

# Antimicrobial resistance

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**Antimicrobial resistance (AMR)** is the ability of a microbe to resist the effects of medication previously used to treat them.

<sup>[2]</sup><sup>[3]</sup><sup>[4]</sup> This broader term also covers **antibiotic resistance**, which applies to bacteria and antibiotics.<sup>[3]</sup> Resistance arises through one of three ways: natural resistance in certain types of bacteria; genetic mutation; or by one species acquiring resistance from another.<sup>[5]</sup> Resistance can appear spontaneously because of random mutations; or more commonly following gradual buildup over time, and because of misuse of antibiotics or antimicrobials.<sup>[6]</sup> Resistant microbes are increasingly difficult to treat, requiring alternative medications or higher doses—which may be more costly or more toxic. Microbes resistant to multiple antimicrobials are called multidrug resistant (MDR); or sometimes superbugs.<sup>[7]</sup> Antimicrobial resistance is on the rise with millions of deaths every year.<sup>[8]</sup> A few infections are now completely untreatable because of resistance. All classes of microbes develop resistance (fungi, antifungal resistance; viruses, antiviral resistance; protozoa, antiprotozoal resistance; bacteria, antibiotic resistance).



Antibiotic resistance tests: Bacteria are streaked on dishes with white antibiotic impregnated disks. Clear rings, such as those on the left, show that bacteria have not grown—indicating that the bacteria are not resistant. Those on the right are fully susceptible to only three of the seven antibiotics tested.<sup>[1]</sup>

Antibiotics should only be used when needed as prescribed by health professionals.<sup>[9]</sup> The prescriber should closely adhere to the five rights of drug administration: the right patient, the right drug, the right dose, the right route, and the right time.<sup>[10]</sup> Narrow-spectrum antibiotics are preferred over broad-spectrum antibiotics when possible, as effectively and accurately targeting specific organisms is less likely to cause resistance.<sup>[11]</sup> Cultures should be taken before treatment when indicated and treatment potentially changed based on the susceptibility report.<sup>[12]</sup><sup>[13]</sup> For people who take these medications at home, education about proper use is essential. Health care providers can minimize spread of resistant infections by use of proper sanitation: including handwashing and disinfecting between patients; and should encourage the same of the patient, visitors, and family members.<sup>[12]</sup>

Rising drug resistance can be attributed to three causes use of antibiotics: in the human population; in the animal population; and spread of resistant strains between human or non-human sources.<sup>[6]</sup> Antibiotics increase selective pressure in bacterial populations, causing vulnerable bacteria to die—this increases the percentage of resistant bacteria which continue growing. With resistance to antibiotics becoming more common there is greater need for alternative treatments. Calls for new antibiotic therapies have been issued, but new drug-development is becoming rarer.<sup>[14]</sup> There are multiple national and international monitoring programs for drug-resistant threats. Examples of drug-resistant bacteria included in this program are: methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *S. aureus* (VRSA), extended spectrum beta-lactamase (ESBL), vancomycin-resistant *Enterococcus* (VRE), multidrug-resistant *A. baumannii* (MRAB).<sup>[15]</sup>

A World Health Organization (WHO) report released April 2014 stated, "this serious threat is no longer a prediction for the future, it is happening right now in every region of the world and has the potential to affect anyone, of any age, in any country. Antibiotic resistance—when bacteria change so antibiotics no longer work in people who need them to treat infections—is now a major threat to public health."<sup>[16]</sup> Increasing public calls for global collective action to address the threat include proposals for international treaties on antimicrobial resistance.<sup>[17]</sup> Worldwide antibiotic resistance is not fully mapped, but poorer countries with weak healthcare systems are more affected.<sup>[9]</sup> According to

the Centers for Disease Control and Prevention: "Each year in the United States, at least 2 million people become infected with bacteria that are resistant to antibiotics and at least 23,000 people die each year as a direct result of these infections."<sup>[18]</sup>

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## Definition

The WHO defines antimicrobial resistance as a microorganism's resistance to an antimicrobial drug that was once able to treat an infection by that microorganism.<sup>[3]</sup> A person cannot become resistant to antibiotics. Resistance is a property of the microbe, not a person or other organism infected by a microbe.<sup>[20]</sup>

## Causes

Bacteria with resistance to antibiotics predate medical use of antibiotics by humans,<sup>[21][22][23]</sup> however, widespread antibiotic use has made more bacteria resistant through the process of evolutionary pressure.<sup>[24][25]</sup>

Reasons for the widespread use of antibiotics include:

- increasing global availability over time since the 1950s
- uncontrolled sale in many low or middle income countries, where they can be obtained over the counter without a prescription, potentially resulting in antibiotics being used when not indicated.<sup>[26]:1060</sup> This may result in emergence of resistance in any remaining bacteria.

Antibiotic use in livestock feed at low doses for growth promotion is an accepted practice in many industrialized countries and is known to lead to increased levels of resistance.

<sup>[27][28]</sup> Releasing large quantities of antibiotics into the environment during pharmaceutical manufacturing through inadequate wastewater treatment increases the risk that antibiotic-resistant strains will develop and spread.<sup>[29][30]</sup> It is uncertain whether antibacterials in soaps and other products contribute to antibiotic resistance, but they are discouraged for other reasons.<sup>[31][32]</sup>

## Human medicine

Increasing bacterial resistance is linked with the volume of antibiotic prescribed, as well as missing doses when taking antibiotics.<sup>[33]</sup> Inappropriate prescribing of antibiotics has been attributed to a number of causes, including people insisting on antibiotics, physicians prescribing them as they feel they do not have time to explain why they are not necessary, and physicians not knowing when to prescribe antibiotics or being overly cautious for medical and/or legal reasons.<sup>[34]</sup>

Up to half of antibiotics used in humans are unnecessary and inappropriate.<sup>[6]</sup> For example, a third of people believe that antibiotics are effective for the common cold,<sup>[35]</sup> and the common cold is the most common reason antibiotics are prescribed<sup>[36]</sup> even though antibiotics are useless against viruses. A single regimen of antibiotics even in compliant individuals leads to a greater risk of resistant organisms to that antibiotic in the person for a month to possibly a year.<sup>[37][38]</sup>

Antibiotic resistance increases with duration of treatment; therefore, as long as an effective minimum is kept, shorter courses of antibiotics are likely to decrease rates of resistance, reduce cost, and have better outcomes with fewer complications.

<sup>[11]</sup> Short course regimens exist for community-acquired pneumonia<sup>[39]</sup> spontaneous bacterial peritonitis,<sup>[40]</sup> suspected lung infections in intense care wards,<sup>[41]</sup> so-called acute abdomen,<sup>[42]</sup> middle ear infections, sinusitis and throat infections,<sup>[43]</sup> and penetrating gut injuries.<sup>[44][45]</sup> In some situations a short course may not cure the infection as well as a long course.<sup>[46]</sup> A BMJ editorial recommended that antibiotics can often be safely stopped 72 hours after symptoms resolve.<sup>[47]</sup> Because individuals may feel better

