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Immunisation

We now have the curious paradox that while we have never had a better opportunity to protect our children and grandchildren against a wide range of diseases, with products of remarkable quality, some members of the public regard the benefits of immunisation as a matter of debate.

In combating the views of the anti-immunisation groups, both education and the attitudes and beliefs of health-care workers are critical.

The triumph of immunisation

Ian Gust

My father, who was born in Poland in 1898, only received one vaccine in his childhood, which was designed to protect him against smallpox. In Radom, as elsewhere, infectious diseases were regarded as an inescapable part of growing up, and there were regular outbreaks of diphtheria, pertussis, measles, mumps, rubella and chickenpox, causing fear, inconvenience and significant mortality. At that time, around 30% of all deaths occurred in children under the age of 5 years, with tuberculosis, pneumonia and diarrhoeal disease the biggest killers.

The advances in vaccine development during my lifetime have been extraordinary, so that although smallpox vaccine is no longer used, my grandchildren are being immunised with 11 vaccines that protect them from 15 diseases caused by 37 different strains of bacteria or viruses, a truly astonishing accomplishment. In the last 65 years, widespread use of vaccines has contributed to an almost 20-fold reduction in mortality in children under 5 and to an almost 30-year gain in life expectancy.

Those advances have been accompanied by fundamental changes in the way that vaccines are manufactured and regulated, and in recent years, a concerted effort to ensure that the benefits that children in the developed world enjoy are more widely shared.

It's an intriguing story.

History

Pre-World War II

While vaccination has a long history, its application to large populations is relatively recent. The earliest verifiable attempt to protect against small pox (variola) originated in India and China in the 16th century and was known as variolation. It involved inoculating susceptible individuals with the fluid from pustules collected from mild cases. Variolation was introduced to England in 1721 by Lady Mary Montagu, who had observed the practice while serving as the wife of British ambassador in Constantinople. Because of inconsistences in the inoculum and variation in individual responses, the results of variolation were quite variable; although most recipients were protected, a small proportion developed smallpox and died.

Immunisation was given a firm scientific basis when the English physician Edward Jenner noted that milkmaids who developed cowpox (vaccinia) from handling the udders of infected cows seemed to be protected against smallpox. Jenner was able to pass cowpox from person to person and to demonstrate that vaccinated individuals were resistant to challenge with smallpox. Jenner began to offer vaccination from a barn on his property, and in a famous paper published in 1798 predicted that it would eventually result in the eradication of the disease, a prediction which took more than 150 years to achieve.

After Jenner, the field of vaccinology lay fallow for almost a century until Louis Pasteur established the germ theory of disease.

During the course of his studies on pathogenic microorganisms, Pasteur developed a crude mammalian tissue-based vaccine against rabies and a crude inactivated vaccine against anthrax.

While a handful of vaccines (rabies, smallpox, typhoid, cholera) existed at the turn beginning of the 20th century the idea of mass immunisation was still contentious.

In 1899, Almoth Wright suggested that all British troops heading to the Boer War by sea be immunised against typhoid fever. The proposal met stern opposition. Wright was vilified and much of the vaccine thrown overboard. Tragically, there were 58,000 cases of typhoid among the troops and 9,000 deaths.

In the 1930s and 40s formalin-inactivated preparations of diphtheria and tetanus toxin were developed and found to provide protection against these diseases.

When these vaccines were introduced into public health programs for children in the industrialised world, they saved many lives.

Subsequently it was shown that some viruses could be adapted to growth in embryonated hen's eggs, which made possible the development of vaccines against influenza, yellow fever and Japanese B encephalitis.

From the time of Pasteur until World War II, most research on new vaccines was conducted in universities and government- funded research institutes, or by the military. Most vaccine production was carried out in unregulated or lightly regulated government-owned facilities like the Lister Institute in the United Kingdom, the Pasteur Institute in Paris or the Commonwealth Serum Laboratories in Melbourne, with the government finding itself in the unique position of producer, regulator and purchaser of the final product.

Post-World War II

The golden era

World War II was followed by a golden era of vaccine development and a radical transformation of the industry. The catalyst

was the discovery of penicillin which, when added to streptomycin in culture media, made it possible to maintain mammalian cells in the laboratory for weeks at a time, allowing the propagation of many common viruses.

