JENNER'S LEGACY

Creating vaccines for the future

Over the last few years, the pace of new vaccine introduction has accelerated, and the prospects are that there are going to be even more vaccines coming on stream. These new vaccines will not just prevent infectious diseases but may also prevent malignant disease and treat chronic conditions. Our national immunisation programme is well placed to benefit.

KEY POINTS

- When the NHS was founded 60 years ago, children were offered only two vaccines (smallpox and diphtheria).
- In the early post-war years, serious illness and deaths of children due to infections, such as measles, poliomyelitis, mumps and whooping cough, were common and widely feared.
- Vaccinations against 10 diseases are now routine in childhood.
- These 10 vaccines save the NHS around 150,000 quality-adjusted life years per annum at a cost to society of £6.6 billion. Over the life of the NHS, that would come to almost £400 billion at today's prices.
- Potential new vaccines against infection on the horizon include:
  - (within three years) wider spectrum pneumococcal, influenza, meningococcal B and ACWY vaccines
  - (within five years) a vaccine against *Clostridium difficile*
  - (within five to 10 years) a group B streptococcus vaccine, and new vaccines for tuberculosis, cytomegalovirus and meticillin-resistant *Staphylococcus aureus* (MRSA)
  - (over 10 years) a vaccine against respiratory syncytial virus.
- New vaccines to treat cancer, diabetes and addictions are being researched. So too are new methods of giving vaccines.
- Vaccination is one of the most significant life-saving public health issues in the history of humankind and has the potential to be exploited even further to relieve human suffering.

Smallpox was the first infectious disease to be prevented by vaccination. It came largely through the work of Edward Jenner (1749–1823), a physician in Gloucestershire, who tested local folklore that milkmaids did not get smallpox ('my face is my fortune, Sir, she said', according to the old nursery rhyme). Milkmaids were believed not to catch smallpox and suffer death or the pockmarked skin associated with it. This was because they had been infected with the milder cowpox infection during their milking of cows.

Famously, Jenner took smears of a cowpox pustule from the hand of a local milkmaid, Sarah Nelmes, and inoculated a boy, James Phipps, who remained immune to smallpox.

In 18th-century England, smallpox accounted for one in 10 of all deaths. Jenner did not actually discover the cowpox link but he showed that cowpox could be transferred from person to person to create a vaccine that was easily available. He also evaluated the technique and published his work in a scientific report.

Box 1: The Member of Parliament for Finsbury's views on the statue of Edward Jenner in Trafalgar Square, 1858

"Cow-pox was a very good thing in its proper place, but it had no business amongst the naval and military heroes of the country. Everybody who heard of this statue spoke of it with ridicule and disgust; and if the Government should not feel justified in stopping the work, he trusted that the House would pass a resolution calling upon them not to pollute and desecrate the ground by erecting a statue there to the promulgator of cow-pox throughout the country."

British Medical Journal, 1858

It was not without risk, because the technique of scratching the person's arm was done by vaccinators who did not understand the importance of sepsis. In 1853, the vaccination of infants against smallpox in England was made compulsory. Jenner's method of vaccination spread worldwide, saving hundreds of thousands of lives, and is widely regarded as one of the most important developments in the history of medicine. It is ironic that in 1858 his statue was removed from Trafalgar Square on the grounds that it did not merit inclusion with the great military figures on the other plinths (see Box 1).

In systematic laboratory research, Louis Pasteur (1822–95) developed and used vaccines against anthrax (in 1882) and rabies (in 1885). In dramatic circumstances, Pasteur (who was a chemist, not a doctor) vaccinated on separate occasions two children who had been savaged by rabid dogs. They survived without rabies symptoms. From these beginnings, the science of vaccination, an understanding of the immune system, and the development of a wide range of vaccines, developed.

Vaccine programmes in the NHS

When the NHS was established 60 years ago, most children were offered just smallpox and diphtheria vaccines. That was the totality of the vaccine programme in this country. Smallpox vaccination was eventually phased out as the disease became so rare (eventually eradicated) that the risks of vaccination outweighed any benefit.

