Newer vaccines in the Universal Immunisation Programme

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Abstract

Vaccines are important preventive medicines for primary healthcare and critical for a nation's health security. In India the Universal Programme of Immunization (UPI), launched in 1985, included six childhood vaccines. A well thought out immunisation schedule must be epidemiologically relevant to the country's health status, covering only diseases that are public health problems and for which effective vaccines are available. There has been pressure from the drug industry to include all newly developed vaccines in the government's UIP, even though the clinical and epidemiological justification for their inclusion is debated. Many developed countries have included several other new vaccines in their regular immunisation programmes. These trends are used as a justification by the industry to include these vaccines in the Indian UIP in the future. All these vaccines need not, and cannot, be given universally. This paper looks at some vaccines which are newly included in the UIP schedule, or which may be included in the near future.

Vaccines are important preventive medicines for primary healthcare and are critical for a nation's health security (1). The World Health Organization (WHO)'s policy under its Expanded Programme of Immunization (EPI), in line with the call for "Health for All by 2000", recommended universal immunisation of all children against six vaccine-preventable diseases (VPD) to reduce child mortality. The EPI was launched in India in January 1978 with the objective of (i) reducing mortality and morbidity from vaccine-preventable diseases of childhood and (ii) achieving self sufficiency in the production of vaccines (2). In the beginning, the EPI included six childhood vaccines: Bacillus Calmette-Guerin, tetanus toxoid, diphtheria-pertussis-tetanus (for children below 2 years), diphtheria-tetanus (for children above 2 and as booster dose), the oral polio vaccine, and typhoid (1).

Universal Programme of Immunization

A revised version of the EPI, the Universal Programme of Immunization (UPI), was launched on November 15, 1985 and included vaccines for six diseases, namely tuberculosis, paralytic polio, diphtheria, pertussis, tetanus and measles, all of which have a major impact in India (2). The typhoid vaccine, which is of low efficacy, was replaced by the measles vaccine, which is of much greater relevance for India. The National Health Policy, 1983, set the goal of universal immunisation by 2000 but this has not been achieved (3). As per data from the National Family Health Survey-III (2005-06), UIP coverage countrywide was just 44% compared to 36% (1992-93) and 42% (1998-99) in previous surveys. Even in Kerala, coverage had actually declined to 75% from 80% (1998-99)(4). The Ministry of Health in its 10th Plan document pointed out that one of the main reasons for this failure was the focus on the campaign mode of programmes in health (3).

Every country has its own immunisation schedule according to what is operationally feasible and socially acceptable (2). A well thought-out immunisation schedule must be epidemiologically relevant to the country's health status and should include only diseases or public health problems for which effective vaccines are available. The vaccines should be immunologically effective and should be given at the right time at appropriate intervals to give maximum protection (2). The United States does not include the BCG vaccine since tuberculosis is not a major problem there. The United Arab Emirates includes the meningococcal vaccine since it is a problem there.

Although international agencies such as the WHO and the United Nations Children's Fund (UNICEF) promote global immunisation drives and policies, the success of an immunisation programme in any country depends more upon local realities and national policies. This is particularly true for a huge and diverse developing country such as India, with its population of more than 1 billion people, and 25 million new births every year (1).

The methods used by economically well-off nations to gain control over poor countries by accessing their markets and creating a demand for medical technologies including vaccines, irrespective of local needs, have been documented extensively. As a new product is being readied, research is published to highlight the number of deaths in the country caused due to the absence of that vaccine (5) The term "public-private partnerships" disguises the role of the pharmaceutical company in such research (5). Many western countries have added several new vaccines to their regular immunisation programmes. These include vaccines for influenza type B, meningitis, chickenpox and a single vaccine for measles, mumps and rubella (MMR). In the last case, our national programme includes only the measles vaccine; the MMR vaccine is costly, marketed by private firms and an optional vaccine in India. These trends are used as a justification by the industry to lobby for inclusion of these vaccines in the Indian UIP (1). Aggressive promotional campaigns for the new vaccines, and their quick adoption by industry-friendly private medical practitioners, have already made these vaccines akin to fast-moving consumer goods. The industry, which enjoys all the benefits of economic liberalisation, sees no contradiction in seeking a captive market for its new vaccines through the government-sponsored UIP while at the same time failing to meet its social responsibility (1).

