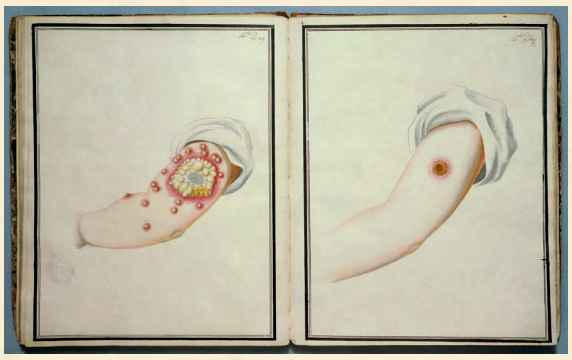
THE HISTORY OF VACCINE DEVELOPMENT

Vaccines protect against infection by helping the immune system learn how to identify harmful bacteria and viruses.

Before vaccination....



(left) arm after variolation; (right) arm after vaccination.

A technique called **variolation** was used. Powdered or dried smallpox scabs were rubbed into cuts to produce a mild infection.

Variolation worked, but there were risks. Those variolated could contract the more severe form of smallpox and die, and could transmit the disease to others.

Other diseases could also be transmitted by inserting infectious material into open wounds.

Edward Jenner 1749-1823

English doctor

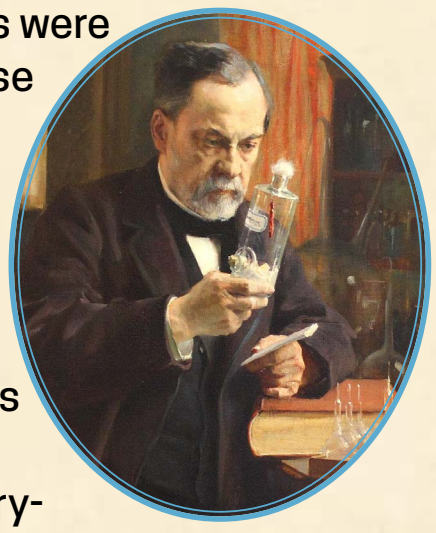
Jenner used scabs from cowpox, a virus closely related to smallpox, to vaccinate James Phipps, aged 8, in 1796. Cowpox is similar but less dangerous than smallpox. Phipps' cowpox infection protected him from smallpox.

Jenner called the new method 'vaccination' after 'vacca' the Latin word for cow, because of the origin of this first vaccination from the cowpox virus.

Louis Pasteur 1822-1895

French microbiologist

Pasteur theorised that microbes were the main cause of infectious disease. From the 1870s, Pasteur and his co-workers produced the first laboratory-developed vaccines for chicken cholera, anthrax vaccine, and rabies.



Pasteur's vaccines were based on attenuating (weakening) live bacteria and viruses.

Robert Koch 1843-1910

German physician

Koch was a co-founder of microbiology. Koch and his co-workers identified and were able to culture (grow) many important bacterial causes of disease.

Members of his school preferred vaccines based on killed bacteria. They were among the first to realise the role of antigens and antibodies in building up immunity against a disease.

1885 Pasteur tests active immunisation against rabies

1890s Bacterial culture techniques lead to the first vaccines against bacterial diseases

1950s Cell tissue techniques for viruses enable new vaccines for polio, measles, mumps, rubella and chickenpox

1980 Smallpox is eradicated

1988 Start of global polio eradication initiative

1994-2001 Successful Rinderpest eradication campaign

2016 Highest vaccine coverage ever!

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Typhoid and Public Health

What is typhoid fever?

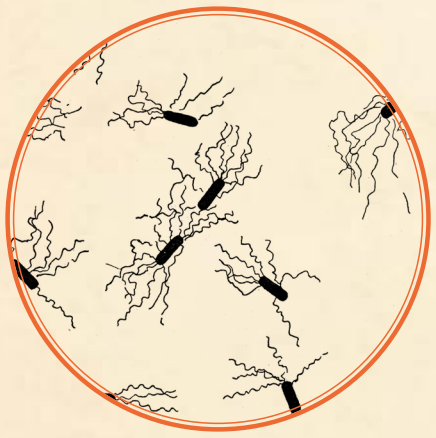
It is caused by the bacterium *Salmonella enterica* serovar Typhi which spreads from person to person via contaminated food and water and can cause severe illness and death.

A small number of typhoid survivors can also turn into healthy carriers and spread the disease without showing any signs of sickness.

Irish cook Mary Mallon ('Typhoid Mary') was a healthy carrier who spread typhoid to the families employing her. The press sensationalised her case. Mallon was imprisoned twice and died in quarantine.

PREVENTING TYPHOID

In the 19th century, the prevention of 'filth-associated' diseases like typhoid became a rallying call for officials and a new generation of public health specialists.



Between 1880 and 1884, German bacteriologists identified typhoid fever's bacterial cause.

