New combination vaccines: backdoor entry into India's universal immunization programme?

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The recent trend in the Indian vaccine industry to move towards expensive new combination vaccines despite mounting shortages in the supply of affordable primary vaccines is a cause for concern. Combination (cocktail) vaccines and multivalent vaccines are meant to provide protection against multiple diseases, with lesser number of doses. In principle, it is a good idea, to the extent that it shortens the immunization schedule and makes it more convenient to the health workers as well as the people. A time-tested example is DTP, a traditional cocktail vaccine meant for simultaneous protection against diphtheria, tetanus and pertussis, all of which are primary vaccines administered under the Universal Immunization Programme (UIP) of the government. However, considering that all vaccines are not needed for all people in all places at all times, the choice of vaccines to be combined becomes a contentious issue. For example, only a few vaccines (DTP, OPV, Measles, BCG, TT, DT) are universally administered under the UIP through the bulk procurement mechanism of the government, supported by the United Nations Children's Fund (UNICEF) and World Health Organisation (WHO). All other vaccines that do not qualify for universal vaccination are purchased locally on a need basis. However, a cursory glance at the new combination vaccines that are currently available in the Indian market reveals that virtually all of them have combined at least one universally administered vaccine with other non-UIP vaccines (Table 1). This is what raises suspicion that private vaccine manufacturers are using the combination vaccines as a means to push non-UIP vaccines into the UIP through the backdoor.

The latest example of this trend in India is the announcement on 19 August 2005 by the Hyderabad-based Indian company, Shantha Biotechnics Ltd, to launch its first combination vaccine 'Shantetra' against diphtheria, tetanus, pertussis and hepatitis B (http://economictimes.indiatimes.com/articleshow/1205210.cms). In April 2004, the company announced its plans to develop Hepatitis B–DTP combination vaccine with the help of soft loans from the Indian Governments' technology development board (TDB) and the public-sector Exim bank to the tune of Rs 9 crores and Rs 20 crores respectively[1]. Interestingly, the availability of DTP, a UIP vaccine (unlike the more controversial Hepatitis B vaccine or its combination), has declined tremendously over the last decade (http://www.unicef.org/publications/index_4442.html), a problem that seems to have opened up opportunities to the private vaccine manufacturers to fill the void with a 'value-added' combination, rather than supplying DTP alone (Table 2). This trend is also true for other private companies, including domestic ones such as Serum Institute of India, Panacea Biotec, etc. and multinational companies (MNCs) such as Glaxo Smithkline (GSK)[2] and others (Tables 1 and 3). These examples should be seen in the context of the changing nature of the vaccine industry in India (as well as globally) during the past decade and their adverse impact on the Indian government's stated policy objective of self-reliance in vaccine development and self-sufficiency in vaccine production, especially for primary UIP vaccines[3].

Vaccine development and immunization constitute critical components of the public-health policy in any country – more so in developing countries where the government makes and/or buys most vaccines. Yet, recent decades have witnessed a growing gap between demand and supply of primary vaccines[4], attributable in part to the decline of the public sector[5] and the disinterest of the bourgeoning private sector in primary vaccines in favour of more lucrative new vaccines, such as that for Hepatitis B[6], or their combinations. These new vaccines are being pushed into the universal vaccination kit of the government despite the controversy over poor clinical or epidemiological evidence[7,8]. This growing influence of the private sector is a part of an international trend, and has attracted substantial debate[6–9].

The UIP of the Indian government is primarily meant to prevent epidemics. WHO recommends mass vaccination of Hepatitis B vaccine only when prevalence is 2% or more in a population. Accordingly, some countries adopted selective Hepatitis B immunization, whereas others opted for universal immunization, based on epidemiological data and cost–benefit analysis[6,7]. However, in India we do not have any data on incidence or prevalence, and estimates based on small sample data from a few blood banks and hospitals and undue reliance on HBsAg positivity rather than HBeAg positivity raised more questions than answers[7,8,10–12]. The corrected HBsAg positivity data indicate very low incidence and mortality risk below 0.1%[8]. Thus, the disease burden could be several folds less than that of diarrhoea, tuberculosis, malaria, acute respiratory diseases, nutritional disorders or cancer.

