GAVI and Hepatitis B immunization in India

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Key messages:

The Global Alliance for Vaccines and Immunization (GAVI) supports Hepatitis B immunization in India in better-performing states, where the Indian government has introduced a program that follows the standard DTP immunization schedule. While only one out of four deliveries in India takes place in hospital, Indian health authorities have decided to provide birth doses of Hepatitis B vaccine for hospital deliveries only. This fails to address the key challenge of transmission of Hepatitis B from mother to child at birth. The introduction of routine antenatal screening for Hepatitis B would facilitate selective immunization with birth doses of Hepatitis B vaccine to high-risk infants born to mothers who are chronic carriers. Routine screening could simultaneously provide important data on Hepatitis B prevalence and transmission in Indian populations, which is necessary in order to make well-informed decisions on immunization schedules and accurate estimates of disease burden.

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Abstract:

In cooperation with Indian health authorities, the Global Alliance for Vaccines and Immunization (GAVI) is introducing Hepatitis B vaccination into the national immunization programme of India. This article describes the concerns and interests of major stakeholders in the programme, including GAVI partners and the Indian government, and summarizes Indian debates that have emerged in reaction to the planning and implementation of the pilot phase of the project. It also discusses the plans for the second phase of the project, to introduce Hepatitis B vaccination into the immunization programmes of eleven 'better performing' Indian states. In conclusion, this article suggests as an alternative approach to combating Hepatitis B in India to introduce routine antenatal screening on a nationwide basis, and provide birth doses of the Hepatitis B vaccine to infants most at-risk, i.e. those born to mothers who are Hepatitis B carriers. It also suggests that in a populous country such as India, where there may be large variations in prevalence and transmission of Hepatitis B among different populations, it is ill-advised to use country-level figures as guidelines for recommendations on the administration of birth doses of Hepatitis B vaccine.

INTRODUCTION

The Global Alliance for Vaccines and Immunization (GAVI) has emerged rapidly into the field of child immunization and achieved an unprecedented impact on immunization programmes in recipient countries around the world, fuelling debates about the principles, strategies, methods and results of the new 'global alliances' to combat communicable diseases among the poor. This article investigates GAVI's contribution to India; a project aimed to introduce the Hepatitis B (HepB) vaccine into India's routine immunization programme. It investigates the interests and concerns of GAVI's major stakeholders as well as Indian government policies and priorities, and the implications of these priorities as reflected in the pilot project design and planning of the follow-up phase of the programme. Recent plans of the Indian government aim to introduce the HepB vaccine into the routine immunization programmes of eleven 'better performing' Indian states, administering the monovalent vaccine in conjunction with DTP (diphtheria, tetanus and pertussis). According to these plans the first dose of HepB vaccine is to be administered at the age of six weeks, with the second and third doses administered at ten and fourteen weeks. The plans do not provide for antenatal Hepatitis B screening or routine administration of birth doses of HepB vaccine to the infants most at-risk, i.e. those born to mothers who are carriers of the Hepatitis B virus (HBV).

This articles starts with a basic introduction to the Hepatitis B disease and the available methods of screening and vaccination. It then describes the GAVI Alliance and the organization of Indian immunization services, with a particular focus on HepB immunization. After giving an overview of the GAVI project in India, the article describes the programming choices involved in the project planning, and reviews the

questions raised in Indian debates about the project. The major issues include the use of monovalent versus multivalent (combination) vaccines, the question of disease burden, prioritization of resources and demand on the health care system, and finally the choice of immunization scheduling. This raises the significant question of prevalence and endimicity, especially the relative importance of perinatal HBV transmission among various Indian populations.

GAVI has received criticism for its programmes on several accounts, including inadequate recipient country ownership (McKinsey 2003), local fragmentation in programme implementation (Hardon and Blume 2005), rushed decision-making, problems in the reliability of basic immunization coverage data, high transaction costs and severely limited health system support (ISS insignificance in comparison to total health budgets in recipient countries) (see for instance Brugha et.al. 2002), lack of synchronization with national health system development or other international processes (e.g. sector-wide approaches, poverty reduction strategies and debt relief programmes) (Ollila 2003), problems concerning financial sustainability and overburdening of health budgets in recipient countries (Kaddar et.al. 2004; Lele et.al. 2005) and lack of independent assessments (Lele et.al. 2004). The present paper does not attempt to assess these more general criticisms, but takes an in-depth look at the debates raised by GAVI's contribution to one particular country: India. In order to evaluate these debates it is necessary to investigate how GAVI partners and the Government of India (GOI) have designed the project, but it is equally essential to understand the complexities of HBV, which has a major bearing on the potential results of the project.

