REVIEW

PRIORITIES AND CHALLENGES FOR HEPATITIS B CONTROL IN THE PHILIPPINES AND THE IMPORTANCE OF A VACCINE DOSE AT BIRTH

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Abstract. The Philippines annual birth cohort of over 2 million is the second largest in the Western Pacific Region; 44% of births occur outside health facilities. With third dose infant hepatitis B (HB) vaccine coverage of 43% in 2006, erratic vaccine supply, and lack of policies or processes for universal HB vaccine birth dose delivery, a substantial burden of preventable chronic HB infection continues to occur. Funding, policy, technical and immunization delivery developments now make substantial progress in HB control in the Philippines possible. These developments can help expand access to trained birth care and essential postnatal care for mothers and their newborn.

INTRODUCTION

Hepatitis B (HB) is a major cause of morbidity and mortality worldwide. The World Health Organization (WHO) estimates more than 2 billion people have been infected, about 360 million are persistently infected, and it causes 500,000-700,000 deaths worldwide each year, almost all of them related to the long-term sequelae of cirrhosis and hepatocellular carcinoma (HCC) (WHO, 2004). HB is the most contagious among common blood-borne viruses. Studies, particularly in East Asia, have shown that about 25% of individuals chronically infected with HB since childhood and 15% chronically infected since after childhood die prematurely from cirrhosis and/or liver cancer (Goldstein *et al*, 2005). HB is second only to tobacco as a known cause of fatal human cancer. Naturally infecting only humans, HB is potentially eradicable.

The burden of HB disease disproportionately affects sub-Saharan Africa and the Asia-Pacific region. With 28% of the world's population, the Western Pacific region has nearly half the world's chronically infected persons, an estimated 160 million people (WHO, 2006a). A recent model for HB disease burden and the effects of immunization developed at the US Centers for Disease Control and Prevention (CDC), estimates that in 2000, there were 620,000 HB-related deaths globally, of which 325,000 (52.4%) were in the Western Pacific region (Goldstein *et al*, 2005). In the absence of immunization, 2.2% of children born in the year 2000 in the Western Pacific region would be expected to

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die prematurely as a result of HB (Goldstein *et al*, 2005). In this region, HB causes about 890 deaths daily, a mortality rate similar to tuberculosis (WHO, 2006a).

A HB vaccine was first licensed in 1981. While substantial progress has been made toward making this safe, effective vaccine available to all the world's children, progress has been slow, and incomplete. The WHO recommended in 1992 childhood HB immunization be included in the national immunization programs of all countries (WHA, 1992). Many obstacles, such as high cost and lack of combination vaccines to enable vaccine, have been overcome. According to the WHO and United Nations International Children's Emergency Fund (UNICEF) global immunization coverage estimates for August 2006, with three doses of HB vaccine for infants has increased from 3% in 1992 to 55% in 2005. This is significantly lower than the three-dose diphtheria-tetanus-pertussis (DTP3) vaccine coverage in 2005 of 78% (WHO, 2006b), despite the availability of combination vaccines including DTP and HB. As of September 2006, 158 countries had integrated HB vaccine into their routine infant immunization schedules (WHO, 2006b).

In 2002 the Western Pacific became the first WHO region to have HB immunization included in the national immunization programs of all 37of its member countries and areas (Clements *et al*, 2005). In September 2005, the Western Pacific also became the first region to set a time-bound goal for reducing the rate of chronic HB infection from its pre-immunization average of 8-10% to less than 2% among 5-year-olds by 2012 (WHO, 2006a). This 2012 goal is an interim milestone towards the final regional goal of less than 1% hepatitis B surface antigen (HBsAg) prevalence among 5-year-olds (WHO, 2005).

Perinatal mother-to-child HB transmission plays a more important role in East and Southeast Asia than in any other global region. This is not only because the carrier rate is high among adults, including women of childbearing age, but about 40% of women are highly infectious, being hepatitis B e antigen (HBeAg) positive. The circulating level of HB virus deoxyribonucleic acid (HBV DNA) is the best marker of viral replication and infectivity, but this test is not widely available, so the presence or absence of HBeAg is most commonly used as a marker of infectivity, especially in serological surveys. Without effective preventive measures, between 3 and 5% of infants born in the region will acquire chronic HB infection perinatally (WHO, 2006a).

