CONTINUOUS MEDICAL EDUCATION

Global Viral Hepatitis Strategy: Issues with Hepatitis B Immunization in India

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Citation

Pathni AK, Pathni R. Global Viral Hepatitis Strategy: Issues with Hepatitis B Immunization in India. Indian J Comm Health. 2017; 29, 3: 308-313.

Source of Funding: Nil **Conflict of Interest:** None declared

Article Cycle

Received: 16/08/2017; **Revision:** 26/08/2017; **Accepted:** 15/09/2017; **Published:** 30/09/2017

Abstract

Hepatitis B vaccination, a key component of the recently adopted Global Viral Hepatitis Strategy, has been plagued by various issues since its introduction under the National immunization program in India. While the concerns relating to the inclusion of the vaccine under the Universal Immunization Program, the vaccination strategies adopted and prevention of mother to child transmission of hepatitis B have been largely resolved, data from recent research has underscored the need for regular monitoring of immunological and epidemiological outcomes of the vaccine. Controversies surrounding the safety and efficacy of the recently introduced combination pentavalent vaccine have highlighted that besides reinforcing surveillance of adverse events following immunization in the public sector, the private health sector in the country needs to be supported in this activity by increasing awareness and strengthening public-private collaboration

Keywords

Hepatitis B; immunization; Pentavalent vaccine; AEFI; Global Viral Hepatitis Strategy

Introduction

As countries gear themselves to meet the challenges of an ambitious set of Sustainable Development Goals by 2030, the World Health Organization has developed three global health sector strategies to tackle HIV, viral hepatitis, and sexually transmitted infections. On 28th May 2016, at the 69th World Health Assembly, Governments worldwide unanimously voted to adopt the first ever Global Viral Hepatitis Strategy 2016-21 with the overarching goal to eliminate viral hepatitis as a public health threat by 2030 (1). Hepatitis B virus (HBV) vaccination is one of the essential interventions under this strategy, with a global target of increasing routine childhood vaccine coverage to 90% by 2020 (2). India has over 40 million HBV carriers and accounts for 10%–15% of the entire pool of HBV carriers globally. It has been estimated that, of the 26 million infants born every year in India, over one million run the lifetime risk of developing chronic HBV infection (3). There are varying reports of overall rate of HBsAg positivity among the general population in India, ranging between 2%–4.7% (4). A meta-analysis of the prevalence of HBV had estimated that the population weighted point-prevalence of hepatitis B among nontribal and tribal populations was 3.07% (95% CI: 2.5–3.64) and 11.85% (CI 10.76–12.93) respectively and the overall prevalence was 3.70% (CI: 3.17–4.24), corresponding to a chronic carrier rate of 2.96% (5).

The Government of India introduced the hepatitis B immunization program as a pilot project in 2002–03; and extended it to 10 States in 2007–08 (6). In 2011–12, the HBV vaccine was included in the Universal Immunization Program (UIP) in the entire country (7). However, various issues and controversies have dogged the inclusion of the vaccine under the National program, culminating in the submission of a petition against the combination pentavalent vaccine to the Prime Minister's Office in November 2014 by a group of eminent doctors and academicians (8). This article attempts to review the available evidence and summarize these issues in a coherent and objective manner.

Hepatitis B Vaccination

Inclusion of the HBV vaccine under the National Universal Immunization Program: The vast majority of chronic carriers remain completely asymptomatic throughout their lives. Without evidence of significant morbidity and mortality due to HBV in the country, the introduction of the vaccine under the National UIP has been questioned in the past (9-11). Long term consequences of HBV infection depends on the chronicity of infection which in turn depends on the age at acquisition of infection – the younger the age at infection, the greater is the likelihood of development of chronicity. Among children who are under 5 years of age at the time of infection, fewer than 10% are symptomatic. However, 80%–90% of infected infants, and 30%–50% of children infected between 1–4 years of age, develop a chronic infection. In contrast, while 30%–50% of adults are symptomatic when first infected, only 2%–5% go on to develop a chronic infection (12). Persons with chronic infection often do not become sick from their infection for decades after becoming infected, but are at risk for developing either hepatocellular carcinoma (HCC) or cirrhosis, hence contributing to significant morbidity and mortality. Globally, 30% of cirrhosis and 53% of HCC has been attributed to chronic HBV infection (13).

Studies have shown that the pool of chronic carriers of HBV in India is built up in childhood and then maintained in older children and adults, underscoring the need for completing hepatitis B immunization during infancy (14). It is estimated that every year, more than 25,000 people die in India because of liver cancer (15). A systematic review of published studies estimated that the population attributable fraction of liver cancer deaths was 67% for HBV, 17%–19% for hepatitis C virus (HCV), and 71%–72% for HBV and/or HCV. The annual attributable number of liver cancer deaths was approximately 17,000 for HBV; 4,500 for HCV; and 18,500 for HBV and/or HCV (16).

