

# Antibiotic resistance

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## Abstract

Antimicrobial resistance (AMR) is a critical threat to global health and has been identified as a leading cause of mortality worldwide. Resistance rates continue to increase among bacterial pathogens while the pipeline for new antibiotic development may be failing to produce enough new and/or novel antimicrobials. After only eight decades of antibiotic use, bacterial infections that once were easily treated are becoming untreatable. The successful outcomes of many surgical procedures and immunosuppressive treatments depend on antibiotic prophylaxis and the ability to treat infective complications. Consequently, AMR threatens to undermine and reverse many advances in modern medicine. Areas of particular concern are carbapenem- and third-generation cephalosporin-resistant Gram-negative organisms, rifampicin-resistant *Mycobacterium tuberculosis*, fluoroquinolone-resistant enteric pathogens, methicillin-resistant *Staphylococcus aureus* and *Neisseria gonorrhoea* resistant to third-generation cephalosporins and/or fluoroquinolones. Antibiotic resistance correlates with antibiotic use, so improved antimicrobial stewardship, with better prevention and diagnosis of infection, can help to conserve the currently available antimicrobial agents. Significant global action and investment, from both public and private sector funding, is still required if the development of new anti-infectives is to keep pace with increasing resistance.

**Keywords** Antibiotic resistance;  $\beta$ -lactamase; carbapenem-resistant; extended-spectrum  $\beta$ -lactamases; gonorrhoea; methicillin-resistant *Staphylococcus aureus*; multidrug-resistant tuberculosis

## Definition of antibiotic resistance

Antibiotic resistance in pathogenic bacteria can be defined microbiologically or clinically.

*Microbiological resistance* relies on laboratory testing, whereby an organism is categorized as sensitive or resistant to an antimicrobial agent based on the application of a set cut-off point. Phenotypic testing breakpoints standardized by the European Committee on Antimicrobial Susceptibility Testing are most commonly used in the UK.

The most frequently used qualitative testing methodology is the disk diffusion method. This involves placing antibiotic-

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## Key points

- Antimicrobial resistance is a growing global problem requiring international action and global investment to protect existing antimicrobials and develop new agents
- The growth of antimicrobial resistance can be reduced by: basic hygiene; provision of improved infrastructure such as water supply; good antibiotic stewardship, to prevent resistance developing; and careful infection control measures, to prevent transmission of resistant organisms
- Areas of particular concern are carbapenem- and third-generation cephalosporin-resistant Gram-negative organisms, rifampicin-resistant *Mycobacterium tuberculosis*, fluoroquinolone-resistant enteric pathogens, methicillin-resistant *Staphylococcus aureus* and *Neisseria gonorrhoea* resistant to third-generation cephalosporins and/or fluoroquinolones

impregnated discs on a pure culture of the target organism and measuring the zone in which bacterial growth is inhibited. Zone sizes are compared with clinical breakpoints; a larger zone means the antibiotic is more active.

Quantitative methods are more precise and allow determination of the minimum inhibitory concentration, which is the lowest concentration of antibiotic that completely inhibits the growth of an organism. Quantitative methods include agar dilution, broth dilution and gradient methods.

Some laboratories use automated systems that involve inoculation of antimicrobial dilution trays or cards, followed by incubation and monitoring of bacterial growth. These automated systems can process many samples simultaneously, test multiple antimicrobials against a bacterial isolate and interface with electronic records, making results quickly available to clinicians.

*Clinical resistance* refers to a level of antimicrobial activity correlated with a high likelihood of therapeutic failure when a drug is used to treat a person's infection. The test cut-offs for determining clinical resistance can vary depending on the clinical setting (e.g. site of infection, drug dose).<sup>1</sup>

Although phenotypic testing remains key to antimicrobial susceptibility testing, molecular assays detecting genes known to confer resistance are increasingly used in clinical laboratories. Molecular methods have significantly quicker turn-around times than conventional testing methods and can provide specific information about the presence of genes with particular epidemiological or infection control significance.

