



PENICILLIN
1928 - 20

ANTIMICROBIAL RESISTANCE: UP AGAINST THE ROPES

Antibiotics have given us the upper hand over many infectious diseases for the last 60 years. Inappropriate and unnecessary use has now reduced their effectiveness. Closer control is needed to protect their usefulness, and new antibiotics need to be researched and developed.

KEY POINTS

- Antibiotics are life-saving drugs, but many bacteria are now resistant to them.
- In some diseases, because of resistance, the last line of defence has been reached.
- Resistance is caused by excessive use of antibiotics: bacteria evolve and block antibiotic attempts to destroy them.
- Antibiotics are also used in large quantities on animals, adding to the threat of resistance.
- Even though these drugs are becoming less effective, fewer companies develop new antibiotics because they yield only small profits.
- Potential solutions include public education, improved prescribing by doctors, tighter regulation of use in animals, and more research into new drugs.

On an autumn day in 1928, Alexander Fleming, a microbiologist working at St Mary's Hospital in Paddington, noticed a strange phenomenon in a Petri dish that had accidentally been left lying on a lab bench. A ring had appeared around a colony of mould. Bacteria were not growing within it. The discovery of what would become the drug penicillin had a profound impact on humankind.

A variety of different drug compounds can selectively kill bacteria, or prevent their replication. These medicines – antibiotics – can cure many common and some serious illnesses, and make many operations and transplant procedures much safer.

Antibiotic resistance

An antibiotic's effectiveness is not a permanent state. Bacteria develop resistance to antibiotic attack by acquiring new characteristics through genetic mutation or transfer. Within eight years of its first widespread use, penicillin was ineffective against the majority of cases of *Staphylococcus aureus* in hospitals.

The same evolutionary pressures that enabled the human race to adapt, survive and thrive allow bacteria to change and



resist the threats to their survival. Bacteria, however, reproduce at rates thousands of times faster than more complex organisms. Evolution for them is in 'fast forward' and so the process of gaining and spreading resistance happens very rapidly.

Every time an antibiotic is used, it potentially becomes less effective in the population as a whole. Overuse and inappropriate use of antibiotics reduce their efficacy and their ability to cure human disease.

A world without antibiotics

Over the last 80 years, society has grown accustomed to the security that medicines give. Before modern antibiotics, simple infections had life-threatening potential. The blister from the ill-fitting shoe, the scratch from the thorn bush, the chesty cough could all progress to life-threatening infections. Minor infections could develop unchecked and lead to bloodstream spread, and often death. Without antibiotics, the only hope was that the body's natural defences would fend off the infection.

Today, many infections are merely a source of inconvenience or minor discomfort. If the antibiotics that we take for granted today were to cease working completely, the burden on society and individuals would be very great.

Lives saved by antibiotics

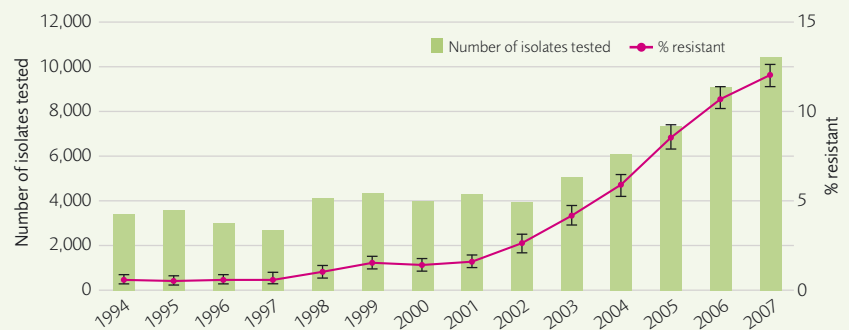
The total number of lives saved by antibiotics each year is large. Three examples of conditions that would often be fatal without antibiotic treatment – 12,000 cases in one year alone – are bacterial meningitis, osteomyelitis and pneumonia (see Table 1).

Table 1: Patients admitted to hospital each year with severe conditions caused by bacteria, requiring antibiotic treatment

Disease	Number of hospital admissions
Bacterial meningitis	1,269
Osteomyelitis (bacterial bone infection)	3,971
Pneumonia (where bacteria are confirmed as the cause)	6,834