Since the formation of the Global Alliance for Vaccines and Immunization (GAVI) in 1999, as an international coalition of multiple funding agencies with vaccine manufacturers and non government organisations, the global promotions of vaccinations are decided by GAVI (6). Pharmaceutical companies promote their agendas by funding or otherwise gaining influence over such agencies (5). Based on the WHO-UNICEF scoring system to determine vaccine priority, the following vaccines were recently included in the list as high priority vaccines: pentavalent vaccines (DTP-hepatitis B-Hib), mumps, measles, rubella vaccines (MMR), the rotavirus vaccine, pneumococcal vaccines, and injectable and monovalent oral polio vaccines(the polio vaccine is usually against all three strains but the monovalent vaccine is against type 1 strain). Most of these are either combined vaccines (UIP + non UIP vaccines) or pipeline vaccines, in the last stage of clinical trials or in the queue for marketing (7). The combined vaccines are costlier than single vaccines and they almost never have more efficacy than single vaccines (6,8). The tendency to combine EPI vaccines with non-EPI vaccines not only creates an artificial scarcity for affordable EPI vaccines, it also creates a backdoor method for the entry of expensive and perhaps unnecessary non-EPI vaccines into the universal immunisation programme (5).

The rapid growth (8%-10% per annum) of India's current human vaccine market is mainly attributed to the new, high-priced vaccines (9). There has been pressure from the vaccine industry to include these new vaccines in the government's UIP even though the clinical and epidemiological justification for their inclusion is controversial (9).

For every new drug invented, genomics and bioinformatics are used to customise it to suit different populations. But in vaccines, the tendency is to move toward a "one vaccine fits all" regime (1). Though there were no attempts to conclusively establish that the imported vaccines actually suited the Indian strains of the pathogens, these vaccines were adopted. Also, the undue emphasis on the statistics of vaccine "coverage", rather than the immune protection achieved, makes it seem that spending money on vaccines is more important than actual disease prevention (1).

The government of India does not have access to quality data and high quality expert advice. Even those with expertise on the matter do not tread an independent path, fearing the wrath of their international donors (10). Immunisation matters are left to manufacturers and international organisations, to "guide" and decide what is to be introduced in our market. Governments and academic associations remain mute spectators. Hence, broadly speaking, two nexuses are operating at present -- one between international health agencies and the government, and another between vaccine companies and academic associations. The former has far-reaching consequences on public health while the latter chiefly affects the practices of the private sector (10).

A major flaw is in the approach to vaccines, which most of the time is "vaccine-targeted" and not "disease-targeted". This flaw is more glaring at a time of resource scarcity when our government is spending merely one per cent of its gross domestic product on health (10). The Ministry of Health also planned to include new vaccines by charging the actual costs from people above the poverty line (3). With epidemiology taking a backseat, government decisions on vaccination are increasingly determined by price competition and supply "push" (by the companies) rather than "pull" (demand) from proven public health needs (9).

Self sufficiency in UIP vaccines

The Ministry of Health and Family Welfare (MOHFW) procures and supplies vaccines for the EPI, and provides logistics and cold chain support to the states (11). Over the last few decades, due to the decline of the public sector and the growing disinterest of the private sector in vaccines, the number of firms supplying EPI vaccines has declined drastically, both in India and abroad. Private manufacturers prefer to sell them as "value-added cocktail vaccines" at exorbitant prices in the open market, rather than supply to the EPI (5).

Vaccine requirements for India's EPI have been met mainly through the public sector's vaccine institutions, as was the case in most parts of the world until the 1980s. However, the Indian public sector failed to introduce new technologies of production (such as for production of tetanus toxoid, Diphtheria Tetanus, or DPT-Diphtheria Pertussis Tetanus) or to expand production to become self-reliant in producing the oral polio vaccine or the measles vaccine. In some cases, indigenously manufactured vaccines were stopped in favour of imported vaccines (1).

