

Leading Article

Immunisation of children: a sound investment for the Millenium

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Historical Background

In the field of vaccine development Jenner and Pasteur easily stand out as the true pioneers. Although Edward Jenner first attempted systematic immunisation against smallpox in 1796, an entire century actually went by

before Louis Pasteur in 1885 administered post exposure rabies vaccine cultured in rabbit spinal cord to a young man severely bitten by a dog. Since then during the last century many other vaccines were developed by researchers¹ (Table 1).

Table 1 - Milestones in vaccine development

Year	Vaccine	Researcher/Developer
1776	Smallpox	Jenner
1885	Rabies	Pasteur
1892	Cholera	Haffkine
1896	Typhoid	Wright
1913	Diphtheria (toxin-toxoid)	Behring
1921	Tuberculosis (BCG)	Calmette & Guerin
1923	Diphtheria (toxoid)	Ramon & Glenny
1923	Pertussis	Madsen
1927	Tetanus	Ramon & Zoeller
1932	Yellow fever	Sellard & Laigret
1937	Influenza	Salk
1949	Mumps	Smorodintsev
1954	Inactivated polio Salk vaccine (IPV)	Salk
1957	Live attenuated polio vaccine (OPA)	Sabin
1960	Measles	Edmonston B (Enders); Schwartz
1962	Rubella	Weller, Nava & Parkmann
1966	Mumps	Weibel, Buynach, Hillemann & Takahashi
1967	Rabies	Wiktor
1968	Meningococcus C	Gotschlich
1971	Meningococcus A	Gotschlich
1974	Varicella	Takahashi
1976	Hepatitis B	Maupas, Hillemann
1978	Pneumococcus	
1979	Hepatitis A	Provost & Hillemann
1980	Haemophilus Influenza type B	
1984	Vi Polysaccharide Typhoid Vaccine	

Global childhood mortality and the expanded programme of immunization (EPI)

Every year almost 10 million deaths occur in children less than 5 years of age and of them over 99% are in developing countries and 70% are caused by measles, pertussis and tetanus in spite of effective vaccines being available for these diseases for many years². It is

important to develop new vaccines but it is even more important to find ways to deliver available vaccines to the poorest children who need them most. Although the development of new vaccines requires research in high-income countries, the provision of vaccines to children in developing, low-income countries depends on financial resources, policy decisions combined with political will and other non-scientific factors.

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Immunisation has substantially reduced child mortality since the WHO began the Expanded Programme on Immunisation (EPI) in 1974. The coverage with the six EPI vaccines has increased from 5% in 1974 to over 80% of children in 25 years.

However, the 2 major causes of deaths in children, pneumonia (2.1 million deaths) and diarrhoeal diseases (2.0 million deaths) cannot be prevented by vaccination in poor countries. In high-income countries new vaccines are being introduced to protect young children from *Haemophilus influenzae*, *Streptococcus pneumoniae* and *rotavirus* and if these vaccines are made available universally there would be a dramatic impact on deaths due to pneumonia and diarrhoea.

In Sri Lanka the EPI programme was formally launched in the late 1970's although the BCG, DPT and oral polio vaccines were available from the 1960s and measles vaccination was introduced island-wide in 1984. As the EPI coverage in Sri Lanka is exceptionally high for a low-income country, deaths due to these diseases have been drastically reduced during the last 3 decades.

Current vaccines

Tuberculosis

Almost 2-3 million adults and about 100,000 children die due to tuberculosis each year. The efficacy of different BCG vaccines varies between 0% and 80% in different populations³. BCG is known to prevent disseminated tuberculosis in children better than pulmonary disease in adults. In Sri Lanka, for this reason, TB meningitis, miliary tuberculosis and bone-joint tuberculosis have become rare in children. Globally as there is a resurgence of TB in HIV infected patients, a more effective vaccine against TB has become a priority and research is underway. BCG should not be given to anyone with symptomatic HIV infection or AIDS. In Sri Lanka, two problems sometimes encountered with the BCG vaccination are "BCGitis" in the left axilla and lack of uptake of the vaccine. If the BCG scar is absent, the vaccine could be re-administered without a prior tuberculin (Mantoux) test if the child is under 1 year and if tuberculin negative in children over 1 year.

