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Efficacy and Safety of Vaccines in Indian Children: a Review

Sunil Karande
Department of Paediatrics, Lokmanya Tilak Municipal Medical College and Lokmanya Tilak Municipal General Hospital, Sion, Mumbai 400 02, India

Nithya J Gogtay
Department of Clinical Pharmacology, Adverse Drug Reaction Monitoring Centre of Government of India, WHO Special Centre for ADR Monitoring, Seth Gordhandas Sunderdas Medical College and King Edward VII Memorial Hospital, Parel, Mumbai 400 012, India

Nilima A Kshirsagar Corresponding Author
Department of Clinical Pharmacology, Seth Gordhandas Sunderdas Medical College and King Edward VII Memorial Hospital, Parel, Mumbai 400 012, India Email: dcpkem@vsnl.com

The immunisation of children in India has resulted in a significant reduction in morbidity and mortality. The current immunisation schedule protects against poliomyelitis, diphtheria, tetanus, pertussis, measles, and tuberculosis. The development of this vaccine programme is discussed and suggestions made to expand the programme to include coverage of hepatitis B.

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Introduction

The Government of India (GOI) established its Expanded Programme on Immunisation (EPI) in January 1978[1]. Initially the EPI offered free immunisation to every child against tuberculosis, poliomyelitis, diphtheria, tetanus and pertussis. In 1985, the EPI was modified as the Universal Immunisation Programme (UIP) with inclusion of the Measles vaccine and increasing the target of immunisation coverage from 80 to 100%[1]. The current official immunisation schedule as recommended by the GOI is shown in Table 1[2]. In recent times many newer vaccines (such as Hepatitis B, *Haemophilus influenzae* type b, Varicella) have been licensed for marketing but have not been included in the UIP.

In India, vaccination is a topic of great public concern. A recent example was the reluctance of parents in the state of Uttar Pradesh to allow their children to have polio vaccinations. The parents had the misconception that the vaccine would induce sterility or worse, even transmit the human immunodeficiency virus[3]. Another scare in the state of Assam was that oral polio vaccination could lead to death, when 946 children developed nausea and vomiting following a mass vitamin A prophylaxis programme. A small number were hospitalised and 16 died[4]. A detailed study found that, contrary to media reports, no oral polio vaccine had been given along with vitamin A. The cause of the adverse events was a vitamin A overdose due to the use of a new measuring cup instead of the usual spoon[5].

Although the risks of vaccine-associated adverse events are extremely low, their occurrence can adversely influence public acceptance of immunisation services. To tackle any immediate

post-immunisation life-threatening event, such as anaphylaxis, it is mandatory for every immunisation clinic to have an emergency resuscitation set up. Monitoring of adverse events is also necessary to identify the UIP programme's errors, if any, for prompt corrective action. For this, state and regional expert teams with an epidemiologist, a paediatrician and a microbiologist have been constituted by health authorities for detailed investigations of severe adverse events. All deaths, especially in clusters, following immunisation are to be investigated within 48 hours[6]. However this is only for vaccines given under the UIP. In India no comprehensive post-marketing surveillance for adverse events to the newer vaccines is being done.

In this article we have reviewed the data available on vaccine efficacy and safety in Indian children, discussed the need for including some newer vaccines in the UIP and the steps needed to improve post-marketing surveillance for adverse events to vaccines in our country.

Bacillus Calmette Guerin (BCG) vaccine

Tuberculosis continues to be a major public health problem in India. It is well known that BCG vaccine does not protect against infection by *Mycobacterium tuberculosis*[7]. Under the UIP, BCG vaccine continues to be recommended to every child within 48–72 hours of birth, before the mother is discharged from the hospital, to ensure maximum coverage (Table 1). Although BCG vaccine does not reduce the prevalence of tuberculosis in the community, two Indian studies have justified its continued use in babies[8,9]. A case-control study found that BCG vaccination is highly effective for protecting children from progressive (non-pulmonary) primary tuberculosis i.e. tuberculous meningitis, bone and miliary tuberculosis and scrofula[8]. Another study not only documented its protective efficacy against tuberculous meningitis, but has also postulated an association between nutritional status and its efficacy. A higher weight for age was associated with a reduced risk of developing tuberculous meningitis[9].