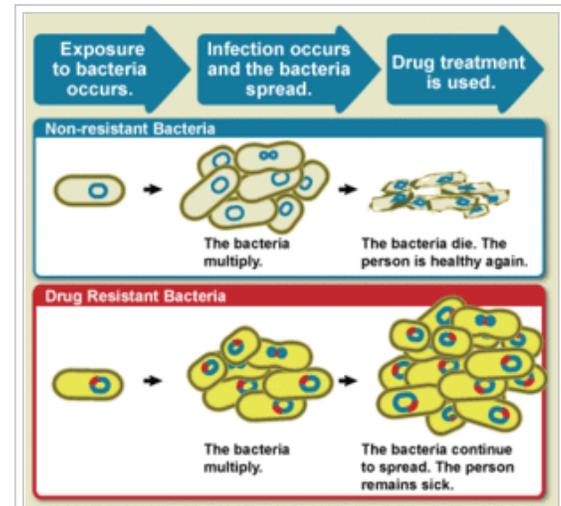
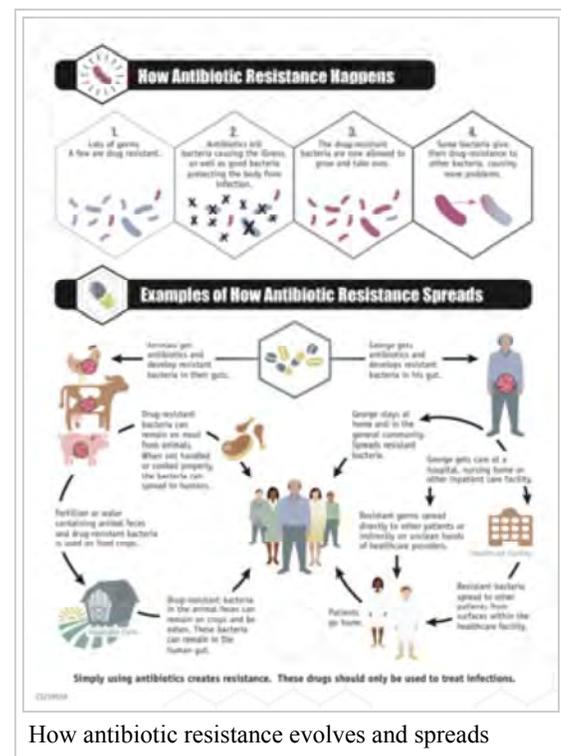


Diagram showing the difference between non-resistant bacteria and drug resistant bacteria. Non-resistant bacteria multiply, and upon drug treatment, the bacteria die. Drug resistant bacteria multiply as well, but upon drug treatment, the bacteria continue to spread.<sup>[19]</sup>



How antibiotic resistance evolves and spreads

before the infection is eradicated, doctors must provide instructions to them so they know when it is safe to stop taking a prescription. Some researchers advocate doctors' using a very short course of antibiotics, reevaluating the patient after a few days, and stopping treatment if there are no clinical signs of infection.<sup>[48]</sup>

Certain antibiotic classes result in resistance more than others. Increased rates of MRSA infections are seen when using glycopeptides, cephalosporins, and quinolones.<sup>[49][50]</sup> Cephalosporins, and particularly quinolones and clindamycin, are more likely to produce colonisation with *Clostridium difficile*.<sup>[51][52]</sup>

Factors within the intensive care unit setting such as mechanical ventilation and multiple underlying diseases also appear to contribute to bacterial resistance.<sup>[53]</sup> Poor hand hygiene by hospital staff has been associated with the spread of resistant organisms,<sup>[54]</sup> and an increase in hand washing compliance results in decreased rates.<sup>[55]</sup>

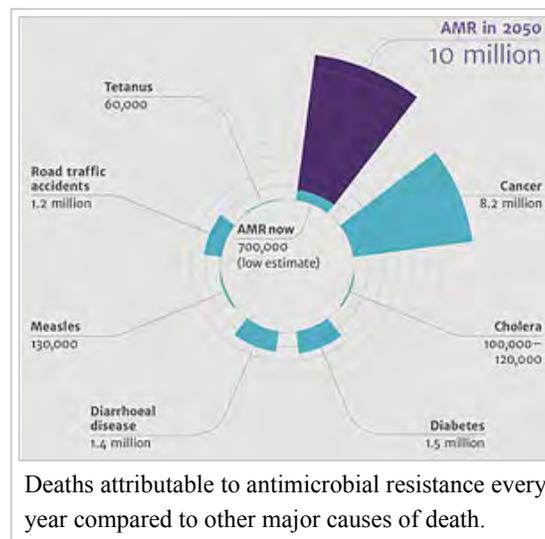
Improper use of antibiotics can often be attributed to the presence of structural violence in particular regions. Socioeconomic factors such as race and poverty affect accessibility of and adherence to drug therapy. The efficacy of treatment programs for drug-resistant strains depends on whether or not programmatic improvements take into account the effects of structural violence.<sup>[56]</sup>

## Veterinary medicine

The World Health Organization concluded that inappropriate use of antibiotics in animal husbandry is an underlying contributor to the emergence and spread of antibiotic-resistant germs, and that the use of antibiotics as growth promoters in animal feeds should be restricted.<sup>[57]</sup> The World Organisation for Animal Health has added to the Terrestrial Animal Health Code a series of guidelines with recommendations to its members for the creation and harmonization of national antimicrobial resistance surveillance and monitoring programs,<sup>[58]</sup> monitoring of the quantities of antibiotics used in animal husbandry,<sup>[59]</sup> and recommendations to ensure the proper and prudent use of antibiotic substances. Another guideline is to implement methodologies that help to establish associated risk factors and assess the risk of antibiotic resistance.<sup>[60]</sup>

## United States

Eighty percent of antibiotics sold in the United States are used on livestock. The majority of these antibiotics are given to animals that are otherwise healthy. Rather, it is normal practice to mix antibiotics with livestock food to promote healthier living conditions and to encourage animal growth.<sup>[61]</sup> The use of antibiotics in animals is to a large degree involved in the emergence of antibiotic-resistant microorganisms.<sup>[62]</sup> Antibiotics are used in food with the intention of not only preventing, controlling, and treating diseases, but also to promote growth.<sup>[6]</sup> Antibiotic use in animals can be classified into therapeutic, prophylactic, metaphylactic, and growth promotion uses of antibiotics.<sup>[63]</sup> All four patterns select for bacterial resistance, since antibiotic resistance is a natural evolutionary process, but the non-therapeutic uses expose larger number of animals, and therefore of bacteria, for more extended periods, and at lower doses. They therefore greatly increase the cross-section for the evolution of resistance.



<sup>[64]</sup> Since the last third of the 20th century, antibiotics have been used extensively in animal husbandry. In 2013, 80% of antibiotics used in the US were used in animals and only 20% in humans; in 1997 half were used in humans and half in animals.

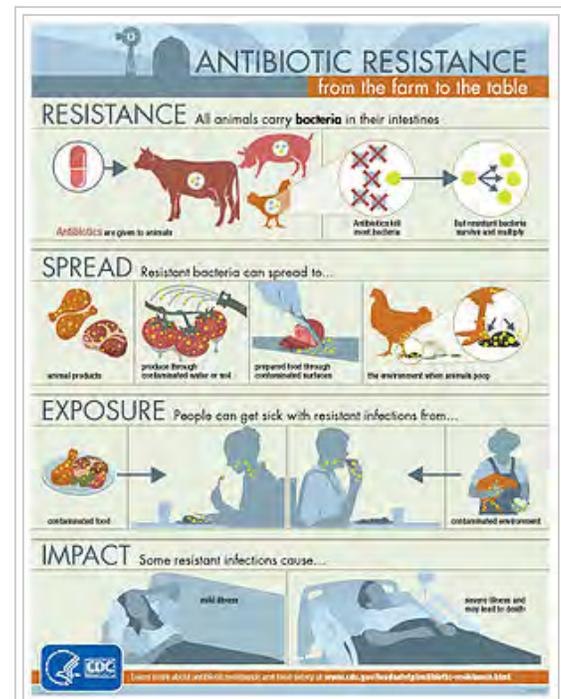
<sup>[65]</sup> Some antibiotics are not used and not considered significant for use in humans, because they either lack efficacy or purpose in humans, such as ionophores in ruminants,<sup>[66]</sup> or because the drug has gone out of use in humans. Others are used in both animals and humans, including penicillin and some forms of tetracycline.

<sup>[67]</sup> Historically, regulation of antibiotic use in food animals has been limited to limiting drug residues in meat, egg, and milk products, rather than by direct concern over the development of antibiotic resistance. This mirrors the primary concerns in human medicine, where, in general, researchers and doctors were more concerned about effective but non-toxic doses of drugs rather than antibiotic resistance.