The event with the most dramatic impact was the successful cultivation of polio virus by Enders, Robbin and Weller in 1948, for which they were subsequently awarded the Nobel Prize.

At that time, polio was a major problem in many industrialised countries, with regular epidemics leaving large numbers of people paralysed, some of whom required artificial ventilation for the rest of their lives.

Enders and his team found that all three strains of polio virus could also be grown in primary monkey kidney cells, which led to the development of a formalin-inactivated vaccine by Jonas Salk (1955) and Albert Sabin's live attenuated vaccine (1962).

The second factor in the post-war explosion in vaccine development, in the United States, was the impact of a visionary engineer and policy maker, Vannevar Bush.

After a distinguished career at the Massachusetts Institute of Technology and the Carnegie Institute, Bush was recruited by President Roosevelt to head the newly formed Office of Scientific Research and Development, whose role was to harness US science to support the war effort.

After the war concluded, Bush produced a seminal report for President Truman entitled 'Science the Endless Frontier', in which he argued for innovation as the engine for economic growth and for consistent government support for basic research.

After delivering his report, Bush joined the board of the pharmaceutical company Merck Sharpe and Dohme, where he advanced the view that viruses were likely to be important causes of disease and therefore worthy of study. He persuaded

the board to establish a virus research institute (the Merck Institute for Therapeutic Research) and to hire a brilliant young scientist, Maurice Hillemann, to head it.

Hilleman was fortunate that Bush had persuaded Merck management to adopt a novel management structure so that in addition to being responsible for basic research, he was given authority over every aspect of product development, including scale-up, manufacturing, clinical investigation and government relations. He used this power and Merck's formidable resources to great effect, developing some 40 viral and bacterial vaccines, many of which are still widely used today.

Vaccine safety

During the 1950s and 60s, vaccine production did not always go smoothly; occasional batches of vaccine failed and significant variations were sometimes found in the reactogenicity and potency of batches, sourced from the same manufacturer.

As vaccines became more widely used, episodes of illness clearly linked to either a failure in the storage of the vaccine, the way in which it was administered or the way it had been manufactured, were noted. In the late 1960s, Sir Graeme Wilson, a former Head of the British Public Health Laboratory Service, published a book entitled *Hazards of Immunization* in which hundreds of such episodes, were recorded. By far the most dramatic was the Cutter incident.

Cutter Laboratories was a small family-owned pharmaceutical company in Berkley California that produced a range of vaccines and blood products. In 1955, it was one of several companies licensed by the US Government to produce the inactivated Salk polio vaccine. One batch of vaccine, which was later found to have been inadequately inactivated, was given to 120,000 children, resulting in a mild illness in around one in three

recipients, 56 cases of paralysis and 5 deaths. An additional 113 cases of paralytic polio and 5 deaths occurred in family contacts.

A government enquiry established that the Independent Regulatory Authority had failed to provide adequate oversight of the production process and had uncritically accepted certain data from the manufacturer. While the immediate consequence was that a number of the officials involved were dismissed or resigned, the longer term consequences were more profound.

As governments strengthened the powers and resources of their regulatory agencies, many commercial vaccine manufacturers looked at their modest profitability and potential liabilities and chose to exit the field. In the industrialised world, most government-funded facilities were closed or privatised, and production moved firmly into the hands of a small number of companies in the private sector.

Regulatory agencies soon found that the regulation of products that are defined by their biological activity rather than their chemical structure was far more complex than the regulation of drugs and had to be designed into the manufacturing process. The obsessive attention to detail required in both the engineering of modern production facilities, documentation of the process and the rigorous testing to validate all the systems had an impact on the time taken to develop new vaccines, the capital involved and ultimately, as shareholders required a return on their investment, the cost of the final product.

In addition to the increased complexity of vaccine production, the number of subjects needed to establish the safety and efficacy of new vaccine increased dramatically.

Jenner's demonstration of the efficacy of vaccination and Pasteur's demonstration of the value of rabies vaccine were each conducted on a single subject. In the 1960s, Enders and Katz's prelicensing studies of the safety and efficacy of the first measles vaccine involved about 400 children.

By the time the first vaccine against rotavirus diarrhoea was licensed in 1998, community expectations had increased, and the vaccine was tested in around 7,000 children. However, when a rare, potentially life-threatening complication, intussusception, was recognised after the vaccine had been administered to more than 100,000 children, regulatory agencies raised the bar even higher. The number of subjects that need to be immunised before a new vaccine is licensed today is between 50 and 70 thousand, a logistical challenge that can take two or more years and cost more than a hundred million dollars!