Table 1. The Government of India's Universal Immunisation Programme schedule

Age	Vaccine
Birth	BCG
6 weeks	OPV + DTPw
10 weeks	OPV + DTPw
14 weeks	OPV + DTPw
9 months	Measles
18–24 months	OPV + DTPw
4.5–5 years	OPV + DT
10 years	TT
16 years	TT

Two doses of tetanus toxoid (TT) are to be given to pregnant women. The first dose is given at the first contact and the second dose 1 month later

BCG induced tuberculin sensitivity is a quantitative characteristic used to judge its efficacy. A study supports the present practice of giving 0.1 ml of BCG at birth. No significant difference in tuberculin sensitivity was observed in normal newborns who received 0.1 ml either at birth or at 4–6 weeks of age[10]. However, newborns who received 0.05 ml at birth had significantly lower tuberculin sensitivity. No local side effects were observed[10]. In India, approximately 25 million babies are born every year of whom 35% are low birth weight (less than 2 kg)[11]. Also malnutrition is widespread. A study has documented that there is no significant difference in the BCG induced tuberculin response of low birth weight babies as compared to normal newborns[12]. Also tuberculin sensitivity is not affected by first and second-degree malnutrition[12].

BCG scar failure has been reported to occur in up to 10% of BCG-vaccinated babies[13]. It was more common when it was given within 48 hours of life. However, the failure of formation of a BCG scar was not equated with a failure of immunisation as the majority (87%) developed cell-mediated immunity, as measured by *in vitro* leukocyte migration inhibition test[13].

Oral Polio Vaccine (OPV)

In India, under the UIP, OPV is to be given to every child at 6, 10 and 14 weeks as a primary immunisation. Booster doses are given at 18 months and at 4½ years (Table 1). Thus five doses have been recommended for every child. The efficacy of OPV to prevent wild poliovirus associated acute poliomyelitis is well documented in India. There was a reduction in the incidence of acute poliomyelitis from 25 per 100,000 children in the pre-EPI era to 16 per 100,000 in 1989 and to 6 per 100,000 in 1992[14]. In India about 16,565 cases of acute poliomyelitis were reported annually during 1987–1991[14].

In December 1995, the GOI launched the National Polio Eradication Programme by implementing an annual two-dose OPV Pulse Polio Immunisation (PPI) programme[15]. All children below the age of

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5 years were to receive two OPV doses on National PPI days, at an interval of about 4 weeks. This was in addition to the routine UIP immunisation. PPI rapidly reduces the size of the susceptible pool of children in a community[15]. It took the policy makers 3 years to realize that with the annual two-dose OPV pulse immunisation wild poliovirus transmission slows down but does not cease[16]. Even in the year 1998, wild poliovirus was isolated from the stools of 2001 children with acute flaccid paralysis[16]. This setback led the GOI policy makers to decide on a four-dose pulse programme. In some states like Uttar Pradesh there was no reduction in acute poliomyelitis cases, largely due to poor implementation of the PPI programme. Instead of improving the inadequate quality of the PPI programme in Uttar Pradesh, a six-dose pulse programme was implemented[16].

This revised PPI strategy has been criticised as it has increased the risk of vaccine-associated paralytic poliomyelitis (VAPP) in Indian children[17]. One case of VAPP is thought to occur for every 400,000 children given the first dose of OPV[18]. In India annually about 25 million babies get their first OPV and one would anticipate about 60 cases of VAPP every year. The risk of VAPP in a child receiving OPV in subsequent doses is about 1 in 2.5 million doses[19]. The GOI is distributing over 500 million doses of OPV annually for about 125 million under-5 children. The number of cases of VAPP in India was 280 in 1998 and 174 in the first half of 1999[16]. These numbers have increased due to the four- and six-dose pulses being given[17]. The GOI does offer free treatment and rehabilitation services to children who develop VAPP, but the parents are not getting any monetary compensation for this adverse event. There is no doubt of the need to continue the PPI programme till poliomyelitis is eradicated in India. However, it has been suggested that three-dose pulses would be just as effective as five or six doses and would reduce the risk of VAPP[17]. A study from Vellore in South India showed that the efficacy of three doses of OPV was 100%, with marked herd effect eliminating disease from a community for up to 9 months[20]. The IAP ,however, recommends a seven-dose regimen (Table 2).