Pertussis

The locally available vaccine is a whole-cell vaccine which is highly effective and inexpensive; however it is associated with more side effects. In the U.K. in the 1970s, due to adverse publicity given to side-effects, the vaccine coverage dropped to about 20% and unimmunised children died of pertussis during outbreaks of it. It continues to cause mortality in unimmunised infants in the U.K. even in 1999⁴. An acellular vaccine has been developed and its use has

been confined to some high-income countries such as Japan because of the cost. The efficacy of acellular vaccines is directly related to the number of antigens it contains, which could vary from one to five.

An absolute contraindication for pertussis vaccination is an adverse reaction such as collapse, shock, fever >40.5°C, seizures or episodes of screaming; a progressive neurological illness is also considered to be a contraindication. Children vaccinated against pertussis, may subsequently develop a pertussis-like illness due to adenoviral infection.

Diphtheria

It is given as a toxoid combined with pertussis and tetanus as DPT. It is well tolerated and side effects such as short-lived local reactions are rare. It is very effective and has almost eradicated the disease from Sri Lanka, except for a few cases of nasal diphtheria.

Tetanus

It is given as an adsorbed toxoid to pregnant mothers during the first 2 pregnancies which has resulted in the virtual elimination of the scourge of neonatal tetanus from most parts of Sri Lanka. It is also given in the EPI as DPT. Tetanus in children is very rare in Sri Lanka although inadequately immunised adults are still at risk. Booster doses are recommended 5 yearly in children and 10 yearly in adults.

Poliomyelitis

The live oral polio vaccine (Sabin) has been used in Sri Lanka since the early 1960s. If the cold-chain is maintained it is very effective. In patients with immune-deficiency, the inactivated polio vaccine (Salk) which is injected is preferred, due to the possible risk of vaccine induced paralysis. Poliomyelitis has been eradicated from the USA since 1974 and from the Americas since 1991 and a strategy of national immunisation days (NID) has been successful in reducing wild virus induced poliomyelitis cases to very low levels in many low-income countries. Although the WHO goal of eradicating the disease by year 2000 has not been achieved, some low-income countries such as Sri Lanka are free of poliomyelitis (the last reported case was in 1992). However the WHO would not clear Sri Lanka totally because the disease is widely prevalent in Tamil-Nadu and the potential for spread is obvious because of frequent travel between the regions. Although Sri Lanka conducted NIDs very successfully in the last few years, the strategy for the future would be sub-national or regional immunisation days in the susceptible areas.

It is of interest to observe that in the USA there are 6-8 vaccine associated paralytic polio cases per year and in

the absence of natural transmission, injectable polio vaccine (IPV) is being considered for the future.

Measles

Immunisation has substantially reduced mortality from measles world-wide; however measles kills 1.1 million children less than 5 years of age every year, despite the availability of an effective vaccine⁵. In high-income countries measles vaccine is usually given at 12-15 months of age because sero conversion rates are higher than in infants; many of these countries use a second dose in older children to increase sero conversion rates. In the U.K. the current recommendation is to give the first dose of MMR (measles, mumps, rubella) vaccine after the first birthday and a second dose just before school entry at 5 years⁶. However, in low-income countries such as Sri Lanka, as many children used to die from measles in infancy (i.e. before 12 months) the vaccine is given at 6-9 months (in Sri Lanka it is given at 9 months).