The cost–benefit studies on Hepatitis B vaccination in India are as equivocal as the incidence estimates[6,7]. The economics of including Hepatitis B under UIP is prohibitive, despite falling prices. Recombinant Hepatitis B vaccine still costs more than three times all the other EPI vaccines put together. The cost of universal Hepatitis B vaccination equals the total budget allocated for health and family welfare – six times the combined budget of the national programmes against malaria, kala-azar, leprosy, AIDS and tuberculosis. However, the budget for safe drinking water and sanitation was only half the expenditure on hepatitis B vaccination[7] in 2001–02.

The price of Hepatitis B vaccine varies a lot in the open market, especially between domestic and MNCs. The cost of Hepatitis B vaccine is several fold (between 15 to 107 times) more than the cost of DTP vaccine in the open market (Table 2). Even if one assumes that private sector offers Hepatitis B at Rs 20 per dose to supply to UIP (http://www.expresspharmapulse. com/20051215/management05.shtml), the total cost of Hepatitis B vaccine for immunizing 2.5 crore children per annum would be double the total cost of all UIP vaccines put together. It costs an additional 50 crores if the Hepatitis B vaccine is bought at open market prices (Table 4).

The usual argument that the combination vaccines produced by domestic compa-

Table 1. Combination vaccines in the Indian market

Company	Combination vaccine	Brand name	Vaccines in the pipeline/plan
Panacea Biotec, Delhi	DTwP–HB	Ecovac four	Polyvalent pneumococcal and meningococcal vaccines; other combination vaccines
	DTwP–Hib	Easyfour	
	DTwP–HB–Hib	Easyfive	
Shantha Biotechnics Ltd, Hyderabad	DTwP–HB	Shantetra (Aug 2005)	DTwP–HB–Hib
Serum Institute of India Ltd, Pune	DTwP–HB	Q-Vac (Aug 2005)	DTwP–HB–Hib
	MMR	Trisevac (1993)	
	Mumps and Rubella (marketed)	(1993)	
	DTwP–IPV	(1986)	
Biological E Ltd, Hyderabad	DTwP	Tripvac	DTwP–HB
GlaxoSmithKline Pharmaceuticals Ltd, Mumbai	DTwP–HB	Tritanrix-HB (Dec2000)	Meningococcal vaccines
	DTwP–HB/Hib	Tritanrix-Hib	
	DTaP-HB–IPV/Hib		
Bharat Biotech International Ltd, Hyderabad			Combination vaccines
Aventis Pasteur Pvt Ltd, New Delhi	Meningitidis type A & C	Meningococcal A & C	

Source: Compiled from the various announcements made by companies either on their websites or in the media.
DTwP: Diphtheria Tetanus whole cell Pertussis; DTaP: Diphtheria Tetanus acellular Pertussis; HB: Hepatitis B; Hib: Influenza type B; IPV: Inactivated Polio Vaccine; MMR: Measles Mumps Rubella.

Table 2. Cost of DTP, HB and DTP–HB vaccines in Indian open market

	Cost of vaccine per dose (in rupees)		No. of doses required for	Cost of vaccine for full immunization (in rupees)	
Vaccine	Public sector	Private sector	full immunization	Public sector	Private Sector
DTP	2.15	3.00	3	6.45	9.00
HB paediatric dose	Not produced	33.83 (SIIL) 85.00 (CHCL) 140.00 (SBL) 181.00 (GSK)	3	Nil	101.49 (SIIL) 255.00 (CHCL) 420.00 (SBL) 543.00 (GSK)
Adult dose	Not produced	52.63 (SIIL) 170.00 (CHCL) 190.00 (SBL) 323.50 (GSK)	3	Nil	157.89 (SIIL) 510.00 (CHCL) 570.00 (SBL) 970.50 (GSK)
DTP–HB	Not produced	50.00 (SIIL) 80.00 (SBL) 225.00 (GSK)	3	Nil	150.00 (SIIL) 240.00 (SBL) 675.00 (GSK)

Source: Compiled from MIMS India December 2005 and Srinivasarao, *Biospectrum*, 7 December 2005.
GSK: GlaxoSmithKline Beecham Ltd, SIIL: Serum Institute of India Ltd; SBL: Shantha Biotechnics Ltd; CHCL: Cadila Health Care Ltd.

nies are almost 3–5 times cheaper than those of the MNCs is also no consolation, because the total cost of immunizing 2.5 crore children even with the lowest priced DTP–HB combination (Rs 375 crores) is far more expensive than the combined cost of DTP and Hepatitis B (Rs 276.22 crores) (Table 4). It is equivalent to double the annual expenditure on the National Tuberculosis control programme (Rs 186 crores during 2005–06).