Without any doubt, the PPI programme has been a great success in most parts of India, except in the northern states of Uttar Pradesh and Bihar, where endemic transmission of wild poliovirus still continues. There was a drastic reduction in the incidence of *acute poliomyelitis* cases from the years 1990–1999, as shown in Table 3[21]. The *acute poliomyelitis* cases include both: (i) *wild poliovirus* proven cases, i.e. clinically diagnosed and proven on stool viral culture; and (ii) *compatible poliovirus* cases, i.e. clinically diagnosed but stool viral culture could not be done. In the year 2001, only 554 children developed acute poliomyelitis (of these 268 were wild poliovirus proven cases) in India[22]. However, in the year 2002, there has been a resurgence of poliomyelitis in India. As of 14 December 2002, 1494 children have developed acute poliomyelitis (of these, 1320 cases were wild poliovirus proven cases)[22].

Table 2. The Indian Academy of Pediatrics Recommended Immunisation schedule

Age	Vaccine
Birth	BCG + OPV + HB
6 weeks	OPV + DTPw + HB
10 weeks	OPV + DTPw
14 weeks	OPV + DTPw
6 months	HB
9 months	OPV + Measles
18–24 months	OPV + DTPw + MMR
4.5–5 years	OPV + DTPw
10 years	TT + HB
16 years	TT

Two doses of tetanus toxoid (TT) are to be given to pregnant women. The first dose is given at the first contact and the second dose 1 month later.

Table 3. Number of acute poliomyelitis cases detected in India

Year	Number of cases
1990	10408
1991	8670
1992	9390
1993	7576
1994	4791
1995	3263
1996	1005
1997	2274
1998	4322
1999	1126

Pulse Polio Immunisation Programme was started in December 1995.

The vast majority of cases (up to 80%) have occurred in the adjoining northern states of Uttar Pradesh and Bihar. Cases in other states outside Uttar Pradesh and Bihar (West Bengal, Gujarat, Delhi, Jharkhand, Madhya Pradesh, Haryana, Rajasthan and Maharashtra) were the result of direct exportation of wild poliovirus from these endemic areas[22]. This resurgence has occurred in large part due to lack of accountability and supervision in the health system and poor routine immunisation[22]. The GOI has already taken steps to correct the situation by strengthening the implementation of the PPI programme in these two states. All vaccinators and supervisors are being retrained and the social mobilisation network is being expanded by increasing the number of supervisors in high risk areas, having more female vaccinators, and having a third team member from the local community in all teams[22]. Lastly, strict attention is being paid to the rapid analysis of surveillance data and use of this data for programme actions[22].

Diphtheria, Tetanus, whole cell Pertussis (DTPw) vaccine

This vaccine is given at 6, 10, 14 weeks of age (primary immunisation) and a booster at 18 months of age (Table 1). The hypotonic-hyporesponsive (HHE) episode that occurs within 48 hours, incidence 1 in 1750 DTPw vaccinations, has led to it being substituted with the DTPa (acellular Pertussis) vaccine in the developed world[23]. Although HHE can also occur after vaccination with DTPa vaccine, the risk is much lower[23]. In India during 1989–1990 more than 18 million children received primary immunisation of DTPw. Of these, 57 developed sudden circulatory collapse and 30 died[6]. However, the GOI cannot afford to replace the DTPw vaccine, as the DTPa vaccine is expensive.

It is important to continue to immunise children against diphtheria and pertussis. Any decline in the DTP immunisation coverage would be disastrous. A recent example is the epidemic of diphtheria in the Newly Independent States of the former Soviet Union causing more than 150,000 cases and 5000 deaths between 1990 and 1996[24]. Most cases (60–77%) and fatalities occurred in adults. A decline in childhood DTP immunisation coverage due to the deteriorated health care infrastructure, decreased public support to immunisation programmes, an altered primary schedule of fewer doses with lower antigenic DTP and giving the second childhood booster of DTP vaccine at 9 years instead of the recommended 6 years led to this diphtheria epidemic[24,25]. Resurgence of pertussis has occurred as a result of parents not immunising their children under the influence of anti-vaccine propaganda. Pertussis incidence was 10 to 100 times lower in countries where high vaccine coverage was maintained (Hungary, the former East Germany, Poland, and the USA) than in countries where immunisation programmes were compromised (Sweden, Japan, UK, The Russian Federation, Ireland, Italy, the former West Germany, and Australia) by anti-vaccine movements[26]. Given the safety and cost-effectiveness of whole-cell pertussis vaccines, far from being obsolete, these vaccines continue to have an important role in global immunisation[26].

