

Original Research

Received 29 May 2026

Revised 28 July 2026

Accepted 06 August 2026

Natural Resources for Human Health
2026, Vol. 6 (14s): 1386–1392

KEYWORDS:

Antimicrobial resistance, Invasive fungal infections, Carbapenemase genes, *Candida auris*, *Aspergillus fumigatus*, Antifungal resistance, Clinical outcomes, Drug development

Antibiotic Resistance and Fungal Infections: Current Challenges in Clinical Microbiology and Therapeutics

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ABSTRACT: Antimicrobial drug resistance and invasive fungal infections have emerged as increasing worries in the disciplines of clinical microbiology and medicine. In this secondary research study, scientific literature available through the databases PubMed, Scopus, and Web of Science published between 2021 and 2025 was analysed. Information on MIC values, resistance genes, and clinical outcomes was collected and analysed through the Joanna Briggs Institute checklist and Braun and Clarke thematic analysis. A total of eight findings were determined. The GRAM study estimates that 4.71 million deaths due to antibiotic resistance occurred in 2021, of which 1.14 million occurred directly. They are the following carbapenemases: KPC, NDM-1, and OXA-48; *mecA*, *vanA*, and *mcr-1*. The number of *Candida auris* infection cases in the USA has grown from 476 in 2019 to 4,514 in 2023, with 90 % fluconazole resistance. The mortality rate in the case of azole-resistant *Aspergillus fumigatus* infections due to CYP51AA mutations (TR34/L98H, TR46/Y121F/T289A) is 60 % in certain patient groups. Antifungal agents are now represented by four different drug classes, and fungal infections in the world result in 3.8 million deaths yearly. Blood culture sensitivity for candidemia detection is only 50 %. According to the WHO 2023 pipeline, there are 97 antibacterial drugs under development, out of which only 12 are truly innovative.

INTRODUCTION

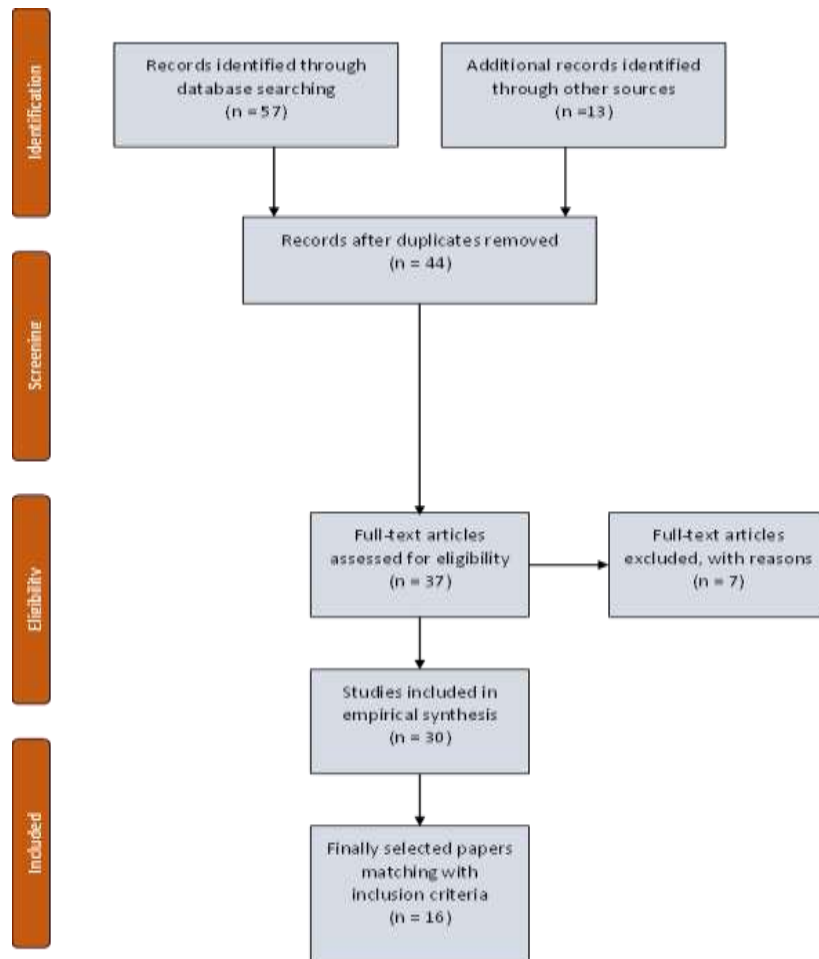
In spite of the fact that there have been years of progress in the field of antimicrobial treatments, the problem of infectious diseases remains a major threat to the well-being of people all over the world. Indeed, the use of antibiotics has completely changed healthcare, allowing surgeries, oncology treatments, and organ transplants that were not possible before their discovery. However, their incorrect use has led to the emergence of many antibiotic-resistant strains of bacteria. Resistance to antimicrobial agents is the most common issue when it comes to the guidelines set up by WHO concerning public health (World Health Organization, 2025). Such bacteria not only make patients sick for a longer period of time, but also put their lives at stake because of infections caused by them. Gram-negative bacteria are especially dangerous, since they possess many methods of resisting antibiotics which can be passed between various species.

