Before the widespread use of antibiotics in the 1940s, it was much more common for women to die from post-childbirth infections, and diseases such as tuberculosis were rife. In addition, farmers often faced losing vast numbers of crops and animals to infectious diseases, leading to serious food shortages, even famine. The discovery and introduction of antibiotics gave us the ability to prevent these tragedies. However, as microorganisms become resistant to antimicrobial treatments, including antibiotics, there is a very real possibility that the drugs we have come to rely upon may become obsolete.

Since 1928, when Sir Alexander Fleming accidentally discovered penicillin growing on a petri-dish of bacteria, antibiotics have saved the lives of millions of people and animals. Their discovery is seen as one of the most important scientific achievements of the 20th century. But overuse and misuse of antibiotics has contributed to the emergence of resistance. Sir Alexander Fleming himself, on collecting a Nobel Prize for his discovery, predicted the dawn of this battle, saying, “It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them…”

England’s Chief Medical Officer Professor Dame Sally Davies warned in 2013 of the “catastrophic effect” of antimicrobial resistance and urged immediate action from global leaders before deaths from routine surgery once again become a common occurrence¹. The World Economic Forum has suggested that antimicrobial resistance (AMR) be added to the global risk register, and the World Health Organization has highlighted the serious implications for global public health in its AMR Global Report on Surveillance². Antimicrobial resistance is one of the Innovative Medicine Initiative’s priorities and a Joint Programming Initiative on antimicrobial resistance was set up in 2011 to streamline European research efforts in AMR.

The UK Research Councils support research, capability and training to pursue a range of strategies to tackle this global problem. Years of research mean that we are now in a better position than ever to understand microbes such as bacteria, viruses and fungi, how they interact with their hosts, and to identify possible routes for alternative diagnostics and treatments. New technologies which could help prevent the spread of bacteria and infections, including smart surfaces and medical dressings, are also being developed. This timeline and series of case studies showcase some of these advances, supported by the Biotechnology and Biological Sciences Research Council (BBSRC), Engineering and Physical Sciences Research Council (EPSRC) and Medical Research Council (MRC). This work lays the groundwork for the cross-Council antimicrobial resistance initiative that was launched in July 2014. This will see all seven Councils working together to tackle AMR. A joined-up, multi-disciplinary approach is essential and so the initiative will coordinate the work of medical researchers, biologists, engineers, vets, economists, social scientists, mathematicians and designers. It is only through tackling the problem at every level and in every environment that we will be able to take the next steps towards a solution.

References
1. Chief Medical Officer annual report: volume 2
2. Antimicrobial resistance: global report on surveillance 2014
   http://www.who.int/drugresistance/documents/surveillancereport/en/
1. Understanding resistant bacteria in context of the host

**2007:** University of Newcastle spin-out company e-Therapeutics Ltd identifies three drugs that are effective against antibiotic-resistant superbugs, including MRSA, using Grid computing and e-science techniques developed during research funded by EPSRC and the Department of Trade and Industry. The company searched through tens of millions of compounds for any that showed action against superbugs in a fraction of the time it would take using conventional drug discovery methods.

**2008:** The first case of a bacterial infection with resistance caused by NDM-1, a powerful enzyme that gives bacteria resistance to most antibiotics, is discovered. MRC-funded researcher Professor Tim Walsh was part of the group that identified the enzyme, which is commonly produced by *Escherichia coli* and *Klebsiella pneumonia*, but can also spread between different strains of bacteria.

**2010:** The EU uses the results of research by BBSRC David Phillips Fellow Dr Mark Webber in two reports on the use of common biocides. During his fellowship, Dr Webber characterised the genetic changes that grant Salmonella resistance to the biocide triclosan and others. There were around 9,000 cases of *Salmonella* food poisoning in the UK in 2010, although three quarters of cases may go unreported.

**2011:** Scientists at the MRC Research Complex at Harwell determine the structure of NDM-1 using the STFC’s Diamond Light Source crystallography facility. Understanding the structure will help researchers develop drugs that could inactivate the enzyme or that are not susceptible to it.

Professor Hagan Bayley at the University of Oxford discovers that the antibiotic-resistance of *Escherichia coli* is not due to the reduced size of OmpC — the channel in the bacteria’s membrane that allows the entry of antibiotics — as is the cause of much resistance, but a change in its electrostatic field.

