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Immunisation: Opportunities and Challenges

DM ***ROBERTON***

Abstract Immunisation provides protection from infective diseases that have previously caused major mortality and morbidity worldwide. Protection from vaccine preventable diseases should be available to all children globally. During the last two decades, global initiatives have led to significant improvement in vaccine availability for all children, but there is still much to be done. New vaccines against encapsulated *Haemophilus influenzae* b (Hib) have led to major changes in the prevalence of diseases due to Hib in developed countries. Further recent developments with conjugate pneumococcal and meningococcal vaccines offer great potential for the future. Acellular pertussis vaccines have reduced reactogenicity in comparison with whole cell pertussis vaccines, and appear likely to have better long term efficacy. Vaccines against rotavirus, RSV, parainfluenza and influenza for use in childhood are in development. There is the real possibility of eradicating infectious diseases such as poliomyelitis and measles in the foreseeable future. Future challenges are to provide vaccines at low cost and in a stable form so that they can benefit all children globally.

Key words Childhood; Immunisation; Vaccines

Introduction

The history of immunisation goes back many centuries, to early attempts to provide immunity against smallpox.

The 20th century saw major development in vaccines, and by the late 1930's effective vaccines against diphtheria, tetanus and pertussis were becoming widely available. The introduction of initially killed, then live, vaccines against poliomyelitis in the 1950's and 1960's had a very marked effect on the incidence of poliomyelitis as a disease. More recent developments have seen the introduction of measles vaccine in most countries of the world, and mumps and rubella vaccine in most developing and developed countries. Vaccines for hepatitis B, initially using plasma derived components, and subsequently recombinant antigens, have been effective. Vaccines against hepatitis A are now available, and combination vaccines to allow easy administration of several vaccines in one injection are now widely used in many countries.

Global initiatives through Unicef have attempted to provide universal childhood immunisation for pertussis, tetanus, diphtheria, poliomyelitis, measles and tuberculosis for children at low cost.[1] The global coverage for receipt of these vaccines for children in the late 1970's and early 1980's was below 20%, and has now risen to between 70% and 80% since the early 1990's. However, there are still major regional differences in vaccine uptake, with children in many of the poorer parts of the world continuing to have very limited access to vaccines. Each year, approximately 130 million children are born globally, with 91 million of these births being in developing countries. Almost 30 million children have no access to immunisation.[2] Nearly 3 million children die annually from eight vaccine preventable diseases (Table 1).[2,3]

As stated by Unicef, an important problem facing immunisation programs is that most vaccine development

Department of Paediatrics, University of Adelaide, Women's & Children's Hospital, North Adelaide, South Australia 5006

DM **ROBERTON** *MD, FRACP, FRCPA*

Correspondence to: Prof DM **ROBERTON**

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Table 1 Global deaths from eight vaccine preventable diseases

Disease	Estimated annual deaths
Poliomyelitis	720
Diphtheria	5000
Pertussis	346 000
Measles	888 000
Tetanus	410 000 (including 215 000 deaths from neonatal tetanus infection)
Haemophilus influenzae b (Hib)	400 000
Hepatitis B	900 000
Yellow fever	30 000
Total	**2 979 720**

Source: Global Alliance for Vaccines and Immunisation, 2001, www.VaccineAlliance.org/reference/globalfund[2]

takes place within the private sector in industrialised countries where the most profitable markets exist. As a result, most vaccines are tailored to diseases occurring in industrialised countries. Yet such diseases occur also in developing countries, and may take a more severe form because of deficient nutrition, lack of medical services and late diagnosis of complications.[4] This has led to a growing immunisation gap between industrialised countries and developing countries, where the prohibitive cost of recently developed vaccines makes them unavailable and where the burden of disease is greatest.

Important initiatives such as the Global Alliance for Vaccines and Immunisation (GAVI) with Unicef are providing financial support and incentives for developing countries to provide uniform immunisation services, and to assist with the provision of vaccines.[2-4]

What is the Ideal Vaccine

The ideal vaccine is highly effective in preventing disease, provides life long protection, can be given at a very early age in life, and is cheap and simple to manufacture (Table 2). Few if any of the currently available vaccines are able to meet these criteria. However, with increasing interest amongst manufactures in the vaccine market, and with competition for the supply of vaccines, costs do reduce with time and more stable and more efficacious forms of vaccine do become available.

Table 2 What are the characteristics of the ideal vaccine?