The primary aim of immunization is prevention of HBV infection and its consequences, especially chronic infection. As the risk of infection begins during infancy, immunization must also start in early infancy. Although infection is mostly asymptomatic in infancy and childhood, the risk of chronic infection is highest in infancy (17). Considering these facts, and because of its safety, efficacy and wide availability, the WHO has recommended the inclusion of HBV vaccine in the national immunization programs of all countries (18).

Selective versus Universal Immunization: Isolated studies among the Indian pediatric population have shown HbsAg positivity ranging from 2.1%-5.2% in the 0-5 year age group (14, 19-21). A study on the role of horizontal transmission among household contacts of patients with HBV-related chronic liver disease in north India showed that the highest HBsAg prevalence was seen in the pediatric age group (1-15 years: 37%) and especially in siblings (48.3%) ($p<0.001$) of household contacts (22). A large study from Northern India documented HBsAg carrier rate in antenatal mothers to be 3.7%. HBeAg was found in 7.8% of these carriers and vertical transmission was observed in 18.6%. Taking into account the low percentage of possible vertical transmission, it has been estimated that HBV infection in India is largely acquired by horizontal transmission in childhood, and perinatal transmission plays a less important role (23).

The spread of HBV from child to child and adult-to-child usually happens in household settings but may also occur in daycare centres and schools as infected children and most chronically infected adults look healthy and are unaware of their infection. The exact mode of horizontal transmission is not defined but as the virus can survive for at least 7 days outside the body and can be found in high titres on objects even in the absence of visible blood, it is suggested that transmission may be due to contact of non-intact skin or mucous membranes with tears, saliva or blood containing secretions or through sharing of towels or toothbrushes (12).

Screening of all pregnant women during antenatal period and selective immunization of infants born to HBsAg positive mothers will not prevent horizontal acquisition of HBV later on in life. In addition, the

cost of screening followed by vaccination is greater than the cost of universal vaccination and impractical in the Indian scenario where antenatal care and hospital delivery are not assured for all pregnant women. Thus the approach of screening followed by vaccination will not prevent a substantial part of even the vertical transmission (9). Accordingly, universal immunization with HBV vaccine has been recommended in the country.

Prevention of mother-to-child transmission of hepatitis B: Mother-to-child transmission of HBV usually happens at the time of birth and the risk of perinatal transmission depends on the HBeAg serostatus of the mother, ranging from 70%–90% for HBeAg positive mothers to 5%–20% for HBeAg negative mothers. In-utero transmission is relatively rare, accounting for less than 2% of perinatal infections and there is no evidence that HBV can be spread by breastfeeding (12).

HBV vaccination and one dose of hepatitis B immunoglobulin (HBIG), administered within 24 hours of birth, are 85% – 95% effective in preventing both HBV infection and the chronic carrier state if the mother is HbsAg positive. HBV vaccine administered alone is 70%-95% effective in preventing perinatal HBV infection (24). Routine infant immunization programs have shown that the currently available vaccines confer as much protection upon the infants as does a combination of vaccine and HBIG, and that the additional expenses for the administration of HBIG can be avoided (25). However, a Cochrane review conducted in 2006 showed that HBV vaccine plus HBIG were more effective than HBV vaccination alone in preventing vertical transmission of hepatitis B (26). The Indian Academy of Pediatrics Advisory Committee on Vaccines & Immunization Practices (IAPCOI) recommends that if the mother is HBsAg positive (and especially HBeAg positive), the baby should be given HBIG along with HBV vaccine within 12 hours of birth. Routine testing for anti-HBsAg levels one month after completion of the immunization schedule is recommended in children born to HBsAg positive mothers and titers >10 mIU/ml are considered protective. Non-responders should be tested for HBV carrier status and if negative, the same three dose schedule should be repeated. Almost all respond to a 3 dose revaccination schedule (27).

Vaccination schedule: The standard three-dose HBV vaccine series consists of two priming doses administered one month apart and a third dose administered 6 months after the first dose. The vaccine is highly immunogenic and seroconversion rates are greater than 90% after the recommended three dose schedule. Increasing the interval between the first and second dose of HBV vaccine has little effect on immunogenicity or final antibody concentration, whereas longer intervals between the last two doses result in higher final antibody concentrations. Based on the latest IAPCOI recommendations for routine use in office practice, the final dose in the HBV vaccine series should be administered no earlier than age 24 weeks and at least 16 weeks after the first dose. However, HBV vaccine schedules are very flexible and there are multiple options for adding the vaccine to existing national immunization schedules, considering the programmatic implications and logistic issues (27). The current national policy in India recommends that children receive 3 doses of HBV vaccine, administered concurrently with DPT and oral polio vaccine at 6, 10 and 14 weeks. In addition, a birth dose is recommended for all newborns (within 24 hours of delivery) for all institutional deliveries. As per 2013-14 data, the HBV vaccination coverage of children was 34% for the birth dose (62% for institutional deliveries) and 71% for the third dose (28). An assessment of HBV vaccine introduction and usage in the country conducted in 2009 concluded that there was a need for focused attention on administration of the birth dose in order to improve coverage (29).

