Vaccines

Christopher Whitty

Gresham College 2021

Millions of people are alive today because of vaccination.

Some would have died in childhood without it.
For others parents, grandparents or other forebears would have died or been permanently disabled.

Examples include:

- Tetanus
- Smallpox
- Diphtheria
- Measles
- Many causes of meningitis
- Polio

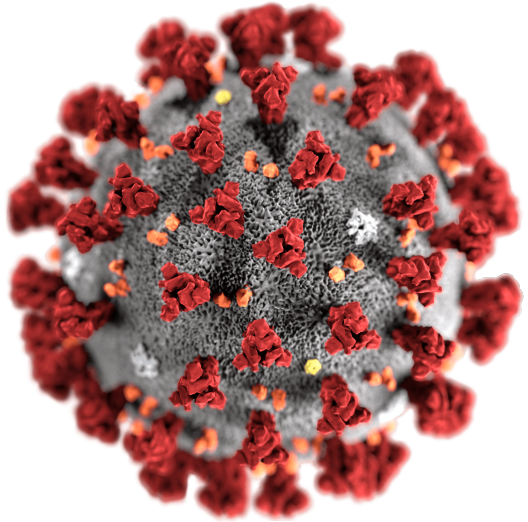
Queuing for smallpox vaccine, Cardiff 1962.
Roath Local History Society.

Epidemics and major adult diseases combatted by vaccination.

- COVID-19
- Influenza
- Ebola

- Pneumococcal disease
- Shingles

- Cervical cancer
- Liver cancer

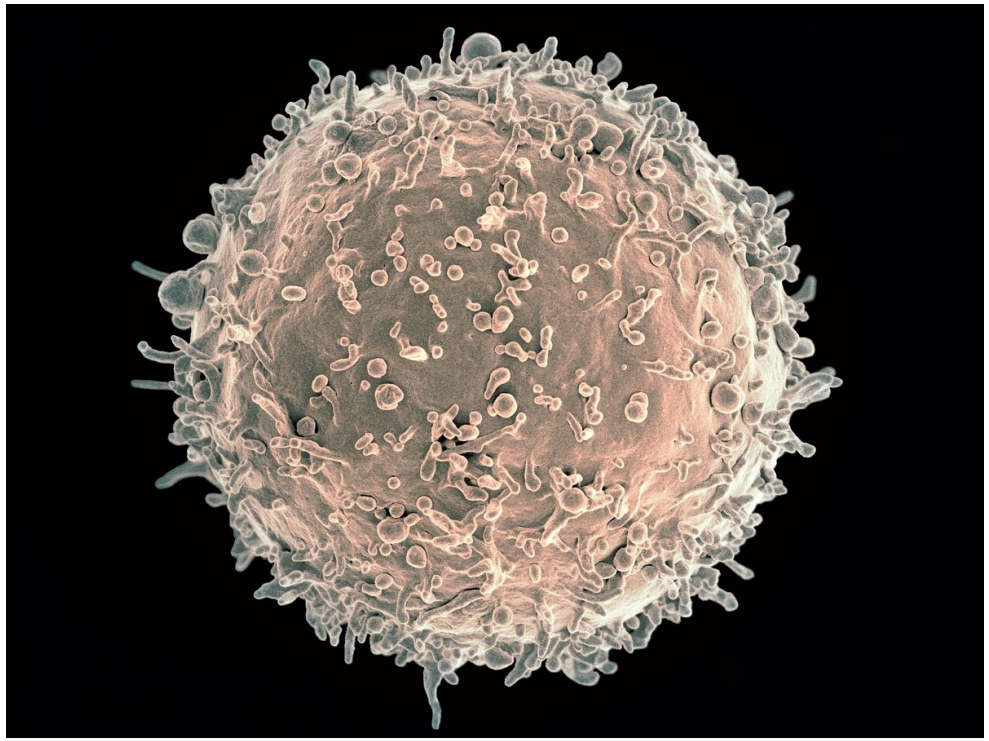


CDC

Celebrating vaccines is also celebrating your immune system. Vaccines harness its huge power.

- Vaccines do not kill viruses, bacteria and neutralise toxins- we do.

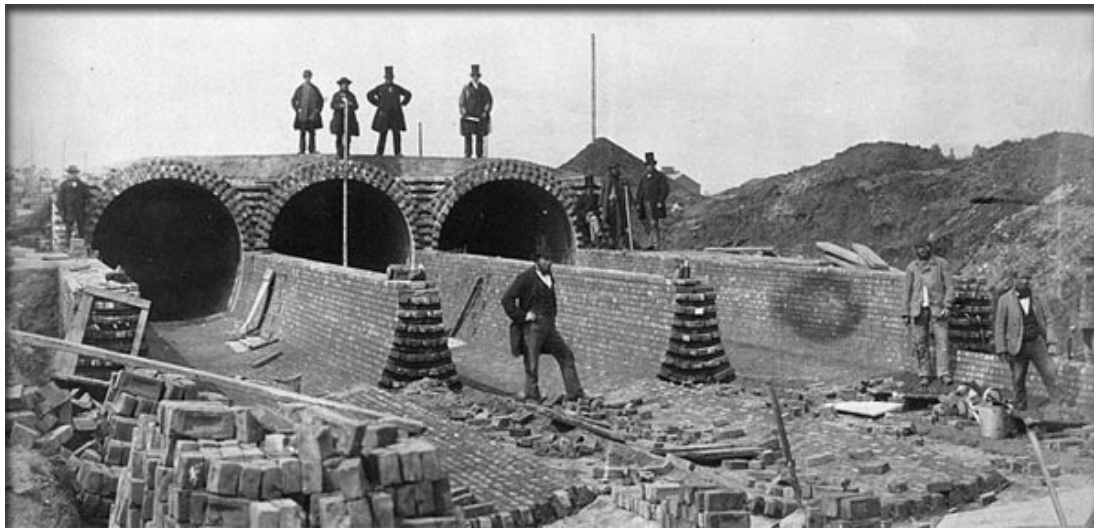
- Vaccines allow our immune system to get ready in advance by mimicking an infection, but much more safely.



Lymphocyte (B-cell). NAID

Vaccines are not the answer to all infectious diseases.

- For some major infections we do not have an effective vaccine. HIV an example.
- For some we have an OK vaccine but also have better countermeasures. Cholera and typhoid control owe more to good sewers than good vaccines.
- Some diseases are not common enough to be worth vaccinating against. E.g. plague, rabies in UK.



Joseph Bazalgette and the London Sewers.

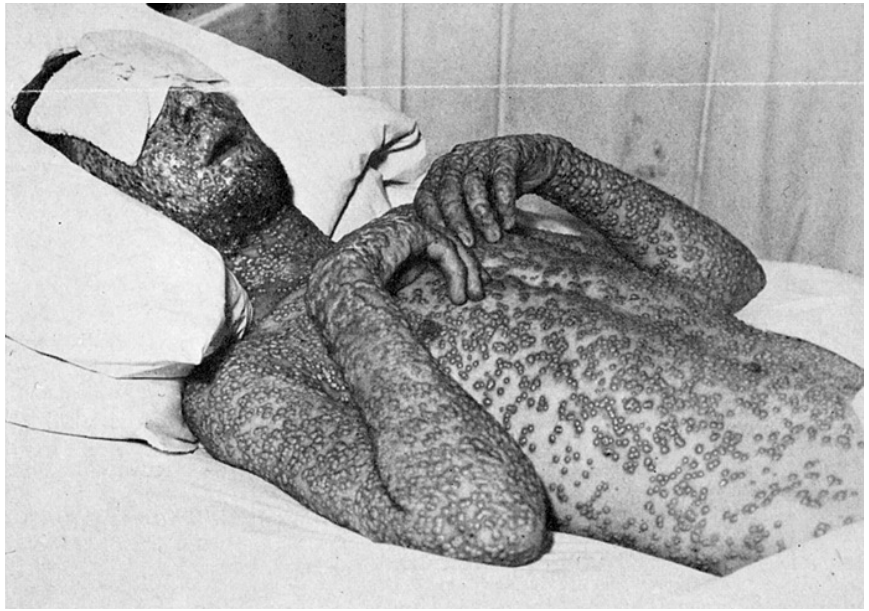
What we need to know to decide to use a vaccine.

- Is the disease a significant risk?
- How effective is the vaccine? And for how long?
- What are the side effects?
- This allows a benefit:risk decision.

Polio. Children's Hospital, Boston Mass

Smallpox was the spur to vaccination.

- An ancient disease with major epidemics in Europe and elsewhere.
- *Variola major* mortality >30%, >80% in infants. Survivors were scarred, up to a third were left blind.
- It was known as early as 480BC survivors were immune- asked to nurse the sick.
- Over 10% of deaths in London in the 1750s.



Variolation.

- An early practice was variolation, developed in Asia and Africa.
- Pus from a pustule inoculated. Around 2% died or caused outbreaks, but much better odds than natural infection.
- Introduced into western Europe 18thC. Lady Mary Wortley Montagu (1689–1762).
- A trial in prisoners in Newgate in 1721. All survived, and were proven immune.

Vaccination. A much safer option.

- The observation dairymaids who had had cowpox did not get smallpox was folk wisdom.
- Dr. Edward Jenner, Gloucestershire country doctor and scientific polymath the first systematically to study this.
- May 14th 1796 cowpox from Sarah Nelms inoculated into 8 year old James Phipps.
- Mild symptoms. When James inoculated with smallpox it did not take.
- Jenner later observed that when smallpox did occur it was milder.

Edward Jenner (1749–1823) and James (Earnest Board)

This observation by Jenner is important. Many vaccines are not all-or-none. And may need revaccination.

Vaccines can:

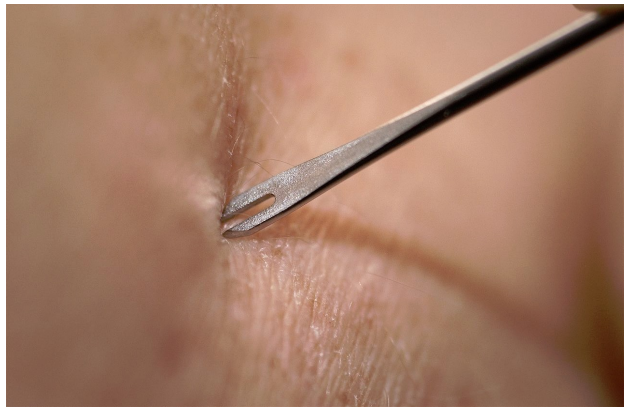
- Prevent infection.
- Prevent significant disease if infected.
- Prevent death even in significant disease.

Many vaccines reduce severity of disease even if not able to stop infection.

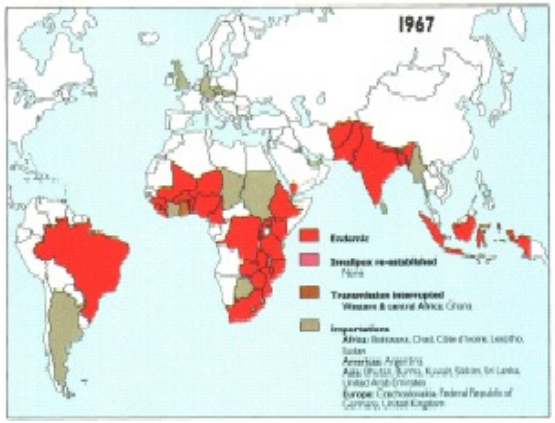
Effects may wane with time.

Two 13 year old boys, one vaccinated, infected same source. Dr Allan Warner, Leicester 1901.

