

## New antibiotics authorized by referral agencies. Brief communication

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### Brief communication

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Antimicrobial Resistance (AMR) has been defined as a public health problem due to the exponential progression of its spread. It will not only cause millions of deaths, but also greater suffering and increased costs for health services, and animal production with serious repercussions on food security. The World Bank has

estimated that if the problem of AMR is not addressed, the global economy may have lost almost 4% of annual Gross Domestic Product (GDP) by 2050, and that the losses will be even greater in low- and middle-income countries. In 2050, this situation could lead 28 million inhabitants to a situation of poverty, within developing

countries, especially due to the effects of drug resistance on the economy, livestock industry and costs of medical services (World Health Organization, WHO, 2021).

The change in the use and/or indications for the use of antimicrobials offered within health centers is of great importance, since innovative and/or new antimicrobials will possibly have the same destination as the current ones and, therefore, they will become ineffective, which would generate a considerable economic impact on the countries and their health systems, since the productivity of patients and their caregivers is altered, by prolonging hospital admissions and care with a higher economic cost. Without tools to adequately prevent and treat drug-resistant infections, and poor accessibility to safe and effective medications, drug resistance and death will increase.

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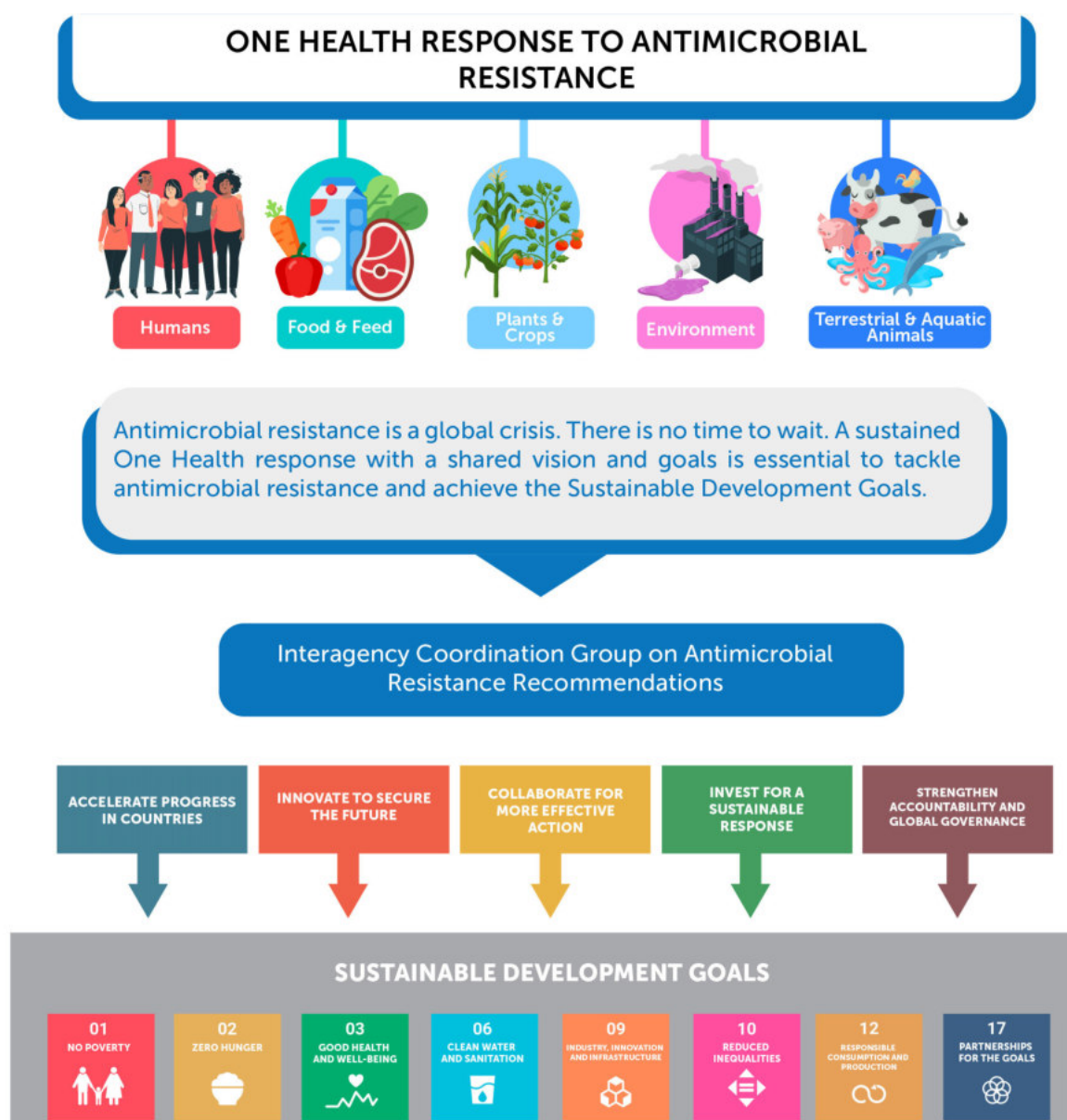
Antimicrobial Resistance (AMR) arises when bacteria, viruses, fungi and parasites change and stop responding to antimicrobials, making it difficult to treat infections and increasing the risk of spreading diseases, developing severe forms of these and even cause death. Due to resistance, antimicrobials become ineffective, making infections increasingly difficult or impossible to treat.