An example is detection of *mecA*, which confers methicillin resistance in most human isolates of *Staphylococcus aureus*. However, the detection of specific genes does not always correlate with expression of the gene *in vivo* and phenotypic testing is generally still required in clinical settings.

## Acquisition of antibiotic resistance

Antibiotic resistance can be intrinsic (i.e. characteristic of all wild-type isolates of that species) or acquired. Examples of

inherent antibiotic resistance include the resistance of Gram-negative organisms to vancomycin, daptomycin and linezolid, and the resistance of Gram-positive bacteria to colistin and aztreonam. *Pseudomonas aeruginosa* is also intrinsically resistant to a wide range of antibiotics including tetracyclines, sulfonamides and most penicillins.

Acquired resistance occurs when naturally susceptible bacteria gain the genes encoding a resistance mechanism. This can occur via mutation or by the transfer of genetic material from other bacteria.

Antimicrobial resistance (AMR) genes are carried on mobile genetic elements. These are either plasmids, which are circular molecules of double-stranded DNA independent of the chromosome, or transposons ('jumping genes') – mobile sequences of DNA that can move to different positions in the genome. Transfer can occur by several methods (Figure 1):

- **conjugation** – direct cell-to-cell contact with plasmid transfer
- **transduction** – transfer of bacterial DNA by a bacteriophage, a bacterial virus that replicates in the bacterial cell and can incorporate a piece of bacterial DNA in the assembled viral particle that is then transferred to the next bacterial cell the virus infects
- **transformation** – uptake of naked DNA from the environment.

The use of antibiotics selects for the bacteria that possess resistance mechanisms, enabling them to pass on the resistance genes vertically.

There is a correlation between antibiotic use and the presence of resistance in both individuals and the wider community. Studies have demonstrated persistence of resistance to an antibiotic for up to a year after exposure, in both the urinary tract (*Escherichia coli*) and respiratory tract (*Streptococcus pneumoniae*, *Haemophilus influenzae*). The probability of resistance at 12 months was also correlated with exposure to a higher number of antibiotics or exposure for a longer duration.

### Mechanisms of antibiotic resistance

The main mechanisms by which bacteria demonstrate resistance to antibiotics are illustrated in Figure 2. Inactivating enzymes are discussed in more detail below.

#### $\beta$ -lactamases and related enzymes

These enzymes can be produced by both Gram-negative and Gram-positive bacteria. They hydrolyse the  $\beta$ -lactam ring of  $\beta$ -lactam antibiotics, rendering them inactive. Penicillinase, which confers resistance to penicillin and penicillin-derived antibiotics, was described in 1940, only a few years after the discovery of penicillin. It is now widespread in many bacteria including *Staphylococcus aureus*.

Extended spectrum  $\beta$ -lactamases confer resistance to synthetic penicillins, such as amoxicillin, as well as first-, second- and third-generation cephalosporins. They can be overcome by  $\beta$ -lactamase inhibitors, such as clavulanic acid, tazobactam and avibactam, as well as some cephalosporins and all carbapenems. They are commonly found in *Enterobacterales* (e.g. *E. coli*, *Klebsiella* spp., *Enterobacter* spp.) and the incidence is increasing. In many countries in Southern Europe rates of

resistance to third-generation cephalosporins are >20% in *E. coli* and 50–75% in *Klebsiella pneumoniae*.<sup>2</sup>

Carbapenemase-producing *Enterobacterales* (CPEs) can inactivate carbapenem antibiotics, as well as all other  $\beta$ -lactams. In bacteria they often coexist with other resistance mechanisms, making treatment extremely challenging. They are split into metallo- $\beta$ -lactamases (e.g. NDM1, VIM, IMP) and non-metallo-enzymes (e.g. KPC, OXA48), which has implications for treatment choices. Importantly, not all carbapenemase-resistant organisms are carbapenemase producing and resistance can be the result of alternative mechanisms such as porin-loss and efflux pumps.