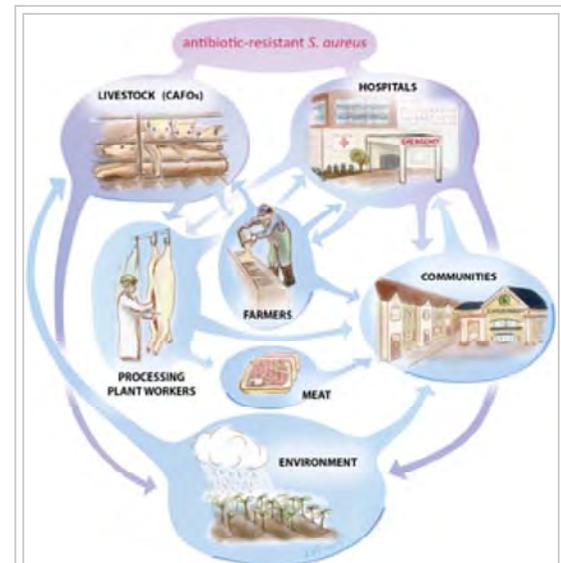
In 2001, the Union of Concerned Scientists estimated that greater than 70% of the antibiotics used in the U.S. are given to food animals (for example, chickens, pigs, and cattle), in the absence of disease.<sup>[65][68]</sup> The amounts given are termed "sub-therapeutic", i.e., insufficient to combat disease. Despite no diagnosis of disease, the administration of these drugs (most of which are not significant to human medicine) results in decreased mortality and morbidity and increased growth in the animals so treated. It is theorized that sub-therapeutic dosages kills some, but not all, of the bacterial organisms in the animal — likely leaving those that are naturally antibiotic-resistant.<sup>[69]</sup> Studies have shown, however, that, in essence, the overall population levels of bacteria are unchanged; only the mix of bacteria is affected. The actual mechanism by which sub-therapeutic antibiotic feed additives serve as growth promoters is thus unclear. Some people have speculated that animals and fowl may have sub-clinical infections, which would be cured by low levels of antibiotics in feed, thereby allowing the creatures to thrive. No convincing evidence has been advanced for this theory, and the bacterial load in an animal is essentially unchanged by use of antibiotic feed additives. The mechanism of growth promotion is therefore probably something other than "killing off the bad bugs".

Antibiotics are used in U.S. animal feed to promote animal productivity.<sup>[28][70]</sup> In particular, poultry feed and water is a common route of administration of drugs, because of higher overall costs when drugs are administered by handling animals individually.

In research studies, occasional animal-to-human spread of antibiotic-resistant organisms has been demonstrated. Resistant bacteria can be transmitted from animals to humans in three ways: by consuming animal products (milk, meat, eggs, etc.), from close or direct contact with animals or other humans, or through the environment.<sup>[71]</sup> In the first pathway, food preservation methods can help eliminate,



All animals carry bacteria in their intestines. Antibiotics are given to animals. Antibiotics kill most bacteria. But resistant bacteria survive and multiply.

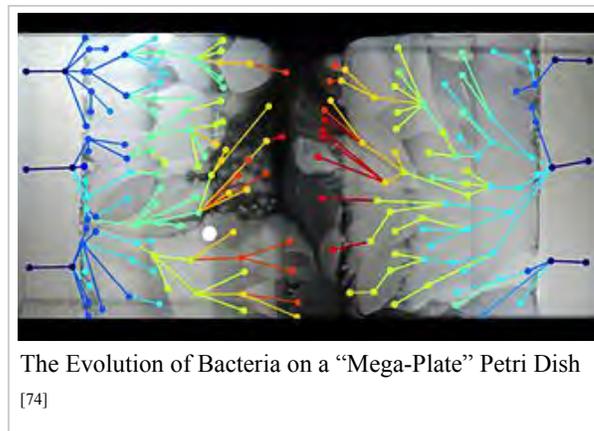


The origins of antibiotic-resistant *Staphylococcus aureus* (CAFO: concentrated animal feeding operations)

decrease, or prevent the growth of bacteria in some food classes. Evidence for the transfer of macrolide-resistant microorganisms from animals to humans has been scant, and most evidence shows that pathogens of concern in human populations originated in humans and are maintained there, with rare cases of transference to humans.<sup>[72][73]</sup>

## Natural occurrence

Naturally occurring antibiotic resistance is common.<sup>[75]</sup> Genes for resistance to antibiotics, like antibiotics themselves, are ancient.<sup>[76][77]</sup> The genes that confer resistance are known as the environmental resistome.<sup>[75]</sup> These genes may be transferred from non-disease-causing bacteria to those that do cause disease, leading to clinically significant antibiotic resistance.<sup>[75]</sup> In 1952 it was shown that penicillin-resistant bacteria existed before penicillin treatment;<sup>[78]</sup> and also preexistent bacterial resistance to streptomycin.<sup>[79]</sup> In 1962, the presence of penicillinase was detected in dormant endospores of *Bacillus licheniformis*, revived from dried soil on the roots of plants, preserved since 1689 in the British Museum.<sup>[80][81][82]</sup> Six strains of *Clostridium*, found in the bowels of William Braine and John Hartnell (members of the Franklin Expedition) showed resistance to cefoxitin and clindamycin.<sup>[83]</sup> Penicillinase may have emerged as a defense mechanism for bacteria in their habitats, such as the case of penicillinase-rich *Staphylococcus aureus*, living with penicillin-producing *Trichophyton*; however, this may be circumstantial.<sup>[82]</sup> Search for a penicillinase ancestor has focused on the class of proteins that must be *a priori* capable of specific combination with penicillin.<sup>[84]</sup> The resistance to cefoxitin and clindamycin in turn was attributed to Braine's and Hartnell's contact with microorganisms that naturally produce them or random mutation in the chromosomes of *Clostridium* strains.<sup>[83]</sup> There is evidence that heavy metals and other pollutants may select for antibiotic-resistant bacteria, generating a constant source of them in small numbers.<sup>[85]</sup>



## Environmental

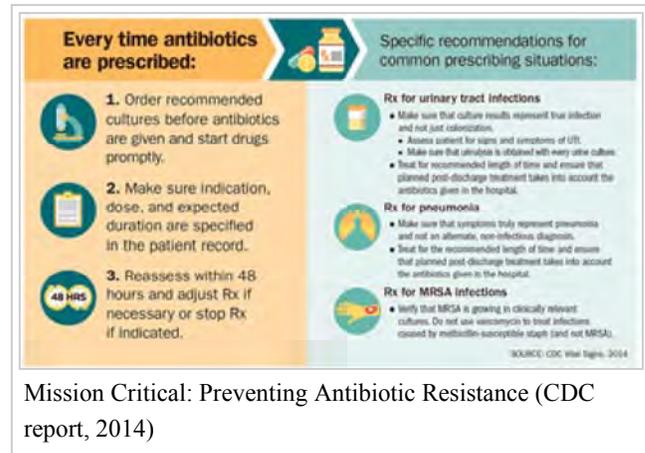
Antibiotic resistance is a growing problem among humans and wildlife in terrestrial or aquatic environments. In this respect, the spread and contamination of the environment, especially through "hot spots" such as hospital wastewater and untreated urban wastewater, is a growing and serious public health problem.<sup>[86][87]</sup> Antibiotics have been polluting the environment since their introduction through human waste (medication, farming), animals, and the pharmaceutical industry.<sup>[88]</sup> Along with antibiotic waste, resistant bacteria follow, thus introducing antibiotic-resistant bacteria into the environment. As bacteria replicate quickly, the resistant bacteria that enter the environment replicate their resistance genes as they continue to divide. In addition, bacteria carrying resistance genes have the ability to spread those genes to other species via horizontal gene transfer. Therefore, even if the specific antibiotic is no longer introduced into the environment, antibiotic-resistance genes will persist through the bacteria that have since replicated without continuous exposure.<sup>[88]</sup> Antibiotic resistance is widespread in marine vertebrates, and they may be important reservoirs of antibiotic-resistant bacteria in the marine environment.<sup>[89]</sup>

## Prevention

### World Health Organization

In 2014, the WHO stated:<sup>[16]</sup>

- People can help tackle resistance by:
  - using antibiotics only when prescribed by a doctor;
  - completing the full prescription, even if they feel better;
  - never sharing antibiotics with others or using leftover prescriptions.
- Health workers and pharmacists can help tackle resistance by:
  - enhancing infection prevention and control;
  - only prescribing and dispensing antibiotics when they are truly needed;
  - prescribing and dispensing the right antibiotic(s) to treat the illness.
- Policymakers can help tackle resistance by:
  - strengthening resistance tracking and laboratory capacity;
  - regulating and promoting appropriate use of medicines.
- Policymakers and industry can help tackle resistance by:
  - fostering innovation and research and development of new tools;
  - promoting cooperation and information sharing among all stakeholders.