Shortages of primary vaccines in developing countries began to emerge in the late 1990s due to the introduction of new, more sophisticated and more expensive vaccines in industrialised country markets, leading to manufacturers phasing out the production of the traditional, less expensive vaccines used in developing countries. Between 1998 and 2001, 10 of 14 major manufacturers partly or completely stopped production of traditional vaccines. The outcome of these developments is that the availability of primary vaccines has decreased dramatically, while their prices have increased (1).

Indigenous efforts to achieve vaccine self sufficiency were jeopardised in January 2008 with the closing down of three public sector units (PSUs) by the MOHFW on the excuse that these units did not comply with the WHO's good manufacturing practices (7,12). As a result, during the year 2009-10, between 25% and 100% of various UIP vaccines had to be procured from private companies. The difference between requirement and supply ranged from 137 lakh doses for the BCG vaccine to 409 lakh doses for the DPT vaccine. Even before the closure of PSUs, UIP vaccines were not available to millions of children born in India, and information obtained under the Right to Information Act gave clear evidence of the impact of reduced coverage (13). Following the closure of public sector vaccine manufacturing units in India, UNICEF announced a Rs 143 crore award to Panacea Biotec, a private manufacturing unit in India,

for its pentavalent vaccine "EasyFive" for supply to the whole country for the years 2008-9.(14) In 2009, UNICEF awarded the company a three-year contract of Rs 1,067 crore) for supply for 2010, 2011 and 2012(15). This five-vaccine combination is much costlier than UIP vaccines. UNICEF's actions facilitated the promotion of the pentavalent vaccine in the country.

If these trends continue unabated, they will lead to serious distortions in the vaccination programmes of India and other developing countries in a similar situation (1). Public health funds must be spent according to public health priorities. There are so many diseases and other health problems which require public health measures (16). Amongst these, money spent on vaccine-preventable diseases is the most effective way of spending public funds. But this does not mean that all safe and effective vaccines available must be given in the public health programme. All these vaccines need not -- and cannot -- be given universally (16). In this background, a critical review was done on newly introduced vaccines in India using available literature.

Hepatitis B vaccine

Humans are the only reservoir of the hepatitis B virus (HBV). The virus is transmitted by percutaneous and per mucosal exposure to infected blood and other body fluids, mainly semen and vaginal fluid (17). The mode of transmission and the risk of acquiring infection are similar for HBV and HIV. The WHO guidelines state that countries with less than 2% prevalence of chronic hepatitis B infection can take up a "selective" vaccination programme (18). The WHO dropped this condition in recent years to favour the introduction of new vaccines (5,17).

Where there is very low endemicity, the economic evidence to enable a rational choice between selective and universal vaccination remains inconclusive (17). There is evidence to suggest that routinely vaccinating high-risk adults in settings such as prisons, sexually transmitted disease clinics, drug treatment centres and needle exchange programmes can be cost effective (17)

A national level consultation of experts held at Delhi on May 14, 2006, reported after a meta analysis that the point prevalence of hepatitis B in non tribal populations was 2.1% (95% CI 1.8-2.5) and this corresponded to a chronic carrier rate of 1.7% (19). The majority of hepatitis B carriers go through life unaware of the presence of hepatitis B surface antigens in their body, and unaffected by it and annually, 10% of the carriers become sero negative (19,17). Hepatocellular carcinoma, the major HBV-related cause of death, is rare in India and constitutes only 1.6% of all cancers. The estimated annual deaths attributable to hepatocellular carcinoma due to hepatitis B is approximately 5,000 (20)

The Hepatitis B vaccine was introduced in 36 selected districts in India on a pilot base in 2002 (6) and in 2007 it was incorporated into the UIP in all districts and was to be given to newborns at the sixth, 10th and 14th weeks (2). There were no studies showing whether this abbreviated schedule proposed for India is actually protective in the long term. To prevent transmission of hepatitis from mother to child, the vaccine should be given as soon as possible, ideally within 24 hours of birth (20). Since 70% of carriers are infected in adulthood, immunisation at birth is not crucial (20). Of the 25 million deliveries occurring annually in India, less than 40,000 mothers are probable carriers. The cost of vaccinating 25 million newborns every year is Rs 250 crore: double the budget for control of tuberculosis which kills 5 lakh Indians every year and more than the cost of all other six vaccines being given to children under the National Immunization Programme (16).