### Why worry now?

AMR has been identified as one of the greatest threats to humankind, and there is a very real risk that the spread of truly untreatable infections will prevent the provision of healthcare as we know it (e.g. operations, transplants). Pan-drug-resistant organisms (those resistant to all known drugs) are being described more frequently and have been identified in all five continents.<sup>3</sup>

The World Health Organization 2024 Bacterial Priority Pathogens List (BPPL) identifies antibiotic-resistant pathogens that pose the greatest threat to public health based on criteria including mortality rate, incidence, trend of resistance, transmissibility and effective antibacterials in development. Pathogens that pose the highest and significant threats are carbapenem- and third-generation cephalosporin-resistant Gram-negative organisms, rifampicin-resistant *Mycobacterium tuberculosis*, fluoroquinolone-resistant enteric pathogens, methicillin-resistant *Staphylococcus aureus* (MRSA) and *Neisseria gonorrhoea* resistant to third-generation cephalosporins and/or fluoroquinolones.<sup>4</sup>

Antibiotic use is expected to triple globally by 2030,<sup>5</sup> as a result of the ageing population, higher rates of co-morbidities, increasing use of complex medical procedures and increased access to antibiotics in low- and middle-income countries. Inappropriate use of antimicrobials is a key driver of rising AMR, as is poor sanitation in low-income countries. Although some new drug combinations are being licensed to treat these resistant infections, drug development has not kept up with the growth of AMR.

### Consequences of antibiotic resistance

AMR has significant consequences for the health of the population as well as economic implications. It is estimated that 1.14 million deaths in 2021 were attributable to bacterial AMR and that 39.1 million deaths globally will be attributable to AMR from 2025 to 2050. The future AMR burden is predicted to be highest in Asia, and sub-Saharan Africa.<sup>4</sup> There is known to be a higher mortality associated with bacteraemia with MRSA or resistant *E. coli*,<sup>1</sup> and as resistance grows, more infections will become untreatable.

As well as the associated mortality and morbidity, the cost of treating infections caused by resistant bacteria is estimated to be 165% higher than treating antibiotic-susceptible infections. This is because of the need for multiple and expensive drugs, longer hospital stays and higher rates of toxicities from the use of less safe antibiotics.