Fungal infections are another type of infection that pose a parallel threat in clinical microbiology. Invasive candidiasis, aspergillosis, and cryptococcosis affect mainly immunocompromised individuals who are undergoing chemotherapy, taking steroid medication, or in intensive care. *C. auris* is a novel form of yeast infection which has developed resistance to a broad spectrum of antibiotics and tends to cause recurrent infections in healthcare facilities (Anandani *et al.* 2025). The capacity of *C. auris* to endure on surfaces, in addition to its resistance to almost all disinfection methods, makes it hard to handle. There has been an increase in the resistance of *A. fumigatus* to azoles in part due to fungicides used in agriculture.

There are only a few drug classes to fight fungal infections, such as azoles, echinocandins, and polyenes. These medications face several limitations, namely toxicity, drug interactions, and poor oral bioavailability. The diagnosis of these infections is hard due to the delay of cultures and their insensitivity (Bassetti *et al.* 2022). The antibiotic development pipeline has also weakened,

since few pharmaceutical companies invest in drugs with limited commercial returns. Together, these factors demand improved surveillance, rapid diagnostics, stewardship programs, and novel therapeutic strategies to protect patient outcomes worldwide.

METHOD



Secondary research methods were employed in this research through the use of peer-reviewed literature on microbiology and clinical studies. To begin with, articles were screened on the PubMed, Scopus, and Web of Science databases. Secondly, articles related to carbapenem resistance, *Candida auris*, and azole-resistant *Aspergillus* were filtered out. Thirdly, the inclusion criteria were set in a way that only articles published between 2021 and 2025 and in English were included. Fourthly, Minimum Inhibitory Concentration, resistance genes and treatment outcomes were extracted systematically. The quality of the data gathered was analysed through the use of the Joanna Briggs Institute Critical Appraisal Checklist for selected studies. Themes of the data were identified and analysed based on the identification of relevant themes (Jia & Stern, 2026). The thematic analysis was done based on the method proposed by Braun and Clarke, which involves familiarisation, initial coding, theme generation and theme review, among other processes. These themes that have been identified include resistance mechanisms, delayed diagnosis, few treatment options and stewardship measures, among others. Ethical approval was not necessary because no primary data was used.

RESULT

Global Mortality Burden of Antimicrobial Resistance

Based on the GRAM study, it is estimated that about 4.71 million people died due to antibiotic resistance in 2021. Out of this number, 1.14 million deaths are due to resistance infections in the year 2021. Predictions show that by 2050, deaths due to infections can be as many as 1.91 million per year without any intervention (GRAM Study, 2021). The associated deaths are

projected to increase to 8.22 million, with a higher incidence among the elderly than the younger population. Based on WHO GLASS reports in 2023, one out of six laboratory-confirmed bacterial infections is resistant.