## Duration of antibiotics

Antibiotic treatment duration should be based on the infection and other health problems a person may have. For many infections once a person has improved there is little evidence that stopping treatment causes more resistance. Some therefore feel that stopping early may be reasonable in some cases. Other infections, however, do require long courses regardless of whether a person feels better.<sup>[11]</sup>

## Antibiotic usage

The Netherlands has the lowest rate of antibiotic prescribing in the OECD, at a rate of 11.4 defined daily doses (DDD) per 1,000 people per day in 2011. Germany and Sweden also have lower prescribing rates, with Sweden's rate having been declining since 2007. By contrast, Greece, France and Belgium have high prescribing rates of more than 28 DDD.<sup>[90]</sup> It is unclear if rapid viral testing affects antibiotic use in children.<sup>[91]</sup>

About a third of antibiotic prescriptions written in outpatient settings in the United States were not appropriate in 2010 and 2011. Doctors in the U.S. wrote 506 annual antibiotic scripts for every 1,000 people, with 353 being medically necessary.<sup>[92]</sup>

## Monitoring

ResistanceOpen, an online global map of antimicrobial resistance developed by HealthMap, displays aggregated data on antimicrobial resistance from publicly available and user submitted data.<sup>[93][94]</sup> The website can display data for a 25-mile radius from a location. Users may submit data from antibiograms for individual hospitals or laboratories. European data is from the EARS-Net (European Antimicrobial Resistance Surveillance Network), part of the ECDC. ResistanceMap, by the Center for Disease Dynamics, Economics & Policy, also provides data on antimicrobial resistance on a global level.<sup>[95]</sup>

## Strategies

Excessive antibiotic use has become one of the top contributors to the development of antibiotic resistance. Since the beginning of the antibiotic era, antibiotics have been used to treat a wide range of disease.<sup>[96]</sup> Overuse of antibiotics has become the primary cause of rising levels of antibiotic resistance. The main problem is that doctors are willing to prescribe antibiotics to ill-informed individuals who believe that antibiotics can cure nearly all illnesses, including viral infections like the common cold. In an analysis of drug prescriptions, 36% of individuals with a cold or an upper respiratory infection (both viral in origin) were given prescriptions for antibiotics.<sup>[97]</sup> These prescriptions accomplished nothing other than increasing the risk of further evolution of antibiotic resistant bacteria.

In a recent years, antimicrobial stewardship teams in hospitals have encouraged optimal use of antimicrobials.<sup>[98]</sup> The goals of antimicrobial stewardship are to help practitioners pick the right drug at the right dose and duration of therapy while preventing misuse and minimizing the development of resistance.

There have been increasing public calls for global collective action to address the threat, including a proposal for international treaty on antimicrobial resistance. Further detail and attention is still needed in order to recognize and measure trends in resistance on the international level; the idea of a global tracking system has been suggested but implementation has yet to occur. A system of this nature would provide insight to areas of high resistance as well as information necessary for evaluation of programs and other changes made to fight or reverse antibiotic resistance.

On March 27, 2015, the White House released a comprehensive plan to address the increasing need for agencies to combat the rise of antibiotic-resistant bacteria. The Task Force for Combating Antibiotic-Resistant Bacteria developed *The National Action Plan for Combating Antibiotic-Resistant Bacteria* with the intent of providing a roadmap to guide the US in the antibiotic resistance challenge and with hopes of saving many lives. This plan outlines steps taken by the Federal government over the next five years needed in order to prevent and contain outbreaks of antibiotic-resistant infections; maintain the efficacy of antibiotics already on the market; and to help to develop future diagnostics, antibiotics, and vaccines.<sup>[99]</sup>

The Action Plan was developed around five goals with focuses on strengthening health care, public health veterinary medicine, agriculture, food safety and research, and manufacturing. These goals, as listed by the White House, are as follows:

- Slow the Emergence of Resistant Bacteria and Prevent the Spread of Resistant Infections
- Strengthen National One-Health Surveillance Efforts to Combat Resistance
- Advance Development and use of Rapid and Innovative Diagnostic Tests for Identification and Characterization of Resistant Bacteria
- Accelerate Basic and Applied Research and Development for New Antibiotics, Other Therapeutics, and Vaccines
- Improve International Collaboration and Capacities for Antibiotic Resistance Prevention, Surveillance, Control and Antibiotic Research and Development

By following are goals set to meet by 2020:<sup>[99]</sup>

- Establishment of antimicrobial programs within acute care hospital settings
- Reduction of inappropriate antibiotic prescription and use by at least 50% in outpatient settings and 20% inpatient settings
- Establishment of State Antibiotic Resistance (AR) Prevention Programs in all 50 states
- Elimination of the use of medically important antibiotics for growth promotion in food-producing animals.

The World Health Organization has promoted the first World Antibiotic Awareness Week running from 16–22 November 2015. The aim of the week is to increase global awareness of antibiotic resistance. It also wants to promote the correct usage of antibiotics across all fields in order to prevent further instances of antibiotic resistance.

[100]

## Vaccines

Microorganisms do not develop resistance to vaccines because a vaccine enhances the body's immune system, whereas an antibiotic operates separately from the body's normal defenses. Furthermore, if the use of vaccines increase, there is evidence that antibiotic resistant strains of pathogens will decrease; the need for antibiotics will naturally decrease as vaccines prevent infection before it occurs.<sup>[101]</sup> However, new strains that escape immunity induced by vaccines may evolve; for example, an updated influenza vaccine is needed each year.

While theoretically promising, antistaphylococcal vaccines have shown limited efficacy, because of immunological variation between *Staphylococcus* species, and the limited duration of effectiveness of the antibodies produced. Development and testing of more effective vaccines is underway.<sup>[102]</sup>

## Alternating therapy

Alternating therapy is a proposed method in which two or three antibiotics are taken in a rotation versus taking just one antibiotic such that bacteria resistant to one antibiotic are killed when the next antibiotic is taken. Studies have found that this method reduces the rate at which antibiotic resistant bacteria emerge in vitro relative to a single drug for the entire duration.<sup>[103]</sup>

## Development of new drugs

Since the discovery of antibiotics, research and development (R&D) efforts have provided new drugs in time to treat bacteria that became resistant to older antibiotics, but in the 2000s there has been concern that development has slowed enough that seriously ill people may run out of treatment options.<sup>[104]</sup> Another concern is that doctors may become reluctant to perform routine surgeries because of the increased risk of harmful infection.<sup>[105]</sup> Backup treatments can have serious side-effects; for example, treatment of multi-drug-resistant tuberculosis can cause deafness or psychological disability.<sup>[106]</sup> The potential crisis at hand is the result of a marked decrease in industry R&D.<sup>[107]</sup> Poor financial investment in antibiotic research has exacerbated the situation.<sup>[65][107]</sup> The pharmaceutical industry has little incentive to invest in antibiotics because of the high risk and because the potential financial returns are less likely to cover the cost of development than for other pharmaceuticals.<sup>[108]</sup> In 2011, Pfizer, one of the last major pharmaceutical companies developing new antibiotics, shut down its primary research effort, citing poor shareholder returns relative to drugs for chronic illnesses.<sup>[109]</sup> However, small and medium-sized pharmaceutical companies are still active in antibiotic drug research.