India's biotech vaccine market, estimated at Rs 300 crores currently, is said to be growing at over 30% per anum (www.shanthabiotech.com/news_1.html) and the market size for the combination vaccine (DTP + HB + Hib) in India is around 20–25 crores (www.shanthabiotech.com/news_2.html). This is a part of the global trend, as combination vaccine segment is expected to be the main driver of growth in the global vaccine market, currently valued at US$3.6 billion.

Owing to tepid demand and falling prices of Hepatitis B vaccine, some manufac-

Table 3. Combination vaccines in international market

Company	Combination vaccine	Brand name	Vaccine launched in the year	Vaccines in the pipeline/ plan
Sanofi-Pasteur, France	DTaP	TRIPEDIA (paediatric)	1996 (first to licence acellular based DTP)	Pneumococcal vaccines
(Sanofi-Aventis Group)	DTaP	Daptacel (up to 7 years age)	2002 (in US market)	IPV based combination vaccines
	DTaP	Adacel (adults)		
	Hib-TT conjugate	ActHIB		
	DTaP–Hib	TriHIBit		
	DTaP–IPV	Quadracel		Cancer vaccines
	DTaP–Hib-IPV	Pentacel	2006	
	Trivalent Hib type A, B, Split virion	Vaxigrip		Preventive and therapeutic AIDS vaccines
	23 valent pneumococcal polysaccharide	Pneumo23		
	Meningococcal A C Y & 135	Menomune-A/C/Y/W-135		
	Meningococcal A C Y & 135-DT conjugate	Menactra		
	Td toxoids-IPV	Td polio adsorbed		
GlaxoSmithKline Biologicals, Belgium	DTaP	Infanrix	1996 (world first)	MMR + varicella
	DTaP–HB	Tritanrix		
	HepA–HB	Twinrix	1996 (world first)	Priorix tetra
	DTwP–HB-Hib	Tritanrix-Hib	1996 (world first)	(MMR Varicella)
	DTaP/Hib	Infanrix+Hib	1997 (world first)	
	DTaP–IPV	Infanrix+IPV	1997 (world first)	Multivalent meningococcal vaccines
	MMR	Priorix	1997	
	DTaP–Hib–IPV	Infanrix+IPV+Hib	1998	
	DTaP (adults)	Boostrix	1999	Multivalent pneumococcal vaccines
	DTaP–HB–IPV	Pediatrix	2000 (world first)	
	DTaP–HB–IPV/Hib	Infanrix hexa	2000	
	HepA–Typhoid	Hepatyrix	2000 (world first)	Pneumococcal + influenza
	Combined ACW135Y polysaccharide meningitis	ACWY Vax	2003 (world first)	
North American Vaccine Inc, Columbia	DTaP	Certiva		
	DTaP–Hib–IPV			
Wyeth-Lederle Laboratories, New York	DTaP	Acel-imune	1996 (second to licence acellular based DTP)	
	DTaP–Hib	Tetramune		
	DTaP–Hib–IPV			
	Pneumococcal 7-valent conjugate vaccine	Prevnar	2000	
Merck & Co, Inc., USA	MMR	M-M-R II		
	MMR–Varicella	Proquad		
	Hib–HB	Comvax		
	Polyvalent pneumococcal	Pneumovax		
*Chiron, Italy	Hib–DT	Vaxem HIB		
	Trivalent influenza vaccine	Fluvirin		