The disease burden associated with HB is under-appreciated. HB is different from other diseases targeted by childhood immunizations. Most infections, particularly in young children, are asymptomatic and unrecognized until a complication (chronic liver disease, cirrhosis, hepatoma) develops. Complications generally develop after decades, typically during mid-adulthood**.** The causative role of HB in liver disease requires laboratory testing and may not be recognized**.** Although HB immunization is primarily targeted at young children, HB infection and its sequelae are not essentially an issue for childhood survival. Pediatricians generally do not see the chronic sequelae of HB infection, even though an estimated 75% of all HB-related deaths follow infection acquired before 5 years of age (Goldstein *et al*, 2005). By preventing chronic infection and its sequelae, the HB vaccine was the first vaccine against cancer. The HB vaccine is the only routine infant vaccine for which the timing of the first dose, within days of birth, is critical.

In every evaluation immunization against HB has been shown to dramatically reduce the burden of both acute and chronic disease, with reductions in acute and chronic hepatitis infections, including fulminant hepatitis, and hepatocellular carcinoma in

older children who were immunized in infancy (Mast *et al*, 2003).

This paper reviews the current situation, challenges and recommended priorities for HB control in the Philippines. It emphasizes the twin importance of sustained, universal high infant HB vaccine coverage with three doses, and of universal administration of the first dose immediately after birth. All the technical requirements to reach these goals are in place including combination vaccines, vaccine vial monitors on all doses of HB vaccine provided through UNICEF, robust evidence of the substantial heat stability of the HB vaccine outside the cold chain (Hipgrave *et al*, 2006), WHO recommendations that the vaccine can be used outside the cold chain to facilitate delivery of the birth dose (WHO, 2006a) and availability of the WHO-prequalified HB vaccine in *Uniject*™ (Becton, Dickinson and Company), a pre-filled non-reusable injection device ideal for use of the vaccine outside cold chain.

HEPATITIS B DISEASE BURDEN IN THE PHILIPPINES

The Filipino population, a little over 85 million, has a HB carrier rate of 9%. More than 7.7 million persons are chronically infected with HB, of whom between 1.1 and 1.9 million are expected to die prematurely of cirrhosis or liver cancer. A 1984 survey of pregnant women found a 9.2% HBsAg positivity rate, with 20.7% of infected mothers being HBeAg positive (WHO, 2007a). These results are essentially the same for Indonesia, Malaysia, Singapore and Thailand as well in the pre-vaccination era according to the CDC model (9% HBsAg positive and 20% HBeAg positive) (Goldstein *et al*, 2005). The model assumes that 90% of infants born to HBsAg positive and HBeAg positive mothers become infected, that 10% of infants born to HBsAg positive but HBeAg negative mothers become infected, and that 90% of infections acquired perinatally become chronic.

Applying this data to the Philippines, with a birth cohort of 2.05 million [based on a 2005 population of 85.24 million and a crude birth rate of 24.09 per thousand per year (WHO, 2006c)], in the absence of immunization, the predicted numbers of chronically infected children as a result of perinatal infection are 30,000 (2.05 million x 0.09 x 0.2 x 0.9 x 0.9) babies born to HBeAg positive mothers, and 13,300 (2.05 million x 0.09 x 0.8 x 0.1 x 0.9) born to HBeAg negative mothers, or a total of 43,000 infants per year.

A recently published WHO Western Pacific Regional Office (WPRO) model predicting seroprevalence for the 2004 birth cohort by birth dose and 3-dose HB vaccine coverage in countries in the Western Pacific region utilizes a similar HBsAg positivity rate of 10% but a higher HBeAg positivity rate of 40% (WHO, 2006a), which is even higher than the 30% figure used by the CDC for high prevalence countries of East Asia, the Mekong and Pacific Islands, which are associated with the highest rates of HBeAg positivity (Goldstein *et al*, 2005). The WPRO model would thus yield a higher number of approximately 80,000 for the number of Filipino infants chronically infected as a result of perinatal transmission in the absence of immunization. Whatever the model, the number is substantial.

Among the 37 countries and areas of the Asia Pacific region, because of the very high birth rate in the Philippines (24.09 per 1,000 population) (WHO, 2006c) the magnitude of the Philippines' birth cohort is second only to China.