There are many instances of interested parties exaggerating the prevalence of Hepatitis B in order to promote the vaccine. The Indian Association of Pediatrics (IAP) which promote these vaccines quotes an article by Thyagarajan et al which estimates the prevalence of chronic Hepatitis B infection in India to be 1.77% by aggregating data from available, published studies in India by different researchers and averaging (8,21). The article is based on a national seminar sponsored by SmithKlineBeecham which markets the Hepatitis B vaccine (21). The authors, based in the United States government's Centers for Disease Control, admitted that the model used to calculate Hepatitis B mortality in India, which enabled them to inflate the figure 50-fold, was flawed (22).

Instead of universal coverage only newborn babies whose mothers are carriers of hepatitis B should get this vaccine selectively within 48 hours (in Indian conditions) of birth, as this infection is passed on to them during birth (16). The IAP schedule is three doses at 0, six and 14 weeks (6).The current UIP schedule recommend a four-dose schedule of the Hepatitis B vaccine, at 0, six, 10 and 14 weeks. In a country like India where less than 40% of mothers deliver in healthcare institutions (4), the extra dose at 10 weeks can be viewed as a luxury and an unrealistic addition to the programme.

Considering the low prevalence of Hepatitis B, and the resource constraints, this vaccine should be limited to babies born to Hepatitis B + mothers. For this purpose, all pregnant women should undergo testing for Hepatitis B as part of the other tests for anaemia and blood grouping. This does not require any additional effort or equipment and the test kit can be bought in bulk by the government for, say, Rs 15-20 (16).

Haemophilus b influenzae

Advocating universal vaccination with Hib, irrespective of an individual country's disease burden and the natural immunity attained within the country against the disease, and not taking into account the rights of sovereign states to decide how to prioritise use of their limited health resources, is an example of the top-down approach of global organisations like the WHO (5).

A prospective surveillance study carried out with 56,153 Indian children under five years of age, over a 24 month period, calculated the annual incidence of Hib to be 7.1 per

100,000 (95% CI 3.1-14.0) :. This project was supported by the Department of Vaccines and Biologicals, WHO (23). The study speculated that the population may have "natural immunity" to invasive Hib disease, which explains the low incidence. The government and public health planners should take note of this latest published study that provides evidence against the need for a Hib vaccine in India (24). A study by the Invasive Bacterial Infections Surveillance Group conducted over four years in six large referral hospitals in India also revealed a remarkably low incidence of Hib disease (25).

Natural immunity due to infections with cross-reacting bacteria may explain the low incidence of invasive Hib disease in India and the reason why this population does not need vaccination with Hib (26). Besides, the cost of the vaccine is so high to that it is not realistic to recommend it in UIP (11).

Rubella

Rubella is a common cause of maculopapular rash illness with fever. The disease has minor complications unless it is contracted in the first trimester of pregnancy (27). The average Indian woman with two pregnancies in her life faces a risk of complications due to rubella for 24 weeks in her whole lifetime (28). Natural rubella infection normally confers lifelong immunity (28). In India about 50% of children acquire rubella antibodies by the age of five years and 80-90% become immune by the age of 15 (29).

Women acquiring rubella in the first trimester of pregnancy can pass the infection to the foetus, resulting in the newborn being born with congenital rubella syndrome (CRS). Reliable statistics on CRS are scant in India but according to the available data its incidence is quite low in India (6,28).

The presence of rubella-specific antibodies in an unvaccinated population is a long-term marker of previous rubella infection. The antibodies persist lifelong and protect the individual from rubella infection (27). A study among unvaccinated girls 10-16 years of age found that 86.5% had antibodies against rubella (27). Another study funded by the Serum Institute of India Pvt Ltd, manufacturers of the MMR vaccine in India, conducted among unvaccinated girls with a mean age of 10.7 years reported that 90% were thus protected despite not being vaccinated (29).