Live vaccinia vaccine led to smallpox eradication by 1980.



1967



1975

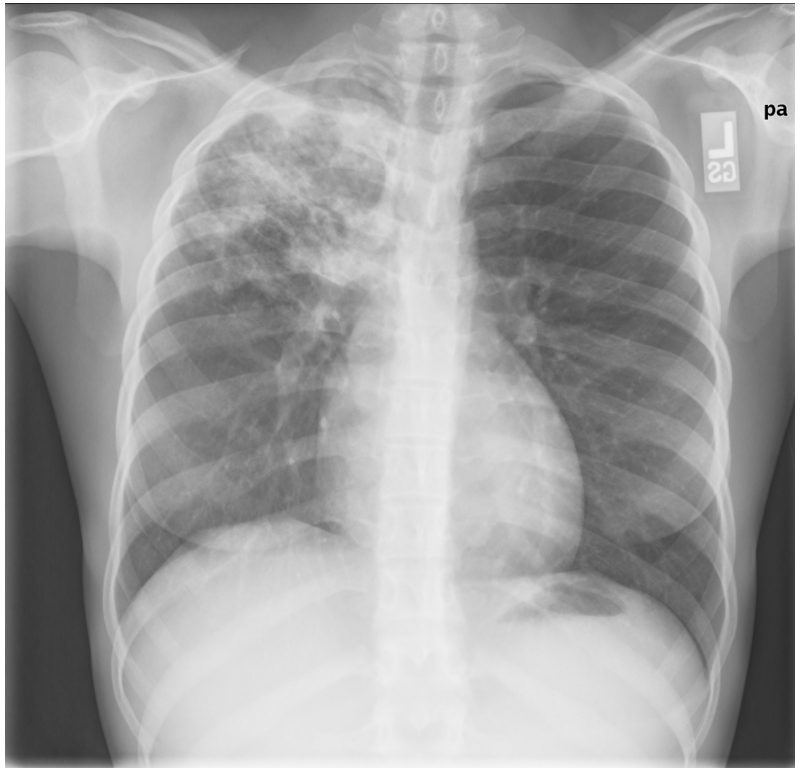
1976-7

- Eradication attempt agreed by World Health Assembly 1959, when 2m a year dying; declared 1980.
- Last continuous case – Somalia October 1977 (last case from lab in Birmingham, 1978).
- Estimated over 300 million deaths during the 20th century.

Inactivated rabies vaccine 1885 (Pasteur and Roux).

- Up to 99% of human cases from dog bites. Globally up to 59,000 cases a year (WHO).
- Death within 10 days of symptoms is virtually inevitable. A terrible disease.
- Initial vaccine from infected rabbit spinal cord after infection.
- Has got steadily safer. Now used pre-infection.
- Vaccination of dogs and foxes.
- The map of human rabies is steadily shrinking.

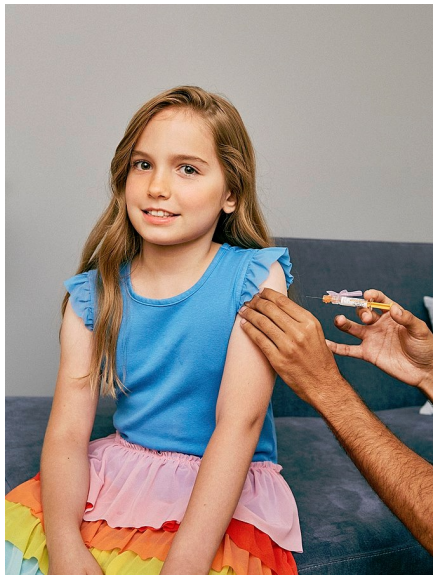
BCG. Live, related (originally bovine) attenuated mycobacteria: tuberculosis and leprosy. First used 1921.



Prof Frank Gaillard, Radiopaedia.org

A vaccine is a way of getting a lasting immune reaction safely. Pre-COVID technologies, some over a century old.

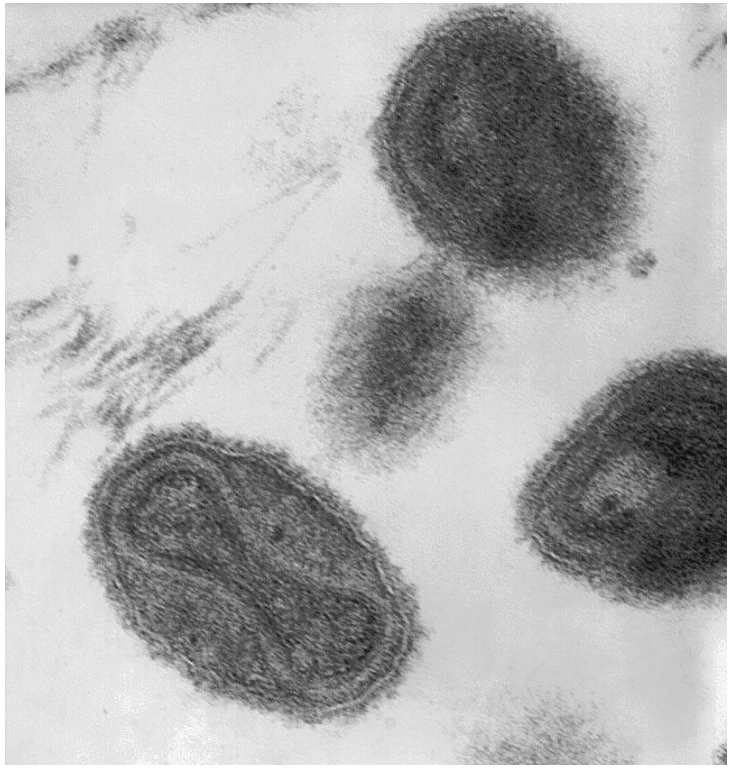
- A live related virus.
- A live, attenuated (weak) virus or mycobacteria.
- An inactivated virus or dead bacteria.
- A toxin (toxoid).
- A bit of protein, complex sugar (polysaccharide) or glycoprotein from the coat.
- Often with something to stimulate the immune system (adjuvant).



USAID/SELF
Mag/Glos NHS

How do vaccines work?

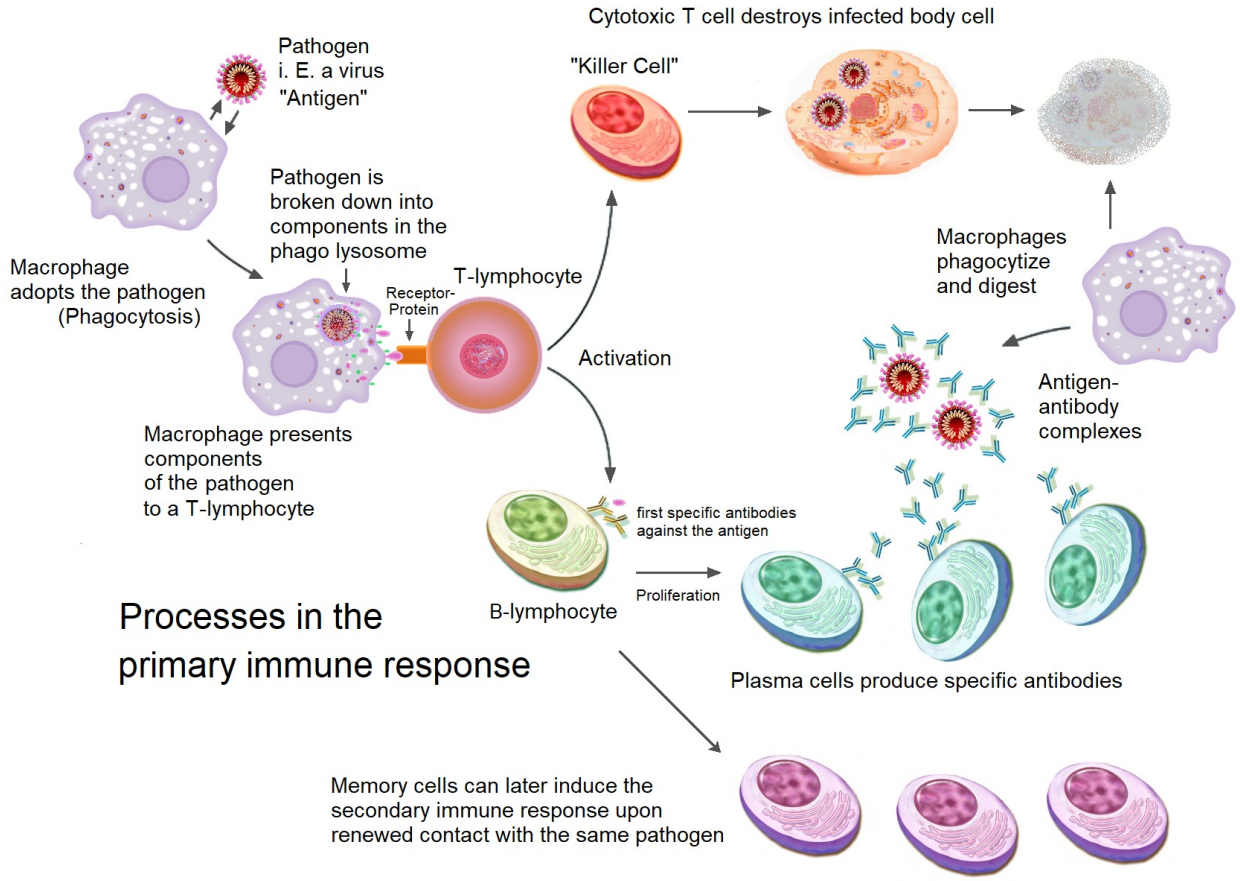
- The body has multiple layers of defence against infection.
- The innate immune system responds to infections non-specifically and without memory.
- The adaptive immune system much more specific. It ‘learns’ an infection and responds. The next time it is ready.



Smallpox. CDC.

Key components of adaptive immune system include:

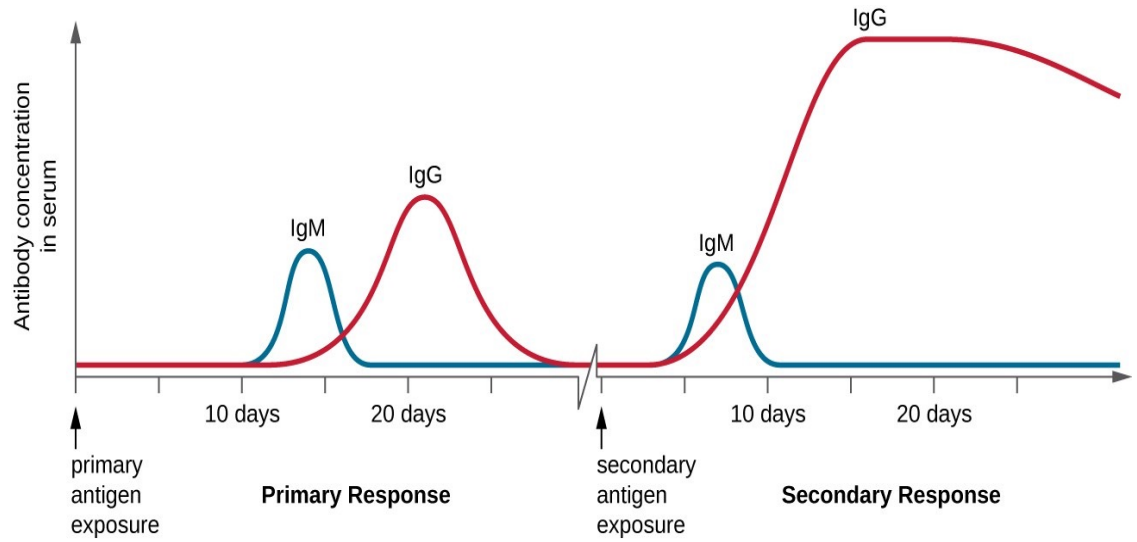
- Antigen-presenting dendritic cells.
- Antigen-recognising T-lymphocytes.
- Killer T-cells.
- Helper T-cells; regulate.
- Antigen-producing B-lymphocytes.
- Memory cells.



