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Fighting antimicrobial resistance

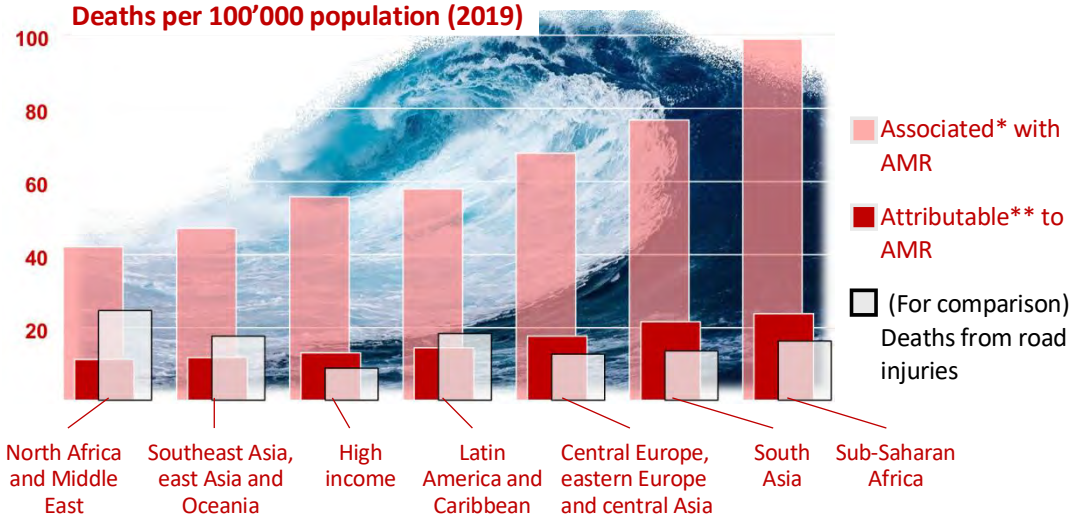
Antimicrobials – including antibiotics, antivirals, anti-fungals and antiparasitics – are medicines used to prevent and treat infections in humans, animals and plants. Antimicrobial resistance (AMR)—including bacterial resistance to antibiotics—poses a profound threat to human health. This newsletter provides an overview of the situation and references for further reading. We thank Valeria Gigante (WHO) and Peter Beyer (GARDP) for their review and comments.

Quick links

A silent pandemic
Drivers of AMR | Resistance levels | Impact
One Health response
Innovation | New actors
Making it happen
References

▶A silent pandemic

The world's first comprehensive assessment of available global data [1] has confirmed that bacterial antimicrobial resistance (AMR) is a leading cause of death around the world. The highest burden, and the largest data gaps, are in low-resource settings.



***Associated deaths**: based on an alternative scenario in which all drug-resistant infections were replaced by no infection.
****Attributable deaths**: based on an alternative scenario in which all drug-resistant infections were replaced by drug-susceptible infections.[1]

Source: Antimicrobial Resistance Collaborators. ***Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis.*** *Lancet. 2022;399(10325):629-655.* doi:10.1016/S0140-6736(21)02724-0 [1]
Source of data on road injuries: Institute for Health Metrics Evaluation. Global Health Data Exchange. Data downloaded from https://vizhub.healthdata.org/gbd-compare/ on 3 October 2022.

Background image by Elias from Pixabay

Drivers of AMR

AMR occurs naturally over time, usually through genetic changes. Antimicrobial-resistant organisms are found in people, animals, food, plants and the environment (in water, soil and air). They can spread from person to person or between people and animals, including from food of animal origin, and will readily travel around the world.

(**Above**) *Drivers of antimicrobial resistance:*[2]

Misuse of antimicrobials and poor infection control in agriculture	*Lack of access to clean water, sanitation and hygiene for both humans and animals*	*Misuse and overuse of antimicrobials in humans*	*Poor infection and disease prevention and control in health care facilities*	*Discharge of waste from health care facilities, pharmaceutical manufacturing and farms*

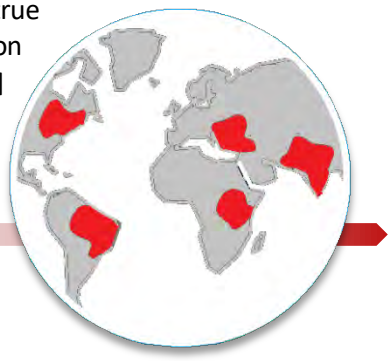
Resistance levels

Global surveillance results indicate that standard antibiotic treatment of common infections is no longer working in many patients.