Another peculiar situation in India is the frequent administration of tetanus toxoid injections to children by private general practitioners. Often parents do not remember the child's immunisation status or carry the immunisation record card with them. Thus, after every injury the child receives a tetanus toxoid injection. Even though tetanus toxoid is a safe vaccine, frequent revaccination is known to cause hypersensitivity reactions[27].

Measles vaccine

Measles is endemic in India. If a child does not receive the vaccine, natural (wild) measles occurs as early as 9 to 10 months of age. Hence children in India receive the measles vaccine at 9 months of age (Table 1). The UIP began in 1985 and by 1995 some 160 million doses of measles vaccine had been given. Mild-to-moderate vaccine reactions are not infrequent and are accepted by parents. From 1986 to 1994, 1762 batches of measles vaccine were tested and found to be satisfactory by the World Health Organisation criteria and released for mass immunisation. After 40 reported incidents of severe reactions or deaths in the field, 59 intact samples of vaccine produced by different manufacturers were tested and found to be safe, i.e. they were not toxic and were sterile. However, on testing reconstituted or used vials, a few were found to be toxic and many were not sterile. Reactions occurred in 115 vaccinees resulting in the death of 79 children. These reactions were characterised by high fever, vomiting and profuse watery diarrhoea resulting in death within 24 hours. Reactions to the vaccines were more likely to be related to the toxic shock syndrome (TSS) due to the use of non sterile syringes and needles and perhaps the use of reconstituted vaccines beyond their specified time for administration resulting in contamination with *Staphylococcus aureus*[28]. To prevent TSS, the GOI has instructed that the measles vaccine should be used within 4 hours after reconstitution and even during these 4 hours it should be kept on an ice pack to maintain

temperature below 8°C. Whenever such vials remain unused they should be destroyed. This has led to a sharp decrease in the incidence of TSS after measles vaccination[6].

Measles vaccine is now produced indigenously and two studies have documented its efficacy and safety[29,30]. The seroconversion rate was 98.4% and mild side effects such as coryza, fever, and diarrhoea and skin rash were observed in about 30% cases[29,30]. Along with the vaccine, children also receive vitamin A (100,000 I.U.). This is done to achieve maximum cost effectiveness and to improve coverage. Use of vitamin A, as a mega-dose, has been shown to reduce occurrence of respiratory tract infections and diarrhoeal diseases in young children and thus improve child survival[31]. Studies done in Indian children have shown that it is safe to give vitamin A along side the measles vaccine[32-34]. There was no significant increase in the incidence of vomiting, loose stools or fever. No child developed a bulging fontanelle[32]. Also the antibody response to measles vaccine was either enhanced[33] or not affected[34]. In malnourished children the immune response was significantly greater with vitamin A co-administration[34].

However, giving the vaccine at 9 months can result in a primary vaccine seroconversion failure in 5–10% children, as against less than 2% if the vaccine is given at 15 months of age[35]. There is also greater risk of secondary vaccine failure, i.e. seroconversion does occur initially but the protective immunity is lost over the next several years. This has led to a concern that measles resurgence will occur in India and a higher age group will be affected[36]. An outbreak of measles occurs if 30% of the population is susceptible. This figure will be reached as 5–10% children have primary vaccine failure, many remain unimmunised and many over the years would develop secondary vaccine failure. In India the measles vaccination coverage is about 66%[37]. Although the vaccine is freely available under the UIP, many parents do not avail this benefit. This has led to a debate for the need for a booster dose at 4–6 years (school entry age) or at 11–12 years of age[36]. A recent study conducted in a community setting has documented the benefit of giving a booster 6 months after the primary dose[38]. The two-dose measles immunisation helps to reduce the chances of measles occurring in a community[38]. However, the GOI has not yet decided whether a booster measles immunisation dose needs to be included in the UIP schedule.

Rabies vaccine

Rabies continues to be an important public health problem in India. Annually about 700,000 people are still given post-exposure rabies prophylaxis using the outdated Semple (sheep brain) vaccine[39]. The reason for the continued use of the Semple vaccine is its low cost. The GOI cannot afford to provide the newer and safer cell culture rabies vaccines free of cost to the public[39]. The Semple vaccine is not safe as it causes demyelinating central and peripheral nervous system side effects in 1 per 3000–7000 vaccinees, with significant residual handicap. Occasionally the adverse reaction can even be fatal[39].