Source: Compiled from the various announcements made by companies either on their websites or in the media.
*Chiron Behringer is one of the world's largest manufacturers of the vaccines; produces all the DTP, HB, Hib, IPV-based combination vaccines, which are marketed worldwide. (http://www.chiron.com/products/vaccines/pedvaccines/index.html).
DTaP: Diphtheria Tetanus acellular Pertussis; HB: Hepatitis B; Hib: Influenza type B; IPV: Inactivated Polio Vaccine; DT: Diphtheria toxoid; MMR: Measles Mumps Rubella; HepA: Hepatitis A; TT: Tetanus Toxoid.

turers like Pfizer and Cadila Healthcare were in a dilemma whether to remain in the business or not. Pfizer, Wockhardt and Biological E Ltd have already pulled out of Hepatitis B vaccine market in India (*Financial Express*, 15 September 2005, http://www.shanthabiotech.com/news_3.htm). The innovative idea of companies to combine Hepatitis B (or other new non-UIP vaccines) with at least one UIP vaccine not only helps them to avert the above situation with assured markets, but also brings legitimacy to enter the national immunization programme. DTP is an ideal partner for such combinations, as DTP itself is a combination vaccine, and it is the most commonly administered vaccine with a

Table 4. Comparative cost calculations of DTP, Hepatitis B and DTP–HB to immunize 2.5 crore children per year in open market in India

Estimated children born every year	2.5 crores
Total cost of UIP vaccines for full immunization per child **through UIP***	Rs 30.00
Total cost of UIP vaccines for full immunization per child in the open market	Rs 80.00
	(in rupees crores)
Total cost of UIP vaccines for 2.5 crore children per annum **through UIP**	30 × 2.5 = **75.00**
Total cost of UIP vaccines for 2.5 crore children per annum in the open market	80 × 2.5 = 200.00
Total cost of DTP on 2.5 crore children per year **through public sector**	6.45 × 2.5 = **16.12**
Total cost of DTP on 2.5 crore children per year through private sector	9.00 × 2.5 = 22.50
Total cost of HB on 2.5 crore children per year by domestic private company	101.49 × 2.5 = 253.72
Total cost of HB on 2.5 crore children per year by Shantha biotech at Rs 20 per dose **through UIP**	60.00 × 2.5 = 150.00
Total cost of HB on 2.5 crore children per year produced by MNC	543.00 × 2.5 = 1357.50
Total cost of DTP–HB on 2.5 crore children per year through private domestic company	150.00 × 2.5 = 375.00
Total cost of DTP–HB on 2.5 crore children per year by MNC	675.00 × 2.5 = 1687.50
Combined cost of DTP and HB for 2.5 crore children per annum in the open market	22.50 + 253.72 = 276.22

*Kale, A. and Phadke, A., Cost-efficacy of selective versus universal Hepatitis B vaccination in India: A critique of Agarwal–Naiks estimation. A pre-publication draft, CEHAT, Pune, 2000.
The table gives only total comparative cost of vaccines and excludes cost of logistics of immunization, syringes, etc.

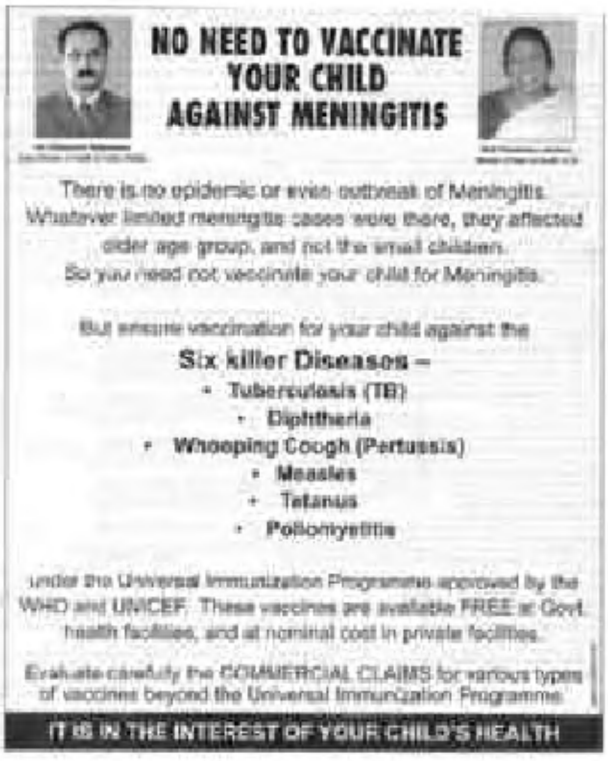

Figure 1. Recent advertisement by the Ministry of Health and Family Welfare warning against 'commercial claims' against various types of vaccines beyond UIP. (*The Hindu*, 7 February 2006.)

worldwide coverage of around 80% and offers life-long protection.