When Schwartz vaccine is given at 4-8 months, sero conversion rates are lower than after vaccination at 9-11 months and more children get measles. However case-fatality rates are lower in the excess cases and the protection against non-measles deaths occurs earlier, so that total mortality is lower with immunisation at 6 months in spite of the lower sero conversion rate⁷. As there is some evidence that the Schwartz measles vaccine reduces mortality from conditions other than measles, the measles vaccination may have to be continued in poor countries even if the disease is eradicated^{8,9}. Measles is a potential target for eradication as there is no animal reservoir and the vaccine is very effective. However as measles is very infectious, vaccination rates of over 95% would be required over many years to achieve that goal.

Measles has made a come-back in Sri Lanka since September 1999. As many vaccinated children have got the disease, a second dose of measles vaccine should preferably be given ideally in the form of MMR vaccine at an appropriate age (e.g. at 3 years). During the recent epidemic as many infants below 9 months have got infected the question of the necessity to advance the age of vaccination has arisen.

Rubella

Rubella vaccine is given routinely to all children in high-income countries in the form of measles, mumps and rubella (MMR) vaccine at about 15 months of age. It has been in use for nearly 30 years. Sri Lanka experienced an outbreak of congenital rubella syndrome in 1994 and 1995 although the rubella vaccine was available in the private sector for about Rs. 55.00 per dose at that time. It is unfortunate that due to lack of awareness, many unimmunised mothers who could have

afforded the expenditure for the vaccine, delivered babies with congenital rubella syndrome. The Ministry of Health made the rubella vaccine available for females between 11-45 years of age in late 1997. However the strategies used to immunise this section of the population were a failure and over a million doses of the vaccine had to be discarded after the expiry date in late 1999 (personal communication). Therefore new strategies have to be developed in the future to provide effective cover. One such strategy would be to include the MMR vaccine in the national EPI schedule, to be given at 3 years of age.

Japanese encephalitis

This disease has raised its ugly head in Sri Lanka during the last 15 years. Initially it was prevalent in the North Western and North Central Provinces but later on spread to Eastern, Western and Southern Provinces as well. The current recommendation is to give initially 2 doses of the vaccine 2 weeks apart to children over 1 year of age, a 3rd dose 1 year later and 3 yearly booster doses thereafter.

It is interesting to note that in Thailand where both Japanese encephalitis and dengue fever are prevalent, adults immunised against the former, when infected by the dengue virus, developed a less serious disease with fewer complications¹⁰. As both are flavi viruses there may be cross-immunity and as there is no effective vaccine against dengue fever as yet, the Japanese encephalitis vaccine may provide an additional beneficial effect for our children.

Other vaccines available in Sri Lanka in the private sector

Measles, mumps, rubella (MMR)

The MMR vaccine is widely used and is in the National schedule of most high-income countries and is administered at about 15 months of age. In the U.K., the current recommendation is to give the first dose soon after the first birthday and the second dose before school entry at five years⁶. There are 3 mumps vaccine strains that have been used in the MMR vaccine. These are the Urabe strain, Jeryl-Lynn strain and the Rubini strain. The Urabe strain was withdrawn in 1992 after an association with increased risk of aseptic meningitis¹¹. In Singapore the Urabe strain was substituted by the Rubini strain during 1993-95¹². However, subsequent disease surveillance revealed that the incidence of mumps had increased during the next 4 years indicating primary vaccination failure. Sharp increases in the incidence of mumps in the 1990s prompted the Swiss Federal Office for Public Health to recommend the use of MMR vaccines containing other mumps virus strains e.g. Jeryl-Lynn, rather than the Rubini strain¹³. As mumps is the commonest cause of viral encephalitis,

although most cases are mild, and as there is multi-organ involvement such as orchitis, pancreatitis, thyroiditis etc. mumps vaccine should be recommended. An ideal solution for Sri Lanka would be to include the MMR vaccine in the National EPI schedule to be given at about 3 years so that there would be a wider coverage for rubella vaccination and a 2nd dose of measles vaccine would also be routinely given.

