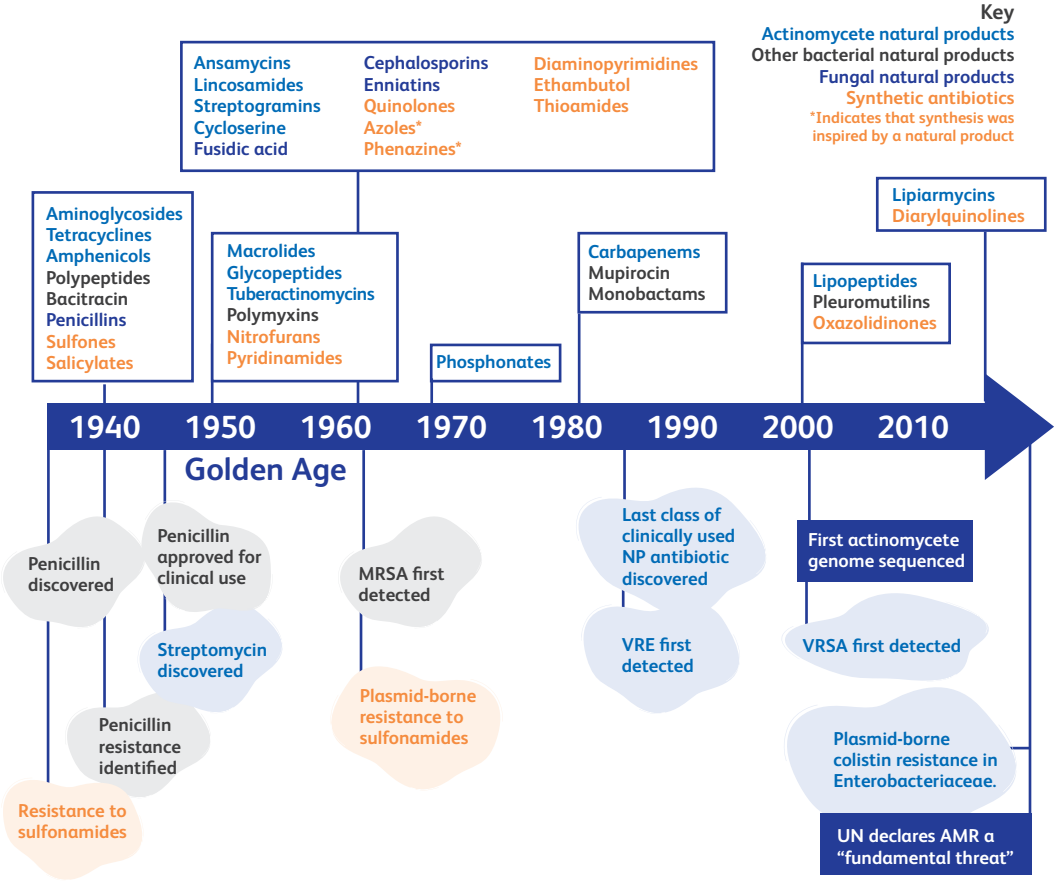
MDR, high-risk pathogens including *A. baumannii* and Enterobacterales (listed as critical in the WHO BPPL) have been implicated in HAIs around the world, leading to high morbidity and mortality. [26] HAIs lead to prolonged hospital stays, and a subsequent further risk of AMR.[26]

MDR bacteria can thrive in healthcare facilities and therefore **surveillance programmes** have an integral role in reducing the burden of HAIs.[27] By ensuring that interventions and policies are tailored according to real-time data on spread,[27] surveillance programmes can help to reduce the need for further antimicrobial use to treat infections, therefore reducing the risk of AMR.

Limited investment in R&D of new antimicrobials

Penicillin discovery in 1928 marked the beginning of the golden age of natural product antibiotic research that reached its height in the mid-1950s.[28] However, since then, there has been a gradual decline in antibiotic discovery and development.