It is necessary to emphasize that the clinical development line for new antimicrobials is exhausted. In 2019, the WHO determined that there were 32 drugs in clinical development capable of combating pathogenic microorganisms that are a priority for the WHO, however, only six were detailed as innovative. Therefore, the lack of access to quality antimicrobials continues to be a problem and the shortage of antimicrobials will affect the health systems of all countries regardless of the levels of development (Source: WHO, 2021).

The current antimicrobial resistance response requires greater political leadership, advocacy, collaboration, coordination and accountability at all levels. Although the effects of antimicrobial resistance on human health and food production have received considerable attention, political commitment and stakeholder participation in these areas at global and national levels remains insufficient. The WHO Interagency Coordination Group on Antimicrobial Resistance has made the recommendations detailed in Figure 1.

**Figure 1. One health, IAGG recommendations and Sustainable Development Goals, SDG**



Source: Report to the secretary-general of the United Nations, april 2019

### Recently authorized authorized antibiotics

According to the results of phase III clinical studies (Pfizer Inc., 2023), the combination aztreonam avibactam (Emblaveo) has been shown to be effective and well tolerated in the treatment of complicated infections caused by aerobic gram-negative organisms, as well as pathogens with resistance to different drugs that produce metallo- $\beta$ -lactamase (MBL), for which there are currently limited or no treatments, also a safety profile similar to that of aztreonam alone. In the REVISIT study where aztreonam- avibactam was compared  $\pm$  metronidazole (MTZ), with meropenem (MER)  $\pm$  colistin (COL) for the treatment of complicated intra-abdominal infections (cIAI), hospital-acquired pneumonia (HAP), and ventilator-associated pneumonia (VAP), good results were obtained in patients with complicated intra-abdominal infections ( cIAI), with a cure rate of 76.4% for the group treated with aztreonam-avibactam  $\pm$  metronidazole (MTZ), compared to 74.0% for those treated with meropenem (MER)  $\pm$  colistin (COL) and in patients with hospital- acquired pneumonia (HAP), and ventilator-associated pneumonia (VAP), the rate of cure was 45.9% for aztreonam-avibactam  $\pm$  metronidazole (MTZ) and 41.7 for meropenem (MER)  $\pm$  colistin (COL). Regarding safety, the studies showed that the adverse events of the combination treatment were similar to those described for Aztreonan alone, in addition, no patient who was treated with the aztreonam-avibactam combination suffered a serious adverse event that was related to the treatment in research.



On March 21, 2024, the European Medicines Agency EMA reported that the Committee for Medicinal Products for Human Use (CHMP) issued a favorable opinion through which it recommended granting marketing authorization in the European Union for the drug Emblaveo, a combination of antibiotics, intended for the treatment of severe hospital-acquired intra-abdominal and urinary tract infections, acquired pneumonia, as well as infections by aerobic gram - negative microorganisms in patients in whom treatments become limited due to the type of infection (European Agency for Medicines (EMA) 2024).