In the United States, drug companies and the administration of President Barack Obama have been proposing changing the standards by which the FDA approves antibiotics targeted at resistant organisms.<sup>[105][110]</sup> On 12 December 2013, the Antibiotic Development to Advance Patient Treatment (ADAPT) Act of 2013 was introduced in the U.S. Congress. The ADAPT Act aims to fast-track the drug development in order to combat the growing public health threat of 'superbugs'. Under this Act, the FDA can approve antibiotics and antifungals needed for life-threatening infections based on data from smaller clinical trials. The Centers for Disease Control and Prevention (CDC) will reinforce the monitoring of the use of antibiotics that treat serious and life-threatening infections and the emerging resistance, and make the data publicly available. The FDA antibiotics labeling process, 'Susceptibility Test Interpretive Criteria for Microbial Organisms' or 'breakpoints' is also streamlined to allow the most up-to-date and cutting-edge data available to healthcare professionals under the new Act.<sup>[111][112]</sup>

On 18 September 2014 Obama signed an executive order<sup>[113]</sup> to implement the recommendations proposed in a report<sup>[114]</sup> by the President's Council of Advisors on Science and Technology (PCAST) which outlines strategies to streamline clinical trials and speed up the R&D of new antibiotics. Among the proposals:

- Create a 'robust, standing national clinical trials network for antibiotic testing' which will promptly enroll patients once identified to be suffering from dangerous bacterial infections. The network will allow testing multiple new agents from different companies simultaneously for their safety and efficacy.
- Establish a 'Special Medical Use (SMU)' pathway for FDA to approve new antimicrobial agents for use in limited patient populations, shorten the approval timeline for new drug so patients with severe infections could benefit as quickly as possible.
- Provide economic incentives, especially for development of new classes of antibiotics, to offset the steep R&D costs which drive away the industry to develop antibiotics.

The executive order also included a \$20 million prize to encourage the development of diagnostic tests to identify highly resistant bacterial infections.<sup>[115]</sup>

The U.S. National Institutes of Health plans to fund a new research network on the issue up to \$62 million from 2013 to 2019.<sup>[116]</sup> Using authority created by the Pandemic and All Hazards Preparedness Act of 2006, the Biomedical Advanced Research and Development Authority in the U.S. Department of Health and Human Services announced that it will spend between \$40 million and \$200 million in funding for R&D on new antibiotic drugs under development by GlaxoSmithKline.<sup>[117]</sup>

One major cause of antibiotic resistance is the increased pumping activity of microbial ABC transporters, which diminishes the effective drug concentration inside the microbial cell. ABC transporter inhibitors that can be used in combination with current antimicrobials are being tested in clinical trials and are available for therapeutic regimens.<sup>[118]</sup>

## Animal use

### Europe

In 1997, European Union health ministers voted to ban avoparcin and four additional antibiotics used to promote animal growth in 1999.<sup>[119]</sup> In 2006 a ban on the use of antibiotics in European feed, with the exception of two antibiotics in poultry feeds, became effective.<sup>[120]</sup> In Scandinavia, there is evidence that the ban has led to a lower prevalence of antibiotic resistance in (nonhazardous) animal bacterial populations.<sup>[121]</sup> As of 2004, several European countries established a decline of antimicrobial resistance in humans through limiting the usage antimicrobials in agriculture and food industries without jeopardizing animal health or economic cost.<sup>[122]</sup>

### United States

The United States Department of Agriculture (USDA) and the Food and Drug Administration (FDA) collect data on antibiotic use in humans and in a more limited fashion in animals.<sup>[123]</sup> The FDA first determined in 1977 that there is evidence of emergence of antibiotic-resistant bacterial strains in livestock. The long-established practice of permitting OTC sales of antibiotics (including penicillin and other drugs) to lay animal owners for administration to their own animals nonetheless continued in all states. In 2000, the FDA announced their intention to revoke approval of fluoroquinolone use in poultry production because of substantial evidence linking it to the emergence of fluoroquinolone-resistant *Campylobacter* infections in humans. Legal challenges from the food animal and pharmaceutical industries delayed the final decision to do so until 2006.<sup>[124]</sup> Fluroquinolones have been banned from extra-label use in food animals in the USA since 2007. However, they remain widely used in companion and exotic animals.

During 2007, two federal bills (S. 549<sup>[125]</sup> and H.R. 962<sup>[126]</sup>) aimed at phasing out "nontherapeutic" antibiotics in U.S. food animal production. The Senate bill, introduced by Sen. Edward "Ted" Kennedy, died. The House bill, introduced by Rep. Louise Slaughter, died after being referred to Committee.

In March 2012, the United States District Court for the Southern District of New York, ruling in an action brought by the Natural Resources Defense Council and others, ordered the FDA to revoke approvals for the use of antibiotics in livestock that violated FDA regulations.<sup>[127]</sup> On April 11, 2012 the FDA announced a voluntary program to phase out unsupervised use of drugs as feed additives and convert approved over-the-counter uses for antibiotics to prescription use only, requiring veterinarian supervision of their use and a prescription.<sup>[128][129]</sup> In December 2013, the FDA announced the commencement of these steps to phase out the use of antibiotics for the purposes of promoting livestock growth.<sup>[65][130]</sup>

Growing U.S. consumer concern about using antibiotics in animal feed has led to greater availability of "antibiotic-free" animal products. For example, chicken producer Perdue removed all human antibiotics from its feed and launched products labeled "antibiotic free" under the Harvestland brand in 2007. Consumer response was positive, and in 2014 Perdue also phased out ionophores from its hatchery and began using the "antibiotic free" labels on its Harvestland, Simply Smart, and Perfect Portions products.<sup>[131]</sup>

## Mechanisms

The four main mechanisms by which microorganisms exhibit resistance to antimicrobials are:

1. Drug inactivation or modification: for example, enzymatic deactivation of *penicillin G* in some penicillin-resistant bacteria through the production of  $\beta$ -lactamases. Most commonly, the protective enzymes produced by the bacterial cell will add an acetyl or phosphate group to a specific site on the antibiotic, which will reduce its ability to bind to the bacterial ribosomes and disrupt protein synthesis.<sup>[132]</sup>
2. Alteration of target site: for example, alteration of PBP—the binding target site of penicillins—in MRSA and other penicillin-resistant bacteria. Another protective mechanism found among bacterial species is ribosomal protection proteins. These proteins protect the bacterial cell from antibiotics that target the cell's ribosomes to inhibit protein synthesis. The mechanism involves the binding of the ribosomal protection proteins to the ribosomes of the bacterial cell, which in turn changes its conformational shape. This allows the ribosomes to continue synthesizing proteins essential to the cell while preventing antibiotics from binding to the ribosome to inhibit protein synthesis.
3. Alteration of metabolic pathway: for example, some sulfonamide-resistant bacteria do not require para-aminobenzoic acid (PABA), an important precursor for the synthesis of folic acid and nucleic acids in bacteria inhibited by sulfonamides, instead, like mammalian cells, they turn to using preformed folic acid.
4. Reduced drug accumulation: by decreasing drug permeability or increasing active efflux (pumping out) of the drugs across the cell surface<sup>[133]</sup> These specialized pumps can be found within the cellular membrane of certain bacterial species and are used to pump antibiotics out of the cell before they are able to do any damage. These efflux pumps are often activated by a specific substrate associated with an antibiotic.<sup>[134]</sup>

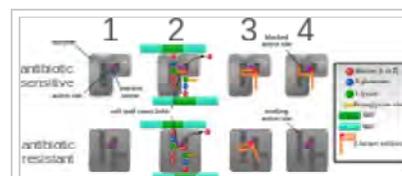
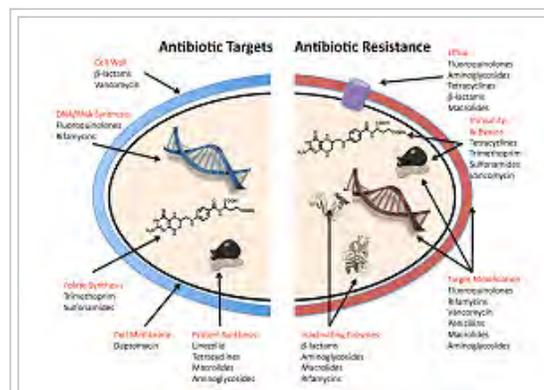


Diagram depicting antibiotic resistance through alteration of the antibiotic's target site, modeled after MRSA's resistance to penicillin. Beta-lactam antibiotics permanently inactivate PBP enzymes, which are essential for bacterial life, by permanently binding to their active sites. MRSA, however, expresses a PBP that does not allow the antibiotic into its active site.