For patients who can afford to buy the newer rabies vaccines, three types of cell culture rabies vaccines are readily available in the Indian market: human diploid cell rabies vaccine, purified chick embryo cell rabies vaccine and purified vero-cell rabies vaccine. Studies in India have documented the efficacy and safety of purified vero-cell rabies vaccine for post-exposure prophylaxis of rabies both in the hospital setting and under field conditions[40,41]. Mild local and general reactions i.e. local pain and redness, mild fever and malaise were observed in about 7% of the vaccinees[40,41]. To reduce the cost of the cell culture vaccines, intra-dermal vaccination has been tried in Indian adults with category I exposure to rabies[42]. Two intra-dermal regimens, the two-site and the eight-site regimens, have been shown to be both effective and safe[42]. However, the eight-site regimen was more immunogenic. The feasibility of using these cost-effective regimens in routine practice needs to be further evaluated under field conditions prevalent in India.

Japanese Encephalitis (JE) vaccine

JE remains endemo-epidemic in India[43]. An epidemiological study from the state of West Bengal[44] has reported that children in the age group 4 to 7 years are maximally affected and the peak incidence of JE is in the months of October to November[43]. The GOI produces 2 million doses of JE vaccine annually whereas 378 million people live in JE prone areas in India[44]. At present there is no clear-cut policy on mass JE vaccination for a community living in a hyper endemic area. Also the vaccine is not available commercially.

The first trial of JE vaccine in Indian children was carried out in the state of Tamil Nadu[45]. A two-dose primary immunisation schedule (7 to 14 days apart) resulted in seroconversion in 73% children. Minor side effects – fever, headache, local tenderness and itching occurred in 55% of the children after each dose and these lasted for 1 to 5 days[44]. A recent study from West Bengal[44] has shown that it is beneficial to routinely immunise the population at risk for JE in endemic areas. The vaccination was started in March in

the form of two doses given at an interval of 7 to 14 days. A booster dose was given 6 months later in September. The seroconversion rate was 84%. There was a concomitant reduction in the estimated incidence and death rate of JE in the study areas[44].

New vaccines

These include the Measles Mumps Rubella (MMR), Hepatitis B (HB), Hepatitis A (HA), Typhoid, *Haemophilus* influenzae type b (Hib), and Varicella-Zoster (VZ) vaccines, which are now commercially available in India. However they are expensive and the GOI has not included them in its UIP schedule. Neither has the GOI formulated any guidelines for these newer vaccines. A pharmaceutical company that wishes to market a newer vaccine will have to research and prove its epidemiological need[46]. The next step is to obtain permission from the Drugs Controller of India (DCI) to carry out pre-licensing trials to document the vaccine's immunogenicity and safety in Indian children. Once the DCI approves the vaccine for sale in the country, the marketing agency obtains the right to promote it. The pharmaceutical company has to invest funds to manufacture the vaccine, research its epidemiological need, immunogenicity and safety, and also promote its sale. The GOI does not offer any financial support. However, the GOI does take stringent vigilant steps to ensure vaccine quality. Every batch of imported vaccine needs to be cleared by the Central Research Institute at Kasauli, which is the GOI's national control authority[46].

The Indian Academy of Pediatrics (IAP) has taken the initiative to formulate immunisation policies, guidelines and recommendations for the newer vaccines[47,48]. The IAP continues to endorse and support the UIP and its immunisation schedule, recognising the fact that it provides the *basic minimum* immunisation needs of all children in India[47]. The IAP, however, believes that this schedule *must be supplemented* with additional doses of OPV and DTPw and two newer vaccines (MMR and HB vaccines). We too feel that the IAP immunisation schedule, shown in Table 2, would be beneficial to children in India. Until the time that the current GOI's UIP schedule gets revised, the IAP has advised that all doctors should strongly recommend the MMR and HB vaccines to parents who can afford them[47]. For all the other newer vaccines – HA, Typhoid, Hib and VZ vaccines the term "optional" has been used[47,48]. This means that the doctor should discuss their benefits with parents who can afford them. The conversation should lead to the decision to give or not to give an optional vaccine. The doctor should record that such a conversation took place and that the final decision was taken jointly or unilaterally by the parents[49]. Also, the IAP has classified optional vaccines into two categories, namely those (the oral and injectable typhoid vaccines), which are to be actively promoted, and others (HA, Hib and VZ vaccines), which are not to be actively promoted by its members[47,48]. These IAP guidelines have been timely. With the pharmaceutical companies actively propagating the newer vaccines, parents even from the lower middle class and especially in cities have become aware of their availability and are seeking these vaccinations at private clinics in spite of their comparatively higher cost[50,51].