- A Sustainable Development Goals (SDG) indicator monitors the proportion of patients with bloodstream infections (BSI) caused by resistant forms of two common pathogens. In 2019, **37%** of BSI due to *Escherichia coli* were resistant to 3rd generation cephalosporins, and **25%** of *Staphylococcus aureus* BSI were resistant to methicillin.[3]
- The data come from the Global Antimicrobial Resistance and Use Surveillance System (GLASS). The fourth GLASS report [3] includes data reported to WHO in 2020 from almost 25 000 surveillance sites in 70 countries. It shows worrying resistance rates to many treatments, including last-resort antibiotics.
- **High resistance rates are reported from low- and lower-middle-income countries** (LMICs), and need to be investigated.[3] Antimicrobial consumption has increased in LMICs in recent years.[4]

Impact

- Bacterial AMR is estimated to have caused **1.27 million deaths in 2019**.[1] The true burden could be greater: without effective antibiotics patients are missing out on surgery and other medical procedures that require antimicrobial prophylaxis.[5]
- AMR is projected to cause a **fall of 1.1%--3.8% in global GDP by 2050**. The losses could be as large as those provoked by the 2008–2009 global financial crisis, and they will be felt during the entire period through 2050. They will disproportionately affect low-income countries.[6]
- **AMR threatens sustainable development** with regard to health, but also food safety, food security, access to clean water, social protection, equality and other goals.[2]



Illustrations on this page are partly based on visuals from an online course on Antibiotic resistance – the silent tsunami. (Watch the Video).

▶*One Health* response

AMR has multiple drivers, and the fight against it must simultaneously consider humans, animals, plants and the environment. The Quadripartite organisations (FAO, OIE, WHO and UNEP)[1] have developed a Strategic Framework for collaboration on AMR,[7] which is reflected in the newly released One Health Joint Plan of Action.[8] These organizations have provided detailed technical guidance on what is needed to preserve antimicrobial efficacy for the benefit of all people, no matter where they live.

Antimicrobial stewardship [9]	Infection prevention and control [10]	Water, sanitation and hygiene [11]
	**Responsible use in humans** • Ensure sustainable access to essential antimicrobials • Adhere to approved indications and treatment guidelines, including adequate diagnosis • Follow the WHO AWaRe classification* • Guide patients on storage, use and disposal of antimicrobials	• Prevent infections, including health care-associated ones • Vaccination • Ensure universal access to safe water, sanitation, hygiene and health care waste management
	**Responsible use in animals** • Stop the use of medically important antimicrobials** for growth promotion • Supply antimicrobials only when prescribed by a veterinarian • Comprehensive labelling, with precautions for use and disposal • Distribute approved products only, through licensed channels only • Control advertising	• Ensure good management and farm hygiene • Vaccination • Improve hygiene and wastewater management in food production
	**Responsible use in plants** • Use antimicrobial pesticides only as legally authorized • Pesticides that have been legally restricted should not be advertised • Packaging should include instructions to minimize risks to users • Stocks and distribution channels should be controlled	
	**Responsible environmental practices** • Minimize the release of antimicrobials and other chemical substances from households, hospital effluents, animal and manufacturing plant run-off into the environment	• Reduce release of antimicrobials and antibiotic resistance genes into waterways

Source of images: [9]

Two antimicrobial classifications

* **WHO AWaRe classification** [12]

Access: The antibiotics of choice for each of the 25 most common infections. These antibiotics should be available at all times, affordable and quality-assured.

WAtch: most of the "highest-priority critically important antimicrobials" for human medicine and veterinary use. Recommended only for specific, limited indications.

REserve: Antibiotics that should only be used as a last resort when all other antibiotics have failed.

According to an indicator based on AWaRe, at least 60% of antibiotic consumption at country level should be from the 'Access' group by 2023.