Haemophilus

H. influenzae may cause almost as many fatal cases of pneumonia and meningitis as *S. pneumoniae* does. The Haemophilus influenza type B vaccine (Hib conjugate vaccine) has been spectacularly successful in high-income countries in reducing the morbidity and mortality due to meningitis, pneumonia, septicaemia, osteomyelitis and acute epiglottitis¹⁴. However, it's relatively high cost has precluded its inclusion in the national schedules of low-income countries. In a Gambian study, this vaccine reduced x-ray proven pneumonia by 20% and total mortality by 6.1 %¹⁵.

However, vaccines are required in the future to prevent infections due to nonserotypable (unencapsulated) *H. influenzae* and types a c d e and f, besides b. The recommended schedule in the U.K is for 3 doses to be given in infancy together with the DPT (all 4 antigens are available in combination) and for a single dose to be given between 12 and 48 months if not vaccinated earlier.

Hepatitis B

Globally hepatitis B causes about 600,000 deaths every year; most are adult deaths from primary hepatic carcinoma caused by hepatitis B infection in childhood¹⁶. Deaths from hepatitis B could be prevented by immunisation but even USD 1.50 for a course of 3 injections is more expensive than the cost of original 6 EPI vaccines². Since 1991 the WHO has suggested to include it in the routine immunisation schedules of all countries with a high prevalence and over 90 countries have done so^{16,17}. However, the vaccine is not given routinely in many very poor countries where the incidence of hepatitis is high because of the expenditure involved. In Sri Lanka it is at present recommended for patients who receive frequent blood transfusions such as thalassaemics and haemophiliacs. In high-income countries where the genetically engineered hepatitis B vaccine has been extensively used, no adverse effects have been reported.

In Sri Lanka, at present the carrier rate of Hepatitis B is not sufficiently high to recommend routine immunisation. It is offered to individuals at risk such as medical officers and paramedics. There is some evidence to suggest that a primary course of immunisation in immunocompetent individuals provides

adequate immunity for at least 15 years negating the need for booster doses¹⁷. Under these circumstances it is worth considering whether this vaccine should be recommended for infants who could afford it, in case the hepatitis B carrier rate in Sri Lanka increases in the future.

Hepatitis A

Although this vaccine is available, it is not recommended for routine use in children. It is recommended for frequent travellers to areas of moderate or high endemicity or where the period of stay exceeds 3 months. It may have a place for patients who receive frequent blood transfusions or blood products such as haemophiliacs and thalassaemics because the hepatitis A virus could be transmitted through blood products.

Pneumococcus

Pneumococcal infection is estimated to cause 1-2 million deaths a year in children under 5 years in developing countries¹⁸. It is an important cause of pneumonia, meningitis, otitis media and sinusitis. At present in Sri Lanka it is recommended for patients undergoing splenectomy and it would be of some benefit to patients with nephrotic syndrome. The polysaccharide capsular antigens of *S. pneumoniae* do not stimulate a good antibody response in children less than 2 years, which is the age at which the pneumococcus causes greatest morbidity and mortality. Conjugate pneumococcal vaccines are being developed for use in susceptible age groups but are likely to be unaffordable for use in low-income countries.

Varicella

An attenuated live varicella vaccine has been developed and used in Japan for many years and the vaccine was licenced for use in the USA in 1995 where it is recommended for use in children between 12 months to 12 years of age. It has an efficacy of about 90%. In the U.K. it is recommended only for immuno compromised children on a named patient basis⁶. When given to children, the total duration of immunity is uncertain at present and therefore the need for a booster dose later has to be considered. It may be recommended for school children who are scheduled to sit for public examinations and who have not been infected earlier and for sportspersons who have to travel abroad for international competitions.

Meningococcus

The currently available meningococcal vaccine is effective against serogroups A and C, which are the prevalent strains in the Middle East and is therefore recommended for travellers to that region. However the

vaccine is ineffective against Group B organisms which have been responsible for outbreaks in the U.K.