- high efficacy
- lifelong protection
- no adverse effects
- once only administration
- able to be given in combination
- easy administration
- stable in storage
- simple and cheap to manufacture

Current Vaccines

Most developing and developed countries use a vaccine schedule which provides protection against pertussis, diphtheria, tetanus, poliomyelitis, measles, mumps, rubella, hepatitis B and *Haemophilus influenzae* b (Hib) infection using a schedule provided from birth through the first 12 months of life, with subsequent booster immunisations. Variations in the schedules exist, but usually immunisation will commence at the age of 2 months, with the primary series of triple antigen being completed by the age of at least 6 months, in conjunction with the primary series of oral polio immunisation.

Many developed countries have recently moved to using acellular pertussis vaccines in order to reduce the incidence of frequent local and less frequent systemic reactions. In many developed countries, hepatitis B immunisation is commenced at birth, while in others it is provided with a school based immunisation program. The introduction during the 1990's of conjugate Hib vaccines has led to a marked decrease in invasive *Haemophilus influenzae* b infections in early childhood. However, in many countries, the cost of acellular pertussis vaccine and conjugate Hib vaccine has meant that it has had not been economically feasible to introduce these vaccines.

The waning efficacy with increasing age of pertussis immunisation after immunisation with whole cell pertussis vaccine has meant that, in many countries, there is a

significant reservoir of pertussis infection in older children and young adults. In Australia, for example, this is reflected in a significant incidence of pertussis in early infancy. A recent survey from the Australian Paediatric Surveillance Unit has documented 105 cases of pertussis in infancy, infection being at a median age of 8 weeks.[5] The incidence of hospitalisation for pertussis in infancy was 44 per 100 000 live births (95% CI 36-52), and 63% of hospitalisations were for infants less than 2 months of age, who would not yet have been due for pertussis immunisation using the national immunisation schedule. There were four deaths, and many of the hospitalised infants had been in contact with older children or adults who had features of pertussis and who were assumed to have had waning immunity in response to the whole cell pertussis vaccine that was used routinely in the Australian population until the late 1990s.

Assessment of Completeness of Population Immunisation

National immunisation surveys have been useful techniques for determining the uptake of immunisation. The World Health Organisation and others have published league tables of immunisation uptake globally.[6] One of the important aspects of ensuring a high rate of immunisation uptake within a population is adequate support and provision of information to providers. Although some parents question the value of immunisation, provider practices are more important barriers to vaccination than parental attitudes to immunisation.[7] Parent held records and national immunisation databases are important components of recording and encouraging immunisation uptake. A very important aspect of improving uptake is reminder notification, and the use of other health care visits to provide opportunistic immunisation.[8,9]

Similarly, the provision of readily available information and answers to frequently asked questions to parents, guardians and health professionals is an important part of the immunisation process (Table 3).

Storage of Vaccines

The necessary storage conditions for vaccines are provided by manufacturers as a required component of regulatory Product Information approvals. In all countries, maintenance of an appropriate cold chain is important, particularly with respect to live attenuated viral vaccines. For most vaccines, storage temperatures of between 2°C and 8°C are recommended. Some recent studies have shown that storage of vaccines by providers may lead to inadvertent freezing of vaccines.[10] In these studies, more than half of the vaccines were shown to have been frozen when storage conditions were tracked at very frequent intervals by electronic temperature loggers. At 23% of the provider sites studied, vaccine had been stored at temperatures below -4°C.[10]

Studies in our laboratories have investigated the effect on immunogenicity of storage at temperatures below freezing for varying periods of time using an animal model.[11] Some relatively minor effects on antibody titres were shown. Further studies, using a murine lung model of protective efficacy against live Bordetella pertussis infection however have not shown major adverse effects of storage at -3°C or

Table 3 Some websites for information on immunisation for parents and professionals

http://www.cdc.gov/nip/	CDC website for parent questions on immunisation
http://www.nlm.nih.gov/medline plus/childhoodimmunization.html	Medline Plus site on childhood immunisations, with links to NIH, CDC and American Academy of Pediatrics.
http://www.who.int/vaccines-diseases/safety/ index.html	website for health professionals
http://www.health.gov.au/pubhlth/publicat/immu.htm	Site for Dept of Health and Aged Care, Australia, with links to pages for the Australian Immunisation Handbook and Australian Immunisation Schedules
http://www.ncirs.usyd.edu.au/facts/facts.html	Australian National Centre for Immunisation Research and Surveillance
http://www.immunisation.org.uk	NHS/ Health Promotion England website with information for providers and for the public

-6°C for DTPa vaccine.[12,13] Further studies of adverse storage are required for other vaccines.

Immune Response to Vaccines in Infancy

Immunisation During Pregnancy

IgG antibody is transferred across the placenta to the fetus during the second half of the second trimester and during the third trimester of pregnancy. Recognition of this has led to maternal immunisation programs with tetanus toxoid in regions of the world where neonatal tetanus has been an important cause of neonatal mortality.