Today's new vaccines are generally produced in purpose-built plants that take several years to design, construct, equip and validate. The facility which Merck built to produce its HPV vaccine cost several hundred million US$, while the facility that Sanofi has built to manufacture quadrivalent dengue vaccine cost around US$1 billion.

Collectively, these changes have had a significant impact on the time and investment needed to develop and license a new vaccine: the inactivated polio vaccine was licensed seven years after the virus was isolated in cell culture and the first live attenuated measles vaccines, nine years after isolation of the virus. By contrast, both hepatitis A virus and human rotavirus were identified in 1973, and while their development pathways were not particularly challenging, the corresponding vaccines were not licensed until 1993 and 1998 respectively — delays of 20 and 25 years.

The high cost associated with developing a new vaccine limits this activity to a small number of large, well-resourced multinational companies (most modern vaccines have been developed by Merck, Glaxo Smith Kline, Novartis, Wyeth-Lederle and Sanofi) and has an impact on the price.

Whereas some older vaccines such as the trivalent diphtheria, tetanus, pertussis vaccine (DTP) or inactivated polio vaccine (IPV) can be purchased in bulk from generic manufacturers for cents or a few tens of cents per dose, most new vaccines are priced at several tens of dollars per dose. Because development of a new vaccine can cost up to US$2billion, pharmaceutical companies are unwilling to invest their shareholders funds in products that will not likely provide an acceptable return: without government incentives, they have no incentive to develop niche vaccines, irrespective of their public health importance.

Recent developments

Until the 1970s, most human vaccines were composed of inactivated or attenuated bacteria or viruses. The first vaccine to break the mould was the plasma-derived hepatitis B subunit vaccine; pioneered by John Gerin and Bob Purcell at National Institute of Health (NIH) and taken into commercial production by Maurice Hilleman at Merck.

The vaccine took advantage of the fact that the blood of healthy chronic carriers of the hepatitis B virus, in additional to mature virions, contains huge quantities of 22 nm virus-like particles that are made up of the surface antigen of the virus (HBsAg), but do not contain nucleic acid and are non-infectious.

Gerin and Purcell developed an elegant method of purifying these particles by ultra-centrifugation, and Hilleman added a three-step inactivation procedure (pepsin, low PH and 8M urea) known to inactivate all life forms.

After the efficacy of the resultant vaccine had been demonstrated in colony-raised chimpanzees and homosexual men at increased risk of infection, the vaccine was licensed in 1981. Although it was safe and effective, the need to obtain the virus by apheresis of healthy chronic carriers limited the quantity that

could be produced. Here, the vaccine field was the beneficiary of an advance stimulated for another reason.

The signing of the National Cancer Act in 1971 is generally regarded as the beginning of the Nixon Administrations war on cancer. Large sums of money were invested to obtain a better understanding of the pathogenesis of common cancers, and from some of these investments arose the modern science of molecular biology. At the same time the United States was developing a vibrant venture capital industry in which entrepreneurial investors nurtured interesting new technologies that were regarded as too risky for investment by industry.

It was soon found that the gene coding for production of the HB surface antigen could be inserted into yeast cells (*Saccromyces cervisae*) and that these altered cells could produce large quantities of particulate HBSAg that was immunologically indistinguishable from the plasma-derived material. GSK and Merck licensed this technology and used it to develop second-generation HB vaccines, while developing world manufacturers who lacked access to the intellectual property were forced to continue to produce plasma-derived vaccine.

When licensed in Europe in 1993, GSK's yeast-derived HB vaccine had a transforming effect on the industry. Prior to that time, most manufacturers had regarded vaccine production as a public service obligation, a high volume, low margin, predominantly paediatric business with governments the major clients.

The recombinant HB vaccine was not only aimed at adults, but sold for about US$120 for a three-dose course; it quickly established a private market, largely among health-care providers and other adults whose occupations put them at increased risk of infection. It became the first vaccine to register sales of greater than US$100 million pa and gave GSK and other research-based manufacturers confidence that private markets

for vaccines existed and that investing in novel vaccines for children and adults could provide adequate returns to their shareholders.