THE BASICS OF HEPATITIS B

Hepatitis B is a virus attacking the liver, causing an infection that may (although very rarely) lead to acute Fulminant Hepatitis B and lethal liver failure. The acute infection usually gives symptoms similar to Hepatitis A (jaundice), but in many cases it is asymptomatic, especially in children. If the infection is not cleared it develops into a chronic condition. Chronic Hepatitis B causes liver cirrhosis (scarring) and liver cancer, which eventually leads to death in approximately one out of four cases. Chronic Hepatitis B affects more than 350 million people globally, of which 280 million live in Asia. HBV causes 60–80 per cent of the world's primary liver cancer, which is the number one cause of cancer deaths in males in sub-Saharan Africa and much of Asia, and a significant cause of cancer deaths in women.[1]

HBV is transmitted either vertically from an infected mother to her child at birth (perinatal transmission) or horizontally through the blood, semen or other body fluids from an infected person (as with HIV). Among adults unprotected sex is the most common route of transmission, whereas children may also be infected horizontally, through blood contact with infected persons via breaks in the skin. Infants and young children who contract HBV are the most likely to develop a chronic infection. Whereas only 5 to 10 per cent of adults infected with HBV become chronic carriers, about 90 per cent of those infected during their first year of life and 30 to 50 per cent of those infected between one and four years of age become chronic carriers.[2] Studies further indicate that

[1] PATH, Vaccine Resource Library, Hepatitis B. http://www.path.org/vaccineresources/hepb.php (accessed 17 November 2007).
[2] Centers for Disease Control and Prevention, US Department of Health and Human Services, Hepatitis B Fact Sheet, July 27 2007. http://www.cdc.gov/Ncidod/diseases/hepatitis/b/bfact.pdf (accessed 17 November 2007); World Health Organization, Fact Sheet No. 204. www.who.int/mediacentre/factsheets/fs204/en/print.html (accessed 17 November 2007).

among chronic HBV carriers since birth about 25 per cent die prematurely due to the long-term consequences of HBV infection whereas the equivalent figure for those who contract the infection as adults is approximately 15 per cent.

There are several tests available to establish whether a person has been infected with HBV and whether the virus is replicating itself. The Hepatitis B surface antibody (anti-HBs) is the most common test. A positive test for anti-HBs indicates previous exposure to HBV where the virus is no longer present and the person is no longer infectious. Another test is for Hepatitis B surface antigen (HBsAg), a protein antigen produced by HBV and the earliest indicator of infection, disappearing from the blood during recovery. Testing positive for HBsAg indicates an active infection. If another HBsAg positive test is taken after six months, this indicates that the individual is a chronic carrier. In addition, he or she will also often test positive for Hepatitis B e-antigen (HBeAg), which is a viral protein found in the blood only when the virus is replicating itself.[3]

The HepB vaccine was first licensed in the United States in 1981, and has been marketed since as the first vaccine against a major human cancer. The vaccine was initially derived from blood plasma from HBV chronic carriers, and was so costly that its use was very limited. In 1986 recombinant vaccines became available, using HBsAg protein inserted into yeast cells. In 1991 the Global Advisory Group of the World Health Organization (WHO) Expanded Programme on Immunization recommended that the HepB vaccine should be included in national immunization programmes in all countries with a HBV carrier rate of 8 per cent or more by 1995, and in every country by 1997.

This was endorsed a year later by the World Health Assembly. According to WHO/UNICEF data as of 2004,[4] 153 of 192 member states reported having introduced the HepB vaccine into routine immunization schedules.