Data are limited regarding long-term protection for schedules with shorter intervals. Few studies have shown that HBV vaccination at 6, 10 and 14 weeks or 0, 1 and 2 months produces a high seroconversion rate but substantially lower antibody levels than the 0, 1 and 6 months schedule (30, 31). However, WHO recommends the closely spaced schedule, asserting that while longer dose intervals may increase the final anti-HBs titres, it does not impact the seroconversion rates (32).

HBV immunization ought to induce more than 95% seroconversion and significantly lower breakthrough infection frequency than in the unimmunized, and zero incidence of chronic infection (6). However, a recent retrospective cohort study found that vaccination did not reduce HBV carrier rate. HBsAg positivity was seen in 0.15% among the vaccinated compared to 0.17% in those not vaccinated (P = 0.855). In addition, while anti-HBc, a marker of exposure to HBV infection (but not to HBV vaccine),

was higher among unimmunized children (1.79%), it was also present in 1.05% of the immunized children. At 6 and 11 years of age, protective levels of anti-HBs antibody were present only in about 59% and 13% of those immunized respectively (33). Based on the results of this study, the efficacy of the current nationally recommended HBV vaccination schedule was called into question (6). However, the study emphasized that despite the disappearance of anti-HBs, due to immune memory, such immunized individuals continue to be protected against clinical illness as well as chronic HBV infection on exposure to this virus (34-36). Another study showed that proper vaccination was efficacious in reducing the disease burden among tribals of Andaman and Nicobar Islands over a decade (37). It is important to note that these results were of a stand-alone HBV vaccine, and not the combination pentavalent vaccine.

Safety and efficacy of combination pentavalent vaccine: The combination pentavalent vaccine includes vaccines against hepatitis B and Haemophilus influenzae type b (Hib) in addition to diphtheria, pertussis, and tetanus (DPT). GAVI (formerly known as the Global Alliance for Vaccines and Immunizations) and WHO recommended the use of the combination pentavalent vaccine in developing countries to replace the DPT vaccine in order to increase the uptake of the hepatitis B and Hib vaccines in these countries by leveraging the well-accepted DPT vaccine (38). In 2008, the National Technical Advisory Group on Immunization (NTAGI) recommended the inclusion of the combination pentavalent vaccine in the UIP (39). This decision was supported by funding from GAVI to the Government of India for the introduction of the vaccine. However, there were several concerns regarding its safety and efficacy (40).

The combination pentavalent vaccine is not licensed for use by the Food and Drug Administration (FDA) in the USA, nor is it used in other developed countries. Given the background of unexplained deaths associated with the vaccine when it was introduced in other countries of South-East Asia, the NTAGI mandated that initially it be introduced in the immunization programs of two states (Tamil Nadu and Kerala) in order to monitor its safety. In the first six months after the introduction of the vaccine in Kerala, 40,000 children were vaccinated and five of them died of adverse events following immunization (AEFI). By the end of one year, 14 children had died. After the initial pilot, the program was gradually extended to all the other states/Union territories. The pentavalent vaccine from Serum Institute of India (Pentavac) was introduced in the country in December 2011 and 83 serious AEFI were reported by the first quarter of 2013, some of which were associated with fatality (41). The GoI and WHO cleared this vaccine as apparently no causal association between administration of the vaccine and death of children could be found. The IAP also endorsed the continued use of pentavalent vaccine in the UIP (42). However, concerns were raised about the changes effected by the WHO to the AEFI assessment methodology (43).

While the majority of children in India receive immunization through public health facilities, 10%-20% of total immunization in the country is provided through the private sector. The National AEFI surveillance and reporting guidelines that were revised and updated in 2010 envisage a limited role of the private sector reporting (44). In addition, individuals receiving vaccines in the public-sector could receive medical care for AEFI in the private sector. While the government is gradually strengthening the AEFI surveillance for UIP vaccines, and the AEFI surveillance and reporting from the private sector is limited (45).

Conclusion

In keeping with the Government of India's commitment to the 2030 Agenda for Sustainable Development, the inclusion of the HBV vaccine under the country's Universal Immunization Program is indisputable. However, issues related to the vaccine schedule and immunogenicity need to be investigated further. Safety and efficacy issues related to the use of the combination pentavalent vaccine need to be continuously monitored and reported to the appropriate authorities.

Recommendation

Further programmatic research is needed to determine the efficacy of the current recommended HBV vaccination schedule to ensure optimum immunological and epidemiological outcomes. In addition, it is necessary to develop a link to report AEFI cases from the private sector to the public health authorities (46). Hence, besides regular sensitization of public sector healthcare workers at all levels to the AEFI guidelines, there is an urgent need for improving AEFI surveillance in the private

sector by increasing awareness, involvement and strengthening public-private collaboration.

Relevance of the study

A critical analysis of HBV immunization program in India highlighting issues relating to vaccine schedule, efficacy and safety.

Authors Contribution

AKP contributed to the concept, design, literature search, manuscript preparation and review. RP contributed to the design, analysis, manuscript editing and review. All authors read and approved the final manuscript.

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