Sciencia58 2020

Many vaccines need a second, or third, dose to maintain protection.

- The primary vaccination is like a first infection.
- There is a lag phase before response.
- The response to the second vaccine is faster.
- Leads to a more focussed, stronger, and long lasting, immune response.



The 6-in-1 vaccine an example in childhood.

- In UK given at 6, 12 and 18 weeks.
- Tetanus. Toxoid.
- Diphtheria. Toxoid.
- Pertussis (whooping cough). Acellular.
- Polio. Inactivated.
- Hib (*Haemophilus influenzae* type B). Polysaccharide-protein conjugate.
- Hepatitis B. Protein from the surface; HepB surface antigen (HBsAg).

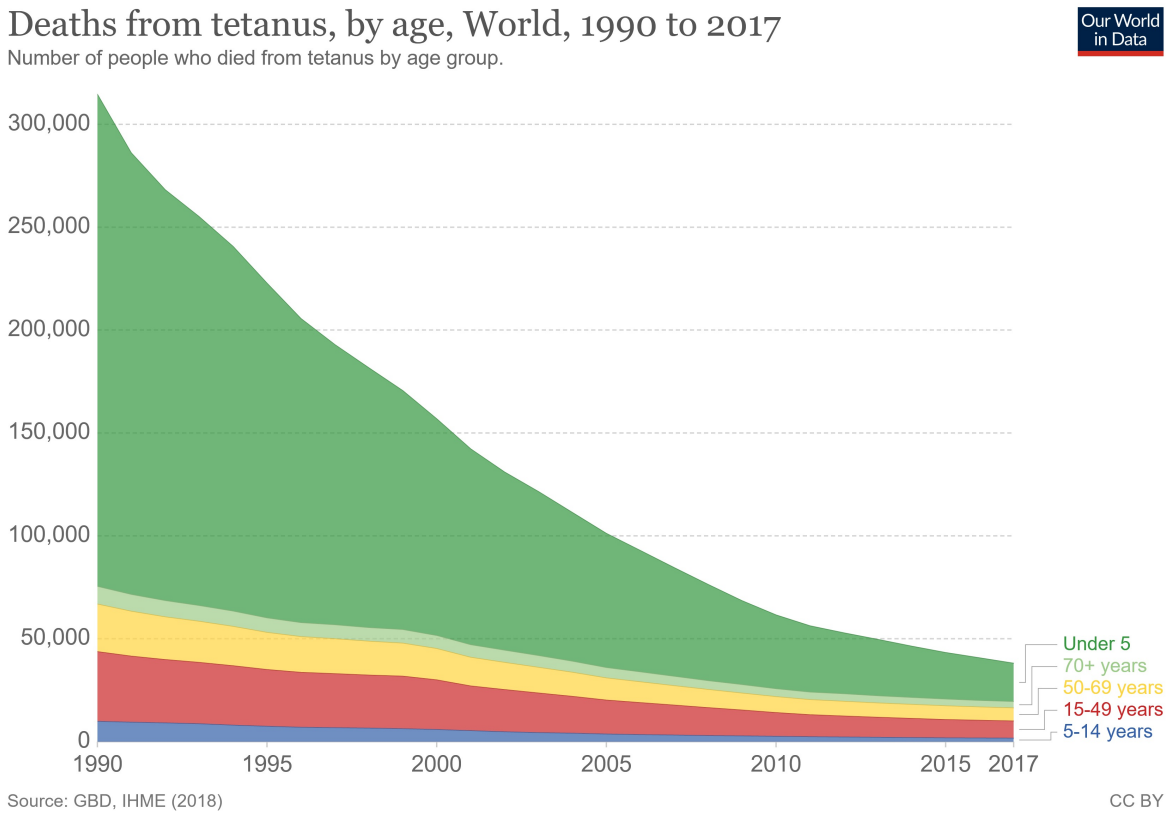
Tetanus, a terrible disease caused by toxin produced by *C. tetani*.

- In rural communities without expert midwifery high infant mortality- up to 50% recorded.
- In some settings tetanus can be the majority of these. Mortality in newborns almost 100%.
- In adults high mortality, exceptionally painful.
- The toxin is inactivated (*toxoid*), and then adsorbed. Developed 1938, introduced widely in 1950s.
- Vaccine is highly effective.
- Does not stop infection- but stops toxin.
- No herd effect.

St Kilda 1880s

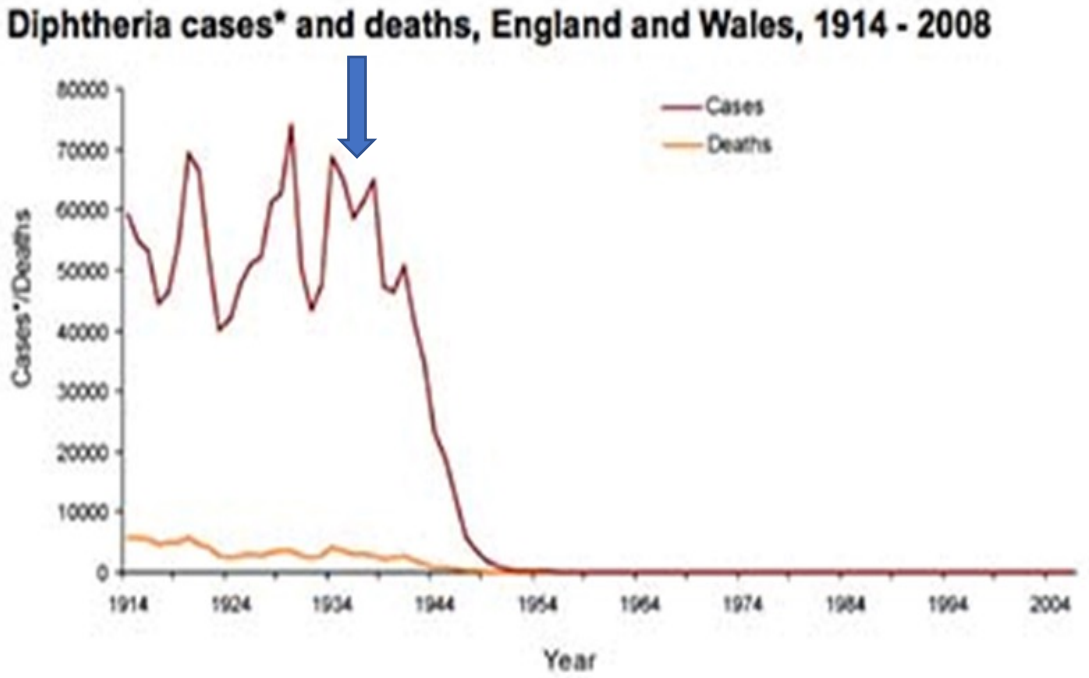
Tetanus vaccine.

- Very safe relative to risk of disease. Severe allergic reaction (treatable) <1/million
- Tetanus was common in rural Europe and North America.
- In 2019 only 4 cases in UK.
- Recent rapid drops in Africa, Asia.
- Maternal vaccination almost eliminated neonatal tetanus.



Diphtheria.

- Diphtheria used to be the third leading cause of death of children in the UK in 1930s.
- Case fatality up to 20%.
- A common throat bacteria, some strains produce toxin.
- Local effects, heart, nerves.
- Vaccine a toxoid.
- First free vaccine England 1940.
- 2480 deaths 1940, 49 in 1950.
- Worldwide massive reduction deaths. Was over 1m a year before 1980s.



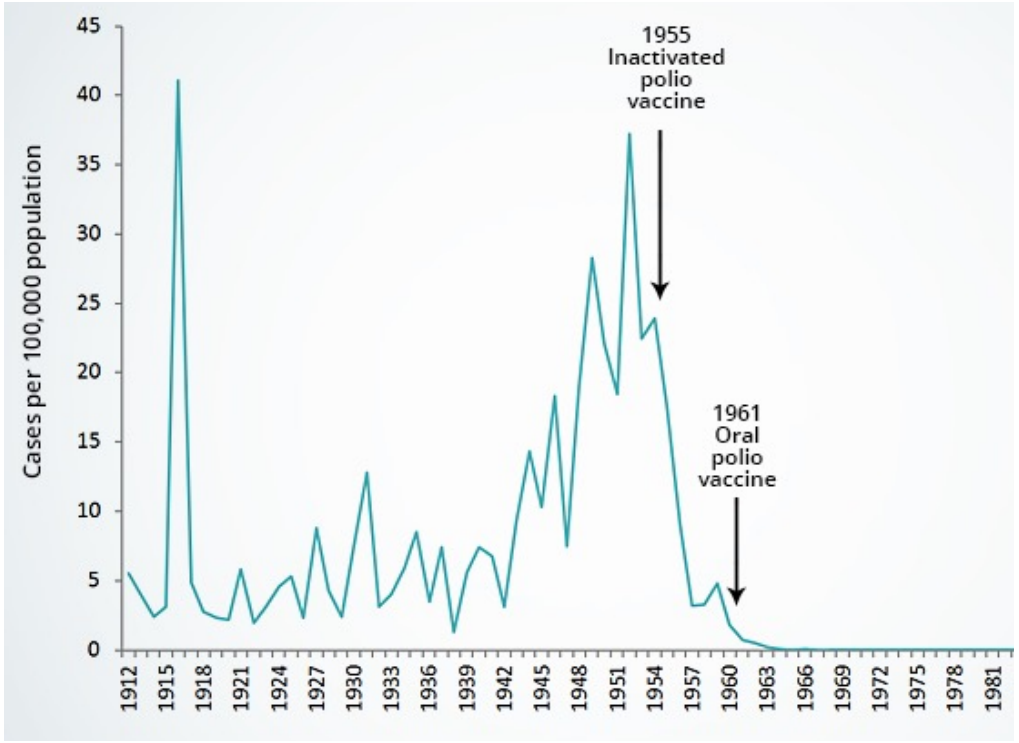
Dileepunnikri

Two polio vaccines- attenuated oral and inactivated injection.