Since then a remarkable range of novel vaccines based on this and other technologies have been developed and licensed, resulting in an exponential growth in sales. In the first eight years of this century, vaccine sales grew threefold from US$6B to US $17B and are predicted to reach US$50B by 2022.

Vaccines produced by the five research-based manufacturers account for more than 80% of the value, but not the volume of sales, which are dominated by generic manufacturers located in the developing world.

Wider use of vaccines

The expanded program for immunisation

The final transforming event for the vaccine industry was the decision by the World Health Organization (WHO) to try and provide the benefits of immunisation to all children in the developing world through its Expanded Program for Immunization (EPI), inspired by the successful campaign to eradicate smallpox and initiated in 1974 at a time when fewer than 5% of children in the world were being immunised. The EPI used donor funds to procure low-cost vaccines against six diseases (tuberculous, diphtheria, pertussis, tetanus, polio and measles) and provide them to the poorest countries. WHO and its sister agency UNICEF help to train local staff and to upgrade facilities for storage and distribution of their vaccine.

While the program was a considerable success, raising the global coverage with these vaccines to about 75% and saving millions of lives, by the late 1980s it became clear that the EPI was under great strain. Uncertainties in funding meant that UNICEF was unable to enter long-term supply agreements with

manufacturers who therefore did not know how much vaccine to produce. Delays in placing orders resulted in intermittent supplies and, on occasions, failure to supply. Worst of all, the system lacked the capacity to fund any of the new vaccines being licensed and used in the developed world.

The challenge of adding the HB vaccine to the EPI

This situation came to a head with the HB vaccine. Although universal immunisation had the potential to save more than one million lives per annum by preventing the fatal consequences of chronic infection (chronic active hepatitis, cirrhosis and primary hepatocellular carcinoma), which are common in the developing world, its incorporation into the EPI was an existential challenge to WHO, who feared it would bankrupt the program and opposed it vigorously. Clearly, the system was broken and needed both a new philosophy and a new source of funds. It also needed a catalyst.

Fortunately, a number of activities were occurring that would lead to a radical overhaul of the system.

In the early 1980s, Fred Prince, at the New York Blood Center (NYBC), showed that flash heating of plasma containing HBsAg not only inactivated adventitious agents but produced a product that was highly immunogenic, thus increasing the number of vaccine doses that could be produced from a litre of plasma. He believed that the process could be transferred to developing country manufacturers, who would be able to produce large volumes of the vaccine at low cost.

Through a Korean American scientist, Seung-il Shin, who had excellent connections to the Korean industry, Prince was introduced to the Chiel Sugar company — a subsidiary of Samsung — which was branching into biotechnology and searching for a lead product that they were prepared to sell at or below cost to establish a market presence.

In the early 1980s, the NYBC licensed Prince's technology to Chiel Sugar, and Prince and Jim Maynard, then Director of the Hepatitis Branch at the Centers for Disease Control (CDC) were enlisted to advise the company on its clinical trial strategy. Cheil were planning to supply the vaccine to the local market at US$5–8/dose, but were persuaded by Maynard and Prince to adopt tiered pricing and to aim at a $1 pediatric dose for sales to the public sector, a dramatic new benchmark.

The second stream of activity arose from WHO's Regional Office for the Western Pacific (WPRO), encouraged by the Regional Director, Hiroshi Nakajima.

In 1981, the WPRO Advisory Committee on Medical Research received a report on hepatitis B, which noted the high prevalence of carriers in the region, the huge impact of primary hepatocellular carcinoma and the potential to reduce the impact of the disease by immunisation.

The Regional Advisor on Communicable Diseases, Takusei Umenai, subsequently convened a meeting of experts to develop a program to define the extent of the problem and devise strategies for its control.

Three new Collaborating Centres for Viral Hepatitis were established to underpin the effort, one at the Tokyo Metropolitan Institute for Medical Science led by Kusuya Nishioka, a second at the Nagasaki Chuo Hospital led by Michito Yano and the third in my laboratory at Fairfield Hospital.

Our efforts were greatly encouraged by Dr Nakajima, who was keen to expand the WHO's influence in China and was looking for a program that would bolster his credentials to become the next Director General.

In 1983, the WPRO Task Force on Hepatitis B proposed that China produce plasma-derived vaccine and arranged to assist in transferring a process developed by the Kitisato Institute in

Japan to four producers located in Beijing, Shanghai, Lanzhou and Wuhan.