** **WHO List of Critically Important Antimicrobials for Human Medicine** (WHO CIA List) [13]

A ranking of medically important antimicrobials for risk management of AMR due to non-human use.

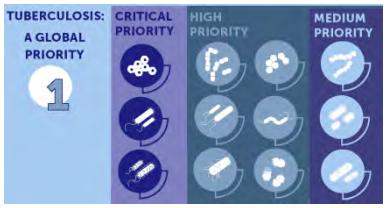
[1] **Quadripartite**: Food and Agriculture Organization of the United Nations (FAO), World Organisation for Animal Health (WOAH, founded as Office International des Epizooties, OIE), World Health Organization (WHO); United Nations Environment Programme (UNEP)

▶Innovation

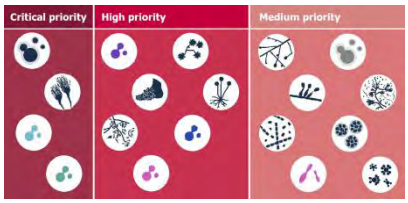
The number of multi-drug resistant pathogens has been increasing relentlessly in past decades. The R&D pipeline has not kept pace with the growing demand for new products. WHO is coordinating R&D on antimicrobial resistance.

What is needed?

- **Treatments** for priority pathogens, including traditional antibacterials and non-traditional ones such as bacteriophages, microbiome-modulating agents, antibodies or immunomodulating agents
- **Vaccines**: Next-generation vaccines against influenza and pneumococcus, new vaccines against malaria, HIV, respiratory syncytial virus, and group A *Streptococcus*, and possibly against other important AMR pathogens [14]
- **Diagnostics** to support the use of existing and new antibiotics, and new rapid tests to cut the unnecessary use of antibiotics [15]



***(Right)** The **WHO bacterial priority pathogens list** [16] identifies those pathogens causing drug-resistant infections for which new products are urgently needed.*



***(Left)** Just released: The first **WHO fungal priority pathogens list** [17]*

The pipeline

Links:
> Clinical antibacterial pipeline
> Preclinical antibacterial pipeline
> Bacterial vaccines

- In 2021 newly approved antibacterial agents, and those in clinical development, were insufficient to address antimicrobial-resistant infections, including those caused by WHO critical pathogens.[2] [18]
- In 2021, relatively few vaccines against priority pathogens were at advanced stages of development. Vaccines could become available in the short term for six pathogens, including two for which the drug development pipeline is insufficient.[19]

The regulatory landscape

Patients who have access to effective antibiotics are less likely to suffer the consequences of AMR. One reason for lack of access is that antibiotics are not registered widely.

Addressing regulatory hurdles can improve access to new antibiotics in emerging markets. Accelerated access pathways should be created for antimicrobials that target serious and life-threatening infections, and regulatory capacities mobilized to deal with the complex trials needed to identify drugs that are effective against drug-resistant pathogens.[20]

***(Above)** A landscape analysis has studied the challenges and opportunities of regulatory approvals of antibiotics in Brazil, India and South Africa.[20]*

[2] **Critical pathogens**: carbapenem-resistant *A. baumannii* (CRAB), *P. aeruginosa* (CRPA), and carbapenem-resistant *Enterobacterales* (CRE)

Innovation (continued)

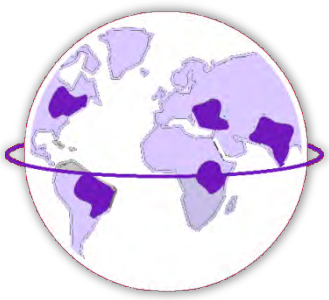
New actors

For pharmaceutical companies, antimicrobials are commercially unattractive. Academia and small biotech companies have been successful in drug discovery but often lack financing to bring a product to market. New actors have stepped up to revitalize the development of new products, but challenges remain.