Figure 8: Antibiotic development since penicillin discovery, adapted from Hutchings et al[28]



Although the discovery and development of new antimicrobial classes since the 1980s has been limited, there have been a number of new antibiotics that have received approval; **since 2010, 29 antibiotics have received marketing authorisation**.[11] Examples include:

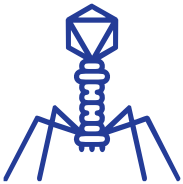
Betalactam and betalactamase inhibitors:

- ceftazidime/avibactam
- ceftolozane/tazobactam
- meropenem/vaborbactam
- imipenem/relebactam

Other types of antibiotics:

- cefiderocol
- plazomicin
- eravacycline
- delafloxacin

The use of these antibiotics therefore needs to be preserved through appropriate use. The affordability and accessibility of new antibiotics are further important factors to consider to ensure that they are available in all settings, including those where resources may be limited.[15]



Even with the development of new antimicrobials, microorganisms continue to develop resistance. Owing to these challenges, a number of non-antibiotic therapeutic strategies are emerging. Bacteriophages, for example, are viruses that infect bacteria[11] and have been used in both humans and animals with positive effects.[29] They are able to target specific bacteria and have been found to have favourable safety and tolerability.[11] Other emerging non-antibiotic therapeutic strategies include antibodies, antibody–antibiotic conjugates, antimicrobial peptides and gene therapy.[11]

Approaches for AMR mitigation

Antimicrobial stewardship requires a coordinated, educated approach

AMS is defined as: "an organisational or healthcare system-wide approach to promoting and monitoring judicious use of antimicrobials to preserve their future effectiveness"[30]

Education around AMS is key to effectiveness:

Clinician education

- Provide clinicians with up-to-date practices and guidelines for the use of antimicrobials
- Ensure clinicians are aware of the local, regional and global threats from AMR

Patient and public education

- Educate patients and the public on how antimicrobials (including antibiotics) should be used, administered, stored and disposed of
- This may be via mass education campaigns, or via direct clinician to patient education[31]

Figure 9: Factors to ensure the appropriate use of antibiotics[13]

Successful AMS programmes require a **multidisciplinary team approach**, ideally including a clinician, pharmacist, nurse and a clinical microbiologist/ laboratory technician.[32] A clinical pharmacologist, an infectious disease physician and/or a nurse with expertise in infections are also recommended if available.[32]

Antimicrobial stewardship at this stage can involve multiple members of the **multidisciplinary team** (Box 3).

Box 3. A multidisciplinary team approach to antimicrobial stewardship[14,33]

Clinical Microbiologists:

- **Choose the right diagnostic pathway** • Choose the appropriate test
- Provide **best practices to optimise diagnostic pathway**
- Notify clinicians as soon as critical results are available
- Provide regular **patient-specific consultations with clinicians** • Perform **surveillance for resistance**

Physicians:

- Consult with the microbiologist to review characteristics of the causative organisms and their susceptibility profiles
- Consider **local susceptibility patterns** when choosing the most appropriate empirical treatment
- **Escalate** promptly in case of detection of resistant organisms and **de-escalate** when possible to narrow spectrum therapy

Pharmacists:

- Surveillance of **adverse events** • **Dose adjustments** as required
- Consider the **appropriateness of recommended treatment**

Nurses:

- **Administration of treatment** in a timely manner • Reporting **adverse events**

The WHO Access, Watch, Reserve (AWaRe) classification can be applied alongside AMS to control AMR and optimise the use of antimicrobials.[34,35]

Box 4: WHO AWaRe classification of antibiotics

Access

– **access antibiotics** have a narrow spectrum of activity, have a lower potential for AMR and are lower in cost. They should therefore be widely available and are recommended for the empiric treatment of most common infections.

Examples: cefazolin, cloxacillin, doxycycline, gentamicin, sulfamethoxazole + trimethoprim

Watch

– the use of **watch antibiotics** should be carefully monitored to avoid overuse. They have a higher potential for AMR and therefore are more commonly used in hospitals.

Examples: cefotaxime, ceftazidime, ceftriaxone, ciprofloxacin, meropenem, piperacillin + tazobactam, vancomycin

Reserve

– **reserve antibiotics** should only be used as a last resort to treat severe infections caused by MDR pathogens.