The project, which was supported by the Arab Gulf Fund, led to a Chinese vaccine being licensed in 1987.

The role of the International Task Force for Hepatitis B Immunisation

The third stream involved the activities of a small Seattle-based non-government organisation, the Program for Appropriate Technology and Health (PATH).

In 1984, a consultant to PATH's office in Indonesia became aware that President Suharto's Minister for Foreign Affairs and golf partner, Adam Malik, was dying of liver cancer and had asked the Minister of Health whether there was anything that could be done about the disease.

PATH conducted a detailed study, which led them to Maynard and Prince.

In April 1986, while I was on study leave at the NIH, Jim gave a lecture at the NYBC in which he argued for a global approach to control of hepatitis B. This was followed by a long dinner at a restaurant on Second Avenue and the decision to form a group, the International Task Force for Hepatitis B Immunization (ITFHBI), to catalyse the process, with PATH providing the organisational infrastructure. It was a brave, even foolhardy venture, which in a short time brought us into conflict with both public health authorities and with industry.

One of the ITFHBI's first actions was to contact Ken Warren, Director of Health Services at the Rockefeller Foundation, who not only provided $50,000 of seed money but encouraged us to approach John Breur, a Warren protégé who had just been appointed CEO of the McDonnell Foundation and was looking for a lead project that might reduce the burden of cancer.

A proposal was drafted — with considerable input from Mark Kane, a young epidemiologist then based at CDC — asking for $2.5m over three years to study the feasibility of delivering the HB vaccine under field conditions and to develop data to support the incorporation of the vaccine into the EPI.

It envisaged demonstration projects in four countries with immunisation of up to a million children.

If successful, we planned to begin the program in Indonesia in November 1986. As the McDonnell Board met in St Louis to consider the proposal, Jim and I flew to the tiny island of Lombok, which the Indonesian government had identified as an appropriate and challenging test site, where we received a phone call that the grant had been successful — which we toasted with coconut juice.

Soon after the Task Force met in Kenya to discuss its modus operandi. Its initial members were Jim Maynard, Xu Zhi Yi, Benji Ayoola, Allain Goudeau, Fred Prince, Violet How, Palmer Beasley and myself.

Rich Mahoney from PATH became secretary and Jim Maynard resigned from CDC and moved to PATH's office in Seattle to assume overall responsibility for the program.

The first important issue for the Task Force was to enter into discussions with industry regarding procurement of the vaccine to be used in the Indonesian study, which exposed it to the complex relationships between government, the bureaucracy and the private sector.

It was decided to seek tenders and to accept the lowest bid, provided that the successful tenderer signed a written undertaking to provide the vaccine to the public sector at the tender price.

It was a brave decision as we could have had no takers and been forced to purchase the vaccine on the open market. In the end, four companies entered the process, one each from the

United States and Europe and two from Korea, including the Korean Green Gross, who offered the vaccine in multidose viral for 95 cents per paediatric dose.

The award of the tender was a seminal moment for the field, as it meant that WHO and UNICEF could no longer use price as a reason for not recommending use of the vaccine.

The next challenge was to show that it was possible to integrate the HB vaccine into the EPI without damaging the rest of the program. While the ITFHBI ultimately conducted demonstration projects in China, Indonesia, Thailand, Kenya and Cameroon, the project in Lombok provided the steepest learning curve and the most critical data.

At the start of the study, Lombok had a population of 2.7 million (of whom 40% could not read or write Bahasa Indonesian). Most were ethnic Sasaks with a per capita income of around US$80 pa. While the birth rate was 3% pa, it was accompanied by an official infant mortality rate of 120/1,000 live births, the highest in Indonesia, with fewer than half of all births reported to local authorities. The EPI program was just being established in Lombok with fewer than 50% children receiving three doses of oral poliovaccine and only 19% receiving measles vaccine.

The vast majority of births occurred at home, mostly delivered by traditional birth attendants. HB was hyperendemic, with around 10% of the population, chronic carriers.

With the funds from the McDonnell Foundation and a matching grant from the Australian Aid Agency (AIDAB), the project was initially conducted in 18 villages and expanded to 118 over the next two years. Because of the high rate of mother-to-baby transmission and the fact that the first contact with the health system did not occur until six weeks of age, we decided to attempt to deliver the first dose of vaccine within a week of

birth. This required establishing a system of birth notifications, arranging home visits and modifying the EPI schedule.