Over the first half of the 20th century, vaccines against the common childhood infectious diseases were gradually developed and made available to the population. The major problem during this period was the lack of any official programme to offer the vaccines. As a result, population coverage rates were not high enough to prevent spread. So-called 'herd immunity' is necessary to interrupt the spread of diseases like poliomyelitis, measles and whooping cough. For herd immunity, it is usually necessary to achieve vaccine coverage rates of 90% or higher although this depends on the epidemiology of the disease and on the vaccine.

The advent of 'call and recall' systems based on child health records and supported by computerisation introduced from the mid-1980s enabled appointments and reminders to be sent to parents as children reached the appropriate age for particular vaccine(s).

This, together with targets for general practices and active national

management of the immunisation programme, enabled relatively high levels of coverage to be achieved and maintained. In addition, as new vaccines emerged and were adopted, they have been integrated into the existing programme rapidly and without major disruption.

In the last 20 years, five new vaccines have been introduced into the routine immunisation programme and a sixth, the human papilloma virus vaccine, to prevent cervical cancer, will be introduced later this year. This is a marked change of pace compared with the previous 200 years, in which eight routine childhood immunisations had been built up: smallpox, diphtheria, pertussis, tetanus, polio, BCG, and individual measles and rubella vaccines.

Many of the diseases which are now routinely vaccinated against were not monitored 60 years ago when the NHS was founded. So valid estimates of the cases averted and lives saved are difficult to make. However, the cost to society of not vaccinating as we do today can be estimated. A quality-adjusted life year is a statistical measure. It is the equivalent of one year with a good quality of life. If the current 10 routine vaccinations were withheld from a year's worth of children, over their lifetimes they would lose 150,000 quality-adjusted life years. If that were multiplied by the 60 years of the NHS, the 9 million quality-adjusted years of life lost would cost almost £400 billion at today's prices.

Box 2: Vaccines introduced to the routine immunisation programme in the last 20 years

- 1988: measles, mumps and rubella (MMR)
- 1992: *Haemophilus influenzae* b (Hib)
- 1999: meningitis C
- 2006: pneumococcus (which causes some types of pneumonia)
- 2006: a combined *Haemophilus influenzae* b and meningitis C vaccine (Hib-MenC)
- 2008: human papilloma virus (HPV) vaccine, to prevent cervical cancer

New vaccines

The vaccines of today are very different to those of just one generation ago. At the start of the 20th century, producing vaccines used very basic technology. Smallpox vaccine was made by growing live virus on calfskin. In 1952, Jonas Salk produced inactivated polio vaccine, but he did not get a Nobel Prize for his discovery. The 1954 Nobel Prize for Physiology or Medicine went to John Enders, Thomas Weller and Frederick Robbins for the invention of cell culture, the critical step that led the way for the production of most of the viral vaccines in use today.

The next significant step came with the first genetically engineered vaccine – hepatitis B vaccine. Another breakthrough came with conjugation, the joining together of a polysaccharide target with a carrier protein. This led to safe and effective vaccines against *Haemophilus influenzae* b, group C meningococci and seven different strains of pneumococci. Together, these modern vaccines were capable of eliminating three of the four causes of bacterial meningitis. The human papilloma virus vaccine is produced using insect viruses to make proteins that reassemble into virus-like particles which cannot replicate themselves.

Box 3: New vaccines on the horizon

Short term (within three years)
- Influenza (wider spectrum)
- Meningococcal ACWY and meningococcal B
- Further pneumococcal *(Streptococcus pneumoniae)* strains

Medium term (within five years)
- *Clostridium difficile*

Medium to long term (within five to 10 years)
- Group B streptococcus
- Tuberculosis
- Cytomegalovirus
- MRSA

Long term (over 10 years)
- Respiratory syncytial virus
- Some cancer treatment vaccines

Vaccines on the horizon

The decision whether to adopt a new vaccine can be complex. For example, vaccines are available against the virus that causes both chickenpox and shingles. However, if young children were vaccinated against chickenpox, this might increase the incidence of shingles in adults. A programme to vaccinate young children against chickenpox and older individuals to boost their immunity to shingles is currently being assessed.