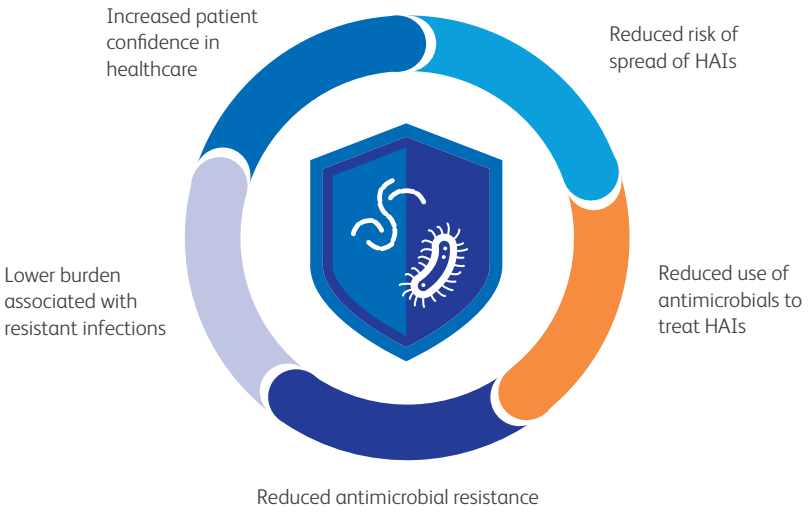
Examples: ceftazidime + avibactam, colistin, fosfomycin, linezolid, meropenem + vaborbactam

Infection prevention and control (IPC) is essential to reducing AMR and preventing HAIs[36]

Surveillance systems are recognised as a vital and essential component of IPC and help to guide IPC interventions.[27] IPC measures may be increased as a result of **active surveillance**, where patients at risk of colonisation are actively searched and measures taken to prevent widespread transmission in hospitals.[37] Active surveillance allows **early identification** of "silent reservoirs" of MDR organisms, and is recommended for high-risk patients at the time of admission.[37]

Surveillance systems can therefore help in delivering **effective IPC, ensuring the delivery of quality healthcare and optimised antibiotic use** (Figure 10).

Figure 10: The impact of high-quality IPC and the link to AMS[25]



Scaling up vaccines for common infections is another key part of IPC; **paediatric vaccines could prevent 181,500 annual deaths** associated with community-acquired resistant bacteria in LMICs.[15]

Diagnostic stewardship

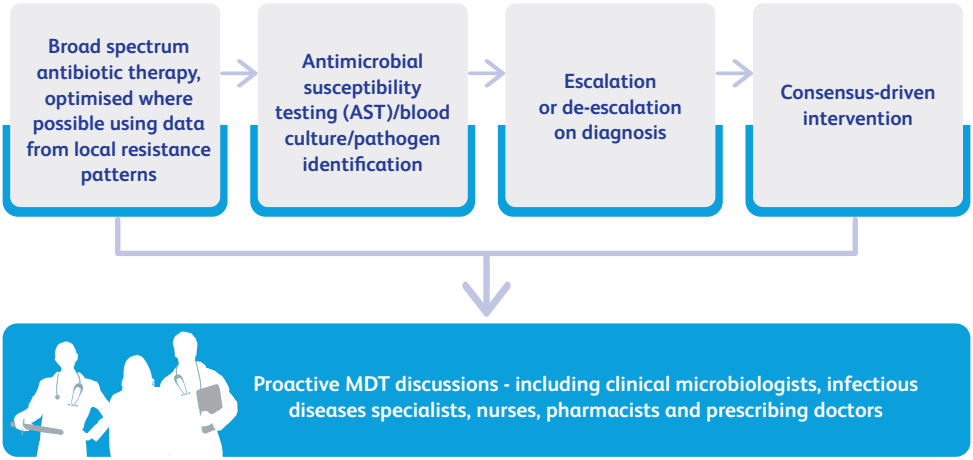
Diagnostic stewardship = ordering the right tests, for the right patient, at the right time[14]

Diagnostic tools can help improve patient outcomes and limit the risk of AMR.[14]
The diagnostic tool should be:[14]

- **Rapid** – results provided in a short amount of time
- **Accurate** – results that are close to the true value
- **Sensitive** – tools that correctly identify patients with a condition/disease
- **Specific** – tools that can correctly identify patients who do not have a condition/disease, therefore reducing false positives

To reduce inappropriate or suboptimal therapy, robust **local epidemiological data**,[21] **rapid diagnostic approaches**,[38] and **implementation of AMS**, with subsequent escalation or de-escalation once diagnostic tests confirm the nature of the causative organism and its susceptibility profile,[14] is key.