THE IMPORTANCE AND FEASIBILITY OF A VACCINE DOSE AT BIRTH

Achievability of vaccine coverage

The risk of chronic HB infection and the

likelihood of acute clinical disease, is closely related to the age at infection. The risk of acute disease increases with age of infection: about 1% for perinatal infections, 10% for early childhood infections, and 30% for infections occurring after the age of 5 years (Goldstein *et al*, 2005). The risk of fulminant HB infection is similar, with an estimated rate of 0.1% during the perinatal period and 0.6% for later infections (Goldstein *et al*, 2005). Development of chronic HB infection, in contrast, varies inversely with age, occurring in approximately 90% of perinatal infections, 30% of early childhood infections, and <5% of infections after 5 years of age (CDC, 2006). The risk of chronic infection in otherwise healthy immunocompetent adults is no more than 1-2%, and those who do develop an acute hepatitis illness, largely immunologically mediated, rarely go on to develop chronic infection.

In the Western Pacific region, using the US CDC model to estimate HB disease burden and the effect of different immunization scenarios, 26% of HB-related deaths are estimated to occur as a result of perinatal infection, the highest proportion of any WHO region, compared with a global average of 21% (Goldstein *et al*, 2005). This model can be downloaded from the internet (http://aim-e-learning.stanford.edu/en/vaccines/hepb/assessBurden/model/index.html) and is useful to examine the effects of different immunization scenarios. The model estimates that in the Western Pacific region, with 90% 3-dose vaccine coverage but without a dose at birth, 63% of HB-related deaths that would otherwise occur could be prevented. However, this proportion increases to 83% with 90% coverage with a birth dose of HB vaccine (Goldstein *et al*, 2005). As discussed below, a large body of field data demonstrates an even greater benefit of an early dose than predicted by this model. This is probably because in the model, only a birth dose delivered within 24 hours is assumed to be effective against perinatal infection, while in reality, gradually declining, but important protection is afforded even by a first HB vaccine dose delayed several weeks after birth. An additional factor is likely to be herd immunity. Young children infected with HB typically have a high viral load and are generally highly infectious; reducing this number has a disproportionate benefit in lowering infectious pressure in a community.

In well-resourced settings, the gold standard for preventing perinatal transmission of HB to babies of infected mothers is a first dose of HB vaccine together with a dose of HB immune globulin (HBIG) within 12 hours of birth (CDC, 2005; NHMRC, 2003). However, this requires antenatal testing of mothers to determine HBsAg status, reliable communication and action on positive findings by delivery staff, and in practice is limited to hospital settings. HBIG is expensive and the supply is limited. These factors make maternal HB screening and selective immunization impractical in all but a few countries and impossible on a population basis in developing countries.

However, a large body of data shows that a much simpler, more feasible approach is effective: giving a HB immunization dose immediately after birth. In a comprehensive review of prevention of perinatal HB transmission, Andre and Zuckerman (1994) demonstrated that in a large number of studies using different vaccines and different schedules in different settings, vaccine plus HBIG was 85-95% effective, and vaccine alone given at birth was 65-95% effective, in protecting infants born to carrier mothers. More recent studies of vaccine alone, using recombinant vaccines (involving more highly immunogenic vaccines than some earlier plasma-derived vaccines) showed an efficacy of more than 90%. In studies which

included direct comparison of vaccine with or without HBIG, HBIG added only 2-5% protective efficacy compared with vaccine alone. Such data led the WHO to recommend: "*In most countries the most feasible strategy for preventing perinatal HBV transmission involves giving a dose of hepatitis B vaccine to all infants at birth*" and "*The efficacy of giving recombinant hepatitis B vaccines alone is similar to that of giving hepatitis B vaccine with HBIG*" (WHO, 2001).

Many studies show the additional protection afforded by a timely HB birth dose, consistently demonstrating a higher level of protection afforded by a first dose administered within 7 days of birth rather than later (Goudeau *et al*, 1983; Lee *et al*, 1986; Monna *et al*, 1988; Schalm *et al*, 1989; Resti *et al*, 1991; Marion *et al*, 1994; Ruff *et al*, 1995; Mahoney *et al*, 1996). Some notable examples from other parts of the Western Pacific region include the following. In Lombok, Indonesia, a poor largely rural setting similar to many parts of the Philippines, the baseline carrier rate in children younger than five years of age was 6.2%. Four years after the start of a model HB immunization project which achieved approximately 90% coverage with three doses, a serosurvey including 2,548 children demonstrated that in those who received the first HB immunization (HB1) more than 7 days after birth, the carrier rate was reduced to 3.0%, however, it was reduced to 1.4% in those who received HB1 within 7 days of birth ($p<0.001$) (Ruff *et al*, 1995).