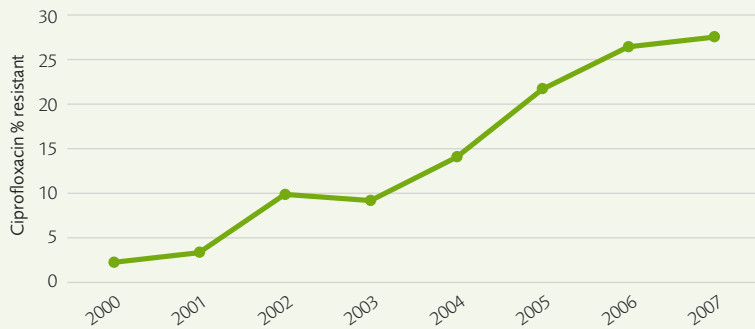
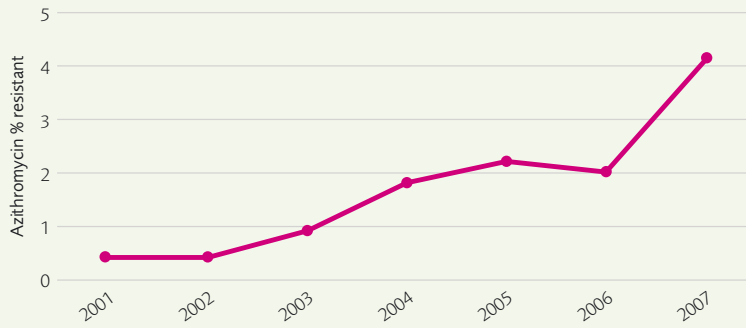
Source: Hospital Episode Statistics 2006/07

Figure 1: Resistance to cefotaxime in *E. coli* bloodstream infections is rising



Source: Health Protection Agency, 2008

Figure 2: Resistance to azithromycin and ciprofloxacin has increased in *N. gonorrhoeae* in the United Kingdom



Source: Gonococcal Resistance to Antimicrobials Surveillance Programme

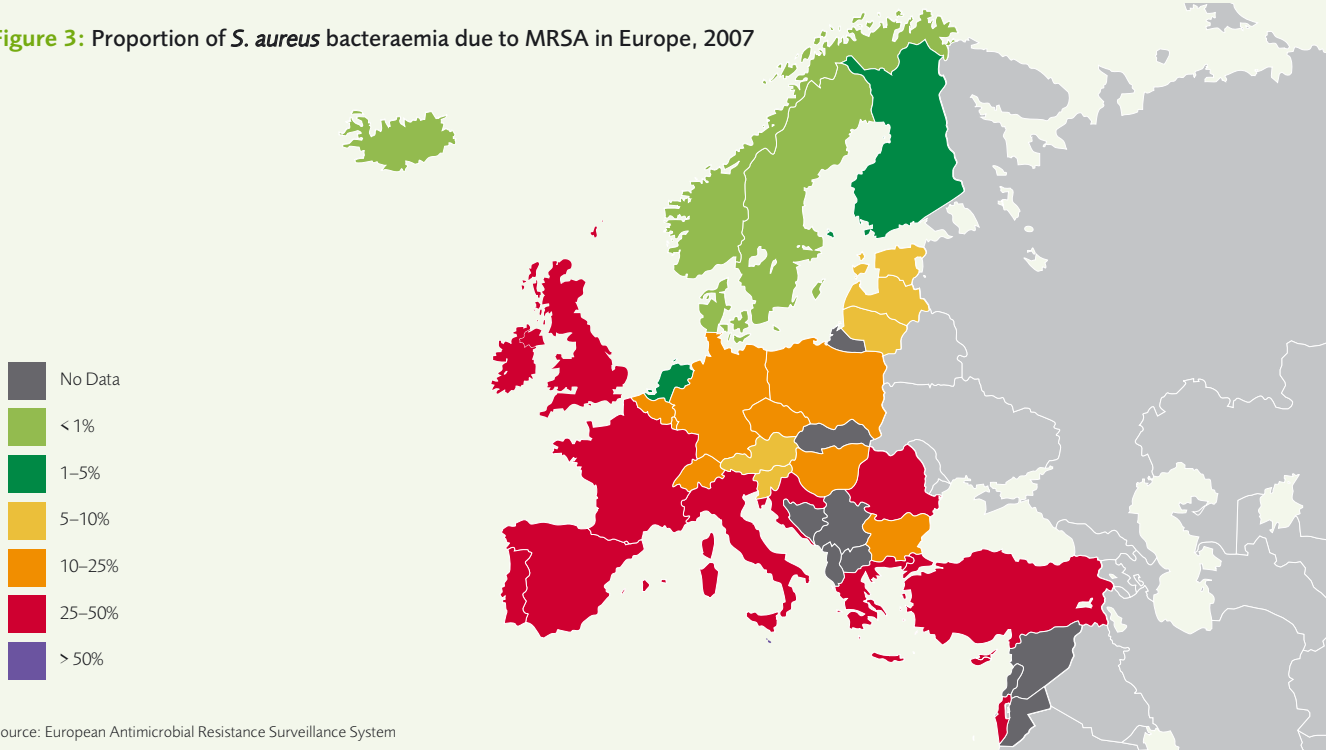
The resistance picture in England: some examples

E. coli is a bacterium that is a common cause of food poisoning and urinary tract infections. Resistance levels to the antibiotic cefotaxime have gone from 1% to 12% in the last 10 years (see Figure 1).

