Leaders

Immunisation policies – successes, failures and the future

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Introduction

The development of vaccines to prevent infectious diseases is one of the most significant achievements of medical science. Few other interventions, prophylactic or therapeutic, can boast its success either in terms of prevention of morbidity or cost-effectiveness of the measure. Over 80% of the world's children now receive at least three primary immunisations during the first year of life, resulting in the prevention of around three million childhood deaths each year. In North America and Western Europe, deaths from the former childhood killers—measles, pertussis, polio, diphtheria, and tetanus—are now virtually unknown.

Much of this success has been achieved with vaccines produced by relatively primitive technology and without a proper understanding of the immunological mechanisms underlying protection. The empirical approach of developing live attenuated vaccine strains of naturally virulent viruses by serial passage in non-human tissue or host was surprisingly successful, as witnessed by the highly effective oral poliomyelitis (Sabin) vaccine. The Sabin strain, selected for its lack of neurovirulence in monkeys (a property which was subsequently confirmed by its administration to Sabin's susceptible wife, two daughters and their three playmates¹) proved to be an almost a perfect vaccine. It was cheap, effective by the oral route even in very young infants, immunised contacts via faecal/oral spread, and had an extremely low rate of reversion to virulence—about one per million doses distributed. Poor thermostability was its only major failing. Many years later, when the technique of nucleotide sequencing became available, the relatively few point mutations in the poliovirus genome responsible for attenuation were identified,² allowing an understanding of the molecular basis of neurovirulence and illustrating the sophisticated genetic engineering that could be achieved by systematic work in an animal model.

For bacterial vaccines, the simple process of formaldehyde inactivation of the exotoxins of *Corynebacterium diphtheriae* and *Clostridium tetani* proved equally successful, with the resulting toxoids retaining their protective epitopes but losing their toxic activity. The subsequent successful combination of diphthe-

ria and tetanus toxoids with whole-cell pertussis vaccine, and the discovery that aluminium salts acted as an adjuvant, led to the first combined vaccine (DTP) which has been used worldwide to considerable effect for over 50 years. More recently, the development of glycoconjugation technology, which allows polysaccharide to be converted from a T cell independent to a T cell dependent immunogen by covalent coupling to a protein carrier, has extended the range of vaccine preventable bacterial infections in children. With the right choice of carrier protein, saccharides such as the polyribosyl-ribitol phosphate of *Haemophilus influenzae* type b become immunogenic in children under two years of age, eliciting protective IgG antibodies in serum and inducing immunological memory. In countries where *H influenzae* type b conjugate vaccines have been introduced, invasive *H influenzae* type b disease in infants and young children has virtually disappeared.^{3 4} Similar technology has now been applied to polysaccharides from *Neisseria meningitidis* group C and *Streptococcus pneumoniae* and conjugate vaccines containing these antigens are already in clinical trials in children in a number of countries.

Apart from such technological achievements, understanding of the epidemiological impact of vaccination programmes has grown, with equal weight now being placed on the implementation strategy and the quality of the vaccine. The global initiative to eradicate smallpox is a good example of what can be achieved with the right strategy. In 1967, when the World Health Organisation (WHO) initiated the eradication programme, there were about 20 million cases of smallpox and around 1.5 to 2 million deaths worldwide. Within 10 years the last wild case had been recorded in Somalia. The lessons learned during the eradication of smallpox are now being applied to poliomyelitis for which there is a WHO target of global eradication by the year 2000. The importance of maintaining high vaccine coverage, supplemented by mass vaccination campaigns to interrupt disease transmission in endemic areas, has been shown in the Americas where the last confirmed case of paralytic poliomyelitis occurred in Peru in August 1991.⁵ Institution of active surveillance systems to identify and investigate all cases of

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acute flaccid paralysis has been an essential component of the programme as it provides the proof of interruption of transmission required for certification of poliomyelitis eradication.

Efforts are also being made to eliminate measles from the Americas by the campaign approach. A number of Latin American and Caribbean countries have conducted mass campaigns during the past few years and, in some cases, succeeded in interrupting transmission,⁶ at least in the short term. However, the elimination of measles is proving more difficult than initially anticipated due to the highly infectious nature of the virus and its ability to maintain transmission in susceptible subgroups despite high levels of herd immunity in the population as a whole. The unexpected resurgence of measles in the USA in 1989–90, where coverage rates in excess of 90% had been sustained for a number of years, caused 46 000 reported cases, 9000 hospital admissions and 130 deaths, and was largely the result of poor immunisation coverage in pre-school children.⁷ The laws requiring documentation of vaccination for entry to school ensured high vaccine uptake but not until five years of age, allowing measles to continue to circulate in pre-school children. In the UK, there have been renewed efforts to interrupt measles transmission with the mounting of a national campaign which took place in November 1994 and immunised seven million children aged 5–16 years within one month. The impetus for this initiative was the need to avert a major epidemic of measles predicted to occur in 1995/6.⁸ This was the consequence of poor uptake of single antigen measles vaccine in the 1970s and 80s, followed by high coverage with measles-mumps-rubella (MMR) vaccine since 1988. The successful MMR programme greatly reduced the incidence of measles and as a result older unvaccinated children no longer acquired natural measles and remained susceptible until adolescence. This pool of susceptible school children provided the potential for a major resurgence of the disease. The effect of the campaign has been to reduce the level of susceptibility to measles in the school age population from over 10% to around 3%,⁹ a level at which transmission of measles is interrupted. Absence of transmission in the school age population has been confirmed by the intensive laboratory investigation of clinically suspected cases using the non-invasive diagnostic technique of measles IgM detection in saliva by an antibody capture radioimmunoassay¹⁰ and measles virus genome by PCR and nucleotide sequencing. The development of molecular epidemiology, which uses viral genotyping methods to identify the probable geographical origin of a case, promises to be of great value as a surveillance tool.¹¹