The recommendation of the WHO Expanded Programme on Immunization is universal childhood immunization with three doses of HepB vaccine. In countries where perinatal transmission of HBV is important (i.e. all countries with a carrier rate of 8 per cent or more) the first of these should be given within twenty-four hours of birth, to protect against perinatal transmission (WHO 2002a). The overall effectiveness of HepB vaccination is 95 per cent when properly administered (WHO 2002a: 48). As for protection against perinatal transmission, a birth dose of the HepB vaccine and two follow-up doses together with one dose of Hepatitis B immune globulin (HBIG) administered within twenty-four hours of birth is 85 to 95 per cent effective in preventing both HBV infection and the chronic carrier condition, while vaccination alone is 75 to 95 per cent effective (Mahoney and Kane 1999). For the birth dose, only monovalent vaccine can be given, whereas for subsequent doses there is a choice between monovalent and multivalent (combination) vaccines.

In the planning of a Hepatitis B vaccination programme the decision-making process involves choosing between monovalent and combination vaccines, selective and universal immunization, and scheduling to include a birth dose versus scheduling to combine HepB with DTP or other vaccinations. The decision to include the HepB birth dose in a national immunization schedule requires policy makers to factor in the cost

[3] American Association for Clinical Chemistry, Lab Tests Online, Hepatitis B. http://www.labtestsonline.org/understanding/analytes/hepatitis_b/test.html (accessed 17 November 2007).

effectiveness or 'value-added', which means considering the relative contribution of perinatal transmission to the disease burden in their country against the cost of the scheme, including the additional resources required to administer the birth dose. The additional resource requirements may be substantial, especially in areas with limited health care system capacity.

THE GAVI ALLIANCE

Public private partnership (PPP) has emerged as the new formula for health aid provision, especially when it comes to the task of 'combating' communicable disease among the world's poor. The principles, strategies, methods and impacts of the new 'global alliances' has been the topic of heated debate in the community of international NGOs and donors, development policy makers and academics. GAVI has received a fair share of the attention, which is not surprising considering its rapid emergence, funding power and unprecedented impact on immunization decision-making in recipient countries. Since its inception in 2000, GAVI has become the world's most significant global health programme, a leading funder of immunization programmes in developing countries and a major proponent of the 'alliance' model of public private partnerships in health aid.

GAVI is an alliance of private foundations (with the Bill and Melinda Gates Foundation as the major contributor), multilateral organizations, the pharmaceutical industry, donor and recipient countries. GAVI provides country assistance for: (i) immunization services to strengthen delivery capacity, (ii) promoting new and underused vaccines (HepB, Hib and Yellow Fever), and (iii) improving injection safety. In the first

[4] PATH, Vaccine Resource Library, Hepatitis B. http://www.path.org/vaccineresources/hepb.php (accessed 17 November 2007).

five-year phase (Phase I), countries with a per capita gross national income of less than US$1,000 and a DTP-3 coverage rate below 80 per cent were eligible for Immunization Services Support (ISS) grants.[5] As of October 2001, ISS grants represented 28 per cent of total GAVI awards of US$ 113 million, whereas vaccine procurements represented 72 per cent (Brugha et.al. 2002: 11). The ISS scheme was evaluated in 2004 (Chee et.al. 2004), and since 2007 GAVI has provided Health System Support (HSS) grants to 'encourage and enable countries to identify infrastructure and resource weaknesses that are barriers to the achievement of immunization and other public health goals'.[6]

The GAVI Board sets the programmatic policies for the Alliance and monitors all programme areas. It is made up of members representing developing country governments, industrialized country governments, research and technical health institutes, industrialized and developing country vaccine industry, civil society organizations, the Bill & Melinda Gates Foundation, the World Health Organization (WHO), UNICEF and the World Bank Group. The GAVI Alliance Executive Committee was established in 2003 to enhance the strategic decision-making abilities of the Board. Standing Advisory Groups of the GAVI Alliance are the Independent Review Committee, GAVI Working Group, Regional Working Groups and the Monitoring and Evaluation Technical Advisory Group (METAG).

Indian critics have claimed that vaccine industry participation in GAVI was obtained 'on the specific assurance that it would open up developing country markets for newer vaccines', whereas the industry has contributed little to GAVI in return (Kumar

[5] DTP-3 coverage indicates the share of children who have received all three recommended doses of the DTP vaccine.
[6] GAVI website. http://www.gavialliance.org/about/in_technologies/index.php (accessed 23 November 2007).

and Puliyel 2007: 189, citing Hardon and Blume 2005). Such criticisms are dismissed by GAVI (Godal 2002; Le Calvez 2007) with arguments that investments by the GAVI Alliance and other organizations are needed to ensure that appropriate vaccines are developed, manufactured, and accessible to citizens of the developing world. Godal (2002) maintains that vaccine supply is a valid concern for which GAVI provides a much needed stability to delivery systems and demand creation. As for allegations that GAVI is creating profitable new outlets for vaccine manufacturers: 'If the public sector can work to help make the developing-country vaccine environment more attractive to vaccine manufacturers, children living in the poorest countries will have access to better and more effective vaccines' (Godal 2002).