Neisseria gonorrhoeae, a sexually transmitted bacterium that causes an uncomfortable genital discharge, has shown increased resistance to both ciprofloxacin and azithromycin (see Figure 2).

Levels of methicillin-resistant *Staphylococcus aureus* (MRSA), although improving, are also high in the United Kingdom when compared with other parts of Europe (see Figure 3).

Figure 3: Proportion of *S. aureus* bacteraemia due to MRSA in Europe, 2007



Source: European Antimicrobial Resistance Surveillance System

Increasing, and worrying, levels of resistance are developing in other bacteria, including klebsiella and campylobacter.

In some cases, such as some resistant *Acinetobacter baumannii* and certain extended spectrum beta-lactamase (ESBL)-producing bacteria, there are only one or two antibiotics left that work. These are the last lines of defence against such infections.

A faltering pipeline of new drugs

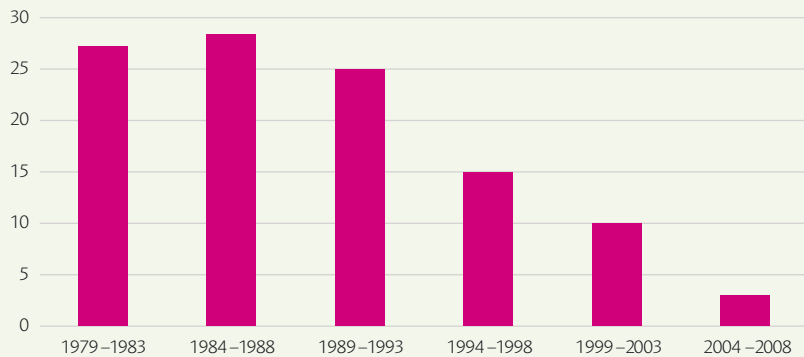
The future availability of new antibiotics to counter antibiotic resistance is less certain. After the initial optimism of the 1940s, 50s and 60s, new antibiotic drug discovery has fallen strikingly. The number of new antibiotic compounds licensed each year has fallen considerably over the last 20 years. Only three new classes of antibiotics have been licensed in the United Kingdom in the last five years (see **Figure 4**).

Pharmaceutical companies are only likely to bear the high cost of new drug development if they make a profit. Antibiotics give a lower return on investment than most other drugs. They are usually used in short courses, compared with chronic disease drugs that are long-term or lifelong treatments. Fewer drug companies are spending money on developing new antibiotics. Prices are set high as drug companies try to claw back the cost of research and development.

In pursuit of profit, drug companies aggressively market new products to ensure that they are prescribed as often as possible. The latest drugs, to which resistance has not yet been developed, should be held in reserve as a last resort. A profit-driven market cannot be relied upon to meet society's needs.

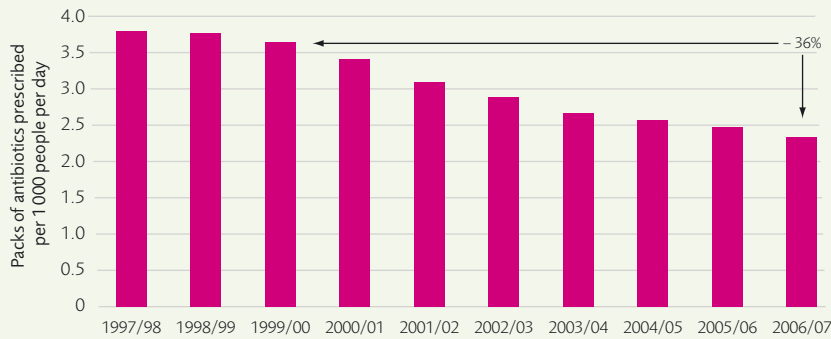


Figure 4: The number of new antibiotics licensed in the UK is falling



Source: Medicines and Healthcare products Regulatory Agency

Figure 5: Outpatient antibiotic use has fallen since the start of the national campaign in Belgium



Source: Goossens et al, 2008

Learning from experience elsewhere

Although England has one of the lower rates of antibiotic prescribing in Europe (14 daily doses per 1,000 people per day, compared with a European average of 18), there are still too many antibiotics prescribed.