A major education campaign was developed to alert people to the dangers of HB and the benefits of immunisation. Because of the level of illiteracy this was mainly conducted through meetings, reinforced by messages on the radio or from the mosques, plus posters and cartoons.

We also explained the benefits of immunisation to the district governor, local health officials, village leaders and members of the Indonesian Women's Movement (the PKK) and local vaccinators.

Over the course of the project, more than 19,000 people were trained, and much to the surprise of local administrators, mothers readily accepted home visits from the vaccinators, which also provided the opportunity to address other health issues.

Despite numerous obstacles and implementation issues, the study demonstrated that the HB vaccine could be integrated into the EPI and that the first dose could be administered within a week of delivery.

Not only did more than 90% of the children receive three doses of vaccine at birth, 6 and 14 weeks, but the uptake of other EPI vaccines actually exceeded the levels obtained in villages in which HB vaccine was not being offered. Most importantly, the HB carrier rate fell from around 10% to less the 2%. The Indonesian government was so impressed that from 1991 it began to expand the program nationwide, albeit without the birth dose, which it was thought would be difficult to deliver.

The ITFHBI was able to replicate the basic findings of the Lombok study in China, Thailand, Kenyaand Cameroon, countries with different carrier rates and different infrastructure, and was energetic in publicising these results and their implications.

Jim Maynard was a particularly effective advocate; a tall man with an imposing presence and a booming voice, he was like a force of nature, with the added attribute of, like Lord Nelson, being able to avoid arguments that he did not want to acknowledge by metaphorically raising a telescope to his blind eye.

As the Task Force began to publicise its results, it ran into vigorous criticism from some pharmaceutical companies who were concerned that its activities would have an adverse effect on the price of the vaccine. Eventually, the power of the data and a groundswell of opinion forced WHO to reexamine its opposition to the vaccine, and the vaccine companies to adopt a tiered pricing structure, with sales in the developed world subsidising lower prices for poorer countries. A joint WHO-Taskforce meeting at Yaounde, Cameroon in October 1991 called for the HB vaccine to be added to the EPI program, a call endorsed by EPI's Global Advisory Group later that year, by the World Health Assembly in 1992 and finally implemented by WHO two years later.

The most important lesson from the battle to introduce the hepatitis B vaccine into the EPI is that it is often necessary to challenge the orthodoxy of the day. Prior to that time, WHO and UNICEF were satisfied in doing the best they could with the resources that were available, without asking 'How do we mobilise the resources we need to do the job that needs to be done?'

It also demonstrated the power of advocacy, especially when the advocacy is backed with compelling data.

Recent developments

Despite the availability of low-cost HB vaccine, it was not possible to deliver the vaccine more widely by trying to divide the existing pool of funds into smaller and smaller pieces.

Clearly what was needed was a bigger pie.

A World Bank (WB) study commissioned by Amy Batson, drew attention to the cost of developing a new vaccine, the risks manufacturers undertake, and the link between a company's profitability and its ability to invest in the development of new products, issues that public health authorities had previously been loathe to confront. The report also drew attention to the then dysfunctional relationship between supplier and purchasers, each of which had a different set of assumptions, that make accurate planning impossible.

While the report provided the WB, UNICEF and WHO with greater insight into the realities and economics of vaccine development, it was only with the creation of the Global Alliance for Vaccines and Immunization (GAVI) and the Global Fund that it has been possible to establish productive relationships between manufacturers, funders and end users, purchase vaccine for the poorest countries, and to roll new vaccines out globally.

Established in 2000, GAVI is a public–private partnership bringing together developing country and donor governments, WHO, UNICEF, the WB, the vaccine industry, research agents, the Gates Foundation and private philanthropists.

Under the inspired leadership of Seth Berkley, it has been remarkably effective in establishing novel funding strategies, purchasing vaccines and saving lives, so that despite a significant increase in the population, infant mortality has declined.

During its two most recent funding cycles (2011–2015 and 2016–2020), GAVI, with the generous support of Warren Buffet, the Gates Foundation and many national governments, has raised almost US$15b which has been, or will be, used to provide vaccines to more than 540 million children, with the saving of almost 10 million lives and an enormous amount of illness and economic loss — a remarkable achievement.