Antibiotic resistance can be a result of horizontal gene transfer,<sup>[135]</sup> and also of unlinked point mutations in the pathogen genome at a rate of about 1 in  $10^8$  per chromosomal replication. Mutations are rare but the fact that bacteria reproduce at such a high rate allows for the effect to be significant. A mutation may produce a change in the binding site of the antibiotic, which may allow the site to continue proper functioning in the presence of the antibiotic or prevent the binding of the antibiotic to the site altogether. Research has shown the bacterial protein LexA may play a key role in the acquisition of bacterial mutations giving resistance to quinolones and rifampicin. DNA damage induces the SOS gene repressor LexA to undergo autoproteolytic activity. This includes the transcription of genes encoding Pol II, Pol IV, and Pol V, which are three nonessential DNA polymerases that are required for mutation in

response to DNA damage.<sup>[136]</sup> The antibiotic action against the pathogen can be seen as an environmental pressure. Those bacteria with a mutation that allows them to survive live to reproduce. They then pass this trait to their offspring, which leads to the evolution of a fully resistant colony. Although these chromosomal mutations may seem to benefit the bacteria by providing antibiotic resistance, they also confer a cost of fitness. For example, a ribosomal mutation may protect a bacterial cell by changing the binding site of an antibiotic but it will also slow the process of protein synthesis.<sup>[132]</sup> Additionally, a particular study specifically compared the overall fitness of antibiotic resistant strains of *Escherichia coli* and *Salmonella typhimurium* to their drug-sensitive revertants. They observed a reduced overall fitness in the antibiotic resistant strains, especially in growth rate.<sup>[137]</sup>



A number of mechanisms used by common antibiotics to deal with bacteria and ways by which bacteria become resistant to them.

There are three known mechanisms of fluoroquinolone

resistance. Some types of efflux pumps can act to decrease intracellular quinolone concentration.<sup>[138]</sup> In Gram-negative bacteria, plasmid-mediated resistance genes produce proteins that can bind to DNA gyrase, protecting it from the action of quinolones. Finally, mutations at key sites in DNA gyrase or topoisomerase IV can decrease their binding affinity to quinolones, decreasing the drug's effectiveness.<sup>[139]</sup>

Antibiotic resistance can also be introduced artificially into a microorganism through laboratory protocols, sometimes used as a selectable marker to examine the mechanisms of gene transfer or to identify individuals that absorbed a piece of DNA that included the resistance gene and another gene of interest. A recent study demonstrated that the extent of horizontal gene transfer among *Staphylococcus* is much greater than previously expected—and encompasses genes with functions beyond antibiotic resistance and virulence, and beyond genes residing within the mobile genetic elements.<sup>[140]</sup>

For a long time, it has been thought that, for a microorganism to become resistant to an antibiotic, it must be in a large population. However, recent findings show that there is no necessity of large populations of bacteria for the appearance of antibiotic resistance. We know now that small populations of *E. coli* in an antibiotic gradient can become resistant. Any heterogeneous environment with respect to nutrient and antibiotic gradients may facilitate the development of antibiotic resistance in small bacterial populations and this is also true for the human body. Researchers hypothesize that the mechanism of resistance development is based on four SNP mutations in the genome of *E. coli* produced by the gradient of antibiotic. These mutations confer the bacteria emergence of antibiotic resistance.

## MCR-1

In November, 2015, a Chinese team first described MCR-1 gene after finding the gene in pigs and pork. It became a matter of concern when it was discovered that it could be transferred to other organisms. MCR-1 was later discovered in Malaysia, England,<sup>[141]</sup> China,<sup>[142]</sup> Europe,<sup>[143]</sup> and the United States.<sup>[144]</sup>

## NDM-1

NDM-1 is an enzyme that makes bacteria resistant to a broad range of beta-lactam antibiotics.

NDM-1 was first detected in a *Klebsiella pneumoniae* isolate from a Swedish patient of Indian origin in 2008. It was later detected in bacteria in India, Pakistan, the United Kingdom, the United States,<sup>[145]</sup> Canada (<http://www.healthzone.ca/health/newsfeatures/article/850906>) and Japan ([http://www.boston.com/news/health/articles/2010/09/08/japan\\_confirms\\_first\\_case\\_of\\_superbug\\_gene/](http://www.boston.com/news/health/articles/2010/09/08/japan_confirms_first_case_of_superbug_gene/)).

According to A *Lancet* study, NDM-1 (New Delhi Metallo-beta-lactamase-1) originated in India, The study came to a conclusion that Indian hospitals are unsafe for treatment as Nosocomial-infections are common and with the new super-bugs on rise in India, It can be dangerous.

## Organisms

### Bacteria

#### *Staphylococcus aureus*

*Staphylococcus aureus* (colloquially known as "Staph aureus" or a "Staph infection") is one of the major resistant pathogens. Found on the mucous membranes and the human skin of around a third of the population, it is extremely adaptable to antibiotic pressure. It was one of the earlier bacteria in which penicillin resistance was found—in 1947, just four years after the drug started being mass-produced. Methicillin was then the antibiotic of choice, but has since been replaced by oxacillin because of significant kidney toxicity. Methicillin-resistant *Staphylococcus aureus* (MRSA) was first detected in Britain in 1961, and is now "quite common" in hospitals. MRSA was responsible for 37% of fatal cases of sepsis in the UK in 1999, up from 4% in 1991. Half of all *S. aureus* infections in the US are resistant to penicillin, methicillin, tetracycline and erythromycin.

This left vancomycin as the only effective agent available at the time. However, strains with intermediate (4–8 µg/ml) levels of resistance, termed glycopeptide-intermediate *Staphylococcus aureus* (GISA) or vancomycin-intermediate *Staphylococcus aureus* (VISA), began appearing in the late 1990s. The first identified case was in Japan in 1996, and strains have since been found in hospitals in England, France and the US. The first documented strain with complete (>16 µg/ml) resistance to vancomycin, termed vancomycin-resistant *Staphylococcus aureus* (VRSA) appeared in the United States in 2002.<sup>[146]</sup> However, in 2011, a variant of vancomycin has been tested that binds to the lactate variation and also binds well to the original target, thus reinstating potent antimicrobial activity.<sup>[147]</sup>

A new class of antibiotics, oxazolidinones, became available in the 1990s, and the first commercially available oxazolidinone, linezolid, is comparable to vancomycin in effectiveness against MRSA. Linezolid resistance in *S. aureus* was reported in 2001.<sup>[148]</sup>

Community-acquired MRSA (CA-MRSA) has now emerged as an epidemic that is responsible for rapidly progressive, fatal diseases, including necrotizing pneumonia, severe sepsis, and necrotizing fasciitis.<sup>[149]</sup> MRSA is the most frequently identified antimicrobial drug-resistant pathogen in US hospitals. The epidemiology of infections caused by MRSA is rapidly changing. Since 2000, infections caused by this organism have emerged in the community. The two MRSA clones in the United States most closely associated with community outbreaks, USA400 (MW2 strain, ST1 lineage) and USA300, often contain Panton-Valentine leukocidin (PVL) genes and, more frequently, have been associated with skin and soft tissue infections. Outbreaks of CA-MRSA infections have been reported in correctional facilities, among athletic teams, among military recruits, in newborn nurseries, and among men that have sex with men. CA-MRSA infections now appear endemic in many urban regions and cause most CA-*S. aureus* infections.<sup>[150]</sup>

#### *Streptococcus and Enterococcus*

*Streptococcus pyogenes* (Group A *Streptococcus*: GAS) infections can usually be treated with many different antibiotics. Early treatment may reduce the risk of death from invasive group A streptococcal disease. However, even the best medical care does not prevent death in every case. For those with very severe illness, supportive care in an intensive-care unit may be needed. For persons with necrotizing fasciitis, surgery often is needed to remove damaged tissue.<sup>[151]</sup> Strains of *S. pyogenes* resistant to macrolide antibiotics have emerged; however, all strains remain uniformly susceptible to penicillin.<sup>[152]</sup>

Resistance of *Streptococcus pneumoniae* to penicillin and other beta-lactams is increasing worldwide. The major mechanism of resistance involves the introduction of mutations in genes encoding penicillin-binding proteins. Selective pressure is thought to play an important role, and use of beta-lactam antibiotics has been implicated as a risk factor for infection and colonization. *S. pneumoniae* is responsible for pneumonia, bacteremia, otitis media, meningitis, sinusitis, peritonitis and arthritis.<sup>[152]</sup>