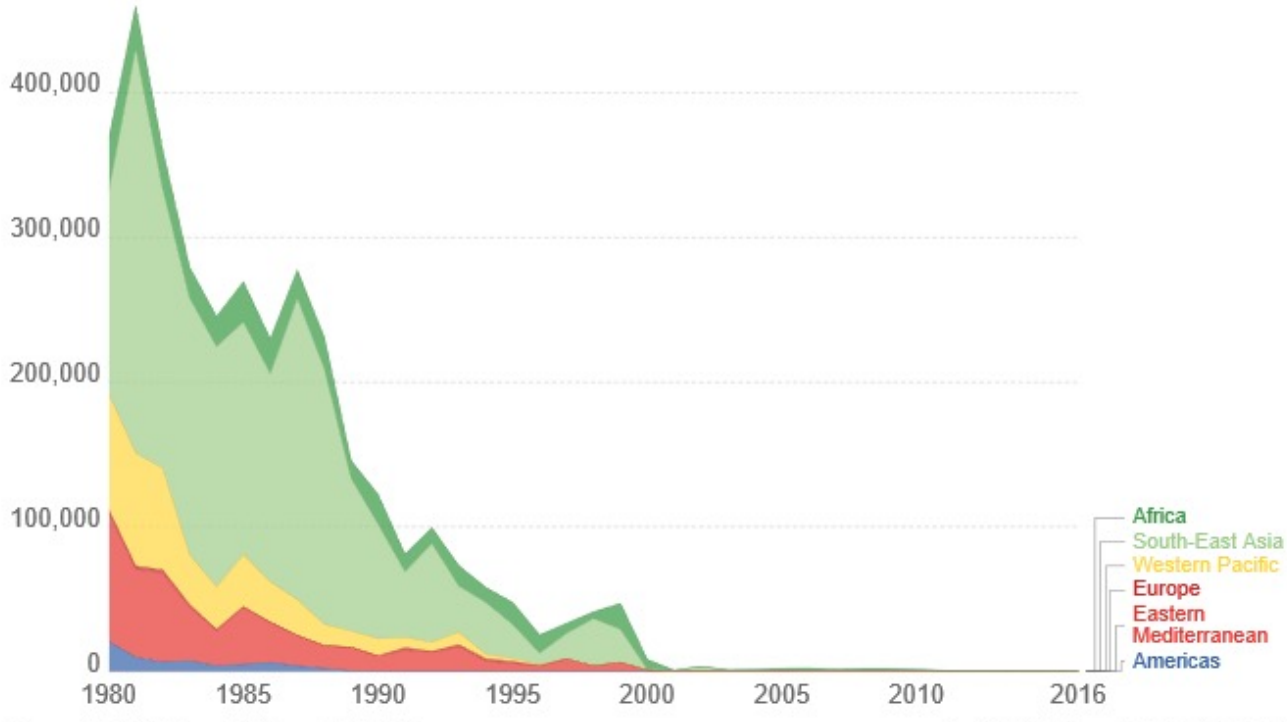
- Polio a paralysing disease. Was very common.
- Jonas Salk inactivated vaccine- 1950s.
- Albert Sabin oral attenuated to the 3 polio strains. Replicates in the gut, but not nerves.
- Pro oral: easy to give, acceptable, good immunity, some spread possible.
- Con oral: very rarely (about three per million doses) can cause paralysis.

Children's Hospital, Boston, Mass.
RareHistoricalPhotographs.com

Polio cases in the US 1912-1980, and globally 1980-2017.

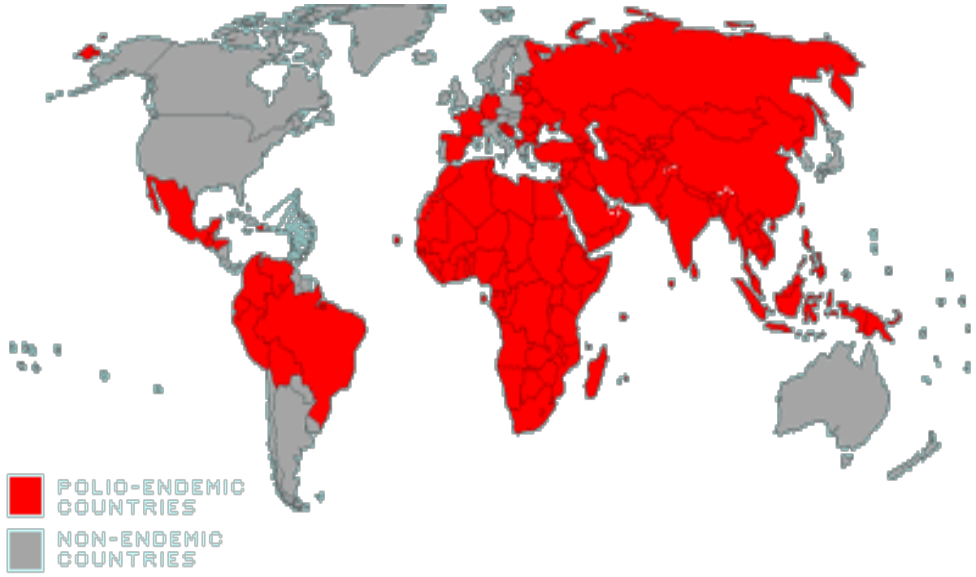


US Census Bureau- cases/100,000

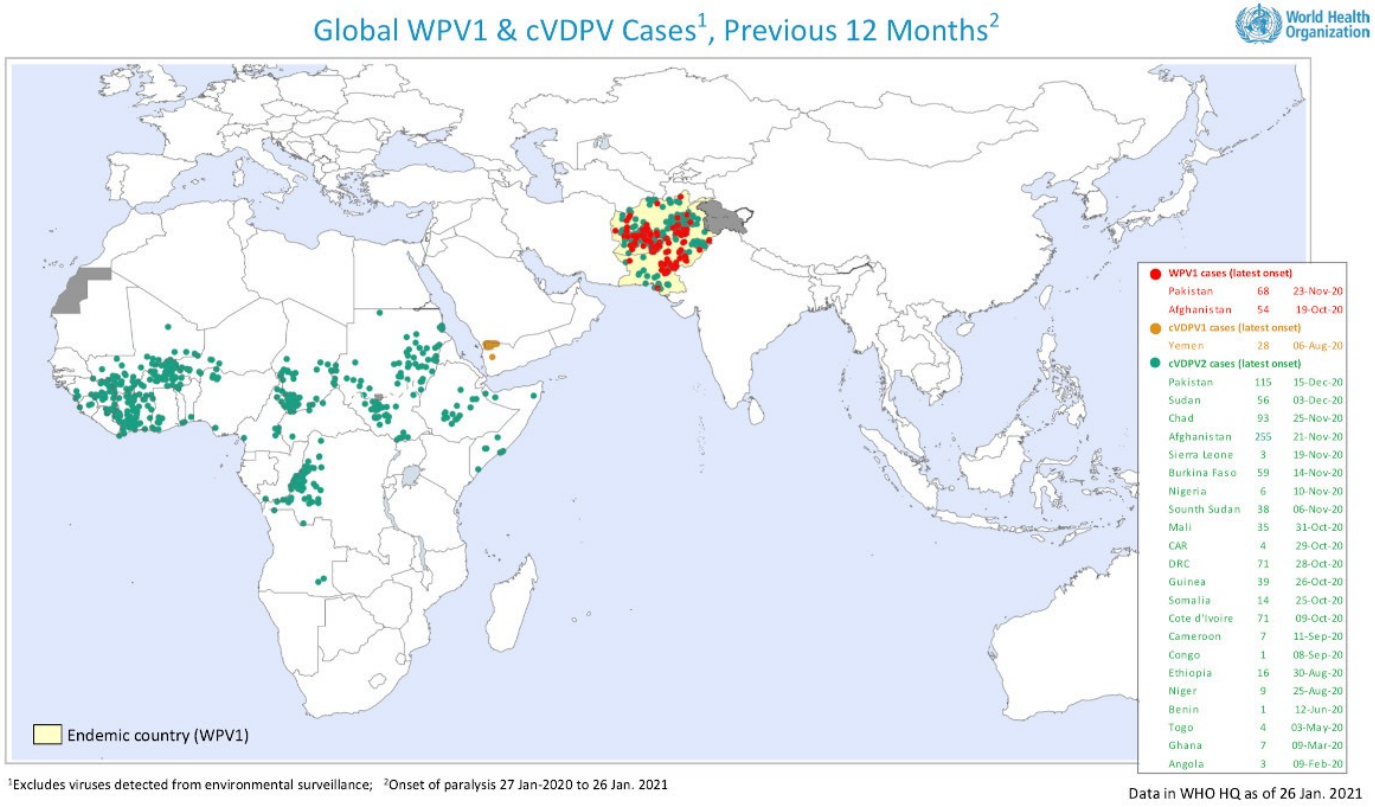


Number of estimated paralytic polio cases globally. Our World in Data / WHO / Tebbens

350,000 wild cases in 1988; 140 in 2020 (WHO). Eradication tantalisingly close.



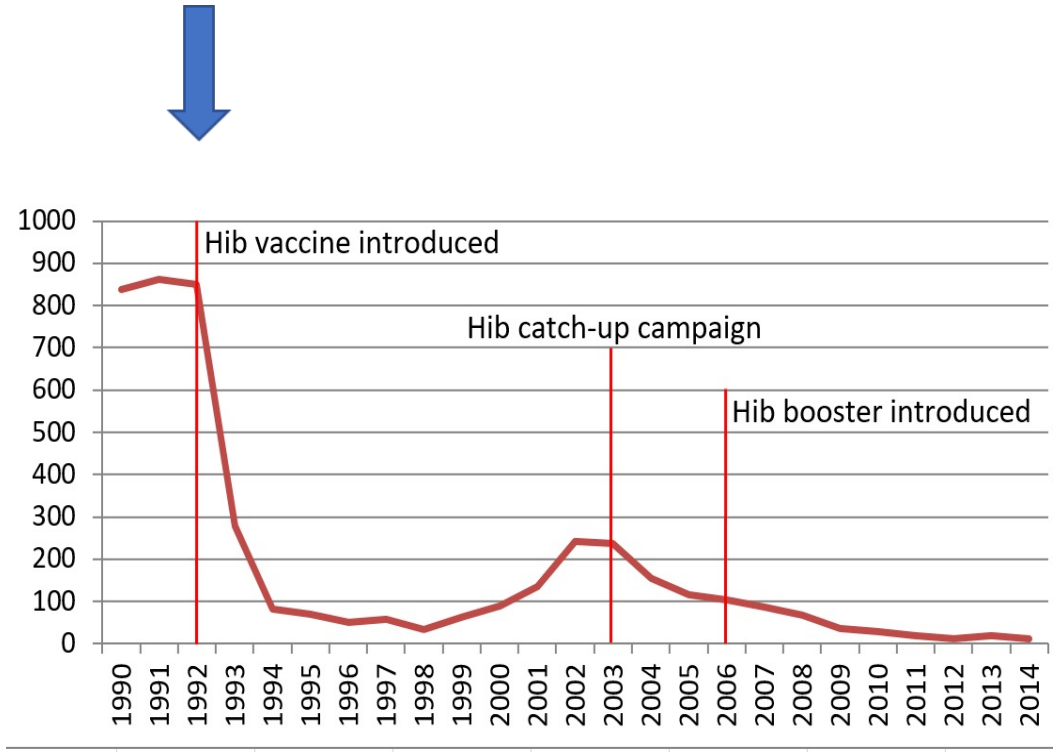
1988



140WPV 99cVDPV

Haemophilus influenzae b (Hib). Meningitis, pneumonia.

- Was commonest cause of meningitis in children under 4 years.
- 1:20 died, 1:5 left with serious neurological disability.
- Hib conjugate vaccine introduced in UK, Ireland 1992. Reduced incidence >90%.
- In 1991 759 reported cases of invasive Hib in children <5 in England. By 2014, there only 2 confirmed cases in this age group.
- Also reduces carriage.
- Global programme since 2014.