**2012:** The gene which grants one strain of MRSA found in hospitals resistance to a range of antibiotics also reduces the bacteria’s ability to secrete the toxins that cause illness, according to a BBSRC and MRC-funded study led by Dr Ruth Massey at the University of Bath. The results also highlight the problem of changes from its normal form to a slow-growing antibiotic-resistant form as part of its natural lifestyle to ensure its survival.

Bacteria transmit resistance genes to other bacterial strains by way of plasmids — small loops of DNA. Carrying these plasmids is commonly thought to reduce a bacterium’s fitness, so removal of antibiotic pressure should reduce the number of resistant bacteria. However, in a BBSRC and MRC-funded study, Professor Laura Piddock and Dr Mark Webber at the University of Birmingham discover that the plasmid pCT persists in the absence of antibiotics because it has evolved to have little impact on the host. They conclude that resistance genes will persist even with careful rationing of antibiotics.
In an MRC-funded study, Professor Gad Frankel at Imperial College London uses a mouse infected with bacteria genetically modified to produce light to show how an infection moves around the body in real time\textsuperscript{12,13}. Regular CT scans of the mouse could show how different vaccines and antibiotics change the way bacteria take over parts of the body.

2013: A research team from the Universities of Nottingham, Birmingham and Newcastle, funded by EPSRC and BBSRC, discover that artificial materials based on simple synthetic polymers can disrupt the way in which bacteria communicate with each other. The findings\textsuperscript{14} open up the possibility to influence microbial behaviour by controlling their ability to form productive communities, which could be exploited to prevent the release of toxins during the spread of infection.

MRC-funded Professor Guy Frankel at Imperial College shows how enteropathogenic Escherichia coli (EPEC), a pathogenic strain of E.coli which is a common cause of infant diarrhoea in the developing world, interferes with the host cell’s normal antimicrobial response\textsuperscript{16}. EPEC injects a toxin into host cells during infection. This blocks the cell’s ability to send messages to the immune cells, preventing a response and subsequent death of the infected cells, allowing the bacteria to survive and spread.

2014: BBSRC-funded researchers at the MRC Centre for Molecular and Biomolecular Informatics (CMBI), identify the pathway behind the ‘stringent response’, the mechanism E.coli use to survive when under stress, such as when deprived of nutrients or in the presence of antibiotics\textsuperscript{18}. When under stress, bacteria produce guanosine tetraphosphate (ppGpp), which instructs the bacteria to stop growing and to use minimal resources. The CMBI researchers show that a protein called NtrC plays a central role in the process by controlling the level of ppGpp.

Researchers at the MRC Centre for Molecular Bacteriology and Infection (CMBI) study ‘persister’ cells in Salmonella, visualising them for the first time using a fluorescent protein produced by the bacteria. Persister cells are a non-replicating form of the bacteria and ‘lie low’ to evade antibiotic action\textsuperscript{19}. See ‘Antibiotic-evading bacteria’.

A common mutation in Salmonella grants the bacteria resistance to an important class of antibiotics, the fluoroquinolones, and also increases its resistance to many other antibiotics and the biocide triclosan, according to research by Professor Laura Piddock and Dr Mark Webber at the University of Birmingham\textsuperscript{15} and supported by BBSRC and the MRC.

P. aeruginosa infection is one of the most common causes of death in cystic fibrosis patients.

Professor Laura Piddock at the University of Birmingham sequences the plasmid pCT, which confers antibiotic resistance to bacteria carrying it. She concludes that the plasmid’s success lies in its stability in a range of hosts, the lack of a fitness cost to the host bacteria — meaning that carrying the plasmid has no detrimental effect — and efficient transfer between bacterial hosts\textsuperscript{20}.

Researchers at the London Centre for Nanotechnology, University College London, show how drug-binding mechanically weakens bacterial cells and leads to their death, whilst unravelling how the antibiotic vancomycin works. Vancomycin is one of the few effective treatments for MRSA. The study was funded by EPSRC, BBSRC and the Royal Society.