Year	Deaths directly attributable to resistance	Deaths associated with resistance
2019	1.2 million	4.95 million
2021	1.14 million	4.71 million
2050 (forecast)	1.91 million	8.22 million
Projected change, 2021 to 2050	Almost 70 percent rise	75 percent rise

Table 1. Temporal Trends and Projections of Resistance Linked Fatalities

(GRAM Study, 2021)

Lower respiratory infections, bloodstream infections, and intra-abdominal infections cause the majority of resistance-associated deaths. High age-standardised mortality due to resistance is found in Sub-Saharan Africa and South Asia (Boakye-Yiadom *et al.* 2024). Limited access to culture facilities and second-line antibiotics increases problems in these regions. Resistance causes longer hospital stays, admission to the intensive care unit, and high cost of treatment. Resistance causes a reduction in global gross domestic product by 3.8% in 2050.

Molecular Mechanisms of Bacterial Resistance

Antibiotic resistance may result from enzyme-mediated degradation, target modification, decreased permeability and efflux systems. The extended-spectrum beta-lactamases (ESBLs) are responsible for the inactivation of the third-generation cephalosporins. ESBLs have been isolated frequently in *E. coli* and *K. pneumoniae*. The KPC, NDM-1, and OXA-488 enzymes mediate the hydrolysis of carbapenems, which are the last-resort beta-lactams (Zhou *et al.* 2026). The *mecA* gene encoding for penicillin binding protein 2a with decreased binding affinity towards the beta lactams causes methicillin resistant *Staphylococcus aureus*.

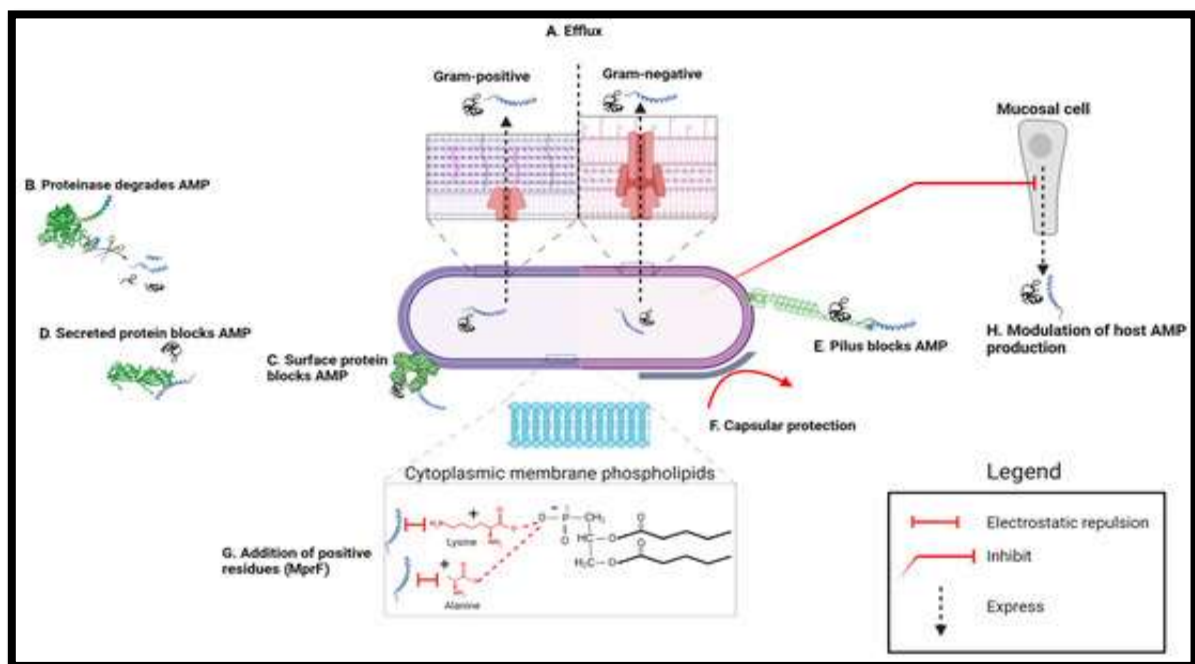


Figure 1: Bacterial mechanisms of AMP resistance not associated with modifications of cell wall structures.