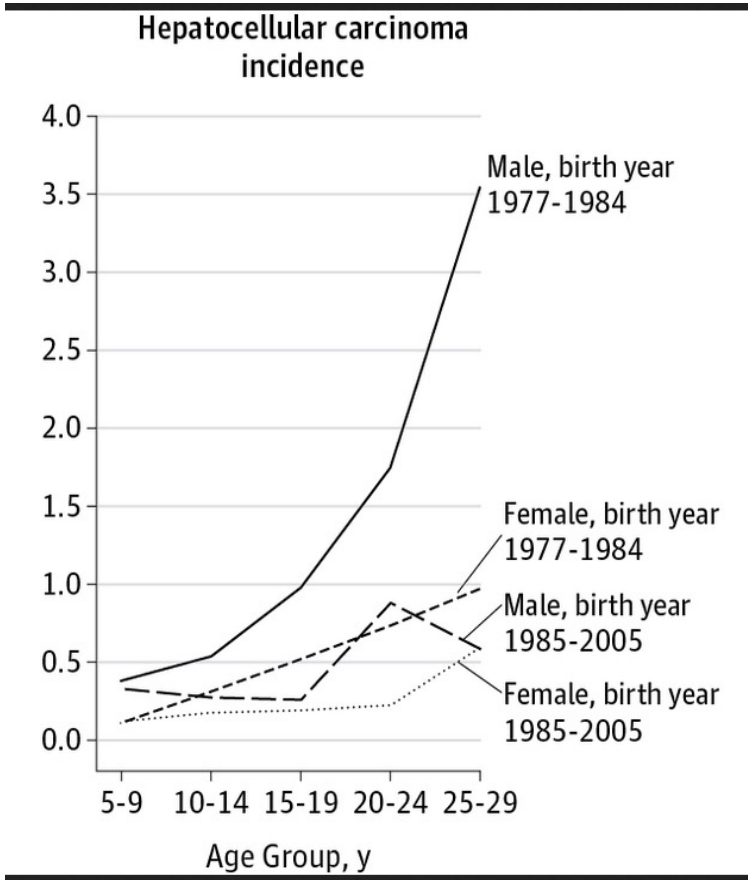


PHE Hib data, 1990-2015.

Hepatitis B and hepatocellular carcinoma (liver cancer).

- Can be passed on mother-to-child, between children, and sexually or IVDU in adults.
- Relatively rare causes of liver cancer and cirrhosis in the UK, a major one in Asia and Africa. High mortality.

- Vaccine 90-95% effective.
- Taiwan Hep B vaccination programme for infants began 1984. Reduced cancer incidence by 80%, mortality by over 90%.



C. Chaing et al JAMA 2013

In addition to the 6-in-1, for babies in UK

8 weeks start:

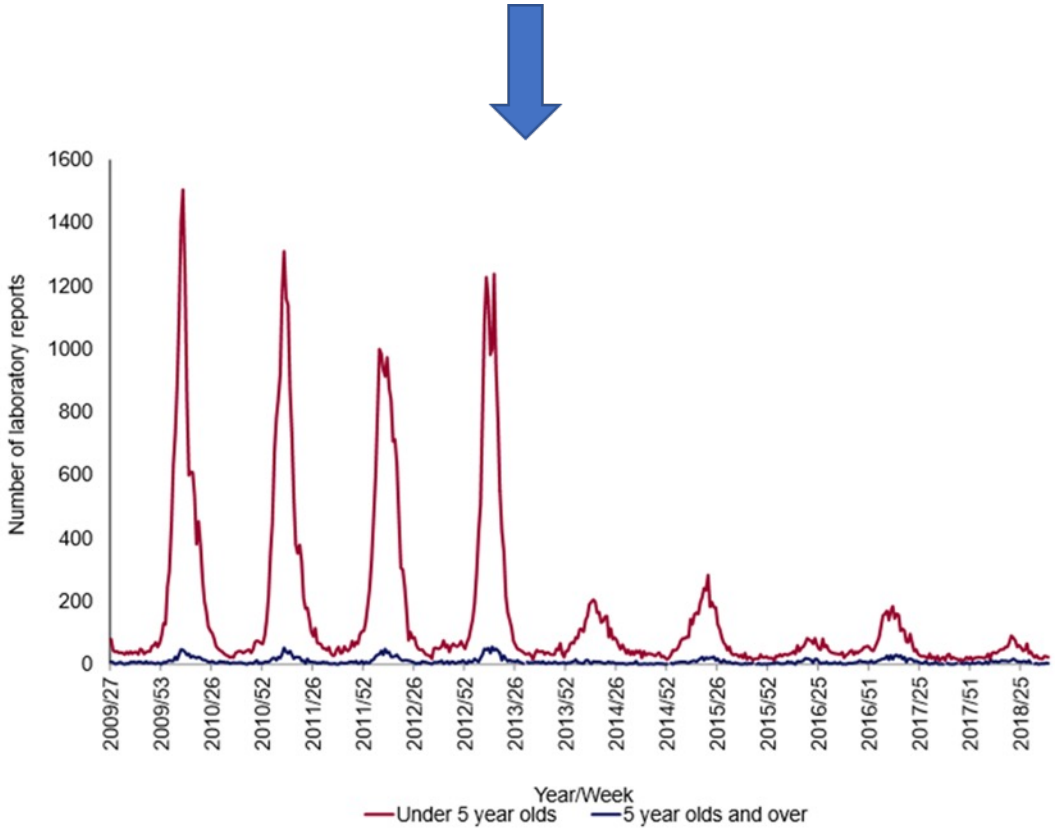
- Rotavirus (R).
- Men B (Meningococcus)

12 weeks start:

- Pneumococcal disease

1 year start:

- MMV; Measles, Mumps, Rubella.
- Men C.



Effect of rotavirus vaccine on under 5 cases.

Vaccines and epidemics.

- Known vaccines against known infections- eg Yellow Fever.
- Adapted vaccines against adapted infectious threats- pandemic flu.
- New vaccines against newly emerging threats. Ebola.
- And new threats- COVID-19.
- Epidemics we might get a vaccine- Zika.
- Epidemics we have struggled to get a vaccine- HIV.

Ebola assay, Army technicians.

Vaccine strategies in epidemics when vaccines often scarce.

- High risk individuals / transmitters.

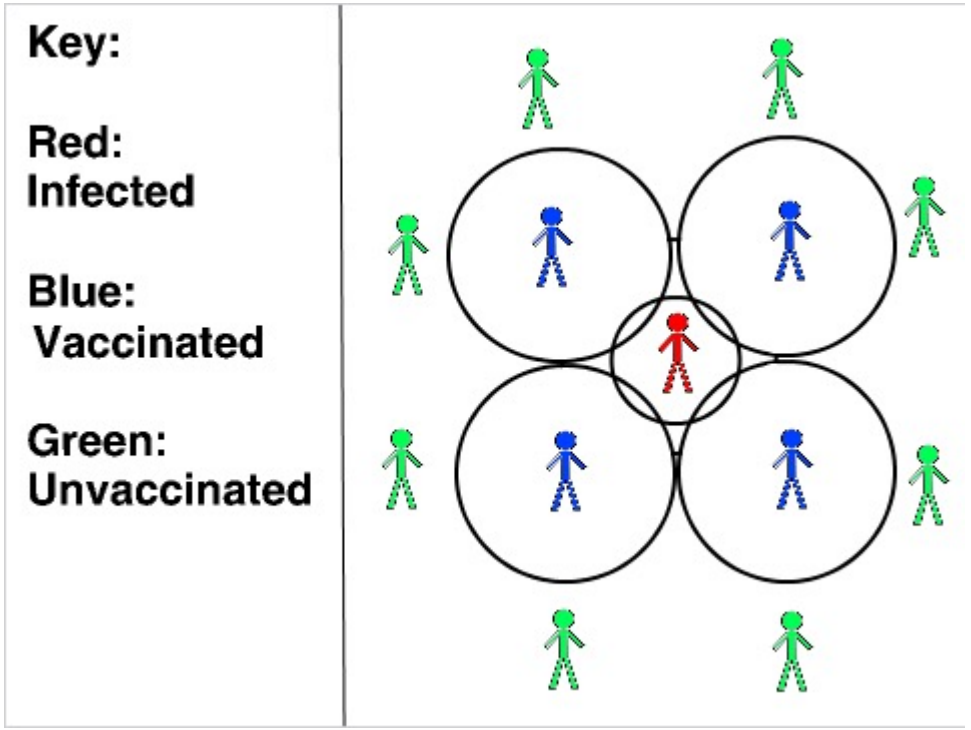
- Ring vaccination.

Fast acting vaccine needed. You have to be able to identify almost all cases.

- Population (herd) immunity.

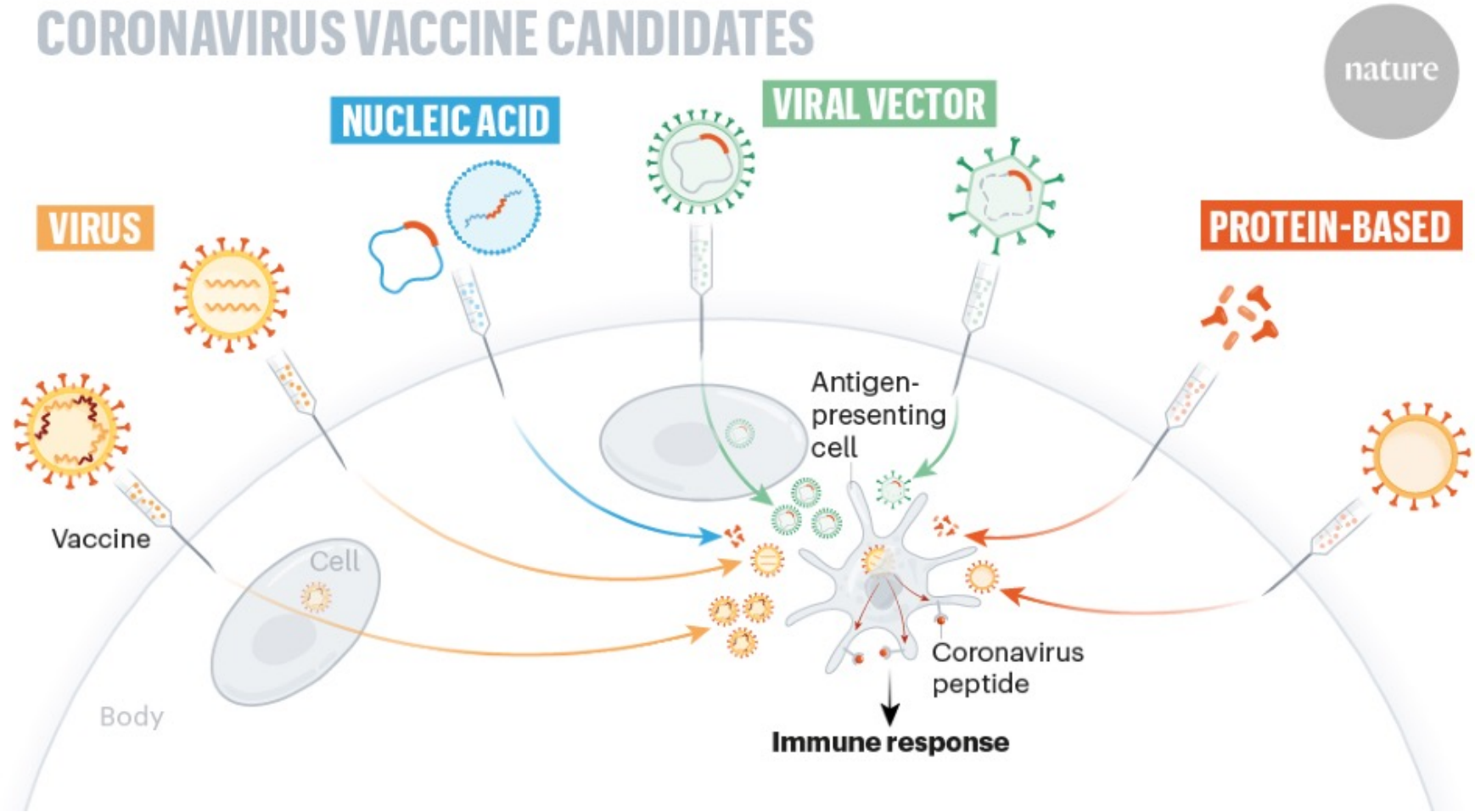
I am protected because my neighbour is protected by vaccine. Needs a high proportion vaccinated.