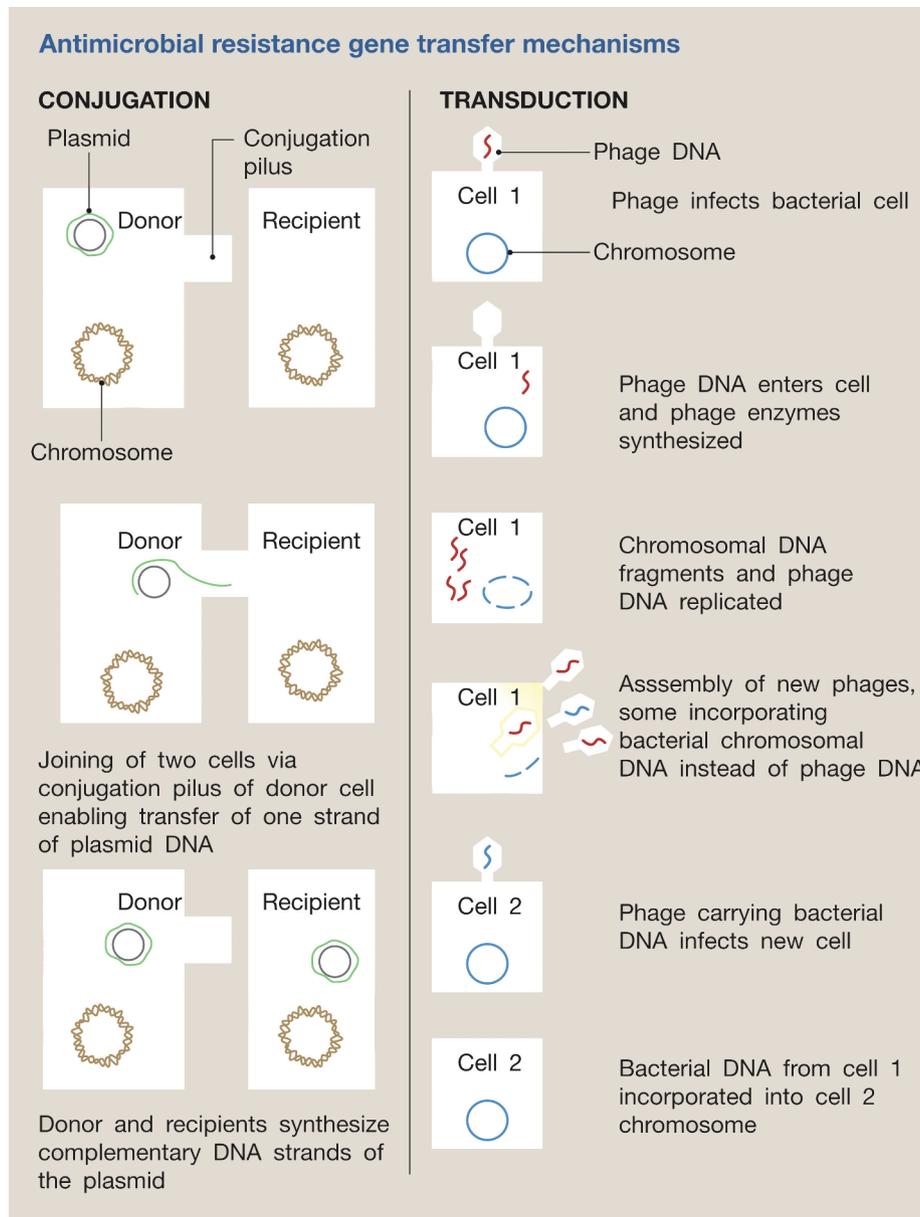


Figure 1

### Specific organisms of concern

#### Carbapenem-resistant *Enterobacterales* (CRE) and third-generation cephalosporin-resistant *Enterobacterales*

CRE and third-generation cephalosporin-resistant *Enterobacterales* pose the highest risk to global health among all multidrug resistant Gram-negative bacteria because of their global prevalence and widespread resistance. Particularly high rates of CRE are found in the Indian subcontinent and parts of Southern Europe (Figure 3). In the UK, overall rates of carbapenemase-resistant *Enterobacterales* remain low but are increasing.

Evidence suggests that patients are colonized with CPE before developing an invasive infection. Early identification of patients infected or colonized with CPE can reduce nosocomial transmission and direct antimicrobial therapy. In UK hospitals, CPE

screening is recommended in particular risk groups including those with previous CPE, multiple hospital treatments or recent hospital stays, and epidemiological links to known CPE carriers.

#### Other multiresistant Gram-negative organisms

Certain non-fermentative Gram-negative organisms, particularly *P. aeruginosa* and *Acinetobacter* spp., cause significant problems, especially in healthcare-acquired infections, including nosocomial outbreaks. These bacteria can live in the environment and colonize the skin; they tend to cause infection when the host is immunocompromised or has a long hospital stay.

These organisms are intrinsically resistant to many classes of antibiotic and are also able to acquire resistance, both by their own high mutation rate and by the transfer of resistance genes via mobile genetic elements from other species. This can make treatment extremely challenging and they have been listed as some of the highest priority pathogens.