BBSRC-funded researchers at the University of Cambridge find the gene responsible for activating the infection mechanism in Pseudomonas aeruginosa when the bacteria encounter low oxygen conditions, such as those found in the lungs of people with severe respiratory illnesses, including cystic fibrosis\textsuperscript{17}.
2. Accelerating therapeutic and diagnostics development

1985:
Researchers at the John Innes Centre (JIC), which receives strategic funding from BBSRC, led by Dr David Hopwood, are the first to produce a 'hybrid' antibiotic using genetic engineering, alongside colleagues from Japan and the USA. The researchers transferred genes associated with antibiotic production between strains of *Streptomyces* bacteria, enabling the bacteria to produce an entirely new antimicrobial compound.

2002:
The *Streptomyces* genome, sequenced by BBSRC- and Wellcome Trust-funded researchers, is published in the journal *Nature*. Researchers subsequently discover a large number of previously-unknown gene clusters in the *Streptomyces* genome that produce ‘specialised metabolites’, potentially including previously-unknown antimicrobials.

2005:
Dr Curtis Dobson founds spin-out company Ai2 to develop an anti-infective coating for contact lenses. The anti-infective arose from Dr Dobson’s BBSRC-funded research at the University of Manchester into a protein that could help protect against the viral infections associated with Alzheimer’s disease.

2009:
Professor Jeremy Lakey co-founds spin-out company OI-Bio, based on BBSRC-funded research at Newcastle University, to develop miniature wireless sensors that can be used to test for a diverse range of infectious diseases in humans. The devices are currently being evaluated by commercial partners in the healthcare industry to test for infectious diseases including flu, HIV and gum disease. Further funding has been provided by the EPSRC and Technology Strategy Board (now Innovate UK) to develop the technology.

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MRC and BBSRC-funded researcher Professor Adam Cunningham at the University of Birmingham begins development of a vaccine against Salmonella. The vaccine development has been licensed to Novartis Vaccines Institute for Global Health.

**2010:**
A team of researchers at the MRC Centre for Molecular Bacteriology and Infection (CMBI), with funding from BBSRC, reveal the structure of a protein called Gp2, produced by the 'bacteriophage' virus T7, which disables E.coli cells. Bacteriophage viruses infect and kill many bacterial species, including those that cause human and animal diseases. See ‘Bacteria-eating viruses’.

Researchers at the MRC Laboratories in The Gambia, in collaboration with scientists in the US, find that infection with H.pylori – the bacterium responsible for gastritis and gastric ulcers – may protect the host against other pathogens, such as tuberculosis.

Funded by the MRC, Dr Andrew Gorringe at the Health Protection Agency develops a vaccine against bacterial meningitis. The vaccine is currently being developed with funding from the Biomedical Catalyst by ImmBio, a vaccine development company based at the Babraham Research Campus.

BBSRC-funded researchers begin to develop a new type of vaccine to protect chickens against coccidiosis, based on a single protein that plays a vital role in the early stages of infection. The coccidiosis parasite, which is widely resistant to antimicrobials, is the most important parasite of poultry globally.

Predatory bacteria with the potential to be used as ‘living antibiotics’ are safe when ingested by chickens, according to BBSRC-funded researchers from the University of Nottingham. When given to live, Salmonella-infected chickens, Bdellovibrio bacteria reduced the number of Salmonella cells by 90 per cent while leaving the birds unharmed.

Scientists at the Institute of Food Research (IFR), which receives strategic funding from BBSRC, adapt the structure of the protein endolysin, derived from a bacteriophage virus, so that it is more effective against C. difficile, a common cause of hospital-acquired infections, while remaining ineffective against beneficial gut bacteria.

**2011:**
A Sheffield University research team produce a gel containing molecules that bind to bacteria and activate a fluorescent dye. The gel will be used in wound dressings to indicate when an infection has developed and will help clinicians to make rapid, informed decisions about wound management as well as reduce the overuse of antibiotics. The research team was funded by the EPSRC and Ministry of Defence. See ‘Wound dressing provides glowing evidence of infection’.

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**2012:**
BBSRC-funded researchers at the MRC Centre for Molecular Bacteriology and Infection (CMBI) demonstrate how Gp2 interacts with the bacteria’s RNA polymerase — an enzyme that enables the instructions in the bacteria’s genes to be read and turned into proteins — to stop it from functioning. The scientists now plan to identify small bacteria could combine two antibiotic molecules to produce a much more effective antibiotic, which works against MRSA.
molecules that mimic the structure and function of Gp2 and use these as the basis for new drugs to combat bacterial infections.