Taking HepB immunization as an example, it is clear that GAVI has played a major role in increasing the demand. When the HepB vaccine was first made available it was priced at more than US$100 per dose, which was far too high for developing countries to introduce the vaccine into their universal immunization programmes. This in turn became an obstacle to its marketability. The procurements of HepB vaccine by GAVI and other organizations (e.g. the Pan American Health Organization Revolving Fund) greatly increased the demand, particularly for the combination vaccines. On the other hand, as new HepB vaccine manufacturers joined the market, competition drove prices down. Until 2004, GlaxoSmithKline was the only manufacturer of HepB combination vaccines to be listed by the WHO as prequalified for purchase by UN agencies. As of November 2007, four other such companies were listed, including one Korean, one Indonesian and two Indian producers. One of them, the Serum Institute of India, was also the developing country vaccine industry representative on the GAVI

Alliance Board in 2003 and 2004. Developing countries represent the largest growth potential for vaccine products today, and the developing world has also become the scene of a truly globalized vaccine industry.

HEPATITIS B IMMUNIZATION IN INDIA

In India the Ministry of Health & Family Welfare is responsible for the planning of health services, providing funding for key components of health programmes, technical and material support to national programmes on communicable disease control, as well as immunization. The bulk of expenditure on public health programmes is borne by the Government of India (GOI) through its own resources, with some funding raised through multilateral and bilateral agencies (GOI 2001). About 85 per cent of immunizations in India are administered by government-funded immunization centres, whereas 15 per cent are administered by the private sector.[7] The latter includes non-profit organizations providing free immunization as well as private clinics charging patients for services.

Several bilateral and multilateral funded programmes have focused on gaps in immunization and health services delivery. In 1999, the GOI negotiated an Immunization Strengthening Project of US$159 million with the World Bank for an International Development Association (IDA) credit of US$143 million, to cover costs for polio eradication, strengthening of routine immunization and new initiatives. The UNICEF-supported Border District Cluster programme also gave high priority to the strengthening of routine immunization (GOI 2001: 2).

As of the late 1990s the HepB vaccine was available in the private sector in most of India's urban areas for a privileged few. In Delhi a pilot Hepatitis B vaccination

programme was started in 1996, using vaccines donated by WHO, to assess the feasibility of including the HepB vaccine into India's Universal Immunization Programme (UIP). Other state level projects led to the introduction of the vaccine into routine immunization schemes in Andhra Pradesh (supported by GAVI through the Vaccine Fund) and Sikkim. These projects all contributed to public awareness and interest in the HepB vaccine, among the medical community, policy makers and the public at large.[8]

A national body called the Inter-agency Coordinating Committee (ICC) was set up in 1995 to coordinate the efforts of various international organizations in India, and avoid duplication. In order to be proactive in its cooperation with GAVI, the ICC decided in 2000 to expand its focus to include all immunization activities, rather than its primary focus on polio eradication (GOI 2001). A smaller Working Group for GAVI was established to work with consultants giving technical support to the UIP and assist the Indian government in its GAVI application, program design and implementation. The members of the working group are WHO, UNICEF, the World Bank, the Children's Vaccine Programme at PATH (PATH-CVP), USAID, the European Commission and DFID, under the chairmanship of the Ministry of Health & Family Welfare.

The first GOI proposal to GAVI was submitted in 2001 and envisaged a phased introduction of the HepB vaccine into the routine child immunization programme, piloted in 15 metropolitan cities and 32 rural districts in 17 states with satisfactory coverage of other UIP vaccines. The ultimate goal of the programme was to reduce morbidity and mortality associated with chronic HBV infection. However, recognizing that the long-term consequences of HBV occur years after infection, short-term goals were defined.

[7] Interview, Ministry of Health & Family Welfare, 15 February 2007.

The principal target was reduction in the prevalence of HBsAg among 3-5 year old children by 55 per cent by 2008, as compared to the prevalence in the pre-vaccine era (GOI 2001).