In the Pacific island country of Palau, the carrier rate in 12-14 month old children was 6.7% [95% Confidence Interval (CI) 1.1-121] in 30 toddlers who did not receive the first of three doses within 3 days of birth, compared with 0.6% among 323 children who did; and in Pohnpei (Federated States of Micronesia) the carrier rate among 78 2-to 4-year-olds who did not receive the first of three doses within 3 days of birth was 2.6% (95% CI, lower limit 0.8) compared with zero among 217 children who did (Mahoney *et al*, 1996).

Even in well-resourced and heterogeneous but generally low-risk settings such as the US and Australia, antenatal HB screening and selective birth immunization of infants born to known carrier mothers has been inadequate and a universal HB vaccine dose at birth for all infants has been a more effective approach, providing the best safety net for high-risk infants (Oman *et al*, 1997; CDC, 2002, 2005; NHMRC, 2003).

Timing of HB1

Few data are available to address how rapidly protection against perinatal transmission declines over time with a delayed first dose, but it is clear that the drop-off in protection is not precipitous. One study showed protective efficacy of 75% when HB1 was given in the second week of life for infants born to HBeAg positive mothers (Lo *et al*, 1985). The 2003 WPRO Regional Plan for HB control estimated protective efficacy against perinatal transmission of a three-dose course when HB1 is given at <7 days at 90-95%, compared with 50-57% for HB1 >7 days (WHO, 2003). It is recommended that the first dose of HB vaccine be given within 24 hours of birth (WHO, 2006a), and while available evidence supports this as a desirable goal, in practice when this is not achievable, the first dose should be given as soon as possible. It is important health staff do not feel that it no longer matters when the first dose is given if it is not possible for it to be given within 24 hours of birth. A secondary target of delivery within 7 days of birth is supported by available evidence.

Enhanced immune response with concurrent Bacillus Calmette-Guérin (BCG)

BCG is the world's most widely used vaccine. An important study in the Gambia

evaluated the influence of immunization with BCG on both antibody and cytokine responses to various other vaccine antigens: diphtheria and tetanus toxoids, poliovirus type 1 and HBsAg (Ota *et al*, 2002). While BCG induces a potent T-helper type 1 (Th1)-type response to mycobacterial antigens, it promoted both Th1- and Th2-type cytokine responses to the unrelated vaccines. BCG at birth at the same time as the first HB vaccine dose significantly increased the antibody, lymphocyte proliferation and cellular immune responses to HB vaccine, with a doubling of the anti-HBs titer achieved after the third vaccine dose. The enhancing effect on HB response was greater than that observed for any other vaccine antigen studied. Thus, when BCG is recommended at birth, as in the Philippines, co-administration with other recommended vaccines, particularly HB, is associated with an augmented immune response.

Ease of delivery of HB1 at birth for infants born in healthcare facilities

Delivering an effective birth dose of HB vaccine requires both a trained service provider able to access the infant and give immunizations at the time of birth, or shortly thereafter, and the availability of a potent vaccine. Both these conditions can be most readily and consistently met in healthcare facilities. Administering injections perinatally is routine. In the Philippines as elsewhere, oxytocin is given to the mother in the third stage of labor, vitamin K is recommended for newborns immediately after delivery and BCG is also recommended at birth. Thus adding an additional postnatal injection for births occurring in healthcare facilities should involve few practical obstacles and minimal incremental cost. Ensuring that all children born in healthcare facilities are provided with a birth dose of HB vaccine should be the first priority for increasing birth dose coverage.

Other maternal and child health providers

Increasing access to trained delivery care, with a target of achieving this for 90% of births by 2015 is an indicator for the Millenium Development Goal (MDG) 5 – reducing maternal mortality by 75% by 2015. The MDGs have been endorsed by all UN member states, including the Philippines. Timely delivery of the HB birth dose can provide a focus and impetus for early contact with mothers, their newborns and health staff (Creati *et al*, 2007). Such contact can have multiple healthcare benefits for both mother and baby (Ruff, 1999; Martines *et al*, 2005; WHO, 2006a), such as education regarding cord care, exclusive and early breastfeeding, and appropriate care for infant illness; micronutrient supplementation including iron, vitamin A, and iodine; additional immunizations such as tetanus-containing vaccine for mothers, and BCG and OPV (in endemic areas) for infants; identification and special care of low birth weight infants; and postnatal maternal care.