Emblaveo is a combination of two fixed-dose antibiotics of aztreonam- avibactam. Aztreonam is classified as a monocyclic beta-lactam, capable of inhibiting the synthesis of the cell wall of bacteria, since it acts on penicillin-binding proteins, on the other hand, Avivactam is recognized for its inhibition activity of non- $\beta$  -lactam beta-lactamase enzymes that It effectively inhibits serine carbapenemases (CP) ( Sader et al. 2020 ), which does not allow some beta-lactamases such as class A, C and D to hydrolyze Aztreonam.

It should be noted that Emblaveo is indicated in adult patients with limited therapeutic options, so it is recommended to consult with a doctor with experience in

the treatment of infectious diseases before using it. Likewise, it is important to mention that the most frequent adverse reactions were anemia, elevation of serum transaminases and diarrhea. As it is a drug that has recently been approved, pharmacovigilance is important with respect to serious and unexpected adverse events that it may present in the course of its use in patients.

The effectiveness of Zevtera (FDA, 2024) for the treatment Staphylococcus aureus bloodstream infections (bacteremia) (SAB) was verified through randomized, controlled, double-blind clinical trials. 69.8 % of participants who received Zevtera showed treatment success, defined as survival, improvement in symptoms, elimination of the bacteria from the bloodstream, absence of new complications (FDA, 2024), versus 68.7% of participants who received the comparator drug; for the treatment of community-acquired bacterial pneumonia (CABP), efficacy was assessed by early clinical response, 91.3% of subjects treated with Zevtera achieved an early clinical response in the assigned period, compared to 88.1% of subjects who were treated with the comparator treatment; For CABP treatment, the main measure of effectiveness was the clinical cure rate at the cure test visit between days 7 and 14, of participants who were treated with Zevtera 76.4% achieved clinical cure, versus 79.3% of those who were treated with the comparator drug.



The Food & Drug Administration (FDA) on April 3, 2024 approved a new antibiotic Zevtera (ceftobiprole medocaril sodium injection), intended for the treatment of adults with Staphylococcus aureus (SAB) bloodstream infections (bacteremia), also for cases of right-sided infective endocarditis; as well as for adult patients with acute bacterial skin and skin structure infections (ABSSSI); and for adult and pediatric patients in the age ranges three months to less than 18 years with community-acquired bacterial pneumonia (CABP) (Food and Drug Administration (FDA) 2024).



The median rates reported in 76 countries are 42% for E. coli resistant to third-generation cephalosporins and 35% for Staphylococcus methicillin - resistant aureus , which represent a major concern. In the case of urinary tract infections caused by E. coli , they reveal that one in five cases showed reduced susceptibility to standard antibiotics such as ampicillin, cotrimoxazole and fluoroquinolones in 2020. This makes it difficult to effectively treat infections.

### Resistance of some bacteria

The global rise in antibiotic resistance poses a significant threat, decreasing the effectiveness of common antibiotics against widespread bacterial infections. The 2022 Global Antimicrobial Use and Resistance Surveillance System (GLASS) report highlights alarming rates of resistance among prevalent bacterial pathogens.

Higher levels of resistance potentially lead to greater use of last resort drugs such as carbapenems, for which resistance is in turn observed in multiple regions. As the effectiveness of these last-resort medications is compromised, the risks of infections that cannot be treated increase. Projections from the Organization for Economic Cooperation and Development (OECD) indicate that resistance to last resort antibiotics is expected to double by 2035 compared to 2005 levels, underscoring the urgent need of sound antimicrobial stewardship practices and improved surveillance coverage worldwide (WHO, 2022).



*Klebsiella pneumoniae* is a common intestinal bacterium, also showed high levels of resistance against critical antibiotics.

## Conclusion

Antimicrobial Resistance (AMR) is an issue of concern for public health systems; therefore, it is important for drug regulatory agencies and the World Health Organization (WHO) to develop new medications that counteract the lack of effectiveness of some of the antibiotics currently used. High surveillance agencies such as EMA and FDA develop guidelines for the pharmaceutical industry that promote research into new antibacterial drugs for the treatment of different infections, as well as educational programs, to promote the rational use of antibiotics and counteract the bad practice of self-medication. Therefore, education in this regard, from health professionals and the population that consumes this type of drugs, is an essential part of reducing AMRs.

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