Multidrug-resistant *Enterococcus faecalis* and *Enterococcus faecium* are associated with nosocomial infections.<sup>[153]</sup> These strains include: penicillin-resistant *Enterococcus*, vancomycin-resistant *Enterococcus*, and linezolid-resistant *Enterococcus*.<sup>[154]</sup>

### ***Pseudomonas aeruginosa***

*Pseudomonas aeruginosa* is a highly prevalent opportunistic pathogen. One of the most worrisome characteristics of *P. aeruginosa* is its low antibiotic susceptibility, which is attributable to a concerted action of multidrug efflux pumps with chromosomally encoded antibiotic resistance genes (e.g., *mexAB-oprM*, *mexXY*) and the low permeability of the bacterial cellular envelopes.<sup>[155]</sup> *Pseudomonas aeruginosa* has the ability to produce 4-hydroxy-2-alkylquinolines (HAQs) and it has been found that HAQs have prooxidant effects, and overexpressing modestly increased susceptibility to antibiotics. The study experimented with the *Pseudomonas aeruginosa* biofilms and found that a disruption of *relA* and *spoT* genes produced an inactivation of the Stringent response (SR) in cells with nutrient limitation, which provides cells be more susceptible to antibiotics.<sup>[156]</sup>

### ***Clostridium difficile***

*Clostridium difficile* is a nosocomial pathogen that causes diarrheal disease worldwide.<sup>[157][158]</sup> Diarrhea caused by *C. difficile* can be life-threatening. Infections are most frequent in people who have had recent medical and/or antibiotic treatment. *C. difficile* infections commonly occur during hospitalization.<sup>[15]</sup>

According to a 2015 CDC report, *C. difficile* caused almost 500,000 infections in the United States over a year period. Associated with these infections were an estimated 15,000 deaths. The CDC estimates that *C. difficile* infection costs could amount to \$3.8 billion over a 5-year span.<sup>[159]</sup>

*C. difficile* colitis is most strongly associated with fluoroquinolones, cephalosporins, carbapenems, and clindamycin.<sup>[160][161][162]</sup>

Some research suggests the overuse of antibiotics in the raising of livestock is contributing to outbreaks of bacterial infections such as *C. difficile*.<sup>[16]</sup>

Antibiotics, especially those with a broad activity spectrum (such as clindamycin) disrupt normal intestinal flora. This can lead to an overgrowth of *C. difficile*, which flourishes under these conditions. Pseudomembranous colitis can follow, creating generalized inflammation of the colon and the development of "pseudomembrane", a viscous collection of inflammatory cells, fibrin, and necrotic cells.<sup>[4]</sup> Clindamycin-resistant *C. difficile* was reported as the causative agent of large outbreaks of diarrheal disease in hospitals in New York, Arizona, Florida and Massachusetts between 1989 and 1992.<sup>[163]</sup> Geographically dispersed outbreaks of *C. difficile* strains resistant to fluoroquinolone antibiotics, such as ciprofloxacin and levofloxacin, were also reported in North America in 2005.<sup>[164]</sup>

### **Carbapenem-resistant Enterobacteriaceae**

As of 2013 hard-to-treat or untreatable infections of carbapenem-resistant Enterobacteriaceae (CRE) were increasing among patients in medical facilities. CRE are resistant to nearly all available antibiotics. Almost half of hospital patients who get bloodstream CRE infections die from the infection.<sup>[15]</sup>

### **Multidrug-resistant *Acinetobacter***

*Acinetobacter* is a gram-negative bacteria that causes pneumonia or bloodstream infections in critically ill patients. Multidrug-resistant *Acinetobacter* have become very resistant to antibiotics.<sup>[15]</sup>

### **Drug-resistant *Campylobacter***

*Campylobacter* causes diarrhea (often bloody), fever, and abdominal cramps. Serious complications such as temporary paralysis can also occur. Physicians rely on ciprofloxacin and azithromycin for treating patients with severe disease although *Campylobacter* is showing resistance to these antibiotics.<sup>[15]</sup>

### ***Salmonella* and *E. coli***

Infection with *Escherichia coli* and *Salmonella* can result from the consumption of contaminated food and water. Both of these bacteria are well known for causing nosocomial (hospital-linked) infections, and often, these strains found in hospitals are antibiotic resistant because of adaptations to wide spread antibiotic use.<sup>[165]</sup> When both bacteria are spread, serious health conditions arise. Many people are hospitalized each year after becoming infected, with some dying as a result. Since 1993, some strains of *E. coli* have become resistant to multiple types of fluoroquinolone antibiotics.

Although mutation alone plays a huge role in the development of antibiotic resistance, a 2008 study found that high survival rates after exposure to antibiotics could not be accounted for by mutation alone.<sup>[166]</sup> This study focused on the development of resistance in *E. coli* to three antibiotic drugs: ampicillin, tetracycline, and nalidixic acid. The researchers found that some antibiotic resistance in *E. coli* developed because of epigenetic inheritance rather than by direct inheritance of a mutated gene. This was further supported by data showing that reversion to antibiotic sensitivity was relatively common as well. This could only be explained by epigenetics.<sup>[166]</sup> Epigenetics is a type of inheritance in which gene expression is altered rather than the genetic code itself. There are many modes by which this alteration of gene expression can occur, including methylation of DNA and histone modification; however, the important point is that both inheritance of random mutations and epigenetic markers can result in the expression of antibiotic resistance genes.<sup>[166]</sup>

Resistance to polymyxins first appear in 2011.<sup>[167]</sup> An easier way for this resistance to spread, a plasmid known as MCR-1 was discovered in 2015.<sup>[167]</sup>

### ***Acinetobacter baumannii***

On November 5, 2004, the Centers for Disease Control and Prevention (CDC) reported an increasing number of *Acinetobacter baumannii* bloodstream infections in patients at military medical facilities in which service members injured in the Iraq/Kuwait region during Operation Iraqi Freedom and in Afghanistan during Operation Enduring Freedom were treated. Most of these showed multidrug resistance (MRAB), with a few isolates resistant to all drugs tested.<sup>[168][169]</sup>

### ***Klebsiella pneumoniae***

*Klebsiella pneumoniae* carbapenemase (KPC)-producing bacteria are a group of emerging highly drug-resistant Gram-negative bacilli causing infections associated with significant morbidity and mortality whose incidence is rapidly increasing in a variety of clinical settings around the world. *Klebsiella pneumoniae* includes numerous

mechanisms for antibiotic resistance, many of which are located on highly mobile genetic elements.<sup>[170]</sup> Carbapenem antibiotics (heretofore often the treatment of last resort for resistant infections) are generally not effective against KPC-producing organisms.<sup>[171]</sup>

### *Mycobacterium tuberculosis*

Tuberculosis is increasing across the globe, especially in developing countries, over the past few years. TB resistant to antibiotics is called MDR TB (Multidrug Resistant TB). Globally, MDR TB causes 150,000 deaths annually.<sup>[172]</sup> The rise of the HIV/AIDS epidemic has contributed to this.<sup>[173]</sup>

TB was considered one of the most prevalent diseases, and did not have a cure until the discovery of Streptomycin by Selman Waksman in 1943.<sup>[174]</sup> However, the bacteria soon developed resistance. Since then, drugs such as isoniazid and rifampin have been used. *M. tuberculosis* develops resistance to drugs by spontaneous mutations in its genomes. Resistance to one drug is common, and this is why treatment is usually done with more than one drug. Extensively Drug-Resistant TB (XDR TB) is TB that is also resistant to the second line of drugs.<sup>[173][175]</sup>

Resistance of *Mycobacterium tuberculosis* to isoniazid, rifampin, and other common treatments has become an increasingly relevant clinical challenge. (For more on Drug-Resistant TB, visit the Multi-drug-resistant tuberculosis page.) Evidence is lacking for whether these bacteria have plasmids.<sup>[176]</sup> Also *M. tuberculosis* lack the opportunity to interact with other bacteria in order to share plasmids.<sup>[176][177]</sup>