Coverage with the HB vaccine birth dose can provide an indicator for coverage of trained delivery care.

Heat stability of HB vaccine

A substantial body of data has accumulated documenting that HB vaccine is heat-stable. Studies in Indonesia and Vietnam have shown potency maintained when the vaccine is stored at ambient temperatures for up to 1 month. One study in China showed potency and protective efficacy were retained for vaccine stored for up to 3 months outside the cold chain (Hipgrave *et al*, 2006). Most HB vaccine used in developing countries and all HB vaccine procured by UNICEF comes from the manufacturer with a vaccine vial monitor (VVM) attached to each vaccine vial. These are labels with a heat-sensitive central square that turns dark on exposure to heat, enabling health staff to

verify visually at point of administration that the vaccine has not been exposed to excessive heat. While HB vaccines are highly heat-stable, like other alum-adjuvanted vaccines, they are sensitive to being damaged by freezing. The potency of HB and other freeze-sensitive vaccines is likely to be compromised more by exposure to freezing than by exposure to heat (Hipgrave *et al*, 2006). Where cold chain management is suboptimal, the HB vaccine is likely to be safer outside than inside the refrigerator.

The use of VVMs means the HB vaccine can be taken outside the cold chain to facilitate vaccination outside healthcare facilities. The WHO has recently recommended use of HB vaccine outside the cold chain to increase timely birth dose coverage, and provided guidelines on implementing this approach (WHO, 2006a). We believe the recommendation the vaccine not be stored outside the cold chain for more than 1 month is overly restrictive. VVMs provide a reliable indicator of exposure to heat. We propose, provided the vaccine is not at risk of freezing outside in a cold climate, the HB vaccine can be kept outside the cold chain as long as the VVM indicates vaccine potency has not been compromised by excessive heat exposure. This is the approach recommended in the new Philippine policy promulgated in 2006 by the Secretary of Health Duque (DOH, 2006).

In settings like the Philippines where a substantial proportion of infants are born outside healthcare facilities, the ability to take the HB vaccine beyond the cold chain dramatically increases the feasibility of reaching all infants with a dose of HB vaccine soon after birth. This can occur by midwives taking the vaccine with them when they deliver infants at home as part of their standard kit for home deliveries (Otto *et al*, 1999), by a community-based birth notification system which enables outreach visits by health staff to newborns in their homes within days of birth (Ruff *et al*, 1995), or by parents being encouraged to bring their newborn to their local health worker in the first few days after birth.

The WHO estimated 29% of the Western Pacific regional birth cohort of 23.1 million, 6.8 million infants, are born outside a healthcare facility annually (WHO, 2006a). Assuming a low risk of perinatal infection of 3%, 70-90% of which become chronic, and with 25% mortality, Hipgrave and colleagues estimated that up to 53,000 deaths per year could be avoided in the Western Pacific region if a birth dose of HB vaccine were given to infants born in settings lacking a vaccine cold chain (Hipgrave *et al*, 2006).

***Uniject*™**

The *Uniject*™ is a single-dose, pre-filled, non-reusable, all-in-one injection device which replaces vaccine vials, syringes, and needle(s) for drawing-up and injection. VVMs can be attached to the *Uniject*™. The device was originally developed by the Program for Appropriate Technology in Health (PATH) and is produced by Becton Dickinson (Franklin Lakes, NJ, USA). The *Uniject*™ has been successfully used for outreach administration of tetanus toxoid to mothers and for birth dose HB for infants in several countries (Levin *et al*, 2005). Field studies show that even low level health workers such as traditional birth attendants (TBAs) can be trained in a few hours to use the *Uniject*™ safely and effectively, and that it is strongly preferred by both providers and mothers (Quiroga *et al*, 1998; Sutanto *et al*, 1999; Levin *et al*, 2005).