Ring vaccination.



Tom Griffin, CDC, Alex Szymanski

COVID-19 has seen the fastest development of vaccines ever. Old and relatively new technologies all produced in a year.



Nature 2020

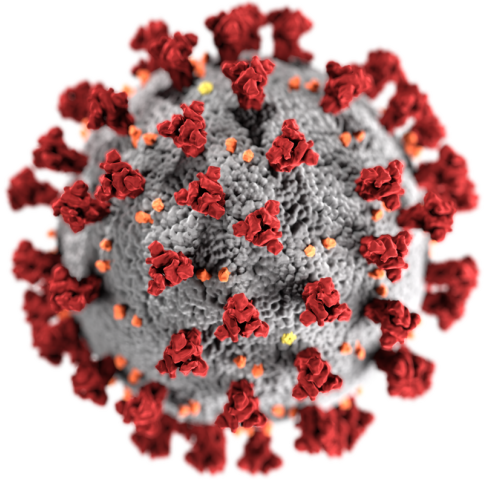
Most target the spike protein the virus uses to enter the cell.

Relatively conventional:

- Whole inactivated virus and adjuvant. Example Valneva.
- Protein and adjuvant. Example Novavax.

More recent technology:

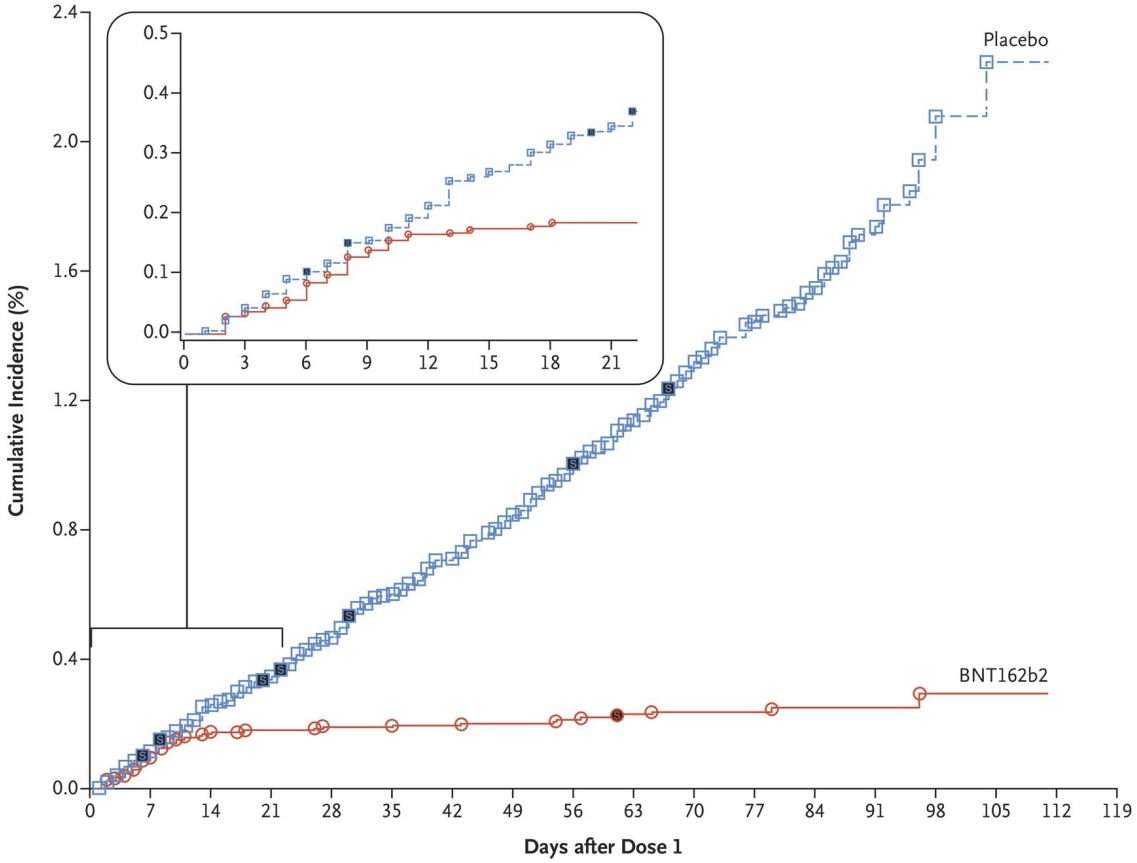
- Virus-vectored. Examples Oxford-AZ, J&J-Jannsen.
- RNA vaccines. Examples Pfizer-BioNTech, Moderna.



NIH, CDC

RNA vaccines.

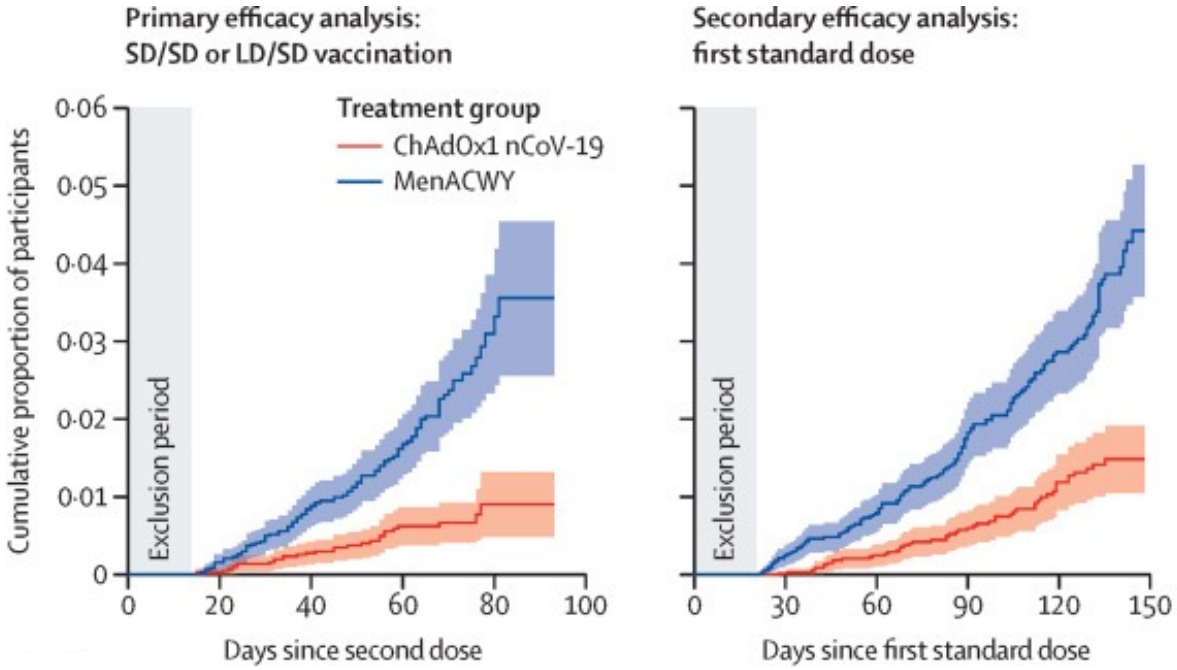
- RNA for the spike protein, which may be in a lipid nanoparticle, injected.
- Incorporated in human cell, which for a time makes the protein.
- Example Pfizer-BioNTech, data R.
- From around 10 days very good protection.
- Advantage it can be reformulated fast.



Polack F et al NEJM 2020

Viral vectored vaccines.

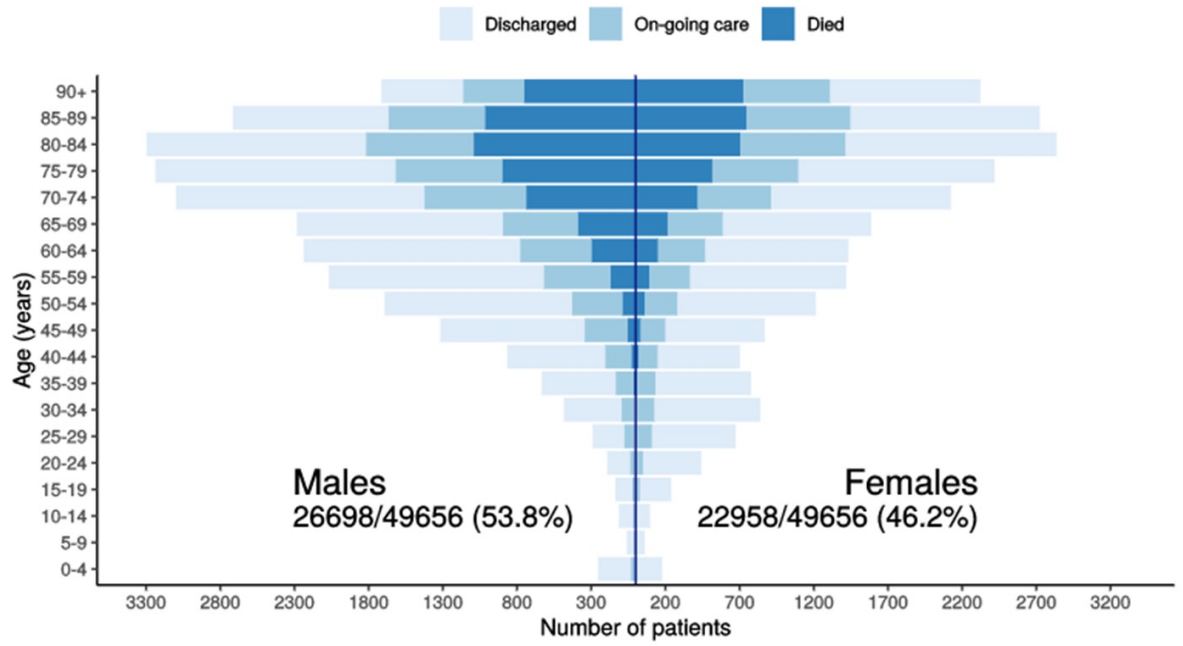
- A relatively harmless virus- generally adenovirus (cold virus).
- Example: Oxford-AZ is ChAdOx1, a non-replicating chimp adenovirus.
- Incorporate genes for COVID spike protein.
- When taken up by the body the protein is manufactured by cells.
- Recognised by immune system.



Voysey M et al Lancet 2021

Vaccination initially mainly protects those vaccinated as relatively few covered.

- Significant population protection will come later (if at all).
- Therefore most impact by vaccinating those at highest risk.
- In the UK those over 70 constitute over 80% of those who died, around 55% of those hospitalised.
- Data at R in hospitalised patients, UK 2021.



Harrison, Docherty, Semple, ISARIC4 / CO-CIN Jan 2021

What we know, and don't, about COVID-19 vaccines.

We know:

- Natural immunity lasts at least 6 months.
- Much lower reinfection- not none.
- Multiple vaccine types with the spike protein reduce infection.
- Good side effect profile.
- Immunity to severe disease probably better than to infection.
- Revising spike protein should be relatively easy.

We don't know (Feb 2021):

Long term protection, especially in elderly.

How easily and rapidly COVID-19 escapes via mutation.