Rubella vaccination is mainly to prevent CRS and not to prevent benign rubella infection (6). For countries wishing to prevent the occurrence of congenital rubella infection including CRS, two approaches are recommended by the WHO : (a) prevention of CRS only, through immunisation of adolescent girls and/or women of childbearing age; or (b) elimination of rubella as well as CRS through universal vaccination of infants, surveillance and assuring immunity in women of childbearing age (28).

In a country like India where the vaccination coverage is below 44%, a strategy of limiting the use of the rubella vaccine to women of childbearing age who are not immune to the virus is essentially free of the risk of altering rubella transmission dynamics, whereas inadequately implemented childhood vaccination runs the risk of increasing the number of adults, including women of childbearing age, susceptible to infection and therefore the possibility of increased numbers of cases of CRS (28).

Haphazard use of the rubella vaccine in young children through public health measures with suboptimal coverage of the target population may be counterproductive as it may shift the epidemiology of rubella with an increase in the number of cases occurring in young adults leading to paradoxical increase of CRS (6). Hence the rubella/ MMR vaccine should not be introduced through public health facilities where immunisation coverage is consistently less than 80% (6), as in India

Rubella vaccines for childhood immunisation as used in the private sector where rubella is not a formal part of the immunisation programmes can affect transmission dynamics and increase susceptibility in women of childbearing age, as recently demonstrated in Greece and in some Latin American countries (28,6).

In India the measles vaccine is already given in the UIP at the age of 9-12 months and the combined mumps-measles-rubella (MMR) vaccine is given at the age of 15 months as an optional vaccine in the private sector. A vaccine trial conducted in India has shown that the MMR vaccine given at the age of 9-10 months has efficacy ranging from 92-100% against these three diseases (30). So giving the MMR vaccine at the age of 15 months following the measles vaccine, instead of giving the MMR at the age of nine months, is an example of wasting our scarce resources for the interest of market forces as India is the largest private manufacturer of the MMR vaccine (11).

Pneumococci

Pneumococci are transmitted by direct contact with respiratory secretions from patients and healthy carriers. Transient nasopharyngeal colonisation, and not the disease itself, is the normal outcome of exposure to pneumococci (31). Middle-ear infections, sinusitis and bronchitis represent the more common non-invasive and less severe manifestations of pneumococcal infection. Information about the burden of pneumococcal disease in adults and elderly people in developing countries is lacking (31). PCV-7, which is currently the only commercially available pneumococcal conjugate vaccine, is licensed in more than 70 countries. The primary dose of PCV-7 consists of three intramuscular doses administered to infants at intervals of at least four weeks, starting at the age of six weeks or later (31). Use in children aged less than five years provides protection for a duration of two to three years (31). PCV-7 covers approximately 50-55% serotypes affecting Indian children, offering about 50 % protection (6). The Indian serotypes 1 and 5 account for about 29% of pneumococcal disease in India and the PCV-7. The vaccine does not contain antigens against these serotypes (6). Relatively little information is available on the outcome of PCV-7 immunisation among children in developing countries.

The following statements in a WHO position paper (31) suggest that the use of the vaccine in India is inappropriate. For pneumonia in children,

> Careful observation is necessary owing to the possibility that conjugate vaccines could result in a significant shift in prevailing pneumococcal serotypes that cause serious disease (p. 95)...[the] use of pneumococcal vaccine should be seen as complementary to the use of other pneumonia-control measures, including appropriate case management and the reduction of exposure to known risk factors, such as indoor pollutants, tobacco smoke, premature weaning and nutritional deficiencies (p. 97)... Changes in the incidence of disease due to non-vaccine serotypes after vaccine introduction need to be evaluated carefully to determine whether they are attributable to the vaccine or to natural temporal changes in serotypes. The replacement phenomenon should be carefully monitored especially in developing countries that have higher rates of nasopharyngeal carriage and disease burden (p. 101).

Using the WHO's standards for radiologically confirmed pneumonia, the efficacy of the vaccine was 35% (95% CI 26-43%) in Gambia and 20% (95% CI 2 -35%) in South Africa (29). These studies showed there was little or no protection against the less specific endpoint of clinical pneumonia (31). The Cochrane database states that PCV 7 does not reduce the incidence of clinical pneumonia (32).