Although the unit cost is higher than standard syringes and needles, economic analysis in Indonesia demonstrated that when the wastage rate for multidose vials is greater than 33%, use of the HB vaccine *Uniject*™ (HB-*Uniject*™) for the birth dose

is cost-saving (Levin *et al*, 2005). HB vaccine birth doses must be given one at a time to babies as they are born, and cannot be grouped in immunization sessions or days. Outside healthcare facilities with large numbers of births, wastage rates for multidose vials of HB vaccine used for the birth dose are inevitably high.

The distinctive nature of the *Uniject*™ and its inherent simplicity make it ideal for use outside the cold chain for outreach delivery.

The only practical disadvantage of *Uniject*™ is it requires eight times the cold chain storage space per dose as a 10-dose vaccine vial. In field use in three provinces in Indonesia, the increased cold chain storage space required for the HB-*Uniject*™ was able met by increased distribution frequency (Levin *et al*, 2005).

For some years, Indonesia had been the only country with a national policy of using the HB vaccine outside the cold chain for the birth dose. Indonesia adopted a policy of using the HB-*Uniject*™ for the birth dose in 1996, implemented progressively, together with a policy supporting use of the HB vaccine outside the cold chain for the birth dose in order to increase coverage (Levin *et al*, 2005; Hipgrave *et al*, 2006). Pilot projects outside the cold chain are in progress in China and Vietnam (Hipgrave *et al*, 2006). Slow progress in this area reflects a number of factors: (a) slow accumulation of ample supportive data; (b) training, support, monitoring and supervision requirements of a significant change in immunization practice; (c) concerns regarding potential program confusion and risks to other vaccines should health workers inappropriately take other vaccines outside the cold chain; and (d) lack of clear supportive recommendations from public health authorities, especially the WHO. The recent WPRO guidelines represent a welcome and clear change (WHO, 2006a), as does Philippine Administrative Order 2006-0015 "Implementing guidelines on hepatitis B immunization for infants" (DOH, 2006). This should lead to more countries adopting policies supporting outreach delivery of HB vaccination outside the cold chain, and expanded demand for HB-*Uniject*™, which is pre-qualified by the WHO and can be ordered through UNICEF, though to date it has not been. While delivering a birth dose of HB vaccine outside the cold chain does not require use of the *Uniject*™, and could utilize monovalent HB vaccine vials (preferably single dose) with standard auto-disable syringes and needles, the HB-*Uniject*™ does have real advantages and is ideally suited for this purpose. It could be argued only the HB-*Uniject*™ should be used by traditional birth attendants (TBAs), or other health workers not qualified to give injections.

Early protection against horizontal transmission

Despite the importance of vertical HB transmission, particularly in the Asia Pacific region, the greatest proportion of chronic HB infection follows early childhood infection. In addition to providing substantial protection against mother-to-infant transmission, timely administration of a birth dose of vaccine also provides the earliest possible onset of protection against horizontal transmission during the perinatal period and beyond. This may occur from infected family members, carers, other children, or by nosocomial transmission, such as via unsterile injections. It is estimated that approximately 16 billion injections are given in developing and transitional countries each year; about 95% for therapeutic purposes and 3% for immunization (WHO, 2006d). The resulting estimated global burden of disease due to injections (WHO, 2006d) is substantial. Twenty-one point seven million develop HB infection, about one-third of all new infections in

developing and transitional countries; 2 million develop hepatitis C infection, about 42% of all new infections; 96,000 develop HIV infection, about 2% of all new infections globally, and 9% of all new infections in South Asia.

Data from the US indicate receipt of a HB vaccine birth dose is associated with an increased likelihood that three doses will be received, earlier administration of the third HB vaccine dose (Yusuf *et al*, 2000;Luman *et al*, 2004); and in some settings, improved completion rates for all other infant vaccines (Lauderdale *et al*, 1999).

Flexibility beyond the birth dose

A HB vaccine birth dose should be followed by at least two subsequent vaccine doses to complete the series (WHO, 2004; CDC, 2005). Since HB vaccine in different vaccine combinations and from different manufacturers can be interchanged, any licensed HB-containing vaccine (preferably a combination vaccine) can be used to complete the course. A four-dose HB vaccine schedule, including a birth dose, does not increase vaccine reactogenicity (Pichichero *et al*, 2002) and is simpler since it allows the same vaccine combination to be given at each of the three primary post-neonatal immunization encounters at which DTP is given, does not result in under-immunization of children who miss the birth dose, and is more beneficial if one or more vaccine doses are less than optimally potent, such as due to damage by freezing.