Other exciting new vaccines are in development, and expected to become available in the short, medium or long term.

Influenza

Every year an estimated 12,000 people die from seasonal influenza in England and Wales. The very young, the very old and those with chronic disease are most at risk. The world is also at risk of pandemic influenza. A pandemic could be caused by a strain of influenza which normally affects other species, such as H5N1 (avian influenza), developing a greater affinity for people. The Spanish influenza pandemic of 1918/19 is estimated to have killed more people than the First World War. The last influenza pandemic was in 1968. The preparations for a new one are a top priority for the government. Until now, influenza vaccines have only been able to protect against the exact strain of the influenza virus to which they are matched. This means that a new strain of influenza can attack large numbers of people, even those who have been vaccinated against pre-existing strains. If a vaccine could be developed which protected against a wide range of known and unknown strains of influenza, then millions of lives could be saved worldwide if a pandemic happened.

After many years of little change in influenza vaccines, the threat of pandemic influenza has galvanised action. Recent technical developments in the use of 'adjuvants' – extra substances given together with the vaccine to improve its effectiveness – have allowed smaller doses of influenza vaccine to be used, increasing manufacturing capacity. These adjuvants have also been shown to enhance cross-protection against different influenza strains. Such vaccines could be available within the next few years.

Vaccines against H5N1 strains of avian influenza are ready for use before or as soon as a pandemic starts. However, we cannot be sure that they will be effective against the exact pandemic strain. There have been discussions about incorporating H5N1 vaccine into seasonal influenza vaccines to prepare the population for a potential pandemic. Other strains are also being considered. Ultimately, the goal will be to develop influenza vaccines that protect against all seasonal and potential pandemic strains.

Meningococcal ACWY and meningococcal B

Meningitis is an inflammation of the tissue that surrounds and protects the brain and spinal cord. Meningococcal bacteria are the most common cause of bacterial meningitis and also cause septicaemia. The main meningitis disease-causing types are B, C, Y and W135.

In this country, since the successful introduction of the meningitis C vaccine in November 1999, around 90% of all bacterial meningitis cases are caused by group B. Given the high levels of meningitis B, a safe and effective vaccine is needed. One avenue of research into developing a vaccine against group B strains, using conjugated vaccine, had to be cut short because the antibodies could target some parts of human cells, raising concerns that the vaccine could attack the human body. Several companies have now developed alternative vaccines and early results look promising.

One combined ACWY vaccine is already licensed and in use in the United States and Europe. Its use in this country will depend on the additional benefit against A, Y and W135 strains since we already have extremely effective control of group C disease.

Clinical trials

Before any drug, including a vaccine, can be given to patients, it must be licensed. To be given a licence, it must be shown to be safe and effective in a series of clinical trials:

Phase 1 trials: a small number of healthy people or patients are given the medicine, closely monitored to find out how it works in the body, and whether side effects increase at higher doses.
Phase 2 trials: patients are treated to establish whether the medicine is effective for the condition or disease and to identify common short-term side effects.
Phase 3 trials: large numbers of patients (hundreds to thousands) are treated to look in more detail at the range and degree of side effects, and to compare the new treatment with existing best practice.

Pneumococcal vaccines

Invasive pneumococcal disease is a serious illness caused by bacteria infecting numerous systems in the body. The vaccine, Prevenar, contains individual components against seven types of pneumococcus, and since it was introduced to this country in September 2006, there has been a marked fall in the reports of the disease caused by these seven types. However, there has been an increase in reports of types not covered by the vaccine. This may be coincidental as some of these types were already

increasing before 2006. Two companies are developing vaccines that give broader protection against pneumococcal strains, with either 10 or 13 strains targeted.

Conjugate vaccines can be particularly powerful by indirectly protecting those who have not been vaccinated. Vaccinated individuals are prevented from carrying bacteria and spreading them to others who are unprotected. A similar effect is emerging for invasive pneumococcal disease. Strains included in the current vaccine are causing less disease even in those who are too old to have been immunised.