Despite such achievements, 17 of the 50 million deaths which occur worldwide each year are still caused by infectious diseases and, in developing countries, infections remain the major cause of morbidity and mortality in children.¹² For the lower respiratory tract and diarrhoeal diseases, which are responsible for

nearly six deaths million per annum, effective vaccines are still awaited. However, for other diseases, effective vaccines exist and the failure lies in delivering them to the population, both because of their cost and the problem of maintaining a cold chain in underdeveloped areas. The killer diseases of childhood—measles, pertussis and tetanus—are responsible for nearly one million deaths in developing countries.¹² Tuberculosis, for which there is an urgent need for an improved vaccine, kills around two million people each year. Recently, however, there have been a number of important initiatives which could dramatically improve the prospect for reducing the global infectious disease burden. The impetus for these initiatives stems from the opportunities arising through innovative methods of vaccine production, coupled with an increasing commitment by the international community to prevention of disease through vaccination. The Children's Vaccine Initiative (CVI), a collaborative venture involving the United Nations, the World Bank, the Rockefeller Foundation, and the WHO, has identified a number of targets for the development of new or improved vaccines, with the overall aim of reducing childhood mortality globally by one third by the year 2000.

The need for an improved measles vaccine which can be administered shortly after birth has been accorded a high priority by the CVI, particularly for developing countries where measles mortality during the first year of life is considerable. Attempts to overcome the poor efficacy of the existing live attenuated vaccine in the presence of maternal antibodies by using high titre preparations have foundered because of the increased general mortality observed in female recipients, which seems to result from an immunosuppressant effect of the vaccine.¹³ Use of an inactivated measles vaccine, which is less likely to be affected by maternal antibody than a live vaccine, has in the past been associated with the occurrence of atypical measles characterised by high fever, severe pneumonitis and an unusual rash following exposure to natural measles.¹⁴ The phenomenon is thought to result from failure of the formalin inactivated vaccine to stimulate antibody capable of blocking the biological activity of the fusion protein of the measles virus, which is necessary to prevent cell to cell spread of paramyxoviruses. Efforts are therefore being concentrated on expressing measles antigens in live canarypox or vaccinia viruses, and on delivering antigen in a non-living vehicle called an ISCOM (immune stimulating complex). An ISCOM is a solid particle made by mixing antigen with a biocompatible detergent and a glucoside (Quil A) derived from the bark of a South American tree. This mixture spontaneously forms a matrix which can trap—by a hydrophobic polar interaction—viral, bacterial or parasitic proteins to form a man made particle around 40 nm in diameter. The ISCOM not only acts as a vehicle for antigen delivery, stimulating both T and B cell responses, but also as a strong adjuvant.¹⁵ Animal studies show that ISCOMs can be administered through the mucosal route, suggesting a potentially wide

application for delivery of future vaccines against respiratory infections or oral delivery of existing vaccines currently given by injection. However, concerns about the safety of agents such as Quil A which have powerful effects on the immune system must be resolved before ISCOMs can enter human trials.

Other targets identified by the CVI are a thermostable oral poliovaccine, which may be achieved simply by substituting deuterium oxide for ordinary water in the vaccine, and a single dose tetanus vaccine, the latter probably being administered by encapsulation in microspheres which release toxoid at a rate determined by the biodegradable properties of the polymers forming its wall.¹⁶ Oral administration may be an option, as microspheres between 5 and 10 mm in diameter are taken up by Peyer's patches and have been shown to induce primary and booster IgG and IgA responses in mice.¹⁶ However, the possibility of adverse reactions to slow release allergens is a potential concern. Another novel technique is the use of naked DNA which can generate immunogens directly from host cells. Injection of plasmid DNA encoding an antigen into muscle can result in sustained expression of the antigen and generation of persistent humoral and cell mediated immune responses.¹⁵ Nucleic acid vaccines expressing viral antigens have been shown to protect against lethal virus challenge in animals, but safety concerns about the potential for integration of plasmid DNA into host cells will need to be addressed before such vaccines can be tried in humans. A number of other novel approaches to vaccine development are being explored, including the use of more potent adjuvants which are capable of inducing protective immunity against intracellular organisms such as those causing malaria, leishmaniasis and AIDS. Oil based emulsions are promising candidates and one, monophosphoryl lipid A (MPL), a fatty acid derivative of a mycobacterial wall, has been tested clinically with a malaria vaccine.¹⁷

The visionary aim of the CVI at its inception was the eventual development of a "supervac-

cine". This would be an oral preparation that is effective immediately after birth, requires only a single administration and provides lifelong immunity against all major infectious diseases. While this dream may not be attainable, there is little doubt that the next decade will bring exciting opportunities for preventing some of the remaining burden of suffering caused by infectious diseases.

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