Bristol physician William Budd proved that typhoid was a waterborne disease in 1856

Wealthier communities began to invest in new infrastructure to provide clean drinking water and safely dispose of sewage.

Alongside better nutrition, hygiene, and new welfare and health care systems, sanitary reforms led to a significant decrease of typhoid.

Alice and Typhoid in Oxford

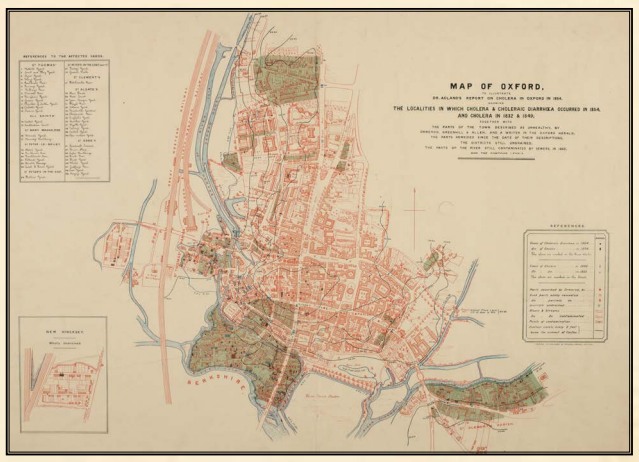
Typhoid was a disease of the poor and of the rich and famous.

One well-connected family to be affected by typhoid was that of Alice Liddell (Alice in Wonderland). Alice's mother, Lorina, nearly died from typhoid fever while living in London in 1848.

After moving to Oxford in 1855, Alice's father, Henry Liddell, used his influence as Dean of Christ Church College to campaign for an overhaul of Oxford's sanitation alongside his friend, physician Henry Acland.

Henry Liddell

Henry Acland



The two Henrys used maps of disease prevalence in Oxford and typhoid outbreaks among undergraduates to push for investment in Oxford's sewage disposal and water supply.

Victorian sanitary reform successfully reduced typhoid in Oxford.

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WHY IS AMR A PROBLEM?

Antimicrobial Resistance

ANTIBIOTICS

Antibiotics and other antimicrobials are important substances that kill or slow the growth of microbes such as bacteria but leave most non-bacterial cells unharmed.

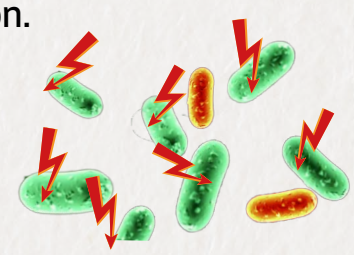
In humans, animals, and plants, these 'magic bullets' can treat and prevent bacterial infections.

ANTIMICROBIAL RESISTANCE

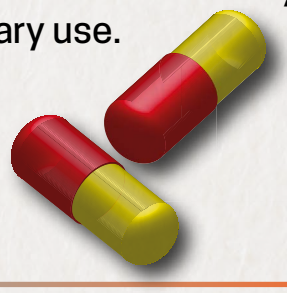
Antimicrobial resistance (AMR) is the ability of microbes like bacteria to resist the effects of antimicrobials. AMR is natural.

Over millennia, bacteria have evolved to resist the antimicrobial substances produced by other organisms. Some bacteria are inherently resistant to certain antibiotics, others can become resistant due to mutations or by acquiring AMR-conferring genes from other bacteria.

AMR is a natural phenomenon. Using antibiotics selects for resistant bacteria and AMR genes, which occur in the population.



