Vaccines
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Millions of people are alive today because of vaccination. Some would have died in childhood without it. For others, parents, grandparents or forebears would have died or been permanently disabled. We take vaccines for granted in high income countries because the effects of not having them are less obvious than they were a generation ago. They have however largely freed us from some of the most dangerous and debilitating infections including tetanus, smallpox, diphtheria, measles, many causes of meningitis and polio to name a few. These are notes to accompany the lecture rather than a direct transcript.

In addition to protecting against many of the most dangerous diseases of childhood, which I will cover in the first half of this talk, vaccines can also combat major epidemics including COVID-19, influenza and Ebola as recent examples. They can significantly reduce important diseases of adulthood such as pneumococcal disease-causing pneumonia and septicaemia, or very unpleasant diseases such as shingles. Several cancers, in particular cervical cancer and liver cancer can be prevented by vaccination.

Celebrating vaccines is really celebrating the immense power of our immune system. Vaccines do not kill viruses, bacteria or neutralise toxins- we do. They use the natural processes of the body to fight infections by getting the immune system ready in advance by mimicking an infection much more safely than natural infection.

Vaccines are not the answer to all infectious diseases. For some major infections we do not have an effective vaccine: an important example is HIV. For some infections we have an adequate vaccine but also have better countermeasures; cholera and typhoid control owe more to good sewers and clean water than vaccines. Some diseases have a reasonable vaccine but are not common enough to be worth vaccinating against at least in high income settings; an example is rabies vaccination for humans in the UK.

In deciding whether to use a vaccine we need to answer three sets of questions. The first is: is the disease a significant risk? If not, vaccination is unlikely to be appropriate. The second is how effective is the vaccine, and for how long? If the protection is only short lived or very limited, then vaccination may not be relevant. The third question is what are the side effects? Vaccination is only appropriate if the risk of being harmed by the vaccine is much lower than the risk of natural infection. All of the vaccines I'll be talking about in this lecture are very safe compared to natural infection. Once we know the answers to these questions, we can make a benefit-risk decision. All of medicine is about risk of no treatment compared to risk of treatment, whether we are talking about major operation for a very dangerous condition, prescribing a drug or giving a vaccine. Benefit versus risk is a central element of medicine.

The spur to vaccination being widely used was smallpox, an ancient disease with major epidemics in Europe and elsewhere. The more common form of the disease had a mortality of over 30% and

over 80% in infants. Survivors were scarred and up to 1/3 were left blind. Over 10% of deaths in London in the 1750s were due to smallpox. It was known as early as 480 BC that survivors were unlikely to get the disease again and were therefore asked to nurse the sick.

Because it was so feared, quite dangerous countermeasures were considered reasonable. An early practice developed in Asia and Africa was variolation. Pus from a pustule from someone with smallpox was inoculated in the hope that it would cause a very limited infection. Around 2% of people inoculated in this way died or caused outbreaks but this is much better odds than natural infection. Variolation was introduced into Western Europe in the 18th century from Turkey by the remarkable Lady Mary Wortley Montague, writer, poet and adventurer. She set up a trial to demonstrate its effect on prisoners in Newgate in 1721; all survived and were proven immune. Variolation became widespread in Europe and North America with the substantial risk of the procedure considered reasonable compared to the even greater risk of not having it.

The great step forward however was the development of vaccination by Dr Edward Jenner. This was massively safer than natural infection with this common, severe disease. Dr Jenner was a Gloucestershire country doctor (broadly equivalent to a GP), scientific polymath (he was elected FRS for his work on cuckoos and studied hedgehog hibernation among other things) and observant physician. The observation that dairy maids who had cowpox did not get smallpox was folk wisdom. Jenner inoculated material from cowpox from Sarah Nelms into eight-year-old James Phipps in 1796. James had mild symptoms and recovered. When James was inoculated with smallpox it did not take. This showed that the much milder disease protected against the more severe one. Jenner spent years promoting vaccination and disseminating it widely including widespread vaccination of poorer citizens.