Measles Mumps Rubella (MMR) vaccine

Both mumps and rubella are endemic in India. No official data is available regarding the prevalence of congenital rubella infection. In a recent report from New Delhi, 10% of schoolgirls aged 9–12 years were sero-negative to rubella[52]. A study from Vellore in South India[53] has reported that response to the MMR vaccine was better when given at or after 12 months of age than when given at 9 months of age. A multi-centre study has evaluated the immunogenicity and reactogenicity of an indigenously manufactured MMR vaccine[54]. The vaccine was given at 15 to 24 months of age to children who had already received the measles immunisation at 9 months. Immunogenicity was found to be excellent. For measles the vaccine acted as an excellent booster. Reactogenicity was low with mild side effects such as local pain and swelling, fever, cough, and transient rash observed in 1–6 % of cases[54].

The IAP has strongly recommended that the MMR vaccine be given to every child at 18 to 24 months of age[47]. This will serve to boost measles antibodies and reduce the incidence of both primary and secondary measles vaccine failure and also give life-long immunity against mumps and rubella[36].

Hepatitis B (HB) vaccine

Hepatitis B is a public health problem in India with a sero-prevalence of 3 to 5% in the general population and 3.3 to 4.2% in the under-5 age group[55]. In India the pool of chronic Hepatitis B surface antigen (HbsAg) carriers is built up in childhood and then maintained in older children and adults. This is because pregnant women are not routinely screened for HbsAg. Also Hepatitis B immunoglobulin (HBIG) is unaffordable to most patients. It is known that the risk of perinatal HB virus infection among infants born to infected mothers ranges from 10 to 85%, depending on each mother's Hepatitis Be antigen (HbeAg)

status[56]. Infants who do become infected have a 90% risk of becoming carriers, and up to 25% will die of chronic liver disease in their adult life[56].

Two Indian studies have shown that simultaneous administration of HB vaccine with other UIP vaccines (BCG, OPV, DTPw) results in adequate seroconversion, without any increase in side effects[57,58]. HB vaccine was given within 12 hours of birth, then at 6 weeks and at 14 weeks[57]. A seroconversion rate of 96% was documented[57]. In the second study, a seroconversion rate of 97% with a 6, 10 and 14 week immunisation schedule was documented[58]. The IAP has recommended a HB immunisation schedule during infancy of day 0 (within 12 hours of birth), 6 weeks (along with OPV_1 and $DTPw_1$), and at 6 months of age[47]. This would result in seroconverting all infants born to HbsAg negative mothers and up to 95% infants born to HbsAg positive mothers[47]. For those children who did not receive HB immunisation during infancy, a 0, 1 and 6 months regimen has been recommended[47]. For *all* children a booster dose every 10 years has been recommended[47].

In India the efficacy and safety of the HB vaccine has also been documented in adolescent school girls[59], in malnourished children[60], and in children with thalassemia major who had received multiple blood transfusions[61]. The vaccine was well tolerated with minor side effects like mild fever and local pain. A recent study has recommended that all pediatric cancer patients be screened for HB infection prior to initiating chemotherapy[62]. In these cancer patients, even with an accelerated HB immunisation schedule (0, 1, 2 and 6 months) with 20 micrograms (double the conventional dose), only one-third of the children seroconverted. This was attributed to the immunosuppression caused by the cancer and the chemotherapy. However, it was felt that the benefits of achieving seroconversion even in 30% outweighs the cost of managing morbidity associated with HB disease in pediatric cancer patients[62].

Recently an indigenously manufactured recombinant HB vaccine (Shanvac-B, Shantha Biotechnics, Hyderabad) has been shown to be safe, well tolerated and highly immunogenic, producing 100% seroconversion in premature babies, low birth weight babies, neonates and infants[63,64]. To reduce the cost a lower dose (5 microgram) was given in premature and low birth weight at 0, 1, 2 and 12 months[63], and in neonates and infants at 0, 1 and 2 months[64]. The UIP vaccines were given as per their regular schedule. However, a booster dose after 5 years has been suggested[63].

Hepatitis A (HA) vaccine

Hepatitis A is endemic in India and is a common infection in children. In childhood the illness is usually mild and it induces life-long immunity. Earlier it had been reported that 90% of Indian children in the age group 5–10 years had anti- HA virus antibodies[65]. With improvement in the living conditions many Indian children are not getting infected with the HA virus. Recent seroprevalence studies in children below 5 years of age have reported that 38% in Mumbai[66] and 32% in northern India[67] are anti-HA virus negative.