Novacta Biosystem’s lead product, NVB302, which is being developed to treat *C. difficile* infections, completes phase I clinical trials, showing it is safe when administered to healthy people 42.

JIC and University of Oxford researchers begin a BBSRC-funded project to investigate whether they can use synthetic biology to remove the toxic side effects of tunicamycin, an antibiotic produced by the soil bacterium *Streptomyces* 43. See ‘New antibiotics from bacterial bioscience’.

MRC-funded researchers at the Wellcome Trust Sanger Institute demonstrate that treatment of *C. difficile*-infected mice with faeces from healthy mice rapidly restores a diverse, healthy microbiota and subsequently cures the disease and removes its contagiousness 44.

MRC-funded researcher Professor Robert Akid at the University of Manchester patents an antimicrobial coating for cementless prostheses, such as hip and knee replacements, to prevent infection 45. The controlled release ensures the antimicrobial is released only at the appropriate time (during and after surgery).

2013:

An EPSRC Interdisciplinary Research Centre 46 is established at University College London to create a new generation of early-warning sensing systems to diagnose, track and prevent the spread of infections, including influenza, antimicrobial resistance and HIV, using mobile communication, nanotechnology, genomics and big data analysis to actively manage outbreaks and prevent infectious diseases.

The world’s largest antibody search engine, CiteAb 47, is founded by EPSRC-funded Dr Andrew Chalmers at the University of Bath. The service, which allows researchers to find antibodies for use in their research, is the largest antibody search engine in a $2Bn antibody industry, and ranked number one by Google. Ranking antibodies by academic citations means CiteAb provides an independent, verifiable guide as to whether an antibody is likely to work in the laboratory, saving both time and money.

Absynth Biologics receives more than £2M through the Technology Strategy Board- and MRC-funded Biomedical Catalyst to take forward to a pre-clinical stage its vaccine against MRSA.

A team led by MRC-funded researcher Dr Martha Clokie at the University of Leicester isolates 40 different bacteriophages — viruses that ‘eat’ bacteria — against hospital superbug *C. difficile*. US pharmaceutical company AmpliPhi Biosciences Corporation are funding the further development of these phages. See ‘Bacteria-eating viruses’.

2014:

Imperial College London scientists, with support from BBSRC, identify how a protein, called P7, produced by a certain bacteriophage virus disables an essential bacterial enzyme called RNA polymerase 48. The viral protein uses a previously-unknown method to disable the RNA polymerase, which is involved in bacterial gene expression, by preventing it from identifying target genes.
Antimicrobial resistance

3. Understanding the real world interactions

2007:
A peptide molecule found in American Bullfrogs is being developed to treat wounds infected with MRSA. Researchers led by Dr Peter Coote at the University of St Andrews find that the bullfrog peptide ranalexin can inhibit MRSA growth when combined with another antimicrobial, lysostaphin. The researchers patent the discovery and aim to develop effective treatments for MRSA-infected wounds.

2010:
Bacteria carried on the surface of leafcutter ants produce a range of antimicrobial compounds, according to a study by BBSRC and MRC-funded researchers from the University of East Anglia, JIC, and The Genome Analysis Centre (TGAC), which receives strategic funding from BBSRC. The antimicrobials help the ants cultivate a fungus that provides them with food, protecting their nest against infection and controlling competing strains of fungi.

2011:
Materials scientists at the University of Birmingham, funded by EPSRC, devise a way of making stainless steel surfaces resistant to bacteria by introducing silver or copper into the surface rather than applying it as a coating. The technique could prevent the spread of superbug infections on stainless steel surfaces in hospitals as well as medical equipment such as instruments and implants, the food industry, and domestic kitchens.

2012:
Researchers at the University of Nottingham, funded by BBSRC and the Wellcome Trust, discover a new class of material that resists colonisation by bacteria. The materials, known as synthetic acrylate polymers, have been licensed to UK company Carnstent Ltd, which is now working with the academics to develop coated urinary catheters.