Since the HB vaccine was added to the EPI in 1994, the number of countries providing it to their children has increased from 17 to 186, with about 80% of all newborn children now receiving the vaccine.

The battle to add the HB vaccine to EPI transformed the thinking of policy makers and provided a pathway for the subsequent introduction of vaccines against Haemophilus influenza type b, rubella and rotavirus, and more recently, the papillomavirus vaccine as the number of vaccines recommended by WHO has grown from 6 to 11.

The dramatic expansion of the EPI has also created huge new markets for generic manufacturers in the rapidly industrialising world. Today more than half the vaccines used by EPI programs are made in China, India and Korea.

The immunisation paradox

My parents needed little encouragement to have their children immunised as both had lost family members from infectious diseases. Later they nursed my older sister through a severe attack of diphtheria, and both of us through the big four — measles, german measles, mumps and chicken pox.

My father's friend, Alan Marshall, who was often in the house and who wrote the inspiring book *I Can Jump Puddle*s about the loss of use of his legs, was a constant reminder of the threat posed by paralytic poliomyelitis.

Our children's generation has had none of these experiences. Widespread use of vaccines has reduced the incidence of many previously common childhood diseases to such an extent that modern parents are largely unaware of their threat.

We now have the curious paradox that while we have never had a better opportunity to protect our children and grandchildren against a wide range of diseases, with products of

remarkable quality, some members of the public regard the benefits of immunisation as a matter of debate.

Much of the information provided by those opposed to immunisation is based on misconceptions, anecdotal data and misrepresentation. It strikes a chord among people who do not have the time or the expertise to review the data, because it plays on fears and prejudices.

There is a natural tendency to ascribe a causative relationship to events that are temporally related and seek an answer to serious illnesses whose aetiology remains unknown. Little surprise that recent scares sought to implicate immunisation as the cause of sudden infant death syndrome, autism and multiple sclerosis.

When you add to that distrust of the medical profession and the motives of the pharmaceutical industry, you have a dangerous mix easily inflamed by media with a voracious appetitive for controversy.

The medical profession is not without blame

In the 1970s, Professor Gordon Stewart, an articulate Scottish epidemiologist, persuaded a generation of British mothers that whooping cough vaccine was associated with brain damage, causing immunisation rates to fall from 81% to 31%, which was followed by two major epidemics and a number of deaths.

It took several public enquiries to exonerate the vaccine and more than a decade before the immunisation rate recovered.

In the United States, with its focus on celebrities and glamour, the leading anti-immunisation advocate is Jenny McCarthy, an ex-Playboy bunny and mother of an autistic child, which she attributes to immunisation. McCarthy is attractive and articulate, and her bizarre conspiracy theories have the support of one of the most influential people in the United

States — Oprah Winfrey. While both Stewart and McCarthy enjoy public attention, I have no doubt that their views are genuine.

By contrast, Andrew Wakefield, who first drew attention to a possible link between the measles vaccine and autism, has been found not only to have falsified the data but to have benefited financially from a relationship with lawyers representing damaged children, and to have potentially benefitted from his interest in an alternative vaccine.

Although now debarred in the United Kingdom he still has many supporters in the United States who refuse to acknowledge the evidence and believe that he is the victim of in giant conspiracy.

What can we do?

First, we must remember that immunisation rates remain high in Australia and that concerns about immunisation are not new.

In combating the views of the anti-immunisation groups, both education and the attitudes and beliefs of health-care workers are critical.

Cuba, which has one of the highest immunisation rates in the world, begins education on the value of vaccines in primary school and repeats the message frequently to students and parents throughout life.

In every country, the attitudes and enthusiasm of doctors and nurses to immunisation is critically important. Although this can be achieved by education alone, incentives to achieve certain targets have proved helpful. Finally, public health authorities have learnt that they need to market the benefits of immunisation in the same way a company might market a new labour-saving device using simple clear messages and the strategic marketing skills of the modern advertising industry.

While government-funded campaigns promoting the benefits of immunisation have sometimes been uninspiring, the recent Australia campaign for measles vaccine and the UK campaign for human papillomavirus vaccine have been spectacular examples of what can be achieved.

There are no easy solutions; while technology may eventually enable us to administer a variety of vaccines in a single encounter, retaining public confidence in the benefits of immunisation and maintaining high coverage rates remains a continuing challenge.