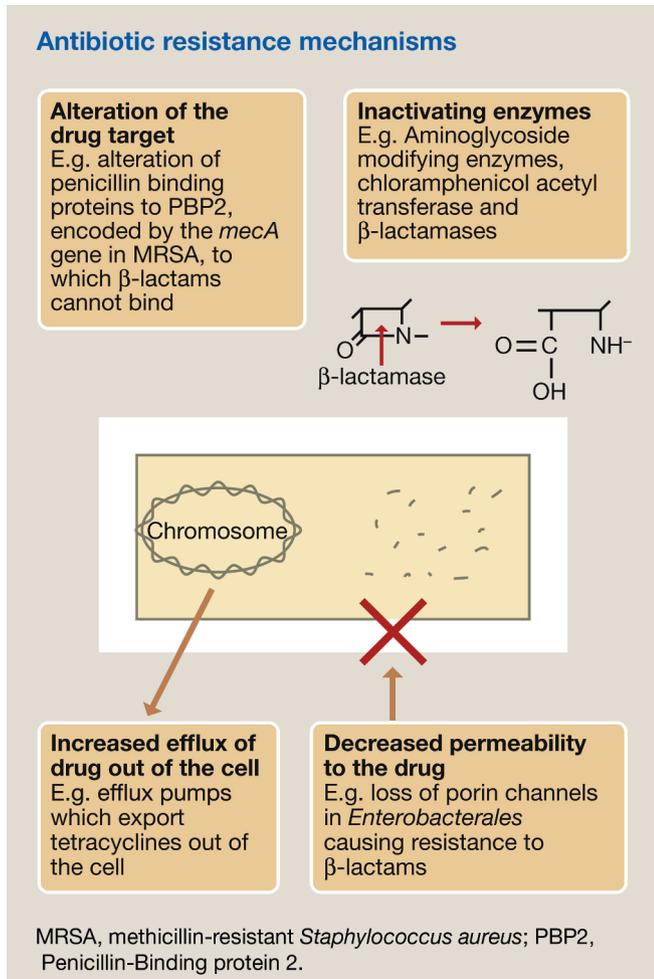


Figure 2

### Rifampicin-resistant tuberculosis (RR-TB)

RR-TB is a critical priority as it poses significant challenges in terms of diagnosis, treatment and management. Treatment regimens for RR-TB are significantly more expensive and toxic than those for drug-susceptible disease.

Multidrug-resistant tuberculosis is defined as having resistance to both rifampicin and isoniazid, whereas extensively drug-resistant tuberculosis demonstrates resistance to these as well as an injectable agent (aminoglycoside) and a fluoroquinolone. Novel drugs like bedaquiline and delamanid may improve the situation. However, resistance to new drugs is already emerging and treatment options for bedaquiline-resistant tuberculosis are extremely limited.<sup>4</sup>

### Fluoroquinolone-resistant *Salmonella* and *Shigella* species

These 'community' pathogens pose a substantial burden, particularly in low- and middle-income countries. *Salmonella typhi* is a cause of enteric fever and estimated to cause 116,800 deaths annually. Increasing resistance to fluoroquinolones is reported in many regions and extensive drug resistance (XDR) is increasing. The British Infection Association (BIA) has published guidelines for the diagnosis and management of enteric

fever in the UK, including patients returning from XDR endemic areas.

Shigellosis is the second most common cause of diarrhoeal mortality globally. *Shigella flexneri* and *Shigella sonnei* are the most common causes and have increasing resistance to fluoroquinolones and multidrug resistance. Outbreaks caused by multidrug-resistant *Shigella* strains among men who have sex with men reflects a shift in epidemiological trends.

### MRSA and glycopeptide/vancomycin-resistant *Staphylococcus aureus*

Globally, MRSA remains a high-priority pathogen and has been identified as one of the leading causes of health-care-associated and community-acquired infections.<sup>4</sup> In the UK, MRSA rates plateaued for several years after a dramatic decrease from peak levels in the mid-2000s. The reasons for the decline are likely to include improvements in antimicrobial stewardship, screening and better line-care programmes.