Figure 11: Steps to reaching a consensus-driven intervention facilitated by proactive discussions between members of the multidisciplinary team[21,38,39]



Standard laboratory microbial culturing techniques, identification and susceptibility testing have a long turnaround time, and this, together with suboptimal practice, **can delay initiation of targeted appropriate antimicrobial therapy**.[14]

There is therefore a need for **rapid**, **sensitive**, **affordable** and **cost-effective** detection platforms for AMR diagnostics.[38] Diagnostic tests are essential for any strategy against AMR; rapid diagnostic tests in particular have been shown to:[38]

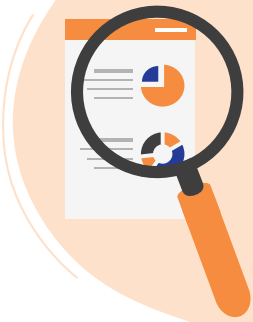
There are a range of current and emerging methods to enable rapid detection of AMR. Established methods include phenotypic and molecular-based techniques:[38]

- Molecular-based assays (e.g., polymerase chain reaction) can detect antibiotic resistant genes,[38] facilitating targeted treatment
- Phenotypic AST can provide clear information about resistance and susceptibility.[19]

While conventional phenotypic tests can take several days for results, new rapid phenotypic AST tests[19] can help to reduce turnaround time.

Rapid identification and susceptibility tests can reduce time to final AST results, preventing delays and avoiding the overuse of broad-spectrum antibiotic therapy.[14]

Surveillance is key to evidence-based, successful AMS programmes[21]



Surveillance data enable the identification of resistance trends, guiding local policies and informing treatment decisions.[21] This ensures that empirical therapy reflects local requirements.

Surveillance tools can gather information from a range of sources as part of routine care provided to patients, and these data can be used to help identify patients at greatest risk of carrying MDR pathogens.[40] The combination of punctual knowledge of circulating pathogens and successful identification of patients at risk can guide clinicians in tailoring **robust**, **data driven empiric** treatments.

Surveillance tools are also useful for creating an early warning system, ensuring that HAI cases are **detected before an outbreak occurs**. Lapses in infection prevention practices can be identified and addressed in a timely fashion. Furthermore, electronic surveillance systems allow data to be transmitted to public health authorities, so that local, regional and national trends can be monitored.[40]

Call to action: an integrated approach to tackling AMR

Tackling AMR requires a **holistic approach**, combining diagnostic stewardship, AMS and IPC.[39,41]

- AST can help inform drug susceptibility for a particular pathogen
- Clinical data should be provided ideally within the first hours of admission for viral infections, or within 24-48 hours for bacterial/fungal infections[39]

- Diagnostic results are interpreted and used to initiate correct and appropriate antimicrobial therapy
- Antimicrobial therapy is optimised based on patient specific factors (e.g., bodyweight), drug specific factors (e.g., pharmacodynamic characteristics) and, where available, results from AST