(Source: Tajer *et al.* 2024)

The *vanA* and *vanB* operons in enterococci alter peptidoglycan by changing the D-alanine-D-alanine structure to a D-alanine-D-lactate structure. The decrease in permeability due to the reduction in porins such as OmpK35 and OmpK36 makes the entry of antibiotics into *K. pneumoniae* difficult. The efflux system includes the AcrAB-TolC and AdeABC systems responsible for the expulsion of various antibiotics from Enterobacterales and *Acinetobacter baumannii* (De Gaetano *et al.* 2023). The *mcr1* genes present on the plasmids cause colistin resistance by modifying the lipid A with phosphoethanolamine.

Carbapenem-Resistant Gram-Negative Pathogens

According to the list of WHO 2024 bacterial priority pathogens, carbapenem-resistant *Acinetobacter baumannii* and Enterobacterales are included in the group of critical pathogens. Mortality from carbapenem-resistant *Acinetobacter baumannii* infections caused by bloodstream infections in intensive care units can be between 40% and 60%. Mortality from carbapenem-resistant Enterobacterales bacteremia can be higher than 30%, especially in the case of delay in treatment.

Resistant pathogen group	Deaths in 1990	Deaths in 2021	Approximate change
Methicillin resistant <i>Staphylococcus aureus</i> (MRSA)	57,200	130,000	More than doubled (about 127 percent rise)
Carbapenem resistant Gram negative bacteria	127,000	216,000	About 70 percent rise

Table 2. Pathogen Level Changes in Lethality Across Three Decades

(GRAM Study, 2021)

According to the CDC report in 2019, there were about 2.8 million antibiotic-resistant infections in the USA each year, along with more than 35,000 deaths annually from them. The resistant *Pseudomonas aeruginosa* is nonsusceptible to fluoroquinolones, carbapenems, and beta-lactams. Colistin is the alternative treatment; however, colistin has serious side effects such as nephrotoxicity in up to 30% to 50% of patients. Ceftazidime avibactam is able to treat KPC and OXA-48 but does not work against NDM metallo-beta-lactamase producers (Lazar *et al.* 2024). Recently, aztreonam-avibactam became available for treatment of metallo-beta-lactamase-producing Enterobacterales. Cefiderocol acts through the siderophore iron uptake system; however, resistant strains are already known. Hospital outbreaks occur due to contamination of sinks, ventilators, and reprocessed endoscopes.

Candida auris and Multidrug-Resistant Yeasts

The fungus was originally isolated from a Japanese patient with an ear infection in 2009. The fungal priority pathogens list of WHO puts it under critical priority level. In the United States, the clinical cases of *Candida auris* increased from 476 in 2019 to 4,514 in 2023 as per surveillance by the CDC. The fungus is resistant to fluconazole in approximately 90 %, amphotericin B in 30 %, and less than 5 % to echinocandins. There are pan-resistant strains reported, which leave clinicians without an active antifungal class to combat it. Azole resistance occurs due to mutations in the ERG11 gene, such as Y132F, K143R, and F126L (Ceballos-Garzon *et al.* 2023). Overexpression of the DR1 efflux pump, with the help of mutations in TAC1B, causes decreased susceptibility to azoles. Echinocandin resistance arises from mutations in the FKS1 hotspot affecting 1,3-beta-D-glucan synthase. It persists on the skin surface of the armpits and groin for months. It survives on environmental surfaces for weeks. Crude mortality of invasive infection is between 30 and 60%.