In GAVI's first five-year phase (2000-2005) funding was allocated on the basis of recipient country birth cohorts, with the exception of maximum allocations of US$40 million each to China, India and Indonesia. Of the total amount allocated to India in Phase I, US$25-26 million was spent on safety AD syringes, while US$15-16 million was spent on supplies of vaccines, procured through UNICEF. The size of these allocations notwithstanding, GAVI and other partners together contribute only 2-3 per cent of India's immunization budget.

GAVI funding is being continued at the same level in Phase II (2006-2015), with India receiving a total of US$100 million over a ten-year period, subject to a mid-term review. The first GOI proposal in Phase II covers the years 2007-2012 and is budgeted at US$86 million. GAVI will provide US$51 million of the total, and the GOI will cover the remaining US$35 million. This will fund a programme to introduce HepB immunization into the UPI of Indian states with DTP coverage of more than 80 per cent. The programme is designed to target the better performing states specifically, so as to 'create an incentive for other states to perform better'.[9] For the second stage of Phase II (2012-2015) the GOI plans to apply for another US$49 million from GAVI, to expand the routine HepB immunization programme to states not covered by the first Phase II project.

According to a background paper prepared for the International Task Force on Global Public Goods (Lele et al., 2005), GAVI's record in integrating immunization

[8] The information on Indian immunization services and programmes is drawn primarily from the 2001 GOI proposal to GAVI (GOI 2001).

programmes into the larger health system has been mixed. The report argues that 'GAVI has focused on the financial sustainability of its own programme but has not been sufficiently involved in debates on overall health policy issues and on the issues of domestic resource availability and resource allocation to immunization vis-à-vis other health sector activities' (Lele et al. 2005: 41). Three problems were cited by the sources interviewed in India: (i) Polio eradication was taking a large share of resources; (ii) the new combination vaccines introduced by GAVI were considered too expensive and it was not politically viable to pilot them in only some parts of the country; and (iii) neither Hib nor HepB were included in the routine immunization programme, there was considerable debate as to India's need for universal HepB immunization, and hence no strong policy consensus on its delivery (Lele et al. 2005: 41). These issues were also brought up by immunization experts interviewed in India in 2007.[10] They suggested that the basic contention between GAVI and the Indian government was that the government prioritized infant mortality reduction, whereas GAVI insisted on the introduction of HepB immunization. According to one interviewee, one of the reasons was that GAVI anticipated a reduction in the unit cost of the HepB vaccine if India with its large birth cohorts included the vaccine in its UIP.

THE DEBATES: MONOVALENT VERSUS MULTIVALENT VACCINES

GAVI has focused on promoting new and 'under-used' vaccines, particularly multivalent (combination) vaccines (DTP-HepB and DTP-HepB-Hib). The argument for using combination vaccines is that it reduces the number of injections required and lessens the

[9] Interview, Ministry of Health & Family Welfare, 15 February 2007.
[10] Interviews with staff of NGOs and the Ministry of Health & Family Welfare, February 2007.

extra demand on health delivery systems. However, the unit cost of combination vaccines is many times those of ordinary vaccines. When the Indian government developed its first GAVI proposal in 2001, the combination DTP-HepB vaccine supplied by GlaxoSmithKline cost nearly US$1.50 per dose, whereas the monovalent vaccine supplied by UNICEF cost about US$0.20 per dose and DTP only US$0.05 per unit. At those prices the cost of using the multivalent vaccine would have come to about four times as much as the monovalent vaccine and DTP vaccines administered separately, considering the cost of syringes as well as the vaccine itself.[11] In 2001 the GAVI board also decided to cap funding to India, China and Indonesia to a maximum of US$40 million each, due to their large birth cohorts. This limited the total funding available to India, and made the cost of the vaccine even more of an issue.

For Indian planners it was evident that even with a considerable reduction in prices, the cost of the multivalent vaccine was far too high to be feasible without continued external assistance (Lele et.al. 2005). However, there was more than simple arithmetic behind the choice of the monovalent vaccine. At least two factors other than price played a role in the decision. One was the likelihood of supply constraints in using multivalent vaccines. In 2001 there were already serious shortages in worldwide supply of multivalent HepB vaccine. Several African countries requesting the combination vaccine in their GAVI proposals had to delay their programmes until the combination vaccine could be supplied or accept the monovalent vaccine instead (Brugha et.al. 2002, Lele et.al. 2004: 27). Secondly, India had its own producers of monovalent HepB vaccine to consider. Although GAVI vaccines were to be procured through UNICEF, the

[11] Interview, India PATH-CVP office, 14 February 2007.

use of the monovalent HepB vaccine in the Indian UIP would boost the sales of India's own vaccine manufacturers.