He also observed the natural history including that after some years smallpox vaccination protection waned to some degree, but that when smallpox did occur later in life in vaccinated people it was milder. These observations by Jenner are important. Many vaccines are not all or none, and they may need revaccination. Vaccines may prevent infection. They may prevent significant disease even if someone does become infected. They may prevent death even in those who have significant disease. Therefore, many vaccines reduce severity of disease even if they're not able to stop infection; this may be important as we consider COVID-19 vaccines. The fact that vaccines may become less effective over time is also important in considering how to deploy them. Revaccination is needed for some, but not all, vaccines due to waning immunity.

Jenner's vaccination gradually reduced smallpox in higher income countries but it remained a major infection right into the 20th century when it is estimated that over 300 million deaths occurred. An eradication attempt was agreed by the world health assembly in 1959 when 2 million people a year were dying. Eradication of this major killing and debilitating disease was declared in 1980.

Early vaccines against other major diseases were developed using a variety of methods. For example, in 1885 Pasteur and Roux developed a rabies vaccine. Rabies is an appalling disease with virtual inevitable death, and it is a terrible death. The initial vaccine was from infected rabbit spinal-cord, and because of the risks was only given to people who have been bitten by potentially rabid dogs so at very high risk of dying. Unlike the vaccinia vaccine for smallpox, which was a live vaccine, the rabies vaccine was inactivated virus. Rabies vaccines have subsequently become much safer and are now used pre-infection when the risks to the person being vaccinated are much lower therefore the vaccine has to be very safe. There is also vaccination of dogs, and wild animals in particular foxes. Using this technique human rabies has been gradually pushed out of much of Europe and other areas.

It was not just viruses that early vaccines were developed against. BCG from live, related (originally from bovine TB in cattle) attenuated mycobacteria provided significant protection in children against

tuberculosis, and has subsequently been found to be highly effective in protecting against leprosy. It was first used in 1921 so this is the centenary of its human use.

A vaccine is a way of getting a lasting immune reaction safely. Pre-COVID technologies, some over a century old include: a live -related virus, a live attenuated (weakened) virus or mycobacteria, an inactivated virus or dead bacteria, an inactivated toxin, a bit of the protein, complex sugar or glycoprotein from the coat of the virus or bacteria. This is often given with something to stimulate a stronger immune response (adjuvant). Vaccines are usually injected but some can also be given by mouth, or up the nose.

So how do vaccines work? The body has multiple layers of defence against infection. They start with simple things including barriers like the skin or mucus. There is then the innate immune system which responds to infections non-specifically and without memory. This is highly effective but not the part of the actively 'learning' system which vaccination aims to involve. What vaccines interact with is the adaptive immune system. This is much more specific. It 'learns' an infection and responds very precisely and effectively next time the same infection represents.

The adaptive immune system is remarkable, and the details would be sufficient for a full lecture. For the purposes of this note however the key thing is to understand the two broad systems which vaccination stimulate. Antigen presenting dendritic cells present the foreign antigen (infection or vaccine antigen) to T-cells. These activate killer T cells which subsequently recognise and destroy infected cells, and B lymphocytes which go on to produce antibodies and lay down memory cells. The relative importance of antibodies from B cells and T cell protection varies by infection.

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 there is a response of antibodies and T-cells. The response to the second vaccine (or second infection) is faster. It also leads to a more focused, stronger and longer lasting immune response. There needs to be a sufficient gap between first and second vaccination.

Childhood Disease: the Example of the 6-in-1 Vaccine

The most widespread use of vaccination outside epidemics is in protecting children from very severe diseases. An example of a childhood vaccine used in the UK is the 6-in-1 vaccine. Viewed as a way of preventing historically devastating diseases it is quite remarkable. It provides extremely good protection against tetanus, diphtheria, pertussis (whooping cough), polio, Hib and Hepatitis B. Two of these involve an inactivated toxin (tetanus and diphtheria). Polio is an inactivated virus. Hib and hepatitis B involve protein and protein polysaccharide antigens. The 6-in-1 vaccine is highly effective and very safe; the question is how dangerous are the diseases? This lecture considers 5 of them.
Tetanus is a terrible disease caused by a toxin produced by the bacteria. Historically it was a major cause of deaths in new-borns in which it has a mortality rate of almost a hundred percent. In adults it is extremely painful and prolonged and also has a high mortality rate. The vaccine does not stop infection but does stop the toxin which does the damage; this protects the individual vaccinated but there is no herd immunity effect. It has led to a massive drop in tetanus cases around the world.