Azole Resistance in Aspergillus fumigatus

There is an estimated number of 2.1 million cases of invasive aspergillosis per year, mainly in cases of hematologic malignancies or severe influenza. Voriconazole and isavuconazole continue to be first-line agents, meaning that azole resistance is clinically significant. It develops because of mutations in the CYP51A gene, particularly TR34/L98H and TR46/Y121F/T289A (Song *et al.* 2026). These mutations are highly linked to environmental exposure to agricultural azole fungicides, such as tebuconazole and propiconazole. Surveillance in Europe indicates a prevalence of about 3 to 6 %, whereas in parts of the Netherlands, it can be even higher. Resistant strains can be acquired by patients without prior treatment with azoles because of their environmental origin. Cross-resistance is common among itraconazole, voriconazole, posaconazole, and isavuconazole. There is an increased rate of mortality at 12 weeks in azole-resistant invasive aspergillosis, up to 60 % in some series. Liposomal amphotericin B is a

second option, although its nephrotoxicity prevents prolonged therapy (Almazmomi *et al.* 2026). There were reported cases of pulmonary aspergillosis in 10 to 15 % of ventilated patients with COVID-19.

Limited Antifungal Drug Classes and Treatment Toxicity

Antifungals used in systemic antifungal therapy include polyenes, azoles, echinocandins, and the pyrimidine analogue, flucytosine. Echinocandins were introduced in 2001, and there have not been any new classes developed in decades since then. Fungi are eukaryotes, which limits the drug targets due to common cellular mechanisms between fungi and humans. Amphotericin B targets ergosterol and leads to nephrotoxicity, hypokalemia, and infusion reaction. Azoles target the 14-alpha-demethylase enzyme that produces lanosterol in fungi. Azoles lead to hepatotoxicity, QT prolongation, and cytochrome P450 interactions. Echinocandins target 1,3 beta-D-glucan synthase but are inactive against *Cryptococcus* and do not cross into cerebrospinal fluid (Huang *et al.* 2025). Monotherapy with flucytosine rapidly develops resistance, and availability in low-income countries is limited. There are 112,000 deaths from cryptococcal meningitis estimated in 2020 with effective treatment strategies being known. Global deaths from the fungal infection account for 3.8 million annually, with 2.5 million directly attributable. The drug rezafungin is approved, while isavuconazole and fosmidomycin are being investigated.

Diagnostic Delays and Surveillance Gaps

Sensitivity of blood culture for invasive candidiasis is about 50%, and it takes a few days to achieve results. Bronchoalveolar lavage fluid culture is not sufficiently sensitive for invasive pulmonary aspergillosis detection. Sensitivity of serum 1,3 beta-D-glucan is about 75%, but this test does not allow identification of the species. The galactomannan test helps in detecting aspergillosis, but previous antifungal prophylaxis decreases its sensitivity. Antimicrobial susceptibility testing of bacteria takes 48 to 72 hours and prolongs empirical broad-spectrum therapy. MALDI-TOF mass spectrometry, Xpert Carba-R, and whole-genome sequencing could decrease the time of identification and detection of resistance (Uitz *et al.* 2024). Delay in proper treatment of candidemia is consistently linked with a significantly increased mortality. Fungal susceptibility testing according to CLSI or EUCAST guidelines is not performed in many laboratories. Outdated laboratory systems are illustrated by misidentification of *Candida auris* as *Candida haemulonii* or *Rhodotorula*. Surveillance of fungi is still very fragmented, and many countries do not have up-to-date information on resistance for policy purposes.

Weak Drug Pipeline and Stewardship Challenges

According to the WHO 2023 antibacterial pipeline review, out of 97 drug candidates, only 32 were found to be active against priority pathogens. Of those 32, only 12 were innovators and very few targeted critical Gram-negative bacteria. The antifungal pipeline was even poorer, with fewer than a dozen drug candidates in advanced clinical trials. Financial losses were among the reasons behind the 2019 bankruptcy of Achaogen and Melinta Therapeutics. According to the CDC, about 28% of all antibiotic prescriptions in outpatient visits in the United States are unnecessary. In the case of the COVID-19 pandemic, 72% of patients have received antibiotics despite 8.6% having bacterial co-infections.