This has led to a concern whether a vaccination programme against HA is needed in Indian children, especially those belonging to the middle and upper class of society. Although fulminant hepatic failure occurs in less than 0.1% of children with HA virus infection, it carries a high mortality rate of 30%[68]. A recent report has stated that HA virus alone or in combination with HB virus or HE virus is responsible for up to 50% cases of fulminant hepatic failure in young Indian children (mean age 4.2 years, age range 1.5–9 years)[69].

The immunogenicity and safety of a commercially available HA vaccine has been documented in Indian children aged 13–18 months of age[70]. Adverse reactions were mostly mild and comprised local pain and erythema[70]. The IAP has stated that this optional vaccine should not be actively promoted by doctors[48]. However, it may be offered to children from the higher socioeconomic strata of society as they are more likely to escape natural infection and remain susceptible at a higher age, which has the attendant risk of serious illness[48,49].

Typhoid vaccine

In India, typhoid fever is one of the five major infection diseases in children in relation to mortality. Typhoid fever also occurs in a large number of children under the age of 2 years[71,72]. Earlier the classical whole cell killed typhoid vaccine was given under the UIP. It has been shown to be immunogenic in children as young as 6 months of age[73]. However this classical vaccine causes local pain, fever and malaise in up to 25–40% of children[74]. Unfortunately, since 1996 the GOI, for reasons unknown, has stopped manufacturing this vaccine for the UIP. Children in India continue to be at risk from typhoid fever and no vaccine is available on the UIP schedule[46,74].

The newer typhoid vaccines – the injectable Vi capsular polysaccharide vaccine and the oral Ty 21a attenuated live vaccine are commercially available. The injectable vaccine cannot be given

to children below 2 years of age since it is not a conjugate vaccine and does not elicit protective immunity. The oral vaccine requires three capsules to be swallowed on alternate days and children below 6 years are usually unable to take capsules. Thus, only a minority of children, get immunised against typhoid fever. Another problem with the oral vaccine is that parents have to buy a packet of three doses at one time. Even if they arrange money to buy the three-dose vaccine, they may not own a refrigerator, which is mandatory to store the next two doses effectively.

There is no published data on the efficacy and safety of these newer vaccines in Indian children. The injectable vaccine is thought to cause local pain, fever and malaise in up to 5% of children and the oral vaccine low, if any, side effects[74]. A recent meta-analysis has shown that the classical whole cell killed vaccine is more efficient than the newer vaccines in preventing typhoid fever[75]. The IAP has made a recommendation to the GOI to make the classical vaccine available under the UIP[46]. Until the time the classical vaccine becomes available, doctors have been recommended to actively promote immunisation against typhoid fever with the newer vaccines in all communities[48,49].

Haemophilus influenzae type b (Hib) vaccine

A preliminary report of prospective multihospital surveillance suggests a substantial burden of severe preventable Hib disease in India[76]. Nearly all isolates of *Haemophilus influenzae* were from infants and meningitis accounted for 69% of isolates. Overall case fatality was 11% and more than 50% of isolates were resistant to chloramphenicol, and up to 40% were resistant to ampicillin, trimethoprim-sulphamethoxazole or erythromycin[76]. Another Indian study has estimated that *Haemophilus influenzae* causes 75 to 100 cases of meningitis per year per 100,000 children below 5 years of age[77]. Both these studies[76,77] suggest that primary prevention of Hib disease by using the conjugated vaccine would be a rational and beneficial intervention in India. However, the vaccine is expensive and the IAP has termed the Hib vaccine as an optional vaccine and stated that doctors should not actively promote it[48,49].

Four studies have documented the efficacy and safety of Hib vaccine in Indian children when given along with the regular UIP vaccines (OPV and DTPw)[78-81]. Common side effects such as mild fever, local pain with redness and induration occurred as they do with routine DTPw vaccination. In two studies[79,81] both the Hib and DTPw vaccines were mixed in the same syringe, and given as a single injection, with no increase in the side effects.