2013:
EPSRC-funded researchers develop a method for quickly detecting infections in children with serious burns. The dressing, developed at the University of Bath with researchers from Bristol’s Frenchay hospital and Bedsshire based AmpliPhi Biosciences, uses dye-filled nanocapsules that burst open in the presence of disease-causing bacteria. Using a UV light, clinicians can quickly check whether there is any infection by seeing if the dressing lights up.

Researchers at the University of Sheffield discover that combinations of bacteria, commonly found in water pipes, can form a ‘biofilm’ that enables other, potentially harmful, bacteria to thrive. The EPSRC-funded study isolated four types of bacteria and found that when any of them grew alongside bacteria called Methylobacterium, they formed a biofilm within 72 hours. The findings mean it should be possible to control the creation of biofilms in water supplies by targeting particular bacteria.

Researchers at the University of Warwick adopt a DNA-based approach to understanding the community of microbes that live in a chicken’s gut. Chickens and other farm animals can act as a reservoir of human pathogens and of microbes that carry antimicrobial resistance genes. The researchers, with support from BBSRC, used high-throughput sequencing to rapidly sequence the DNA of microbes in the chicken gut to identify which bacterial species were present.

Some strains of MRSA that cause disease in humans originate in livestock, according to research led by Professor Ross Fitzgerald at the Roslin Institute, which receives strategic funding from BBSRC. The findings suggest that livestock can act as a potential reservoir of new human epidemic strains of the bacteria. See ‘Making the leap.’
MRC-funded Professor Sharon Peacock at the University of Cambridge uses whole-genome sequencing to analyse an outbreak of MRSA\textsuperscript{58}. Whole genome sequencing of bacterial samples could lead to fewer antibiotics being used as a more specific diagnosis would allow the targeted use of specific antibiotics to treat it. This sequencing also means that researchers can track the spread of infection, helping with infection control and prevention. See ‘Whole-genome sequencing’.

The Chief Medical Officer publishes the second volume of her annual report, focusing on infection and antimicrobial resistance. Professor Peacock writes a section on the use of whole genome sequencing to track the transmission of infections to improve surveillance and control\textsuperscript{59}.

An MRC-funded team at the University of Oxford, led by Dr David Eyre and Dr Sarah Walker, use whole genome sequencing to show that many cases of \textit{C. difficile} infection are caused by bacteria transmitted from people who show no sign of infection, or from environmental sources such as water, animals, or food, rather than from symptomatic patients\textsuperscript{60}. See ‘Whole-genome sequencing’.
4. Behaviour within and beyond the health care setting

2005:
With up to 50 per cent of antibiotic prescribing inappropriate, Professor Peter Davey at the University of Dundee looks at interventions to improve prescribing, such as education, restriction of drugs, guideline implementation and expert approval in an MRC-funded study.

2007:
In an MRC-funded study, Professor David Mant at the University of Oxford shows that antibiotic-resistant bacteria are present in children prescribed the common antibiotic amoxicillin, which although transitory in the children is sufficient to sustain a high-level of antibiotic resistance in the population.

2011:
Pigs on farms with access to the outdoors and a clean, enriched environment are less likely to suffer Post Weaning Multi-systemic Wasting Syndrome (PWMS), which is associated with a certain virus, than those on other farms, according to BBSRC-funded researchers from the Royal Veterinary College. The researchers are now working with the British Pig Executive to develop monitoring systems to help farmers identify animals at risk of PWMS.

2005:
It was previously thought that using less active antibiotics was the best first defence in order to reserve more active antibiotics for more resilient bacteria. In an MRC-funded study, Professor Sebastian Amyes at the University of Edinburgh concludes that using less active antibiotics first — which are generally more likely to cause resistance to develop — results in resistance to the whole class of antibiotics, rendering even the more active types unusable.

2013:
Professor Ian Chopra, director of the Antimicrobial Research Centre at the University of Leeds advocates that new business models for antibiotic development are required. He suggests new methods of screening for compounds, delinking product sales from the companies' return on investment and financing incentives for drug development.

2014:
An international team of researchers, including MRC-funded researcher Dr Tim Felton, recommend individualised antibiotic dosing for critically-ill patients. These patients often exhibit different responses to antibiotic treatment; dosing that does not take this into consideration can lead to sub-optimal treatment and increase antibiotic resistance.