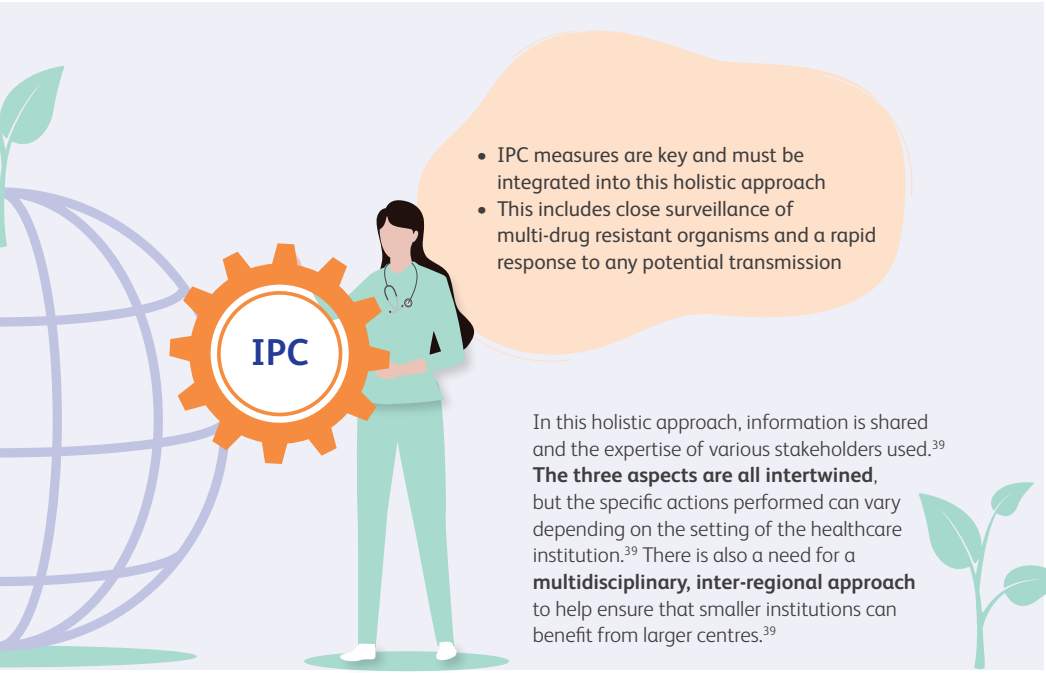
Conclusions

In conclusion, antimicrobial resistance (AMR) poses **a significant threat to global health**, impacting both human and animal populations.

The development of AMR is driven by the misuse and overuse of antibiotics, inadequate diagnostic testing, and insufficient infection control measures. To combat this growing crisis, a multifaceted approach is essential.

Robust surveillance systems are crucial for monitoring AMR trends and guiding effective interventions.

By adopting an **integrated approach** that combines efforts across human, animal, and environmental health sectors, we can mitigate the impact of AMR and ensure the continued effectiveness of antibiotics. It is imperative that we **act now** to safeguard the health of future generations.



- IPC measures are key and must be integrated into this holistic approach
- This includes close surveillance of multi-drug resistant organisms and a rapid response to any potential transmission

In this holistic approach, information is shared and the expertise of various stakeholders used.[39] **The three aspects are all intertwined**, but the specific actions performed can vary depending on the setting of the healthcare institution.[39] There is also a need for a **multidisciplinary, inter-regional approach** to help ensure that smaller institutions can benefit from larger centres.[39]

Glossary

AMR (antimicrobial resistance)
Microorganisms undergo changes when exposed to antimicrobials, making the medicines ineffective

AMS (antimicrobial stewardship)
The responsible use of antimicrobials, promoted through a coherent set of actions

AWaRe (Access, watch, reserve)
WHO classification system to guide the optimal empiric treatment of common bacterial infections

De-escalation
Discontinuation of one or more components of combined empirical therapy, and/or the change from a broad-spectrum to a narrower spectrum antimicrobial

Empirical antibiotic treatment
Initial antibiotic therapy targeted at the most likely causative microorganism

Escalation
Addition of a new antibiotic and/or the change to a broader-spectrum antibiotic

GLASS (global antimicrobial resistance surveillance system)
WHO surveillance system including surveillance of antimicrobial consumption, invasive fungal infections and a One Health surveillance model

HAI (healthcare-associated infection)
An infection that develops while the patient is receiving care in a hospital or other healthcare facility and that was not present or incubating at the time of admission. The infection may also appear after discharge

IPC (infection prevention and control)
Practical, evidence-based approach that aims to prevent avoidable infections. It covers all aspects of healthcare, including hand hygiene, injection safety and surgical site infections

LMIC (low- and middle-income country)
A collective term for low-income-, lower-middle-income- and higher-middle-income countries. These are grouped according to gross national income (GNI) per capita for a specific year

MDR bacteria (multidrug-resistant bacteria)
Bacteria that are resistant to at least one agent in three or more antibiotic categories

Targeted antibiotic Using treatment that is specific and targeted to the causative microorganism, rather than a broad-spectrum approach

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