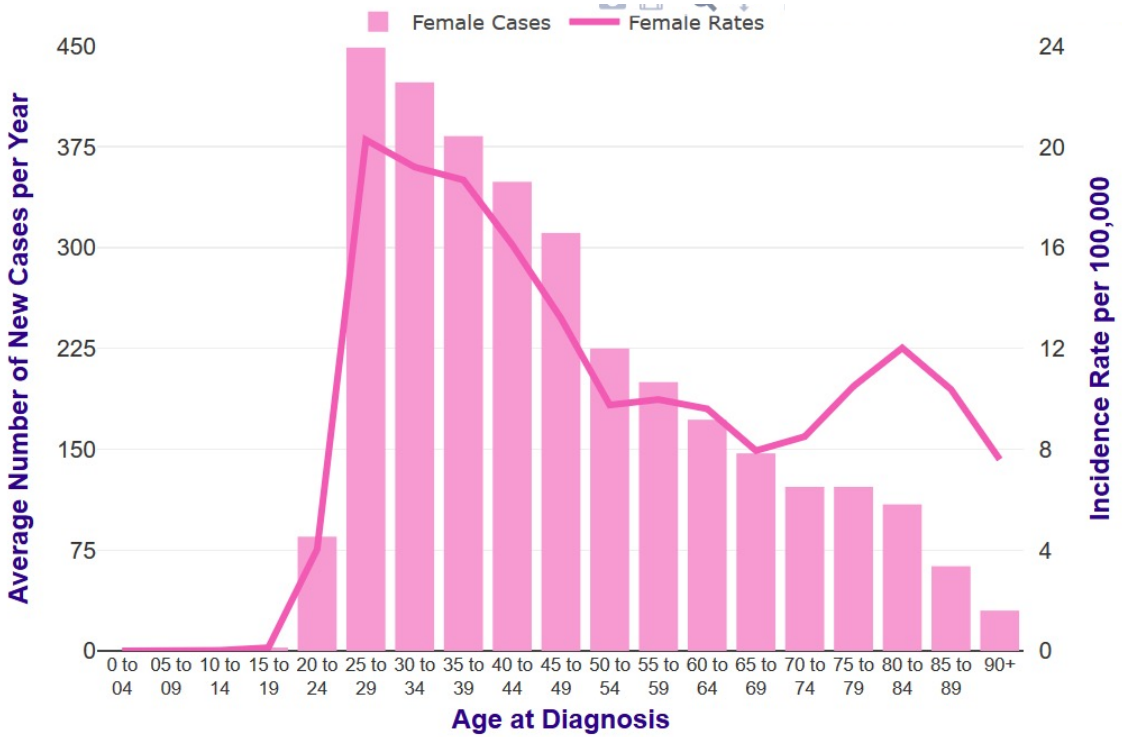
Impact on transmission at an individual level.

Effect on transmission at a population level.

Prevention of adult diseases: cervical cancer.

- Globally around half a million women affected.
- Around 3000 cases a year in UK.
- 1 in 142 UK females will be diagnosed with cervical cancer in their lifetime.
- Often young.
- Almost 100% preventable.

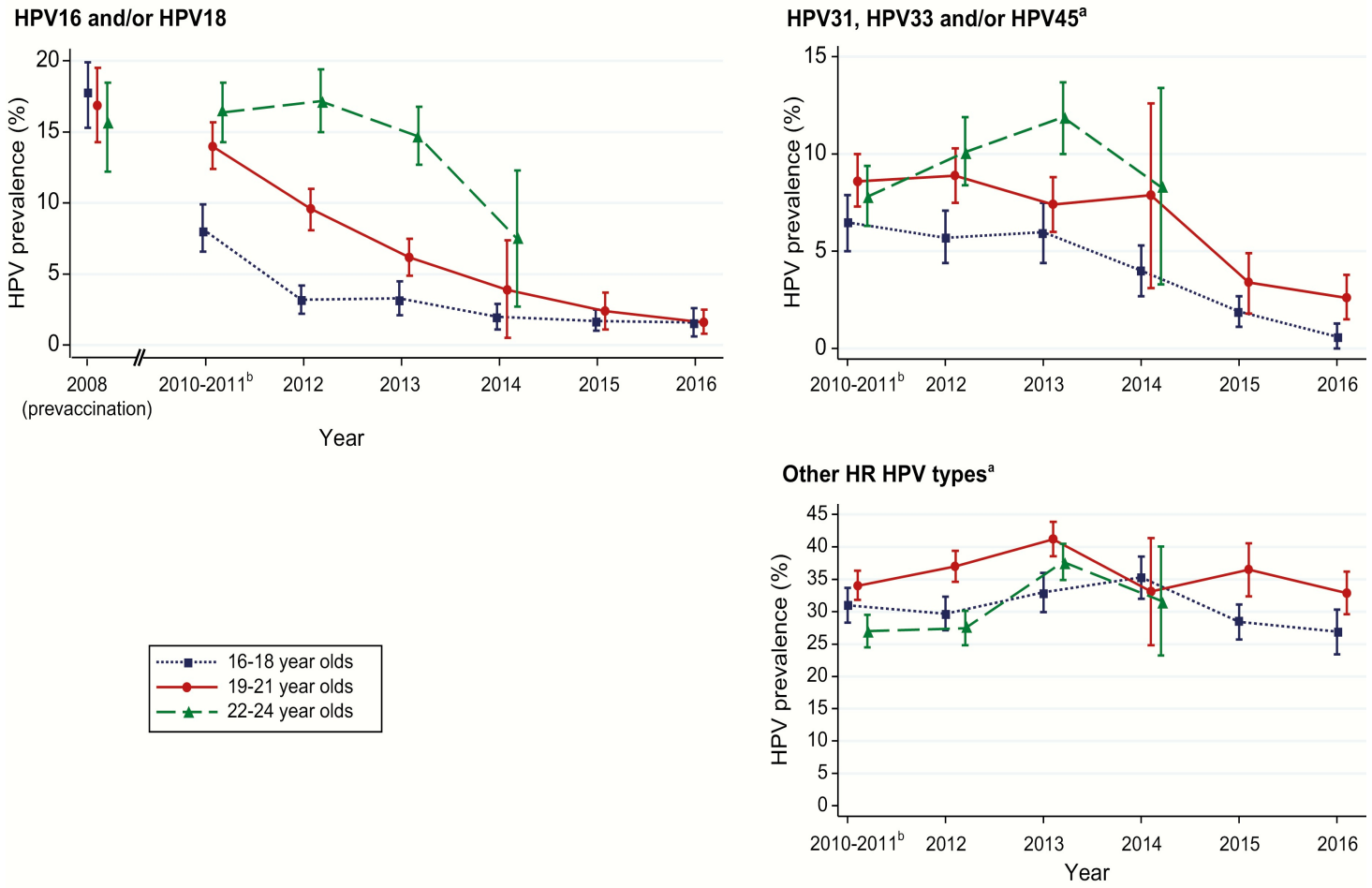
- HPV vaccine and screening.



CRUK

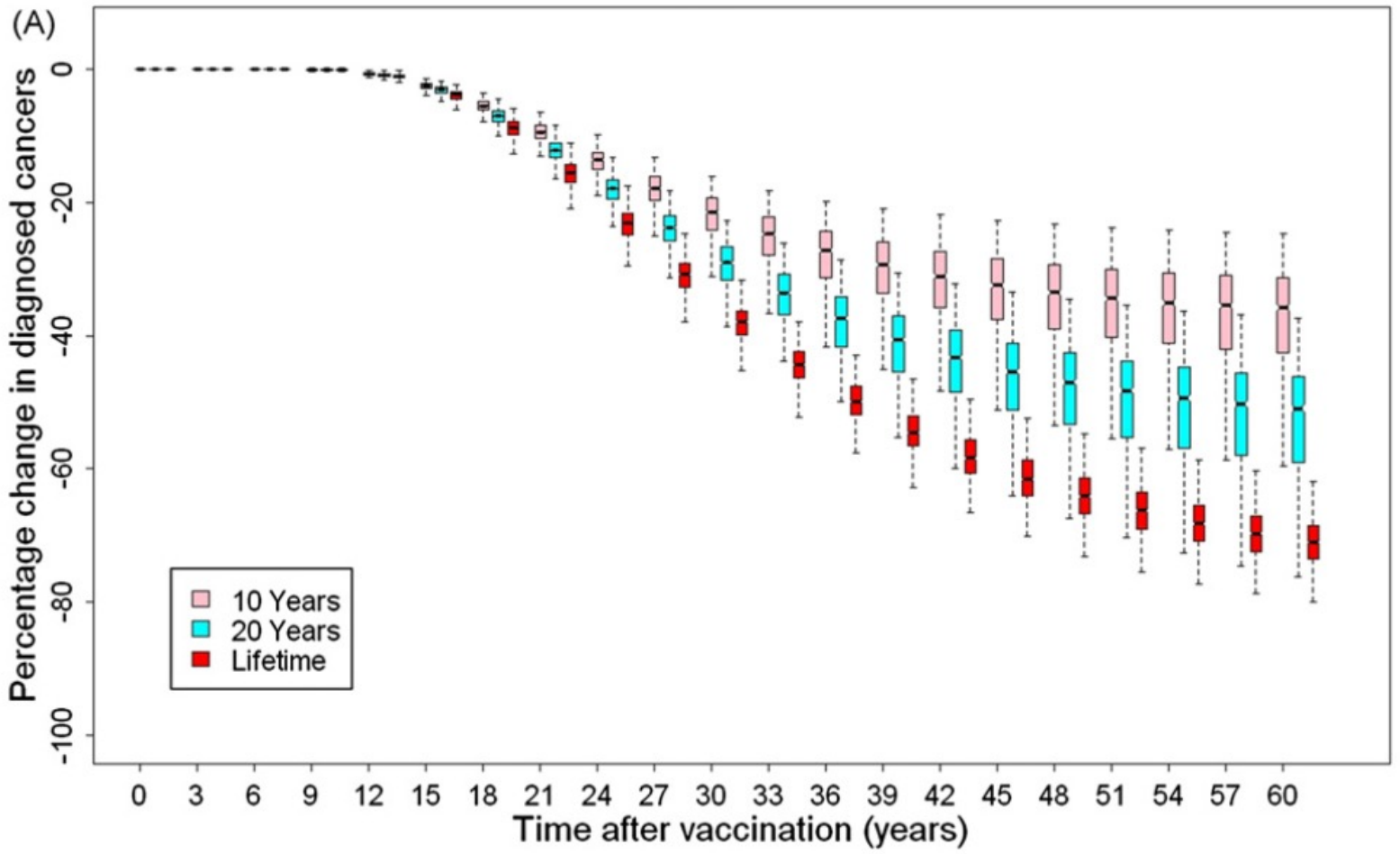
UK vaccine for girls against HPV 16, 18 introduced in 2008.

- Prevalence of HPV16/18 decreased between 2010/2011 and 2016 from 14.0% to 1.6% in 19–21 year olds attending chlamydia screening.
- Vaccine effectiveness for HPV16/18 82%.



Mesher D et al JID 2018. In girls/women for chlamydia screening.

Reduction in cancer depends on how long immunity lasts, what % coverage vaccine. HPV 16, 18 only vaccine model. *(Yoon Hong Choi et al)*



The numbers of deaths vaccines avert is remarkable, especially in lower and middle income countries.