Clostridium difficile

One of the most common and serious causes of healthcare-associated infection is *C. difficile*. These bacteria live in the gut of up to 3% of healthy adults and 66% of infants. However, they rarely cause problems in children or healthy adults, because they are kept in check by other bacteria. When certain antibiotics disturb the balance of bacteria in the gut, *C. difficile* can multiply rapidly and produce toxins which cause illness.

From 2005 to 2006, laboratory reports of *C. difficile* in England increased by 8% to 51,519 cases.

In late 2008, a new vaccine will be tested on patients having elective surgery in the United Kingdom. If the vaccine is effective, it is likely to be available in three to five years. Another *C. difficile* vaccine is at an earlier stage of development. An alternative approach (currently in phase 2 clinical trials) is to produce antibodies to destroy the toxins made by *C. difficile*.

Group B streptococcus

Group B streptococcus is the most common cause of life-threatening infections in newborn babies in this country. It can also cause serious illness and death in pregnant women, the elderly and people with weakened immune systems (such as cancer patients). Reports of bloodstream infections with group B streptococcus increased by 15% between 2005 and 2006.

The bacterium is present in the gastro-intestinal and genito-urinary tracts of up to half of healthy adults. As it is commonly present in the vagina, group B streptococcus is inevitably transmitted to some babies during labour and delivery. When this happens, the bacteria pass into the bloodstream in 3% of babies in the first week after birth. This can lead to pneumonia, septicaemia and meningitis. Overall, 80% of group B streptococci are resistant to the antibiotic tetracycline, and resistance to other antibiotics is increasing.

Developing a suitable vaccine is difficult. Several varieties of group B streptococcus exist across the world, not all of which can be targeted by the same vaccine. There is concern about the risk of birth defects when vaccinating pregnant women, and debate around whether it is better to target non-pregnant adolescents.

Two vaccines are in early clinical trials in the United States. If these prove safe and effective, a vaccine against group B streptococcus could be available within the next five to seven years.

Tuberculosis

Tuberculosis is continuing to rise and, in this country, particularly in London which accounts for 40% of all cases nationally. This is a cause of concern.

The currently available vaccine, BCG, is the most widely administered vaccine worldwide. BCG is largely ineffective at protecting against adult lung disease in endemic areas and a new, more effective tuberculosis vaccine is a major global public health priority. However, BCG does confer protection against the more serious forms of tuberculosis that affect young children, such as tuberculous meningitis, and appears to protect against complications and death in children.

A number of new tuberculosis vaccines are going into clinical trials. These will require very large-scale studies to demonstrate safety and efficacy, especially in immunodeficient people, since they will be needed most in populations where the prevalence of HIV infection is high. These new vaccines are unlikely to appear before 2013.

Cytomegalovirus

Cytomegalovirus is the most common cause of congenital infection in developed countries and also affects transplant patients, patients with AIDS, the elderly and those in intensive care. Around three in every 1,000 babies born in the United Kingdom are born with cytomegalovirus infections. These account for 15% of hearing loss due to nerve damage and 7% of cases of cerebral palsy. Cytomegalovirus infections can also cause learning difficulties and other congenital abnormalities.

The infection can be caught during pregnancy or may be a flare-up of a previous infection. Either can be transmitted to the baby. Half of pregnant women show evidence of past cytomegalovirus infection. Amongst the remainder who have not had it before, 1% will acquire the virus during pregnancy. In 40% of maternal infections the baby is born infected. About 5–10% of infected infants are symptomatic at birth. These infants have a poor prognosis, with 50–90% having major neurological damage. In contrast, an estimated 8–15% of congenitally infected infants without symptoms in the neonatal period have cytomegalovirus-related problems at follow-up.

Vaccines against the infection are being trialled in the United States, and initial results are encouraging. A candidate vaccine may be at least five years away.

Respiratory syncytial virus

Respiratory syncytial virus is the commonest cause of severe respiratory illness such as bronchiolitis and pneumonia in children under two years old. It is also the commonest cause of hospital admissions due to acute respiratory illness in young children. The number of cases peaks every year during the winter months, adding to the burden on health services from seasonal influenza.