Scenario	Projected outcome by 2050
No further policy action (reference)	About 39 million deaths, 2025 to 2050
Regular release of new antimicrobials targeting Gram negative pathogens	Up to 11 million resistance related deaths averted
Deeper health investment, with better severe infection care and wider antibiotic access	Up to 92 million lives saved
Highest regional burden (South Asia)	11.8 million attributable deaths, 2025 to 2050

Table 3. Projected Lives Saved Under Alternative Policy Scenarios to 2050

(GRAM Study, 2021)

About 73% of all global antimicrobial consumption is in farm animals, which creates environmental resistance pools. Similarly, agricultural azole fungicide utilisation maintains resistance in environmental *Aspergillus* populations. Hospital antibiotic

stewardship measures reduce the course of antibiotics by 2 days without affecting mortality rates, according to a Cochrane meta-analysis. A 10% reduction in resistance-related deaths by 2030 is the aim of the 2024 United Nations political declaration.

DISCUSSION

Together, these data support the hypothesis that antibiotic resistance and infection with fungi represent a converging problem in current clinical microbiology and therapy. Bacterial resistance results in significant mortality, and the results from the GRAM study clearly show that resistant infections have become an equally significant cause of death as other infectious causes (GRAM Study, 2021). Mechanisms like carbapenemases, target modification by the *mecA* gene, efflux pumps, and *mcr-1* plasmids are responsible for the increased frequency of treatment failure. Horizontal gene transfer is responsible for their rapid spread, especially of carbapenem-resistant Gram-negative bacteria in intensive care environments. Fungi follow the same pattern, as *Candida auris* and azole-resistant *Aspergillus fumigatus* prove the nosocomial spread of fungi and resistance due to exposure to fungicides in the environment. The agricultural origin of *cyp51A* mutations shows that resistance cannot be controlled only within the hospital setting.

The importance of applying the One Health model that integrates the human, veterinary, and environmental sectors cannot be overstated. There is limited availability of treatment due to the fact that antifungals depend only on four main classes, and the toxicity of polyenes and azoles is a limiting factor. Cefiderocol, aztreonam-avibactam, and rezafungin are some of the new agents that have provided improvement, but resistant strains pose a danger to the sustainability of these agents (Závora *et al.* 2025). Delayed diagnosis worsens the situation because slow culture tests lead to empiric use of broad-spectrum agents, which increase the selection of resistance. Rapid methods such as MALDI TOF, molecular panels, and whole-genome sequencing may mitigate this problem as long as resources are available. Poor surveillance in low-income areas makes it difficult for policymakers to get resistance information.

CONCLUSION

The combination of antibiotic resistance and fungal infections is a major challenge facing modern clinical practice. Infections caused by antibiotic-resistant organisms such as carbapenem-resistant Enterobacterales and *Acinetobacter baumannii* are highly lethal due to the lack of available treatment options. Other organisms that pose additional threats include *Candida auris* and azole-resistant *Aspergillus fumigatus*. Antifungal therapy options are limited; furthermore, drugs have toxic side effects, and diagnostics are slow. The poor antimicrobial pipeline and the improper use of the existing antibiotics by people and animals contribute to the rise of resistance. Effective solutions to the challenges include rapid molecular diagnostics, antibiotic stewardship programs, and global surveillance. There is a need for investments in new antibacterial and antifungal drugs, which should come through government funding and innovative incentives. A One Health approach involving the clinical, veterinary, and environmental sectors is crucial for the control of resistant organisms. International efforts could still ensure the preservation of the efficacy of therapies and increase the survival rates among susceptible individuals.

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