2012:
EPSRC-funded researchers at the University of Leeds discover that superbugs, such as MRSA and C. difficile, not only spread through contact, but they also float on air currents and contaminate surfaces far from infected patients’ beds. Coughing, sneezing or shaking bedclothes can send superbugs into the air, allowing them to contaminate recently cleaned surfaces. This may explain why, despite strict cleaning regimes and hygiene controls, some hospitals still struggle to prevent bacteria moving from patient to patient.

2013:
The Joint Programming Initiative on Antimicrobial Resistance publishes its Strategic Research Agenda. MRC-funded Professors Tim Walsh and Paul Williams were involved in its development.

2014:
MRC-funded researcher Dr Tim Felton, recommend individualised antibiotic dosing for critically-ill patients. These patients often exhibit different responses to antibiotic treatment; dosing that does not take this into consideration can lead to sub-optimal treatment and increase antibiotic resistance.
EPSRC-funded researchers at Newcastle University and the Indian Institute of Technology in Delhi reveal that the spread of antibiotic-resistance at sacred sites along the Ganges is linked to annual human pilgrimages. When thousands of visitors travelled to the sacred sites, levels of resistance genes in bacterial populations were about 60 times greater than other times of the year. The study is helping to understand how resistance gene blaNDM-1 spreads through specific human activity.

The World Health Organization publishes its report, Antimicrobial resistance: global report on surveillance 2014. Professor Tim Walsh was part of the review group.
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34. See: http://www.a-i-2.com/news/?id=18
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Front cover
Petri dishes with cultures of bacteria grown on agar jelly. Credit: M J Richardson. CC BY 3.0 <http://creativecommons.org/licenses/by/3.0/>

Understanding resistant bacteria in context of the host
Image 1: Salmonella invading cultured human cells. Credit: NIAID. CC BY 2.0 <https://creativecommons.org/licenses/by/2.0/>
Image 2: NDM-1 was first identified in Klebsiella pneumonia bacteria. Public domain.
Image 3: Pills. Credit: Thinkstock
Image 5: A scanning electron micrograph of MRSA and a dead human white blood cell. Credit: NIAID. CC BY 2.0 <http://creativecommons.org/licenses/by/2.0/deed.en>

Accelerating therapeutic and diagnostics development
Image 2: Contact lenses. Credit: Thinkstock
Image 4: Vaccine. Credit: iStock
Image 5: A chicken. Credit: Liz West CC BY 2.0 <https://creativecommons.org/licenses/by/2.0/>
Image 6: The connectedness of today’s society. Credit: Thinkstock.

Understanding the real world interactions
Image 1: American Bullfrog Rana catesbeiana. Credit: F00002. CC BY-SA 2.5 <http://creativecommons.org/licenses/by-sa/2.5/deed.en>
Image 2: Surgical instruments. Credit: Thinkstock
Image 3: Cows on Eifee Hill. Credit: John Comloquoy CC BY-SA 2.0 <http://creativecommons.org/licenses/by-sa/2.0/deed.en>

Behaviour within and beyond the healthcare setting
Image 1: Pigs. Credit: Hadyn Blackey. CC BY-SA 2.0 <http://creativecommons.org/licenses/by-sa/2.0/deed.en>
Image 2: The Imperial Antibiotic Prescribing Policy smartphone app. Credit: Imperial College London.
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| Cephalosporins   | Cefalexin   | 1945             | Around 1956           | Resistance to cephalosporins was already present in nature when the antibiotics were developed. This date is based on when researchers identified the specific enzymes that could break down cephalosporin. | Turek, M. (1982) Cephalosporins and related antibiotics: an overview. Review of Infectious Diseases. 4 (supplement). http://cid.oxfordjournals.org/content/4/Supplement_2/S281.full.pdf  
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1. List is based on NHS classification of antibiotics into six broad groups: [http://www.nhs.uk/Conditions/Antibiotics-penicillins/Pages/Introduction.aspx](http://www.nhs.uk/Conditions/Antibiotics-penicillins/Pages/Introduction.aspx), plus the glycopeptides.

2. Resistance to many naturally-derived antibiotics, for example, penicillin, streptomycin, cephalosporin, existed in nature before the antibiotic was discovered.