Early clinical trials are being conducted on a vaccine designed to give active immunity against respiratory syncytial virus and parainfluenza virus type 3. A vaccine is likely to be seven to 10 years away. However, a shorter-lived immunity can be provided by giving the antibodies directly. This is known as passive immunity. Passive immunisation against respiratory syncytial virus is currently available using palivizumab. A more potent antibody has recently been developed and clinical trials are in progress.

Staphylococcus aureus

Surveillance of *S. aureus* bloodstream infections was made compulsory in April 2000. This includes meticillin-resistant *S. aureus* (MRSA). In 2007, the Health Protection Agency received 17,404 reports of *S. aureus* bloodstream infections in England, of which 6,381 were due to MRSA. Between April 2000 and March 2007, reported cases of MRSA bloodstream infections decreased by 12%.

The emergence of MRSA has made an effective vaccine to *S. aureus* an essential tool. A candidate vaccine is in development but availability is likely to be seven to 10 years away.

Vaccines for chronic diseases

As well as using new routes for vaccination, it is hoped that new diseases will be targeted by vaccination in the future.

The United Nations estimated that, in 2005, there were around 40 million people infected with HIV, with 5 million new infections occurring each year, 95% of which occurred in developing countries.

In the United Kingdom, HIV continues to be an important public health issue. It is associated with serious ill health, high costs of treatment and care, and significant mortality. Despite effective treatment and prevention measures, the number of new cases tripled each year over the past decade, meaning that the control of HIV remains a major public health challenge for the near future.

A vaccine against HIV remains the best hope for tackling the epidemic. Research has led to progress in understanding the virus and identifying aspects of the immune system that are essential in building immunity and preventing the infection.

One major obstacle in the development of a vaccine against HIV is that the body's immune system does not respond in the usual way to HIV infection; it does not eradicate the infection or produce long-lasting immunity. Additionally, there remains the issue of multiple HIV strains and subtypes around the world which may hinder the universality of a single vaccine.

Despite extensive research, there is still little progress in developing an effective HIV vaccine. Safety concerns have led to recent trials being suspended, and the vaccine research community is now having to reconsider the best ways forward in tackling this devastating disease.

Therapeutic vaccines treat an existing illness rather than preventing it. There are already two vaccines that prevent cancer – human papilloma virus vaccine and hepatitis B vaccine – and others are being investigated. Much of this work relies on vaccines that are tailored to the individual cancer and patient. Trials of tailored vaccines are currently under way for kidney, skin and prostate cancers and certain lymphomas.

Many issues still need to be resolved. If the vaccine targets are not visible to the immune system, then the cancer cells are not recognised and killed. Another important issue is that cancer cells produce many chemical signals that alter the behaviour of immune cells, changing them to cells that help the tumour to grow. Any new vaccines would need to be given along with agents capable of 'turning off' these chemical signals.

Much research is also being put into vaccines for chronic diseases such as diabetes. Type I diabetes is caused by destruction of insulin-producing cells in the pancreas by the body's own immune system. Vaccines to protect against type I diabetes may work in different ways, particularly making the body's immune system less destructive. These vaccine approaches are all in early development and suitable vaccines are at least 10 years away. Vaccines for drug addiction and smoking cessation have also been proposed.

New ways of giving vaccines

At present, most vaccines are injected beneath the skin or into muscle. New ways to give vaccines more safely and effectively are being developed.

Current research and development in vaccine delivery systems includes the use of needle-free delivery of vaccines. The use of these systems would have the potential benefit of increasing uptake and being less invasive.

One approach to needle-free vaccination involves mucosal vaccination. Mucosal vaccination can produce sterilising immunity, where infection as well as disease is prevented. Mucosal vaccination can be through the mouth (Salmonella, *E. coli*), nose (influenza vaccines), or inhaled through the lungs (nebulised measles vaccine).

Dermal vaccination, using delivery through the skin, is relatively painless and produces better immune responses than intramuscular injection. One form of dermal vaccination is by jet injectors, which use air pressure rather than needles. They were originally used in the 1960s but cross-contamination was a problem. New developments address this, for example using single-dose disposable cartridges. A needle-free jet injection influenza vaccine is being tested in six to 24-month-old children in United States-sponsored studies. Other needle-free techniques such as dermal patches have produced promising results using toxins from cholera.