Other studies have also been undertaken of maternal immunisation during pregnancy. One such study immunised mothers during their third trimester of pregnancy with a conjugate Hib vaccine (PRP-T). Effective transfer of IgG anti PRP antibody was demonstrated in cord blood samples, and there was no apparent significant impact on the later development of IgG antibody concentrations following immunisation in infancy with the same conjugate vaccine.[14] The same study showed a significant increase in breast milk IgA antibody concentration to PRP in those mothers immunised during pregnancy (unpublished results).

Immunisation of Premature Infants

Most immunisation schedules recommend that premature infants commence immunisation according to their birth age rather than their gestational age. A number of studies have shown that the immune response to the usual immunisation antigens is likely to be sufficient to be protective, although in extreme prematurity there are somewhat lower responses, even up to the age of 18 months.[12,15,16] The functional activity of antibody produced by premature infants needs further study.

Combination Vaccines

Combination vaccines are not new. Pertussis, diphtheria and tetanus vaccines have been provided in combination form for several decades. Similarly, oral polio viral vaccine consists of three strains of attenuated live poliovirus, and measles, mumps, and rubella (MMR) have been given in combination for many years in several countries.

With the development of significant numbers of new vaccines, there is a major need to provide further vaccines in combination. Examples are DTPa – hepatitis B, DTPa – hepatitis B – injectable polio virus vaccine (IPV), DTPa – hepatitis B – Hib, and DTPa – hep B – Hib – IPV. An interesting finding has been that antibody concentrations to Hib PRP have tended to be lower when conjugate Hib vaccine is combined with acellular pertussis vaccines in comparison with whole cell pertussis vaccines. Although there has been concern that this may alter the efficacy of Hib vaccine when given in combination with DTPa vaccines, currently there is little evidence to suggest that this will be the case.[17,18]

Recent New Vaccines

Vaccines that have become available recently include varicella vaccine, pneumococcal conjugate vaccine, and meningococcal A and C conjugate vaccines.

Varicella vaccine is now available widely in developed countries, but is part of the universally funded immunisation program in only a few countries. Economic analyses suggest some economic benefit from the provision of varicella vaccine in childhood in some developed countries, but for many countries there are other health priorities which take precedence. Studies are being undertaken of combination of varicella vaccine with MMR vaccine.

A 7 valent conjugate pneumococcal vaccine has been licensed for use in several countries during the last two years. A major efficacy study undertaken in the United States[19] has shown efficacy against vaccine serotype – associated invasive disease of 97%. The conjugate vaccine appears highly effective under the age of 2 years, but unfortunately remains extremely costly.

Conjugate vaccines have become available recently for meningococcal A and C serotypes. Meningococcal C conjugate vaccine has been introduced on a universal basis in infancy in the United Kingdom during the last two years, as well as being provided for immunisation at other ages, particularly in young adult life. No formal prospective studies of vaccine efficacy were undertaken before introduction to the immunisation schedule, but post licensing surveillance suggests an efficacy of 92% (CI 65-98).[20] The economic benefit of meningococcal C vaccine in individual countries depends very much on the local epidemiology of disease. In contrast to Hib and pneumococcal infection, the incidence and prevalence of meningococcal C disease varies within and between countries quite markedly.

Combinations of hepatitis A and hepatitis B vaccine are also available, but are not yet used widely.

When introducing new vaccines to an immunisation

schedule which are to be given at the same time as existing vaccines, or when providing current vaccines in combinations for administration, it is of great importance to ensure that there is not a detrimental effect on the immunogenicity or protective efficacy of the vaccines in the standard schedules.

Vaccines of the Future

Potential vaccines for the near future are listed in Table 4. Trials are underway currently with intranasally administered influenza vaccines, and a rotavirus vaccine was licensed recently for use in the United States, but has been withdrawn from marketing because of concerns about the rare potential for being associated with intussusception in infancy. Phase I and some phase II studies have been undertaken in recent years with new RSV vaccines. Similar studies have been undertaken with new parainfluenza vaccines.

Development of efficacious vaccines for these viral infections will have a significant effect on childhood morbidity and mortality in developed and developing countries. There are significant needs still for vaccines against other organisms such as malaria, and for more effective vaccines against tuberculosis.

The challenges in immunisation for the future remain significant, and are ones of manufacturing, public health policy, and funding for delivery, as well as of basic research. There are major opportunities to further improve the survival and health of the world's children through immunisation.

Table 4 Paediatric vaccines for the near future

- expanded serotype range for pneumococcal conjugate vaccines
- multivalent meningococcal conjugate vaccines
- rotavirus vaccines
- RSV live intranasal adapted/recombinant vaccines
- parainfluenza vaccines
- cold adapted live viral influenza vaccines

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