However, community and hospital MRSA rates are currently rising, and cases of MRSA bacteraemia reported by NHS acute trusts in England increased by 15.6% in 2023–2024 compared with the previous year (Figure 4). In some countries in Southern Europe, >25% of *S. aureus* isolates are resistant to methicillin.<sup>2</sup>

### *Neisseria gonorrhoea* resistant to third-generation cephalosporins and/or fluoroquinolones

Over the years, *N. gonorrhoeae* has become resistant to sulfonamides, penicillin, tetracyclines, fluoroquinolones and the third-generation cephalosporin cefixime. In the UK, surveillance of antibiotic resistance in *N. gonorrhoeae* is monitored through the Gonococcal Resistance to Antimicrobials Surveillance Programme.

Current UK guidelines (published by the British Association for Sexual Health and HIV (BASSH), 2025) recommend a single dose of 1 g ceftriaxone intramuscularly for uncomplicated presentations. Resistance rates to ceftriaxone remain low, but there has been a rise in the distribution of minimum inhibitory concentrations so the recommended dose was increased in 2018 BASSH guidelines.

Effective treatment is required as the consequences of inappropriate treatment of gonorrhoea include progression to pelvic inflammatory disease, infertility and ectopic pregnancies, as well as increased transmission of the organism. HIV transmission is also increased in the presence of active gonorrhoeal infection.

### Vancomycin-resistant enterococci

Enterococci are organisms of relatively low virulence that occasionally cause deep-seated infections such as infective endocarditis, prosthetic joint infection and discitis. Vancomycin-resistant strains can be particularly hard to treat, although antibiotics such as linezolid, daptomycin and tigecycline have activity. Vancomycin resistance in enterococci is encoded by one of several genes (e.g. *vanA*) producing alterations in the peptidoglycan precursor and preventing vancomycin from binding.

### How can antibiotic resistance be overcome?

AMR is a complex problem but we can do something about it. The WHO Bacterial Priority Pathogens List acts as a framework for prioritizing research, development and investment. In 2024,