HEPATITIS B PREVALENCE IN INDIA

The Indian government estimates that India has more than 40 million chronic HBV carriers (GOI 2001). Using this data in a model of disease burden due to HBV, in each birth cohort in India over 1.5 million people develop chronic HBV infection, and nearly 200,000 die of the acute or chronic consequences of the infection. As concluded in the proposal to GAVI: 'Analyses indicate that routine Hepatitis B vaccination of infants in India is highly cost-effective in preventing the economic disease burden on the Indian health system due to Hepatitis B' (GOI 2001).

According to both of India's GAVI proposals, available data indicates that India has intermediate to high endemicity of HBV, with HBsAg prevalence between 2 and 10 per cent among populations studied. The proposals claim that the prevalence does not vary significantly by region (GOI 2001, 2005). However, according to a review of nine studies of HBV prevalence among 21 Indian tribal populations (Murhekar and Zodpey 2005), HBsAg positivity ranged from 1.86 per cent among the Kolli Hill tribes of Tamil Nadu, to a staggering 65.6 per cent among Andaman Islands Jarawas (Murhekar et.al. 2003). The weighted prevalence among the tribal groups studied was 10.15 per cent. Some of these studies were conducted more than 25 years earlier, but as the authors point out: 'in absence of any vaccination program, it does not appear likely that the HBsAg rates could have changed significantly over the years' (Murhekar and Zodpey 2005: 270). A more recent review of 54 Indian studies of point prevalence of HBV (Batham et.al.

2007) confirms the diversity. When tribal and non-tribal populations were analyzed separately the prevalence among non-tribals was 2.7 per cent whereas the prevalence among tribals was 15.9 per cent. The results also showed significant heterogeneity among tribal and non-tribal populations across the country. Although nearly all the studies analyzed in this review were cross-sectional studies indicative of the point prevalence of HBV, an examination of studies that followed up initial HBsAg positive cases for six months revealed that 75 to 80 per cent were found to be chronic carriers (i.e. had continued HBsAg positivity for at least six months). The review therefore assumes that the carrier rate is 80 per cent of the HBsAg point prevalence (Batham et.al. 2007: 669).

In a critical assessment of the estimates of disease burden cited in the government's GAVI proposals, Phadke and Kale (2000) argue that the chronic carrier pool in India is 12.75 million, not the oft-cited 42.5 million. Their estimates are based on the same 19 studies that were used to arrive at the higher figure, excluding studies of dental personnel and blood donors and studies where the numbers tested were unspecified. Phadke and Kale (2000) and other immunization experts call for an evaluation of the cost efficiency of universal HepB immunization in India, arguing that the available data on HBV prevalence is inadequate. The critics further suggest that since perinatal infection is likely to be the most important mode of HBV transmission in India, it is vital to introduce selective immunization of newborns of HBsAg positive mothers.

THE BIRTH DOSE: SELECTIVE VERSUS UNIVERSAL IMMUNIZATION

The key issue in Indian debates on HepB immunization is the controversy between proponents of selective and universal immunization. The Indian government has decided

to provide the birth dose of HepB vaccine for hospital deliveries only, while promising to explore the feasibility of providing the birth dose 'on a larger basis' in the future (GOI 2005: 19). The Indian Academy of Paediatrics also supports universal HepB immunization following the standard DTP schedule. However, some immunization experts disagree with this approach, arguing that HBV should be combated by antenatal HBV screening and provision of birth doses to infants whose mothers are HBsAg positive (Mittal 2003; Mansfield et.al. 2006; Phadke and Kale 2000). Some researchers have argued for universal HepB immunization starting with a birth dose (Jain et.el. 2005),[12] and research has also been carried out to assess the cost-effectiveness of selective immunization (Sahni et.al. 2004).