### *Neisseria gonorrhoeae*

*Neisseria gonorrhoeae* is a sexually transmitted pathogen that causes gonorrhea, a sexually transmitted disease that can result in discharge and inflammation at the urethra, cervix, pharynx, or rectum.<sup>[15]</sup> It can cause pelvic pain, pain on urination, penile and vaginal discharge, as well as systemic symptoms. It can also cause severe reproductive complications.<sup>[15]</sup> The bacteria was first identified in 1879,<sup>[178]</sup> although some Biblical scholars believe that references to the disease can be found as early as Parshat Metzora of the Old Testament.<sup>[179]</sup>

In the 1940s effective treatment with penicillin became available, but by the 1970s resistant strains predominated. Resistance to penicillin has developed through two mechanisms: chromosomally mediated resistance (CMRNG) and penicillinase-mediated resistance (PPNG). CMRNG involves step wise mutation of *penA*, which codes for the penicillin-binding protein (PBP-2); *mtr*, which encodes an efflux pump that removes penicillin from the cell; and *penB*, which encodes the bacterial cell wall porins. PPNG involves the acquisition of a plasmid-borne beta-lactamase.<sup>[180]</sup> *N. gonorrhoeae* has a high affinity for horizontal gene transfer, and as a result, the existence of any strain resistant to a given drug could spread easily across strains.

Fluoroquinolones were a useful next-line treatment until resistance was achieved through efflux pumps and mutations to the *gyrA* gene, which encodes DNA gyrase.<sup>[180]</sup> Third-generation cephalosporins have been used to treat gonorrhoea since 2007, but resistant strains have emerged. As of 2010, the recommended treatment is a single 250 mg intramuscular injection of ceftriaxone, sometimes in combination with azithromycin or doxycycline.<sup>[181][182]</sup> However, certain strains of *N. gonorrhoeae* can be resistant to antibiotics usually that are normally used to treat it. These include: cefixime (an oral cephalosporin), ceftriaxone (an injectable cephalosporin), azithromycin, aminoglycosides, and tetracycline.<sup>[15]</sup>

## Viruses

Specific antiviral drugs are used to treat some viral infections. These drugs prevent viruses from reproducing by inhibiting essential stages of the virus's replication cycle in infected cells. Antivirals are used to treat HIV, hepatitis B, hepatitis C, influenza, herpes viruses including varicella zoster virus, cytomegalovirus and Epstein-Barr virus. With each virus, some strains have become resistant to the administered drugs.<sup>[183]</sup>

Resistance to HIV antivirals is problematic, and even multi-drug resistant strains have evolved.<sup>[184]</sup> Resistant strains of the HIV virus emerge rapidly if only one antiviral drug is used.<sup>[185]</sup> Using three or more drugs together has helped to control this problem, but new drugs are needed because of the continuing emergence of drug-resistant HIV strains.<sup>[186]</sup>

## Fungi

Infections by fungi are a cause of high morbidity and mortality in immunocompromised persons, such as those with HIV/AIDS, tuberculosis or receiving chemotherapy.<sup>[187]</sup> The fungi candida, *Cryptococcus neoformans* and *Aspergillus fumigatus* cause most of these infections and antifungal resistance occurs in all of them.<sup>[188]</sup> Multidrug resistance in fungi is increasing because of the widespread use of antifungal drugs to treat infections in immunocompromised individuals.<sup>[189]</sup>

Of particular note, Fluconazole-resistant Candida species have been highlighted as a growing problem by the CDC.<sup>[15]</sup> More than 20 Candida species of Candida can cause Candidiasis infection, the most common of which is *Candida albicans*. Candida yeasts normally inhabit the skin and mucous membranes without causing infection. However, overgrowth of Candida can lead to Candidiasis. Some Candida strains are becoming resistant to first-line and second-line antifungal agents such as azoles and echinocandins.<sup>[15]</sup>

## Parasites

The protozoan parasites that cause the diseases malaria, trypanosomiasis, toxoplasmosis, cryptosporidiosis and leishmaniasis are important human pathogens.<sup>[190]</sup>

Malarial parasites that are resistant to the drugs that are currently available to infections are common and this has led to increased efforts to develop new drugs.<sup>[191]</sup> Resistance to recently developed drugs such as artemisinin has also been reported. The problem of drug resistance in malaria has driven efforts to develop vaccines.<sup>[192]</sup>

Trypanosomes are parasitic protozoa that cause African trypanosomiasis and Chagas disease (American trypanosomiasis).<sup>[193][194]</sup> There are no vaccines to prevent these infections so drugs such as pentamidine and suramin, benznidazole and nifurtimox and used to treat infections. These drugs are effective but infections caused by resistant parasites have been reported.<sup>[190]</sup>

Leishmaniasis is caused by protozoa and is an important public health problem worldwide, especially in sub-tropical and tropical countries. Drug resistance has "become a major concern".<sup>[195]</sup>

## Applications

Antibiotic resistance is an important tool for genetic engineering. By constructing a plasmid that contains an antibiotic-resistance gene as well as the gene being engineered or expressed, a researcher can ensure that, when bacteria replicate, only the copies that carry the plasmid survive. This ensures that the gene being manipulated passes along when the bacteria replicates.

In general, the most commonly used antibiotics in genetic engineering are "older" antibiotics. These include:

- ampicillin
- kanamycin
- tetracycline
- chloramphenicol

In industry, the use of antibiotic resistance is disfavored, since maintaining bacterial cultures would require feeding them large quantities of antibiotics. Instead, the use of auxotrophic bacterial strains (and function-replacement plasmids) is preferred.

## Society and culture

For the fiscal year 2016 budget, President Obama has suggested to nearly double the amount of federal funding to "combat and prevent" antibiotic resistance to more than \$1.2 billion.<sup>[196]</sup>

Since the mid-1980s pharmaceutical companies have invested in medications for cancer or chronic disease that have greater potential to make money and have "de-emphasized or dropped development of antibiotics".<sup>[197]</sup> On January 20, 2016 at the World Economic Forum in Davos, Switzerland, more than "80 pharmaceutical and diagnostic companies" from around the world called for 'transformational commercial models' at a global level to spur research and development on antibiotics and on the "enhanced use of diagnostic tests that can rapidly identify the infecting organism".<sup>[197]</sup>

## Legal frameworks

Some global health scholars have argued that a global, legal framework is needed to prevent and control antimicrobial resistance.<sup>[198][199][17][200]</sup> For instance, binding global policies could be used to create antimicrobial use standards, regulate antibiotic marketing, and strengthen global surveillance systems.<sup>[17][198]</sup> Ensuring compliance of involved parties is a challenge.<sup>[17]</sup> Global antimicrobial resistance policies could take lessons from the environmental sector by adopting strategies that have made international environmental agreements successful in the past such as: sanctions for non-compliance, assistance for implementation, majority vote decision-making rules, an independent scientific panel, and specific commitments.<sup>[201]</sup>

## See also

- Resistance-nodulation-cell division superfamily (RND)
- Alliance for the Prudent Use of Antibiotics
- Antibacterial soap
- (KPC) antibacterial resistance gene
- Broad-spectrum antibiotic
- Carbapenem-resistant enterobacteriaceae
- Colonisation resistance
- Drug of last resort
- Multidrug tolerance
- Multidrug-resistant Gram-negative bacteria
- New Delhi metallo-beta-lactamase 1

## Footnotes

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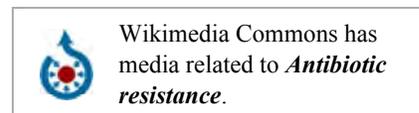
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- Antimicrobial resistance



([https://www.dmoz.org/Health/Pharmacy/Drugs\\_and\\_Medications/Antibiotics/Resistance\\_Issues/](https://www.dmoz.org/Health/Pharmacy/Drugs_and_Medications/Antibiotics/Resistance_Issues/)) at DMOZ

- Animation of Antibiotic Resistance (<http://pharmaxchange.info/press/2011/02/animation-of-antimicrobial-resistance/>)
- CDC Guideline "Management of Multidrug-Resistant Organisms in Healthcare Settings, 2006" (<http://www.cdc.gov/ncidod/dhqp/pdf/ar/mdroGuideline2006.pdf>)

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