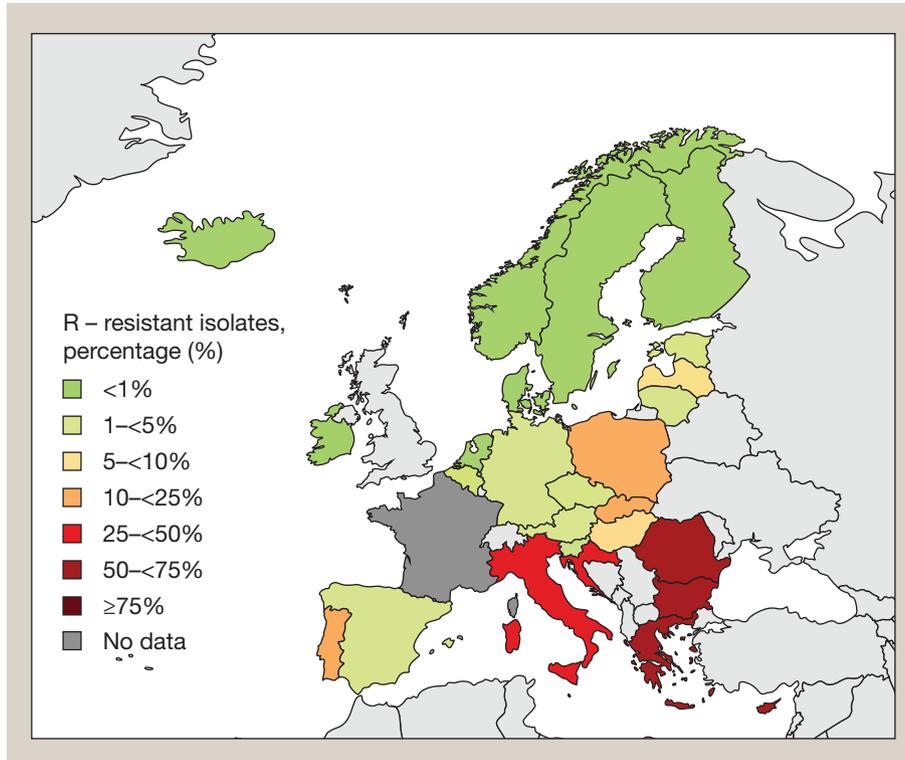
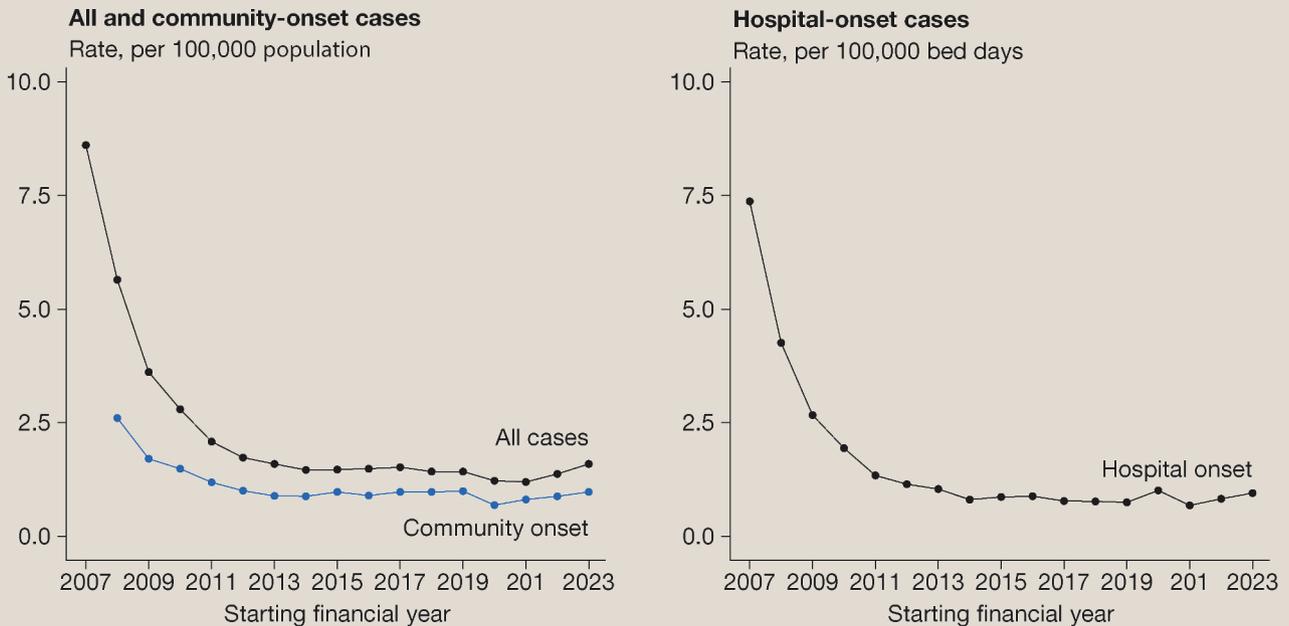


Figure 3 Proportion of isolates of *Klebsiella pneumoniae* resistant to carbapenems, 2023.<sup>2</sup>

**Trends in rates of all-case and hospital-onset MRSA bacteraemia, England, April 2007 to March 2024, by financial year**



Reproduced with permission from UK Health Security Agency. Last updated 2025. Annual epidemiological commentary: Gram-negative, MRSA, MSSA bacteraemia and *C. difficile* infections, up to and including financial year 2023 to 2024. <https://www.gov.uk/government/statistics/mrsa-mssa-and-e-coli-bacteraemia-and-c-difficile-infection-annual-epidemiological-commentary/annual-epidemiological-commentary-gram-negative-mrsa-mssa-bacteraemia-and-c-difficile-infections-up-to-and-including-financial-year-2023-to-2024> (accessed 30 May 2025).

Figure 4

the UK government published a new 5-year national action plan, *Confronting antimicrobial resistance 2024 to 2029*, following on from the first national action plan.<sup>5</sup> The national action plan has four key themes, as follows.