Influenza

Two types of influenza virus are responsible for most clinical illness; influenza A and influenza B. Outbreaks and epidemics are more common with influenza A as experienced locally in 1998. Influenza A viruses are antigenically labile due to changes in the principal surface antigens. Minor changes (antigenic drift) occur progressively seasonally whilst major changes (antigenic shift) occur due to acquisition of new antigens and can result in epidemics or pandemics. Therefore in the U.K. influenza vaccine is prepared each year taking into account the strains of viruses that are currently prevalent⁶. Although an influenza vaccine is available locally it is not recommended for routine use for the above reasons.

Vaccines for the future

Malaria

As the parasite has developed resistance to several antimalarial drugs and the mosquito has become resistant to insecticides, the morbidity and mortality rates of malaria keep on increasing worldwide. Production of an effective vaccine has proved difficult because of the polymorphism displayed by the parasite's proteins. The optimum strategy may be a combination of sporozoite (pre-erythrocytic) and merozoite (erythrocytic) vaccines¹⁹.

Rotavirus

Rotavirus accounts for 80,000 childhood deaths per year globally, because it is the most important cause of severe diarrhoea in children²⁰. In low income countries the most susceptible are young infants in contrast to high-income countries where it occurs later. An oral live attenuated vaccine based on rhesus monkey rotavirus was effective when given at 2, 3 and 4 months of age²¹. It had 50-60% efficacy against severe diarrhoea in children in Peru, Brazil and USA. The tetravalent rotavirus vaccine was licenced in the USA in the 1998 and in the European Union in 1999 but routine use has been suspended because it appears to cause intussusception²².

Rabies

In Sri Lanka, pre-exposure prophylaxis is not offered to children and only post-exposure prophylaxis is available after animal bites. In a preliminary study in Vietnam, pre-exposure rabies vaccination in infancy using 2 doses of purified vero cell rabies vaccine at 2 and 4 months of age produced protective antibody concentrations against rabies²³. In countries such as Sri Lanka where rabies is

enzootic, this option may have to be considered in the future.

HIV

HIV infection. killed 500,000 children in 1997 (and 1.8 million adults). 80% of these deaths were in Africa. Difficulties are being encountered in developing an effective vaccine and currently Phase 3 trials are in progress.

Strategies for the future

Green revolution

Production of functional proteins by genetic engineering of bacteria, yeast, cultured mammalian cells, or large animals is currently in progress but expensive. Hepatitis B vaccine using recombinant DNA is a good example. At present a green revolution is underway with researchers and industry turning to the vegetable kingdom for low-cost large-scale solutions. Plants can be engineered to make foreign proteins either transiently by infection with recombinant plant virus vectors or permanently by making transgenic plant strains. There are plans to make edible vaccines by expressing antigens in fruits and vegetables. A research group headed by Charles Arntzen in USA is currently working towards production of edible vaccines - recombinant proteins expressed in a widely available plant material that does not need cooking, the banana²⁴. Therefore, in this 3rd millenium a banana a day may keep the doctor away!

Global Alliance for Vaccines and Immunisations (GAVI)

The mission of GAVI is "to save children's lives and protect people's health through widespread use of vaccines". Since 1990 a declining proportion of the approximately 130 million children born every year becomes fully immunised with the original six EPI vaccines. While in the early 90s 4 out of 5 children were fully immunised, in 1998 only three out of four children were reported to receive full immunisation²⁵. Although newer vaccines have become available, over 30 million children born every year will not be adequately protected against vaccine preventable diseases. Of those, 25 million live in countries with less than USD 1000 GNP per capita annually. Every year there are 3 million unnecessary vaccine preventable premature deaths. It is considered not only as a health issue but an issue of fundamental equity and human rights. A Global Fund for Children's vaccines has been set up to rectify the problems that have been identified. The Bill and Melinda Gates Foundation has provided the first contribution to the fund through a commitment of 750 million USD over five years²⁶. As Sri Lanka has an annual per capita GNP of 810 USD (i.e. <1000 USD)

and a population of 18 million, it fits into the category of low-income countries that would benefit from GAVI to strengthen its national EPI programme by adding new vaccines, for the benefit of our future children.

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