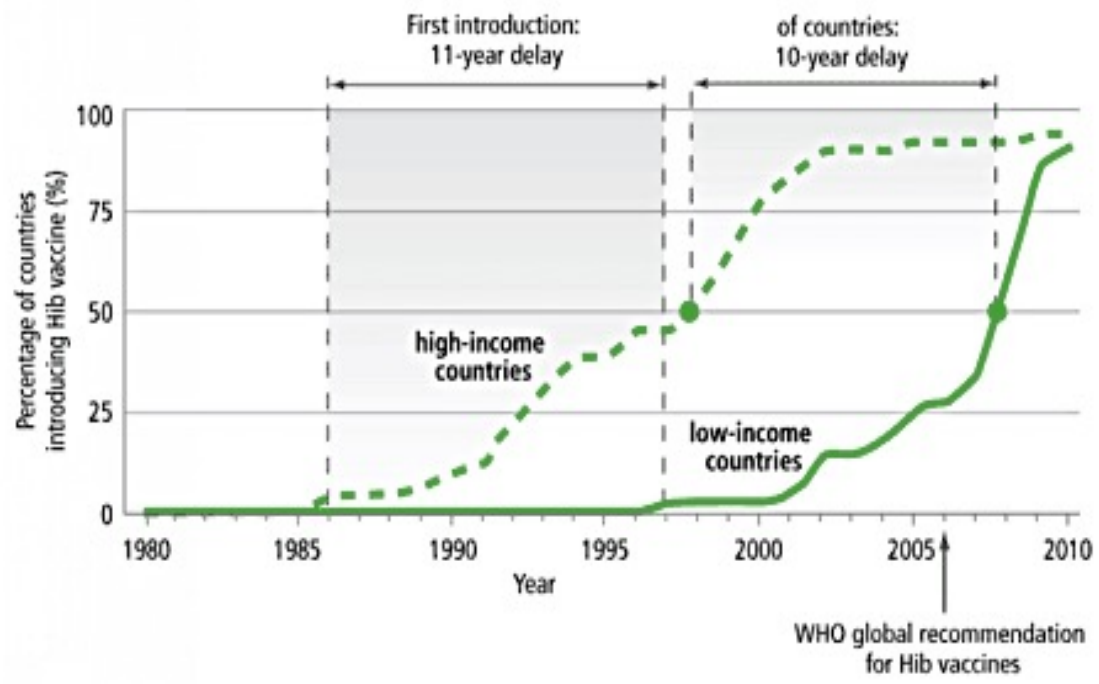
- Recent estimate effect of vaccination against ten pathogens globally:
- Averted 37 million deaths between 2000 and 2019.
- Among children under 5 years, a 57% reduction, most notably from measles.
- *Xiang Li et al Lancet 2021.*

Juliene Harneis/ UNICEF/ CDC

Vaccine preventable deaths in children globally: some examples.

- Pentavalent vaccine against five major infections: Hib, diphtheria, tetanus, pertussis (whooping cough), Hepatitis B.
- Deployed globally since 2014 (GAVI).

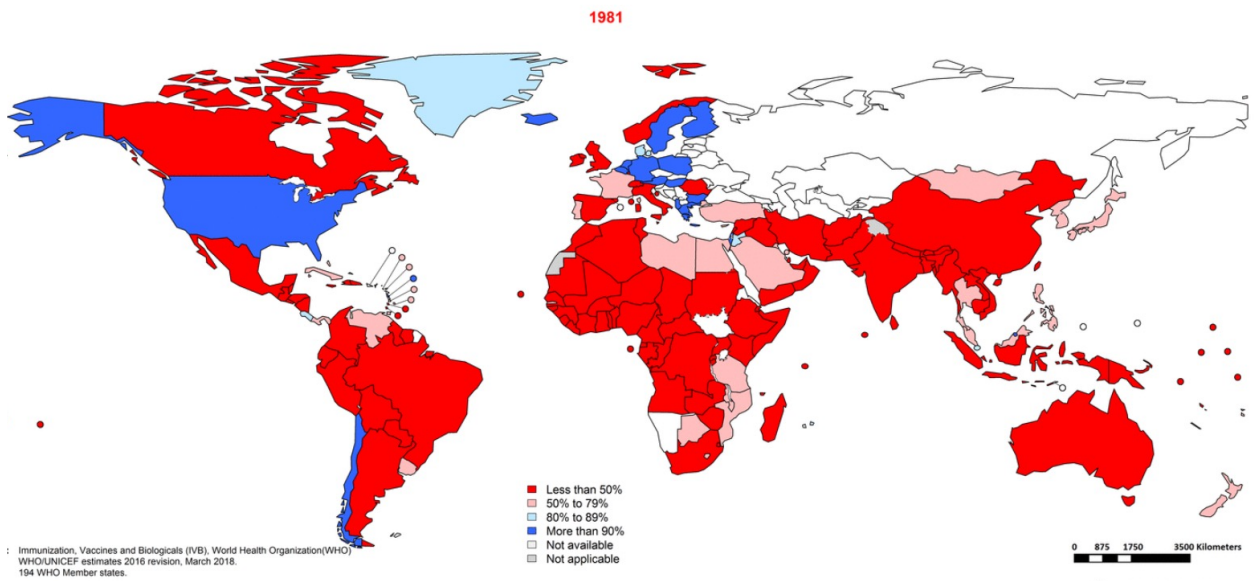
- Pneumococcal and *Haemophilus influenzae* type b (Hib).
- Rotavirus, measles, rubella.

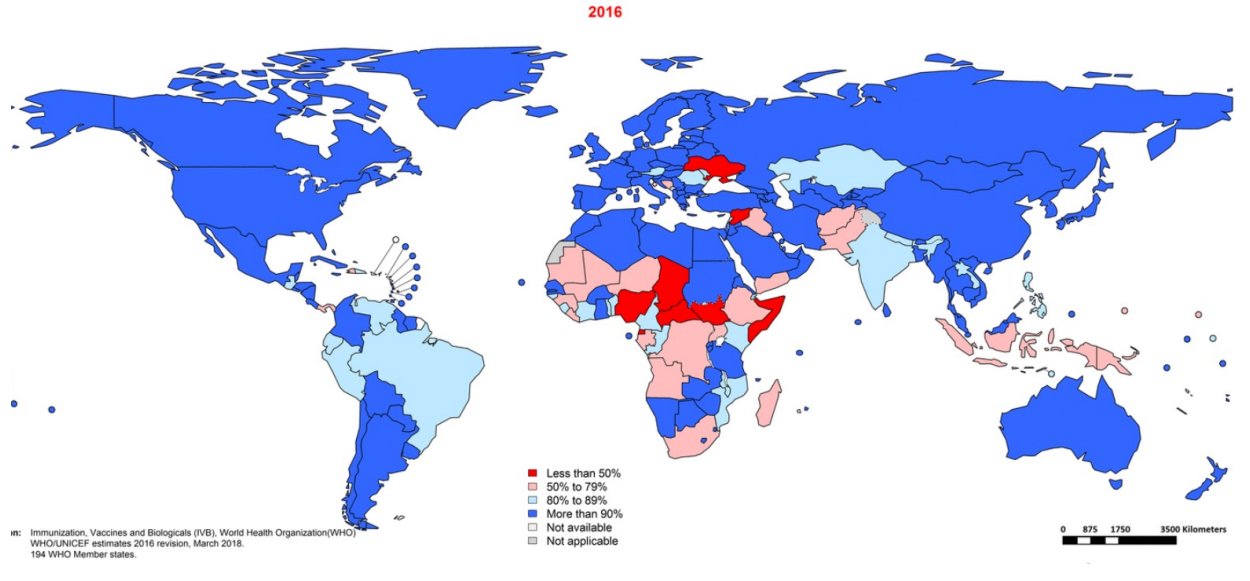


PHE/GAVI

Global coverage of DPT containing vaccines. 1981-2016. <50%, >90%.

WHO

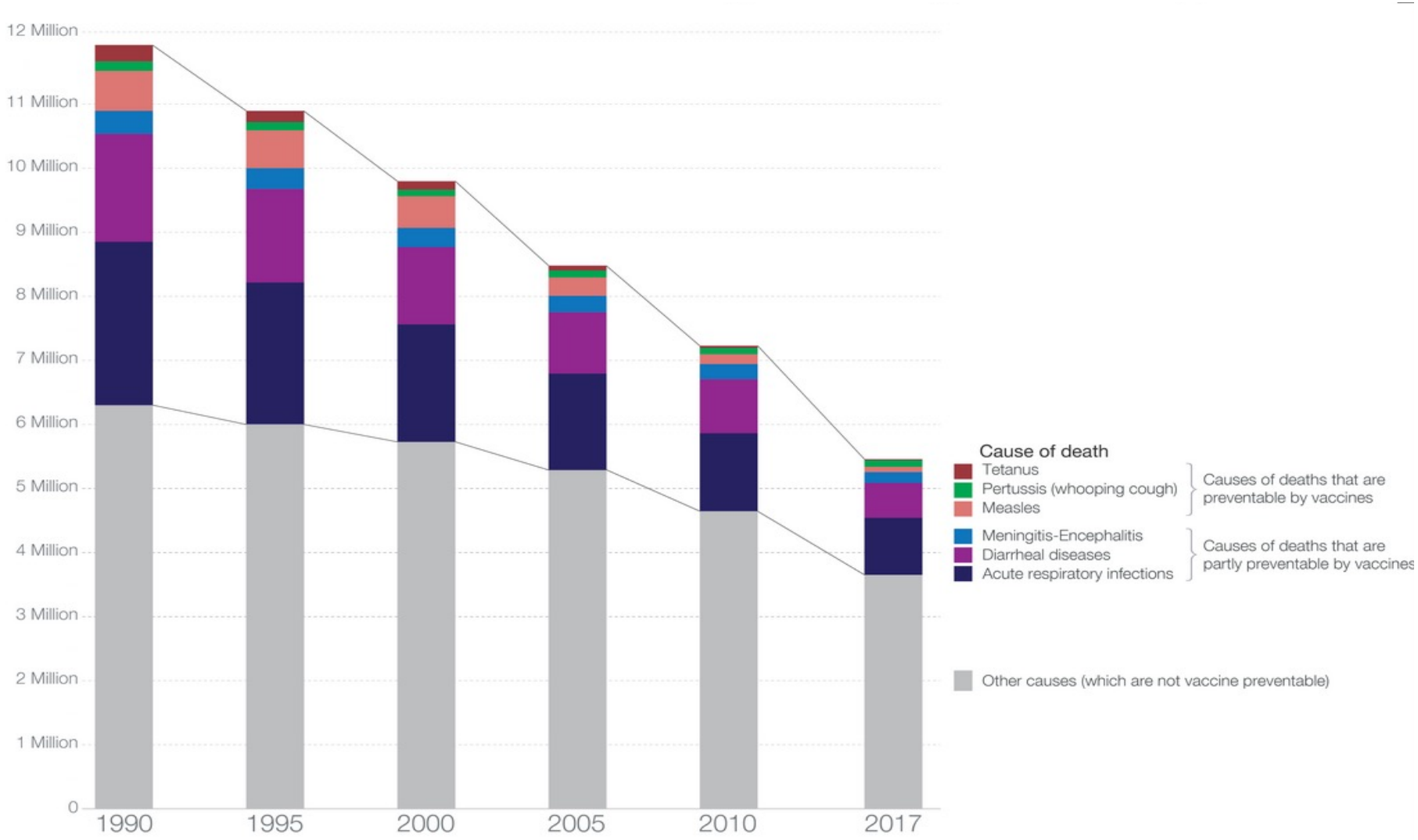




Global number of <5 child deaths by cause- vaccine preventable in colour. 1990-2017. Our World in Data.

12 Million

6 Million



Dr. Jenner's legacy.

- Many of the most feared diseases largely gone- where vaccines are available.
- Substantial protection against multiple childhood infections.
- New and relatively rapid approaches for responding to epidemics.
- Major drops in adult disease continuing, including cancers.
- Vaccine science advancing rapidly.

Edward Jenner, 1749-1823