In a study in Finland, the efficacy of this vaccine against culture-confirmed pneumococcal otitis media was 34%; against acute otitis media regardless of cause the efficacy was only 6-7% (31). The benefit from reducing disease caused by vaccine serotypes was partly offset by an increase in disease caused by non-vaccine serotypes of pneumococci and *H influenzae* (31). Poor nations will need to assess its cost utility carefully (32).

When the news of the WHO supporting the introduction of the 7 valent pneumococcal vaccine in India by Wyeth came, the Drug Action Forum-Karnataka (DAF-K) sent a letter (33) to the WHO director general that the DAF:

> ...would like to bring to your notice facts which are really alarming and indicate the strong influence that profit making vaccine companies have on the esteemed WHO. These unhealthy nexus between WHO and the vaccine industry, we fear will have far reaching negative influence on the lives of millions of children all over the world... **for every four children in whom pneumonia is prevented, two children develop asthma because of the vaccine.** Pneumonia is a mild infection treated with antibacterial agent (Sulfamethoxazole / Trimethoprim) at less than $1 per child, according to the WHO protocol. Asthma on the other hand is often permanent and needs repeated inhaled treatment with bronco-dilators and steroids. Asthma is a condition much worse than the one-off pneumonia which is easily treated and cured... So we expect that the vaccine will be voluntarily withdrawn from the market immediately because of this unacceptable risk

DAF-K suggests that the vaccine should be advised only for high risk group children.

Conclusion

India must evolve its own national strategies to meet its vaccination needs within its budgetary constraints. The suitability of imported vaccines to deal with Indian pathogenic strains also needs to be conclusively established wherever necessary. The health security of a nation of India's size cannot be left to the vagaries of global market forces. By reviving the production of closed PSUs, India can even play a major role in meeting the global shortfall in the vaccines procured by UNICEF.

Second, India needs to strengthen its disease surveillance system. This would help to decide between universal or selective immunisation based on unequivocal scientific evidence. It would also help us respond to the changing disease prevalence scenario on the ground, which may call for a move from universal to selective immunisation or vice versa.

Finally, a strong emphasis on in-house research and development is needed in order to ensure that our production technologies are in tune with the times, and in order to negotiate strategic partnerships with outside scientists or institutions and companies.

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Living unrelated kidney donors: ethical aspects of living kidney donation in Brazil

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Abstract

Brazil has established the largest public kidney transplantation system in the world.46.2% of transplants in 2008 came from living donors. The vast majority of these involved relatives of the recipient; less than 8% came from unrelated donors. In 2008, Brazil's health minister proposed banning unrelated donors in kidney transplantation. A large number of the over 35,000 Brazilians on the waiting list for a kidney would be denied a transplant without the use of unrelated donors. Brazilian culture has a unique feature, the "informal family", that is not legally recognised as a "family entity and is bound by affection rather than genetic or legal ties. It is vital that Brazil establishes a regulated, standardised, and ethical system of organ procurement; creates awareness about transplantation in physicians and the public; upgrades facilities and standardises medical care, and enforces legislation for transplantation. However, outlawing the use of unrelated donors would result in injustice for many patients who seek kidneys.

Introduction

Brazil, which occupies nearly half the land area of South America, is the fifth most populous country in the world. The last census in 2007 revealed a population of 189,987,291. Brazil's current constitution defines it as a federal republic. The country also boasts the world's tenth largest economy at market exchange rates. Economic reforms have given the country new international influence. Brazil is a founding member of the United Nations and the Union of South American Nations. It is a predominantly Roman Catholic, Portuguese-speaking, and multiethnic society.

Of course, Brazil has had some struggles as well. The country is grappling with substantial problems characteristic of the developing world, including enduring poverty, urban violence and widespread social inequity. Brazil has among the highest income inequality discrepancies and poverty rates in the world, although these values are declining. In March 2002, 18.5 million Brazilians were living in poverty. In June 2009, this number had dropped to 14.4 million. The Gini Index, which