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NATIONAL HEALTH POLICY CHALLENGE

Hepatitis B Vaccination in Bangladesh: a Suggestion Based on Current Evidence

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Introduction

The hepatitis B virus (HBV) causes up to a million deaths worldwide and 16 million health care related infections in the tropics each year[1,2], and over 350 million become chronically infected carriers who have no significant liver disease; approximately three quarters of them are in Asia and the western pacific region[3,4]. HBV infection is a potentially life threatening condition as many of the affected individuals progress to chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC)[3].

In infants and children, acute hepatitis B infection is nearly always asymptomatic, whereas in adults it is usually the opposite. But on the other hand, the risk of becoming chronic carriage is much greater in children than in adults; as many as 90% of infants born to Hepatitis B e Antigen (HBeAg) positive mothers become carriers themselves and, therefore, in long term are more likely to develop chronic liver disease[5].

Currently, though several antiviral drugs are used, there is no reliable curative treatment for HBV once it has been acquired and prevention by universal immunization remains the strategy for reducing the number of acute infections, chronic carriage and the long-term burden from diseases such as HCC[4,6].

In 1991, in an attempt to reduce the global impact of HBV infection, WHO recommended that hepatitis B vaccination should be integrated into national immunization programs in all countries[7]. Some Asian countries, for instance, Thailand, have adopted the policy of immunizing children universally against the disease as early as 1992, however many others lagged behind[4].

The true prevalence of Hepatitis B in Bangladesh is yet to be ascertained by a reliable study. Data available from different studies show that it ranges between 0.8 and 5.4% depending on the study design, samples and laboratory methods used[8-10]. These data were based on detection of HBsAg antigen; the rates would have been higher, had they been based on anti-HBc antibody[11]. Relying on these statistics Bangladesh can be categorized as an intermediate endemic zone for HBV[12].

Unfortunately, despite an increased prevalence of HBV infection, the country has not incorporated hepatitis B vaccination into its national childhood immunization policy until recently, most probably because of its economic constraints. Presently it offers three doses hepatitis B vaccine to all babies. It is felt that the current regimen was drawn in on the basis of ongoing uncertainties and disagreements surrounding the vaccine all over the globe.

Uncertainties Surrounding HBV Immunization

The rationale of HBV immunization is illustrated in the box; however uncertainties surrounding HBV immunization do exist, these are:

Box. Rationale of Hepatitis B Immunization

The rationale of HBV vaccination is to prevent:

- Episodes of acute hepatitis B
- Chronic hepatitis B surface antigenaemia
- Chronic hepatitis and the need for therapy
- Hepatocellular carcinoma
- HBV transmission

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• *Duration of vaccine- induced immunity:*

It has been shown that immunization with three doses of HBV vaccine provides acceptable level of seroprotection for at least five years[13]. Titers decreased to <10mIU/mL in between 12.6 and 18.4% of 14-year-old teenagers previously vaccinated at 9 years of age. One month after a booster, >99% of the 14 year olds had titers of ≥10mIU/mL while one year after the booster <1.5% had antibody titers below this level[13]. In addition, vaccination can provide long-term protection for at least fifteen years[12,14]. Although, after vaccination the levels of antibody to hepatitis B surface antigen may decline over time, the necessity to maintain anti-HBs concentrations above a certain titer is not widely accepted, since long term immune memory remains intact even in the absence of detectable antibodies[15].

• *Number of doses needed to achieve efficacy:*

A Turkish study revealed that the anti-HBs titers of >10mIU/mL after 1 month of first, second and third vaccinations were 58%, 70% and 94% respectively[16]. However, it has been observed in other studies that two doses of recombinant HBV vaccine given over 4 or 6 months provide adequate seroprotection (≥10mIU/mL) in ≥95% of adolescent vaccines[13,17]. There were small variations in vaccine response between infants and teenagers. The range of protection for different doses is shown in Table[17]. If we accept that a level of 80-95% seroprotection is sufficient for Bangladesh then a strategy with only two doses would be more economical.

Table 1. Percentage of infants and teenagers/adults responding to 1, 2 or 3 doses of HBV vaccine

Dose #	Infants	Teens and adults
1	16-40%	20-30%
2	80-95%	75-80%
3	98-100%	90-95%

[Adapted from Margolis H *et al.* (copy right free resource)[17]]

• *Acceptability of a universal program:*

The data available from WHO reveal that the uptake of other vaccines in routine immunization schedule can vary in Bangladesh from 83% for DPT3 (Diphtheria-Pertussis-Tetanus vaccine) to 95% for DPT1 [18].Utilizing this experience we may suppose that the acceptability of HBV vaccine will be somewhere between 80 and 95%. The uptake can be increased by improving health education, creating awareness among people in general and among health care providers in particular as well as involving politicians and religious leaders in the vaccination campaign. There were concerns that HBV vaccine could be related to central nervous system demyelinating disorders. However, a later study in France concluded that in the worst case considered the number of complications prevented by vaccination outweighs quantitatively the potential risks[19].