New DNA vaccines use an air-pressured or spring-released 'gene gun' to deliver a biodegradable implant containing the target, for example gold particles covered with DNA. Producing a consistent formulation and accurate dose is difficult.

Risk, public acceptance and communication

The success of the vaccination programme in this country has been remarkable, with many children alive today who would have died in the past from the infectious disease epidemics which were so common. The misery and disability of these diseases is also largely

a thing of the past. As the folk memory of the consequences of diseases like polio now rests with older grandparents, so the fear factor has largely disappeared from the minds of young parents.

Parents now worry much less about the risks of the diseases (because they have never seen a case) and much more about the possible complications of the vaccine. This was the climate into which the totally unfounded scientific claims about autism, bowel disease and measles–mumps–rubella (MMR) vaccine descended. Most medical authorities considered the claim at the outset to be completely unsound and misleading to parents. But it ran and ran in media coverage. Needless anxiety and distress were caused to millions of families and the repercussions were felt in the falling MMR uptake rate. MMR has been a highly effective vaccine used for over three decades and it has an excellent safety profile.

Ten of the 13 authors of the original scientific paper that unfairly discredited MMR formally retracted some of the paper's conclusions, saying: "We wish to make it clear that in this paper no causal link was established between (the) vaccine and autism, as the data were insufficient. However, the possibility of such a link was raised. Consequent events have had major implications for public health. In view of this, we consider now is the appropriate time that we should together formally retract the interpretation placed on these findings in the paper."

The MMR story has some important lessons for the future.

Firstly, the public must be made constantly aware of the dangers of the diseases that vaccines protect against. It is not a risk-free decision to refuse your child a vaccine.

Secondly, health professionals who advise parents on vaccines and give them should have the most up-to-date information on any claims of risks so that they are well informed to answer questions that parents may ask.

Thirdly, the Government must continue to be open about the information it has and offer it freely for independent scientific scrutiny.

Finally, health and medical authorities should not allow themselves to be intimidated or vilified by those pressure groups ideologically opposed to vaccines. They should speak up objectively and honestly in defence of vaccines where the record needs to be put straight.

Conclusion

Vaccine availability and the epidemiology of vaccine-preventable diseases will continue to drive the immunisation programme in the future. It is possible that, with climate change, the United Kingdom could see a return of diseases usually associated with travel abroad.

It will also be vital to ensure that high coverage is maintained for all routinely provided vaccines. Whilst coverage remains high for most vaccines in most parts of the country, it is unacceptably low for all vaccines in London. Efforts are in place to identify and overcome barriers to immunisation. Experience over the last decade has shown how vulnerable the provision of immunisation can be to unfounded safety concerns. Although MMR coverage is rising and parental confidence in the safety of the MMR vaccine is returning, it is realistic to assume that there could be other safety scares in the future.

One of the signs of a responsive and capable immunisation programme is its ability to accept and incorporate change with minimal disruption. The immunisation programme in this country has a proud history in this respect.

Vaccination remains one of the most important developments in the history of humankind. Over the last two centuries, it has already saved hundreds of millions of lives worldwide.

In this country, so many greatly feared diseases of the past are now largely prevented by immunisation that there is a risk of complacency. It is essential that parents and health professionals work together to achieve the high levels of vaccine coverage necessary to prevent potentially life-threatening childhood and adult diseases. Technological innovation in vaccine science coupled with careful assessment of risks and benefits is the cornerstone of vaccine policy in this country.

The prospects of new vaccines coming over the horizon to save more lives, prevent greater rates of illness and disability, and relieve suffering on a much larger scale show that Edward Jenner's work is still inspiring the conquest of disease more than two centuries after his death.

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RECOMMENDATIONS

- As new vaccines get close to being available for implementation, there should be a streamlined process for bringing their benefits to the population.
- There should be a major campaign to reverse the poor vaccine uptake levels in London and other areas of poor coverage.