Varicella Zoster (VZ) vaccine

This is the latest vaccine being marketed in India. Varicella (chickenpox) is a relatively mild illness in childhood. In temperate countries there is almost universal seroconversion, either by clinical or sub clinical infection, occurring by early adolescence[82]. However the epidemiology of varicella in a tropical country like India is quite different. A recent multi-centric study has reported that a significant proportion of adolescents are susceptible to varicella in India[83]. The age-related seroprevalence rate of anti-Varicella Zoster virus antibodies was 29% in the 1–5 year olds, 51% in the 6–10 year olds and 72% in the 11–15 year olds[83]. It is well known that varicella at an older age is a severe illness with a much greater risk of complications. There is no published data on the side effects of this vaccine in Indian children.

The pharmaceutical industry has been advocating vaccinating children at one year of age with this expensive vaccine. The IAP has stated that doctors should not actively promote the vaccine for children below 10 years of age. However, it may be recommended for children above 10 years who have not had varicella previously and only if they can afford the vaccine[48].

Steps necessary to improve the situation

Until recently, in India there was no national body to periodically review the nation's requirement of newer vaccines[46]. The IAP had taken the initiative to form policies and recommendations but its mandate was only restricted to its members. However, the IAP had made a plea to the GOI to introduce HB immunisation in the UIP without any further delay, to make the classical whole cell killed typhoid vaccine available in the UIP schedule and to discontinue use of the outdated Semple rabies vaccine[46]. Also, there is no comprehensive post-marketing surveillance for adverse reactions, however minor, to the newer vaccines. To date there has been only one post-marketing surveillance study to detect adverse reactions to HB vaccine in Indian children which has been conducted by the pharmaceutical company itself[84]. The reason for this is because newer vaccines are generally prescribed by private doctors, who are not duty bound to report adverse reactions to vaccines.

The GOI, under encouragement from the World Bank, has recently constituted the National Technical Advisory Group on Immunisation (NTAGI)[85]. This is a major step forward to improve the immunisation services in the country. The NTAGI has representation from a wide spectrum of important constituencies: the Ministry of Health and Family Welfare, national organisations such as the Indian Council of Medical Research, the National Institute of Biologicals, the National Vaccine Testing Facility, Drugs Controller of India and experts from the IAP, Indian Medical Association and the Indian Association of Preventive and Social Medicine, although non formal members, representatives of UNICEF, the World Health Organisation, and the World Bank will have a presence in the committee as special invitees[85]. The overall purpose of the NTAGI will be to advise the GOI on policies, practices and implementation of the UIP.

It is hoped that the pending issues such as, introducing the HB and MMR vaccines in the UIP, making the classical whole cell killed typhoid vaccine available once again in the UIP schedule, replacing the Semple rabies vaccine by the newer cell culture rabies vaccines, formulating a policy for mass JE vaccination in endemic areas, and starting a Vaccine Adverse Event Reporting System and making it mandatory for the private doctors to report adverse events will now be addressed effectively.

The measure of success of an immunisation programme is not only to measure the vaccine coverage among the eligible childhood population, but to measure the degree of reduction of the target diseases in the community. A functional disease surveillance system is essential if the UIP is to be seen as a successful investment of human power and resources[86]. A practical and low cost model of surveillance is currently being established in the state of Kerala[86]. This district-level disease surveillance model is replicable in developing countries for evaluating polio eradication efforts, monitoring immunisation programmes, detecting outbreaks of old or new diseases, and for evaluating control measures. Such epidemiological data will also help decide if modifications are necessary in the scheduling of routinely given vaccines, for example, whether a booster dose of measles vaccine is necessary or not.

Another avenue which can help update the current UIP immunisation schedule by including newer vaccines, especially the HB, MMR and Hib vaccines is by involving Global Funds in providing financial aid. Although the need for these newer vaccines is immense in developing countries like India, they are not available to children, as the government cannot afford to take this financial responsibility. Once a developing country agrees to devote 0.01% of its gross national product (GNP) to its vaccine procurement, the Global Fund would then step in and take the responsibility to finance the remaining funds[87]. Another suggestion made recently is to make the newer vaccines available free to the poor and to make the middle class pay a nominal amount[85]. Also it has been recommended that the elected representatives of the community should take up the responsibility to provide the newer vaccines to the children in their community[85]. Already in Mumbai, a Member of Parliament has made the HB immunisation available to all children at a very nominal cost. This decentralisation will create a demand for vaccines by the people, which in turn will ensure the quality and the success of a sustainable immunisation programme[85]. The problem of availability of new vaccines can be addressed by visionary thinking, political will, global funding, stringent implementation and networking between the key players involved i.e. the paediatric associations, the pharmaceutical industry and the government. This alone will ensure that children in India can also avail the benefits of the newer vaccines.

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