One might argue that as Hepatitis B vaccine is increasingly becoming a part of the UIP, the entire debate about combining a non-UIP vaccine with that of a UIP vaccine is redundant. However, the reality is exactly the opposite, as indicated by a recent advertisement by the Union Ministry of Health and Family Welfare cautioning the public against 'commercial claims for various types of vaccines beyond the UIP' in the context of meningitis (Figure 1). Given that Hepatitis B is not yet fully a part of UIP and the proposal for its inclusion is facing increasing criticism, combining Hepatitis B with a permanent UIP vaccine like DTP could be a more effective way for the industry to get a piggyback ride into the Indian UIP. The very fact that the Union Government is considering a proposal to include Hepatitis B in UIP (*Times of India*, 6 September 2005) is a classic case of policies being driven by supply push (by the industry) rather than demand pull (public-health need) that pinches heavily on the public exchequer. Moreover, there is no objective justification for WHO's policy support to universal Hepatitis B vaccination in India.

The well-meaning but ill-prepared participation of the government in such combination vaccine development projects, as exemplified by soft loans from the TDB and Exim Bank to Shantha Biotech, lends unnecessary legitimacy to the tactics of the industry. However, one could argue that the government of the day might not eventually include this vaccine in UIP, and Shantha will sell it in the open market to pay back its loan. Indeed, this is how Shantha seems to have paid back its earlier TDB loan for the development of the recombinant Hepatitis B vaccine. GlaxoSmithKline and Panacea

are already selling their Hepatitis-B/DTP combination vaccine for Rs 225 and Rs 109 per dose. But then, the general public who do not get the UIP vaccines through the government for whatever reasons, will be sold an expensive combination, which they might not actually need. Shantha Biotech and Serum Institute of India priced their vaccine at Rs 80 and Rs 50 per dose respectively, claiming that their vaccine gives protection against diphtheria, tetanus, pertussis and Hepatitis B in a single shot and is less expensive compared to vaccines produced by MNCs. Effectively, in the name of adding Hepatitis B protection, whose public-health significance in India has yet to be soundly established, the cost of DTP (combination) vaccine will increase 17 fold or more (Table 2). Companies often use irrational drug-combinations and campaigns to persuade the doctors and the public to adopt their medicines and such trends have also been predicted for vaccines[7,13–15].

The issue at stake is not just economics of vaccination with Hepatitis B or its combination, but also whether we need such a vaccine at all and whether it is immunologically safe and effective[16–18]. Evidence accumulating in the literature suggests that combination vaccines give less protection when compared to their individual counterparts[19–21].

The Indian government should recognize these trends and take the following measures to prevent the distortion of its otherwise credible policy objective of self-reliance in vaccine development and self-sufficiency in vaccine production, especially for primary (UIP) vaccines. First, it should actively discourage any combination of UIP vaccines with non-UIP vaccines, so that government procurement (as well as that of UNICEF) of primary vaccines at affordable prices is not affected. Second, government should not fund any combination of UIP vaccines with non-UIP vaccines, unless it is backed by scientific rationale and offers distinct cost–benefit advantages. Third, all the industries that intend to produce combinations based on UIP vaccines (such as DTP) should be forced to produce their traditional versions at affordable prices to meet shortages for public health purposes. Fourth, the ailing national disease surveillance system should be revived and no new vaccine should be allowed into the universal vaccination programme without sound epidemiological basis and thorough cost–benefit studies. National immunization programmes must be led by scientifically established public health needs and not by mere availability of a vaccine in the market, the lure of new technologies or international fashions. The government cannot afford to leave the health security of a nation of India's size to the vagaries of market forces.

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