According to a report prepared for the WHO Regional Office for South East Asia: '[i]n countries in which a high proportion (>40%) of pregnant women are hepatitis B e antigen (HBeAg) positive (e.g., Asia), incorporating a birth dose for all infants is generally indicated. In countries in which a low proportion (<10%) of pregnant women are HBeAg-positive (e.g., Africa), use of a birth dose is encouraged, if feasible (e.g., in birthing hospitals)' (WHO 2002b: 4). This is complicated in India by the lack of studies of HBeAg prevalence among pregnant women, and the fact that the few existing studies provide widely disparate figures.[13] The Indian government GAVI proposals state that HBeAg prevalence among pregnant women who have tested positive for HBsAG ranges between 12 and 47 per cent, 'with most studies showing 18 per cent or less'(GOI 2001, 2005). In fact, the main background document (WHO 2002b) cites only a handful of

[12] Jain et.el. (2005) suggest that the second dose should be administered at six weeks along with DTP and the third dose at nine months along with the measles vaccine.

Indian studies focusing on HBeAg prevalence among HBsAg positive pregnant women, regarded as the main indicator of the relative importance of perinatal transmission. These few studies, which have formed the basis for HepB programme planning in India, were all conducted in the 1980s and 90s (Biswas et.al. 1989; Gill et.al. 1995; Gupta et.al. 1992; Mittal et.al. 1996; Nayak et.al. 1987; Prakash 1998).[14] The number of women tested in these studies range from 850 (Mittal et.al. 1996) to 8575 (Nayak et.al. 1987). The rates of HBsAg positivity range from 2.5 per cent (Gupta et.al. 1992) to 9.5 per cent (Prakash 1998), whereas the rates of HBeAg positivity among HBsAg positive women were measured at 7.8 per cent (Nayak et.al. 1987), 12 per cent (Gill et.al. 1995; Prakash 1998), 18 per cent (Mittal et.al. 1996), 26 per cent (Gupta et.al. 1992) and 47 per cent (Biswas et.al. 1989). Figures of 18 per cent and lower were found in several studies from North India and Mumbai, whereas the higher figures (26 and 47 per cent) were measured in studies from Chandigarh. This suggests that there may be considerable geographical variations within India in the rate of perinatal transmission, which warrants further studies to resolve the reasons for such differences. A multi-centred study is called for by Tandon et.al. (1996a), also referring to an unpublished study from Madras showing a 34.2 per cent HBeAg positivity rate.

Despite the discrepancies in the early studies, Indian experts who support universal HepB vaccination without the birth dose commonly cite the study by Nayak et.al. (1987) as evidence that only 7.8 per cent of HBsAg positive pregnant women in India are chronic carriers. Based on these figures they argue that perinatal transmission

[13] Contradicting the WHO recommendation (2002b: 4), Toteja et.al. (2007) argue that a systematic review of the literature on Hepatitis B vaccination fails to demonstrate that the carrier rate can be reduced by HBV immunization starting at six weeks.

of HBV is infrequent in India whereas horizontal transmission in early childhood, due to crowded and unhygienic living conditions, is the major cause of HBV transmission among children (see Tandon et.al. 1996b). This view is shared by Aggarwal (2002, 2004; see also Aggarwal and Naik 1994, 1996; Aggarwal and Ghoshal 2004), who argues that selective immunization has a poor effectiveness in preventing HBV transmission because perinatal transmission is responsible for a relatively small share of chronic carriers.

A common estimate circulating in numerous Indian studies during the past two decades is that about one third of HBV carriers in India are the result of perinatal infection, while two thirds are the result of horizontal infection.[15] This is now being challenged. The relative importance of perinatal transmission was a topic of heated debate among Indian experts on HBV at the National Consultative Meeting on Immunization, convened by the Indian Medical Association in May 2006.[16] According to some of the discussants perinatal transmission may account for at least 40 per cent of chronic carriers in India, and perhaps as many as two thirds of the cases. As these debates illustrate, there are major disagreements among Indian immunization experts on the importance of perinatal HBV transmission, and there is clearly a need for comprehensive multi-sited and community-based research on HBV prevalence and transmission. This would help assess the actual risk of perinatal HBV transmission among different populations, and the cost-effectiveness of selective vaccination with the birth dose.

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[14] A more recent study is Chakravarty et.al. (2005), a community study which included HBeAg as well as HBsAg testing of women of childbearing age in eastern India.