Other countries have been successful in reducing the volume of antibiotics prescribed. The Belgian government has made a concerted effort to drive down inappropriate prescription of antibiotics, particularly in the primary care sector. The Belgian Ministry of Health ran a seasonal campaign over the autumn and winter months from 2000 until 2007, which aimed to educate the public about the rational use of antibiotics. It used a combination of booklets, posters and high-profile television and radio adverts. The campaign helped reduce outpatient antibiotic prescription by 36% (see **Figure 5**).

Resistance rates for several common microbes also fell. Erythromycin resistance in *Streptococcus pyogenes*, a common cause of tonsillitis, fell from 17% in 2001 to 2% in 2007.

In France, a similar major antibiotic education campaign produced a reduction in outpatient antibiotic prescription of 23%. Penicillin resistance in *Streptococcus pneumoniae* fell from over 50% to less than 40% during the campaign (see **Figure 6**).



The Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection has run a number of successful campaigns in England. However, education campaigns for both the public and clinicians have not been on the same scale as those in Europe.

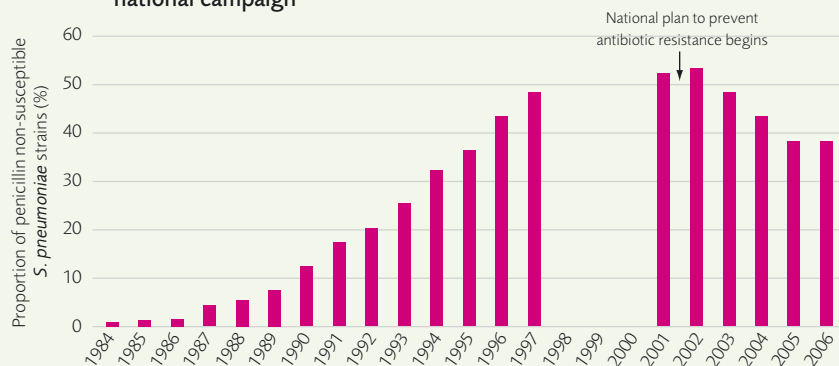
Irresponsible antibiotic use in the agricultural sector

Very large quantities of antibiotics are used in the agricultural industries, particularly in animal husbandry. The total volume of antibiotics used in the United Kingdom for agricultural purposes in 2007 was 387 tonnes.

Some active ingredients authorised for animals are used to treat people too. Large volumes of quinolones and cephalosporins are prescribed by vets, even though they are important for treating human infections.

Resistant bacteria developing in animals could pose a threat to people. Antibiotics must be used in moderation in agricultural settings and only when necessary for animal welfare. A significant step forward has already been made by the European Union-wide ban on the use of antibiotics as growth promoters.

Figure 6: Resistance rates in France have fallen since the start of the national campaign



Source: Eurosurveillance, 2008

Prescription only

Although England has taken significant steps forward in the control of antibiotic usage, recent moves to make certain antibiotics available from pharmacists without prescription must be extended with caution. Azithromycin, an antibiotic used to treat chlamydia, can now be purchased without prescription, provided there is a positive test result for the disease. Although this is an innovative way to deal with the considerable public health implications of chlamydia, further moves to widen access to antibiotics without prescription will need to be balanced carefully against the risks of promoting greater resistance.

A public good

The potency of one of the key weapons in the medical armoury is being eroded. The harm caused by each unnecessary prescription is not visible at the time, and so society fails to take action that is necessary to stop the problem worsening.

Correcting this situation will require a paradigm shift in thinking. The effectiveness of antibiotics should be seen as a common and collective public good.

Every antibiotic expected by a patient, every unnecessary prescription written by a doctor, every uncompleted course of antibiotics, and every inappropriate or unnecessary use in animals or agriculture is potentially signing a death warrant for a future patient.



ACTION RECOMMENDED



"The effectiveness of antibiotics should be seen as a common and collective public good. Every inappropriate use in medicine or agriculture is a potential source of harm or death for a future patient."

- Existing public education campaigns about responsible use of antibiotics should be raised in profile, in line with practice in some other European countries.
- There should be a ban on the use of certain types of antibiotics (quinolones and cephalosporins) in animals, in order to protect their activity in humans.
- Antibiotic packaging should carry a warning, reminding people of the need to take them responsibly and appropriately.
- No further antibiotic classes should be made available without prescription unless there is careful consideration of the potential public health consequences.
- Alert 'flashes' should be added to packaging for antibiotics where resistance levels are rising rapidly.
- Consideration should be given to novel ways to stimulate research and development of new antibiotics, including public–private partnerships.