Diphtheria used to be the third leading cause of death in children in the UK in the 1930s. The case fatality was up to 20% and is caused by a common throat bacterium which sometimes produces a toxin. This has local effects which can lead to children being unable to breathe, and effects on the heart and nerves. It was the first free vaccine in England, in the 1940s, and had a dramatic impact on deaths from diphtheria in the UK and subsequently worldwide. There were over a million deaths a year before the 1980s; now it is a very rare disease.

There are two polio vaccines; a live attenuated oral one and an inactivated one given by injection (used in the 6-in-1). Polio is another terrible disease which cause significant lifelong paralysis in large numbers of children and adults. Polio cases in Europe, the USA and globally have dropped dramatically. In 1988 there were 350,000 world cases; in 2020 there were 140, in two countries. Polio has been tantalisingly close to eradication for several years.

Haemophilus influenzae b (Hib), which is a bacterium (not to be confused with influenza virus) was the commonest cause of meningitis in children under four years until quite recently. 1:20 died, one in five of those who survived were left with serious neurological disability. Hib conjugated vaccine was introduced in the UK and Ireland in 1992 and reduced incidence by more than 90%. There is now a global programme since 2014.

Hepatitis B is globally one of the major causes of cirrhosis and liver cancer. It is relatively uncommon in Europe but very common in much of Asia and Africa. The vaccine is 90 to 95% effective and has led to a substantial reduction in liver cancer where it is deployed.
In addition to the 6-in-1, babies in the UK are given vaccine for the common diarrhoeal disease rotavirus, the major causes of meningitis and septicaemia meningococcus, pneumococcal disease which causes pneumonia and sepsis and MMV against the dangerous diseases measles, rubella and mumps.

Measles in particular is seriously underestimated by many people, with a significant risk of encephalitis (brain inflammation) to vaccinating against it is essential. I have covered measles vaccine in a previous Gresham lecture on brain infections, and pneumococcus on a previous lecture on lung infections so they are not covered in this one.

Vaccines and Epidemics

Vaccines are one of the strongest tools we have against epidemics. There are known vaccines against known infections which cause repeated epidemics such as Yellow Fever. There are vaccines we have to adapt against infections which evolve new strains such as influenza. We develop new vaccines against newly emerging threats; a recent example is Ebola whereas a result of the major West African epidemic we now have developed good vaccines. There is also recent important epidemics where we may well get vaccines but do not have one yet such as Zika. And it is important to stress that there are some major epidemics and pandemics for which we have never got a vaccine, of which the most important is HIV, the last devastating pandemic before COVID-19 (still ongoing).

There are several vaccine strategies which can be used in epidemics in particular when vaccines are scarce which they usually are at the beginning of an epidemic. One is to identify who is at very high risk of dying or catching or transmitting the disease and vaccinate these high-risk individuals. A second, which is only useful under certain circumstances is a technique called ring vaccination. If you have a fast-acting vaccine and can easily identify cases you can vaccinate all their contacts, and the contacts of the contacts in a ring around the infected person. This protects the rest of the population from them. It has been used highly effectively in smallpox and Ebola outbreaks but is not relevant to diseases such as COVID which often have minimal symptoms. Finally, if you can vaccinate a large enough portion of the population, in some cases you can create population (herd) immunity; this should only be an aim of policy with vaccination. For many diseases, population immunity is never attained, and it should not be assumed it can be, even with vaccines.

At the moment the most important epidemic is obviously COVID-19. It has led to the fastest development of vaccines ever. Multiple technologies have been used many of which produced vaccines in under a year. The scale of this achievement cannot be overstated. In addition to well-established methods such as inactivated viruses and protein-based vaccines two relatively new

techniques in terms of human deployment have been used: RNA vaccines and viral vectors. It is important to understand that all of these are simply a way of delivering an antigen to the immune system. The delivery method is different between the different vaccines, but the antigen is similar in most of them which is the spike protein that the virus uses to enter the human cell.