	Funders of R & D		Non-profit R&D organisations
	Public sector	**Private sector**	
Examples	• Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (**CARB-X**) • Biomedical Advanced Research and Development Authority (**BARDA**) • Joint Programming Initiative on Antimicrobial Resistance, (**JPIAMR**) • European Health Emergency Preparedness and Response Authority (**HERA**)	• **AMR Action Fund** Sponsored by a consortium of multinational pharmaceutical companies, WHO and the European Investment Bank • **REPAIR Impact Fund** established by Novo Holdings REPAIR: Replenishing and Enabling the Pipeline for Anti-Infective Resistance	• **Global Antibiotic Research and Development Partnership** (GARDP) Created by WHO and the Drugs for Neglected Diseases Initiative (DND*i*) Builds targeted public-private partnerships [21]
Advantages	Public health focus. Successful in early phases of product development	Significant funding for targeted investments to address health priorities	Long-term commitment to public health goals; collaboration and networking platform
Challenges	Challenges in raising sufficient funding to complete clinical studies and achieve marketing authorization	Focus on shareholder returns. Profit prospects are not sufficient to incentivize R&D to cover global unmet needs	Dependent on public health prioritization and government oversight by funders who allocate public resources [21]

"No one is safe until everyone is safe"

The pandemic of antimicrobial resistance must be fought with global public health needs in mind. Different public-private partnership models may be employed to raise the funding and human resources that are required to develop products and keep them on the market. In any such partnership, government input and oversight are needed to maintain a public health focus. Non-profit organisations like GARDP, that mobilize the support of governments and foundations all along the development process, have a good chance of success. Their approach may encourage governments to create incentives for public and private actors to ensure that effective antimicrobials will reach all those who need them.[21]



▶Making it happen

Countries have affirmed their commitment to fight AMR in a political declaration.[22] In practice, however, this is challenging. Because AMR has multiple drivers, it needs to be tackled on many fronts. Combating AMR requires joint action, with shared responsibilities.

*(**Above**) Different stakeholders have different roles to play in combating AMR.*

"Governments, civil society and the private sector need to be engaged and to collaborate in an unprecedented effort across the human, animal, plant, food and feed production and environmental sectors, based on a shared vision and goals."

Interagency Coordination Group on Antimicrobial Resistance, in its report to the Secretary-General of the United Nations.[2]

Seven years after the release of the 2015 WHO Global Action Plan on Antimicrobial Resistance, WHO has released a comprehensive review on its implementation,[23] documenting key strengths as well as some missed opportunities and shortcomings. Eight factors have been identified that will be needed for joint action against AMR in the future.[24]

1. A governance structure that engages all relevant international agencies, mobilizes financing and ensures accountability
2. Equitable global access to effective antimicrobials
3. Collaboration to curb inappropriate antimicrobial use in healthcare delivery, in food systems and the environment—the One Health approach
4. Meaningful engagement of civil society organizations
5. Resistance to the undue influence of those with financial conflict of interest
6. Clear milestones for progress monitoring and prioritization of investments
7. Adequate funding for implementation of National Action Plans (NAPs)
8. Recognition of AMR as one of the facets of pandemic preparedness and prevention

The theme of this year's World Antimicrobial Awareness Week (WAAW 2022) is 'Preventing Antimicrobial Resistance Together'. We hope that the information in this newsletter will make a small contribution towards this goal.

▶Get involved

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A silent pandemic

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Drivers of AMR — Resistance levels — Impact

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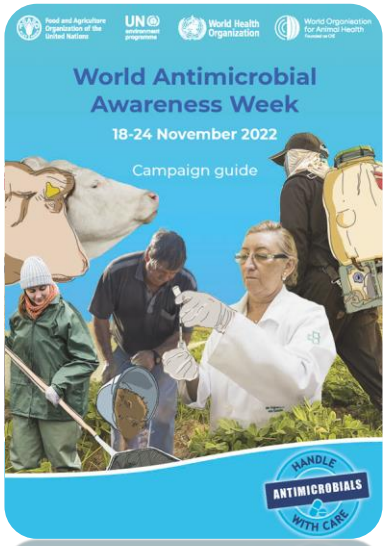
Get involved

World Antimicrobial Awareness Week 2022
18-24 November 2022
Campaign guide

The Quadripartite organisations have jointly developed a campaign guide to support WAAW 2022. The guide is designed to provide information and ideas on how to support the campaign and proposes ways for different stakeholders to engage and develop their own local activities. It includes the campaign theme, key messages, event ideas, social media information and links to various campaign resources.



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