### Reducing the need for and unintentional exposure to antibiotics

Reducing AMR requires a focus on preventing infection in humans and animals. Infection prevention and control interventions should be informed by surveillance and tailored to respond to the context. The UK Health Security Agency publishes the English Surveillance Programme for Antimicrobial Utilization and Resistance report. Scotland and Wales publish separate surveillance reports.

The importance of the built environment is recognized and ensures that understanding of AMR is integrated into estate design rather than as an afterthought. Additionally, it is vital to address AMR in the environment, including wastewater treatment methods and agrochemical stewardship to reduce preventable exposure to antimicrobials.

### Optimizing use of antibiotics

Reducing unnecessary antimicrobial use is key. Antimicrobial stewardship (AMS) comprises core components including correct diagnosis, optimal drug, correct dose, correct time, correct route, optimal duration and timely de-escalation. Artificial intelligence (AI) could support risk stratification and targeting of antibiotic treatment. Access to penicillin de-labelling services ensures patients are not unnecessarily denied this crucial class of antibiotics.

Infection prevention and control and AMS training of all those working in health and social care is imperative. Additionally, it is important to gain public support through campaigns to raise awareness of the negative effects of overuse of antibiotics.

### Investing in innovation, supply and access

There must be a focus on investment in the research and development of new agents to tackle AMR. Improving funding streams for the production of novel antibiotics is vital. The reward is currently low as antibiotics are used for short courses and new drugs are kept in reserve to slow the development of resistance, leading to market failure.

Measures to prevent infection are also vital, including vaccines, as well as healthcare-associated equipment. Additionally, improving diagnostics to reduce the time taken for susceptibility testing can reduce unnecessary broad-spectrum antibiotic use. Methods to distinguish bacterial from viral infections would be of great benefit.

### Being a good global partner

AMR is a worldwide One Health issue. International action is required through a clear strategy, research collaboration and

preparedness. Equitable access to antimicrobials, alternative therapies, vaccines and diagnostics is imperative to tackling AMR. Global standards optimizing the use of antimicrobials in farming and responsible antimicrobial manufacturing are key. ♦

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## TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online [here](#).

### Question 1

A 27-year-old man presented with a 1-week history of fever, myalgia and dry cough and a 4-day history of diarrhoea. He had recently returned from a 1-month trip to Pakistan. On clinical examination, his temperature was 38.8°C, blood pressure 100/60 mmHg, and Glasgow Coma Scale score 13/15.

#### Investigation

- Blood cultures showed Gram-negative bacilli identified as *Salmonella* species, but sensitivities were awaited

#### What is the most appropriate antibiotic regimen in these circumstances?

- Azithromycin
- Azithromycin and meropenem
- Ciprofloxacin
- Vancomycin
- Teicoplanin

### Question 2

A 25-year-old man presented with symptoms of dysuria and penile discharge 3 days after unprotected sexual intercourse. He had no other symptoms.

#### Investigation

- Urethral swab sent for nucleic acid amplification testing was positive for *Neisseria gonorrhoea*; Urethral swab culture results were awaited

#### What is the most appropriate antibiotic choice in these circumstances?

- Amoxicillin 500 mg three times a day for 7 days
- Ceftriaxone 1 g intramuscularly as a single dose
- Ceftriaxone 1 g intravenously once daily for 10 days
- Ciprofloxacin 500 mg as a single dose
- Gentamicin 240 mg intramuscularly as a single dose

### Question 3

A 32-year-old woman was reviewed 48 hours after hospital admission for fever and erythema of the left leg. She had been treated for 3 days before admission with flucloxacillin orally, which was changed to intravenously in hospital. There had been no improvement. She had a history of intravenous drug use.

#### Investigation

- Positive MRSA screen from another hospital

#### What is the most appropriate antibiotic treatment?

- Stop the flucloxacillin and start amoxicillin/clavulanate acid intravenously
- Stop the flucloxacillin and change to doxycycline
- Stop the flucloxacillin and change to meropenem
- Stop the flucloxacillin and start vancomycin intravenously
- Increase the dose of flucloxacillin