This lecture highlights the two new technologies of RNA vaccines and viral vectored vaccines, although other, older, technologies will play an important role in due course. RNA vaccines are the RNA coding for the spike protein which may be put in a lipid nanoparticle. Once injected they are incorporated into human cells temporarily, which for a time make the virus spike protein the RNA codes for. The protein is recognised as foreign by the immune system and after around 10 days begins to produce an immune response. The RNA is broken down and not incorporated into the cell in the long run. A major advantage of RNA vaccines is that they can be reformulated extremely rapidly. This will be important if we get escape variants that evolve to get around the natural immunity.

The viral vectored vaccines like the Oxford vaccine incorporate the genes for the spike protein in a relatively harmless non-replicating virus, generally a human or chimp adenovirus. When this is taken up by the body the protein is manufactured by cells which again cause an immune response.
Both of these new vaccine methods have proved to be very safe. There is a bad reaction rate of 1 to 2/ 100,000 but this can be reversed. Non-severe reactions have been reported at around 3:1000. This is much lower risk than natural infection which has a significant hospitalisation and mortality rate. Therefore benefit-risk is strongly for vaccination.

In initial phases of the rollout of the vaccine there is little or no significant population immunity as too few are vaccinated- this will come later if at all. Therefore, the most impact is by vaccinating those at highest risk. In the case of COVID this is very heavily skewed towards older citizens and those with significant pre-existing health conditions. Those over 70 years old constitute over 80% of those who died before vaccines became available, and around 55% of those who are hospitalised.

We now know a lot about COVID-19 vaccines, but there are several things we still do not know at this point in time (Feb 2021). We know natural immunity lasts at least six months in most people and probably longer; there is much lower probability of reinfection after the first infection but not none; multiple vaccine types with the spike protein reduce infection; immunity to severe disease is probably better than to infection; revising the spike protein to respond mutations should be relatively easy with new technologies. What we don't know: long-term protection, especially in the elderly; how rapidly and easily COVID escapes via mutation; impact on transmission at an individual level; effect on transmission at a population level.

Prevention of Adult Disease By Vaccination

Example of Cervical Cancer

Several major adult infections can be prevented by vaccination. An example is HPV, which causes cervical cancer. Cervical cancer is a major disease of women, particularly young women. The highly effective HPV vaccine given before people become sexually active can provide a very large degree of protection, and screening (discussed in my last Gresham lecture) adds further protection. Over time rates of cervical cancer are likely to go down substantially.

Vaccines in Low and Middle Income Countries

The number of deaths vaccines avert is remarkable, especially in low and middle-income countries. A recent estimate of the effect of vaccination against 10 pathogens globally is that it averted 37 million deaths between 2000 and 2019. Among children under five there was an estimated 57% reduction, most notably from measles. Vaccine deployment has historically been much slower in

low and middle-income countries then high-income countries but is now very extensive particularly for childhood disease. Organisations such as GAVI have played a major part. Vaccines have contributed a major portion of the extraordinary drop of child mortality globally. In 1990 almost 12 million children are estimated to have died under the age of five, the rate is now less than half of that although still far too high. This is one of the great public health triumphs of the last three decades.

The Future

Vaccines science is still progressing, as we have seen with COVID-19. The immune system does many things other than fight infections. In particular it fights cancers. There is a good theoretical reason for thinking that we could use vaccines to help prevent or treat cancers, although so far it has proved difficult to get to work outside those cancers which are driven by infections. The concept of vaccines for cancer is reasonable; I have not covered this in this lecture, but did so in a previous Gresham lecture on infection and cancer. RNA vaccines were initially designed mainly for this potential use.

The impact of vaccines since Dr Jenner's work has been remarkable. Many of the most feared diseases are largely gone where vaccines are available. We now have substantial protection against multiple childhood infections. We have new and relatively rapid approaches responding to epidemics, including an ability to respond rapidly to new ones. There are major drops in adult diseases continuing, including cancers. And the science of vaccines is still advancing rapidly. Quite a legacy.