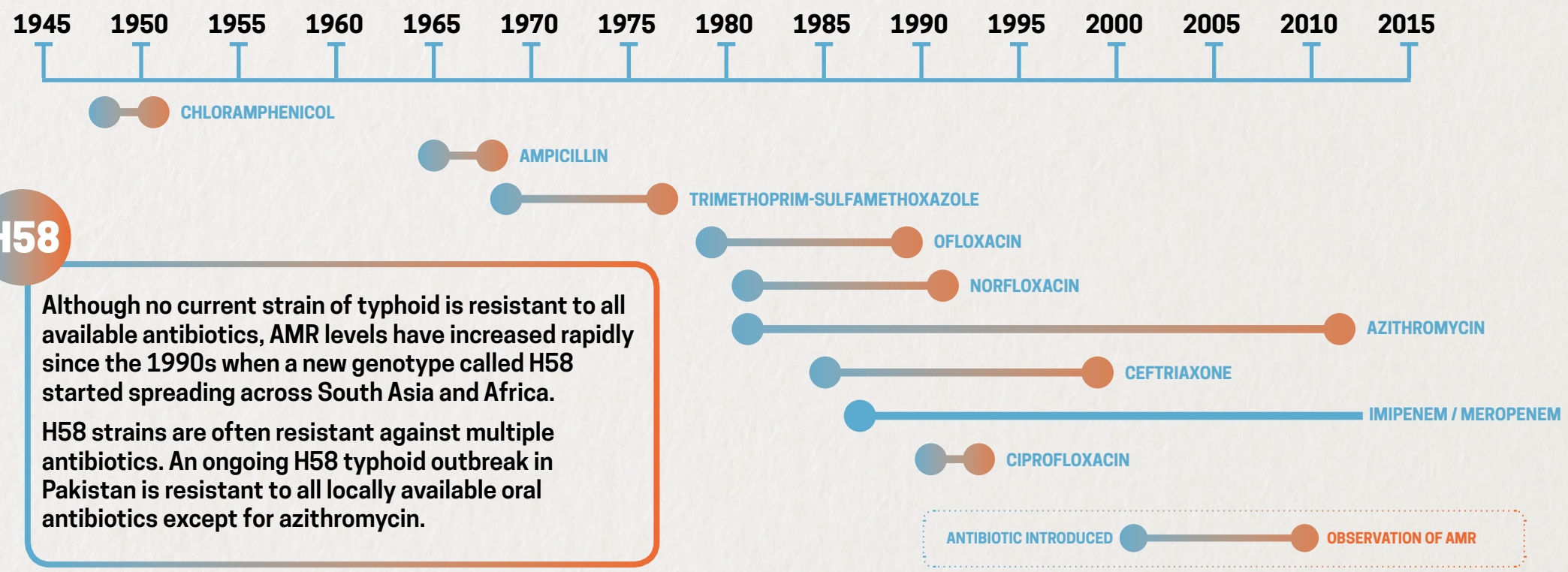
It is important to use antibiotics when they are necessary but we also have to conserve this precious resource by reducing unnecessary use.



We can reduce antibiotic use by preventing bacterial infections with better hygiene, sanitation (clean water and safe sewage disposal), and vaccination.

Case Study | TYPHOID

antibiotic effectiveness/observation of AMR in a typhoid strain



H58

Although no current strain of typhoid is resistant to all available antibiotics, AMR levels have increased rapidly since the 1990s when a new genotype called H58 started spreading across South Asia and Africa.

H58 strains are often resistant against multiple antibiotics. An ongoing H58 typhoid outbreak in Pakistan is resistant to all locally available oral antibiotics except for azithromycin.

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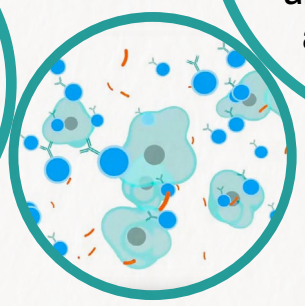
HOW DO VACCINES WORK?

Vaccines protect you by helping your immune system learn to identify harmful bacteria and viruses without making you ill.

Vaccines harness the natural activity of your immune system.

Your immune system recognises structures, called antigens.



Antigens are surface proteins and sugars on the bacterium or virus that are different from any in the body.

White blood cells in your body produce antibodies that can stick to antigens to kill or disable bacteria or viruses.

However, the antibody has to be exactly the right shape.

Producing antibodies of the right shape can take several days. When your body gets rid of the bacteria or viruses, you recover.

Antibodies remain in the blood, and some white blood cells become memory cells so they produce the same antibodies more quickly if the bacteria or virus is encountered again.

CASE STUDY
VACCINE EVOLUTION

As the example of typhoid fever shows, the technology behind vaccines has changed significantly over the past 100 years.

1896

HEAT-KILLED VACCINES

Developed in Britain and Germany in 1896, researchers used heat to kill bacteria and then injected the killed bacteria into humans to trigger an immune response.

Heat-killed typhoid vaccines were first used on a large scale by British troops during the second South African War (1899-1902) but proved unpopular because of adverse side effects and quality problems.

Improved vaccines were used to protect troops and travellers from the First World War onwards.

1970s -1980s

LIVE-ATTENUATED VACCINES

Ty21a is a live vaccine, which can be given by mouth. It is mutated chemically to render it harmless.

Developed and tested during the 1970s and 1980s, it was not used for larger civilian populations because it only offered short-lived protection.

1980s

SUBUNIT VACCINES

Vi capsular polysaccharide vaccine (ViCPS) is an injectable vaccine made from sugars (Vi antigens) from the typhoid bacterium's surface.

Antigens make your immune system learn how to detect an infection and another advantage is that you no longer have to inject actual typhoid bacteria.

Despite its reduced side-effects, it did not have a high uptake in endemic countries because it doesn't work in children under 2, only induces short duration immunity, and does not induce immunological memory.

TODAY

CONJUGATE VACCINES

New typhoid "Vi conjugate vaccines" (TCVs) combine *S.* Typhi's Vi-antigen with a protein, such as tetanus or diphtheria toxoid to create a stronger immune response and longer protection. Unlike the polysaccharide vaccine, TVCs are effective in children under two years of age.

Child vaccinated during 2019 TCV rollout in Pakistan.

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