[15] According to Aggarwal (2004: 66), only about 14 per cent of chronic HBV infections in India are caused by perinatal transmission.

[16] See Report of the National Consultative Meeting on Hepatitis B and The Polio Eradication Initiative http://www.imanational.com/Hepatitis/Report.htm (accessed 18 November 2007) and Discussion by members at the IMA meeting on Hepatitis B http://www.imanational.com/Hepatitis/DiscussionHepatitis.htm (accessed 18 November 2007).

ANTENATAL SCREENING FOR HBV: IMPORTANT SYNERGIES

In India only 25 per cent of deliveries take place in hospitals, but the same national health survey (India, DLHS-RCH, 2002-04) shows that 73 per cent of pregnant women make use of antenatal services at least once during pregnancy.[17] Antenatal check-ups are more common among younger women in the 20-24 age group (78 per cent).[18] In terms of demand and coverage of basic services, a HepB immunization programme targeting those who are most at-risk is feasible provided that training and health systems development support is made available. Such support would have very significant synergy effects for health systems improvement as detailed in the Action Plan for Child Health and Survival of the National Population Policy (GOI 2000). For instance, to improve the accessibility and quality of maternal and child health services, the action plan suggests to deploy community mid-wives and additional health providers at village levels, and provide routine immunization facilities and delivery rooms at sub-centre levels. It suggests that staff of the sub-centres should be responsible for registering every pregnancy and child birth in their jurisdiction, and for providing universal antenatal and postnatal services. The inclusion of STD/RTI and HIV/AIDS prevention, screening and management in maternal and child health services is listed among the action plan's programme development measures, and it would make sense to add on measures for HBV screening and the administration of birth doses of HepB vaccine to this programme.

[17] Reproductive and Child Health, District Level Household Survey 2002-04, (DLHS-2), International Institute for Population Sciences and GOI, Ministry of Health and Family Welfare. http://www.rchindia.org/dlhs_india.htm (accessed 23 November 2007).

In light of the limited information currently available on HBV transmission among Indian populations, and the potentially high risk of perinatal transmission, Indian health authorities should introduce routine antenatal HBV screening and provide birth doses to all infants whose mothers test positive for HBsAg. Through such routine screening HBV carrier rates could be monitored throughout the country, which would provide valuable information on HBV prevalence in different parts of the country and among different populations. Such a programme would also have important synergy effects, especially with measures to prevent HIV/AIDS infection in infants.

CONCLUSIONS

For donors, it should be clear that Hepatitis B is not a childhood disease and support to HepB immunization does not decrease infant mortality. Secondly, it is tempting to interpret high immunization coverage figures such as those provided by GAVI as an indicator of a programme's 'success', but this is not necessarily the case. When it comes to a complex disease such as Hepatitis B, immunization coverage does not translate directly into disease prevention. There are still many unanswered questions regarding the impact of different immunization schedules on disease prevention among particular target groups, especially in populations with high rates of perinatal transmission.

The use of country-level figures in WHO recommendations regarding the administration of the birth dose is inadvisable and potentially misleading to policy makers in developing countries. In large and populous countries such as India it is critical to conduct studies of prevalence and transmission across the country to establish the

[18] India, DLHS-RCH, 2002-04, chapter 4, p. 68. http://www.rchindia.org/dlhs_india/chep4.pdf (accessed 23 November 2007).

degree of geographical variation and identify communities and target groups most at-risk. The limitations of available studies of HBV prevalence in India has been ignored when the share of chronic carriers among the HBsAG positive has been assessed as relatively low. Considering the limited and inconclusive information on HBV prevalence among Indian populations it is far too early to dismiss the importance of perinatal HBV transmission. A good knowledge of HBV prevalence and transmission is necessary in order to make well-informed decisions on HepB immunization, as well as accurate estimates of disease burden.

GAVI has been criticized for its lack of attention to health systems development, which is now being addressed by the Phase II Health Systems Support scheme. Despite these improvements it is important to keep in mind that GAVI was primarily set up to increase vaccination coverage of 'under-used' vaccines such as HepB through their introduction into the universal immunization programmes of recipient countries. GAVI funding does not cover the research and evaluation that is essential to effective programme planning in recipient countries, which are by definition among the poorest countries in the world. This is a major weakness of the 'GAVI formula'.

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