• *Vaccine Failure:*

A small percentage of adults fail to mount an immunological response despite completion of the immunization schedule. The variables associated with vaccine failure are: site of vaccination, obesity, smoking, presence of diseases that alter immune system, medications, age (>40 years) and male sex[17,20]. Preterm babies <2Kgs are also known to show insufficient responses[17].

• *Cost-effectiveness:*

Cost is an important issue for a resource poor country like Bangladesh. Cost analysis done in countries with low endemicity shows that routine infant vaccination against HBV costs about US$1800 per life saved, compared with over US$10000 for coronary artery bypass surgery or pneumococcal vaccination for the over 65s[21]. Economic analysis of vaccinating Asian Americans in Philadelphia was found to be cost-effective and even cost-beneficial with a benefit-cost ratio of 4.4:1[22]. However these data are not adequate enough to justify economic analysis of HBV vaccination in Bangladesh. A separate study to analyze cost benefit/cost effectiveness is recommended for Bangladesh, as its infrastructure of health care and disease prevalence are different from those of resource rich countries.

HBV immunization in Bangladesh- Current Strategy and a New Recommendation

Recently (since late 2004) Bangladesh has started incorporating the HBV vaccination into national immunization program with the schedule of immunizing babies at 6, 10 and 14 weeks of birth. It is certainly a welcome step but the schedule may need to be reviewed.

Immunizing babies at six weeks of life with the first dose of vaccine will leave many at risk babies unprotected in their neonatal period when they need it most. It has been found that about 1.2-3.5% of the pregnant ladies in Bangladesh are HbsAg positives and that 22-38% of them are also HBeAg

positives, so delaying vaccination for the first six weeks will put 70-90% babies at risk of acquiring perinatal infection[8]. Immunizing them in the first twenty-four hours of birth is conceivably the best approach. Bangladesh has already a policy of immunizing children with BCG at birth. To make sense of economics and thus save extra costs both vaccines can be administered at the same time.

Regarding the second dose of hepatitis B vaccine: it can be administered at 6 weeks with other EPI (Expanded Program on Immunization) vaccines at the same sitting, which will save both time and cost. The interval between the first two doses does not necessarily need to be one month as it has long been practiced, a dose interval as long as one year could still be equally effective[20].

It has been established that two doses are quite efficacious giving almost 80- 95% seroprotection in infants (see Table)[17]. Regarding the third dose we think it can be either selective or optional as the level of seroprotection increased by the third dose is very minimum[17]; hence it can entirely be left on the parents' choice. If they want to vaccinate their children with the third dose they should be encouraged to do so depending on their affordability; or this can be reserved only for the babies of HbsAg positive mothers. The third dose can be timed with measles vaccine at 38 weeks.

We think that this two-dose neonatal vaccination strategy plus selective antenatal screening, instead of a universal screening, will probably be a superior and cost effective approach. Another advantage of neonatal vaccination is that, it can pave the way to the cessation of antenatal screening for HBV infection in future. A neonate today is expected to be a 'mother' in a couple of decades, so screening may not be essential at that time for an already vaccinated person. This neonatal approach has been found to be quite effective in some neighboring countries such as Thailand, with a national seroconversion rate of 87.6% within one year of initiation of vaccination and the prevalence of carrier rate decreased drastically from 3.4% to 0.7%[15]. It can be exemplary for Bangladesh.

Further, a reliable multi-centre seroprevalence study needs to be conducted with samples representative of the whole population to determine the exact prevalence of HBV infection; data drawn simply from laboratory report or notification may not reflect the true situation. An epidemiological survey of saliva testing for anti-HBc antibody may be an easy-to-do alternative.

Promising results have been reported with a new aluminium-adjuvanted vaccine that has been shown to produce 99% seroprotection only after two doses; moreover the vaccine was well tolerated by the volunteers in its initial trial in Argentina[23].

A hexavalent combination vaccine that includes among others hepatitis B vaccine has been found to be immunogenic and generally safe in various studies[24,25]; it has been licensed in Europe and America and shown to improve timeliness of immunization[26], its use in Bangladesh could be considered in the future.

Conclusions

Bangladesh needs an effective vaccination strategy against HBV. Infant immunization with two doses is the minimum recommendation. The first dose can be effectively introduced as early as on the first day of life with BCG. To optimize the compliance, second dose can be administered at 6 weeks with other routine vaccines e.g. DPT, Polio etc. The third dose should be optional, however, can be implemented as compulsory for at risk babies and the timing should be at 38 weeks with measles vaccine. Further study is needed to evaluate the cost-effectiveness of this novel policy.

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Competing interests

We declare that we have no conflict of interest.

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