The advantages of a universal HB birth dose are summarized in Table 1.

HEPATITIS B CONTROL IN THE PHILIPPINES

The prevalence of HB infection in the Philippines is high, and HB control warrants being a national priority. The WHO and the Philippine Department of Health estimate 10% HBsAg positivity among Filipino women of childbearing age (DOH, 2006; WHO, 2006a). HB vaccine was first introduced into the Philippine national immunization program in 1991, 10 years after HB vaccines were first licensed. The program was expanded nationwide in 1992, and was planned to expand by 10% per year, from 40% to 100% population coverage by 1999 (DOH, 2006). However, funds have been insufficient to achieve this. Coverage has fluctuated widely depending on vaccine availability. In 2000, when there was no allocation for HB vaccine, coverage was only 3%. In 2001, this increased to 80% but then fell again to 31% in 2002, and has increased progressively reaching 69% by 2006 (Table 2, Fig 1) (WHO, 2007b). This is still 11% lower than the 80% coverage in 2006 for the third dose of oral polio vaccine and DTP scheduled at the same time. In 2005, HB3 coverage was more than 10% lower than DTP3 coverage in 171 of 188 (91%) districts (WHO, 2007b).

While HB vaccine supply and coverage are improving, this failure to consistently provide sufficient vaccine for a priority vaccine included in the national immunization program represents a public health failure and is incompatible with the Philippine government's ethical and legal obligations under the Universal Declaration of Human Rights and the Convention on the Rights of the Child, to provide essential and feasible preventive primary healthcare (Ruff, 1999).

Inadequate and widely fluctuating HB vaccine supplies has been compounded by the use of a less than optimal immunization schedule, with the first dose being given at 6 weeks with the first DTP vaccine, rather than at birth, reducing the chance of preventing mother-to-infant transmission (DOH, 2006).

Table 1
Advantages of a universal hepatitis B vaccine dose at birth.

- Highest efficacy against perinatal infection, with or without HBIG
- Immunogenic, protective, well-tolerated and safe
- No interference with any other concurrent vaccines at any time
- Enhanced HB antibody and cellular immune responses (both Th1 and Th2) when vaccine birth dose is given with BCG
- Readily achievable, requiring minimal additional resources for children born in healthcare facilities with capacity to store and administer vaccine
- Other injections targeted during labor (oxytocin) and in the immediate postnatal period (vitamin K, BCG) make it easy to add HB vaccine at minimal cost
- A birth dose is synergistic with increasing access to trained delivery care (Millenium Development Goal 5) and with the Integrated Management of Childhood Illness (IMCI) strategy for essential postnatal care
- For babies born outside healthcare facilities with the capacity to give immunizations, a universal dose at birth:
  - Provides an impetus and platform for early contact between mothers, their newborn and healthcare staff
  - Facilitates multiple benefits of such early contact through a comprehensive care package for mothers and neonates
  - Heat stability of HB vaccine and attached vaccine vial monitor (VVM) enable vaccine to be taken outside the cold chain without compromising effectiveness *eg* for active outreach delivery in the home
  - The *Uniject* HB vaccine pre-filled non-reusable injection device is ideal for outreach delivery; is pre-qualified by the WHO and can be ordered from UNICEF
- Outreach vaccine delivery can strengthen primary healthcare services
- Provides the best safety net for highest risk infants: those born to carrier mothers
- Avoids the need for expensive and difficult-to-implement antenatal HB screening
- Optimal even in low prevalence settings
- May improve coverage of subsequent vaccine doses and completion of the vaccine course
- Provides earlier onset of protection against horizontal transmission, including from unsafe injections
- Can be followed by 3 or 4 doses of any HB-containing vaccine or combination vaccine
- Proven feasibility even in challenging settings
- No disadvantages

Promising recent developments

In the past few years, there has been growing interest among many in the Philippines to improve HB control. The immunization schedule recommended by the Philippine Pediatric Society, Pediatric Infectious Disease Society of the Philippines, and Philippine Foundation for Vaccination has for the past 7 years recommended the first HB vaccine dose be given at birth. At the 5th Philippine National Immunization Conference in 2004, organized by the Philippine Foundation for Vaccination, a resolution recommending routine HB immunization of all infants at birth was overwhelmingly supported, and endorsed by a wide range of health professional associations (Philippine National Immunization Conference, 2005).

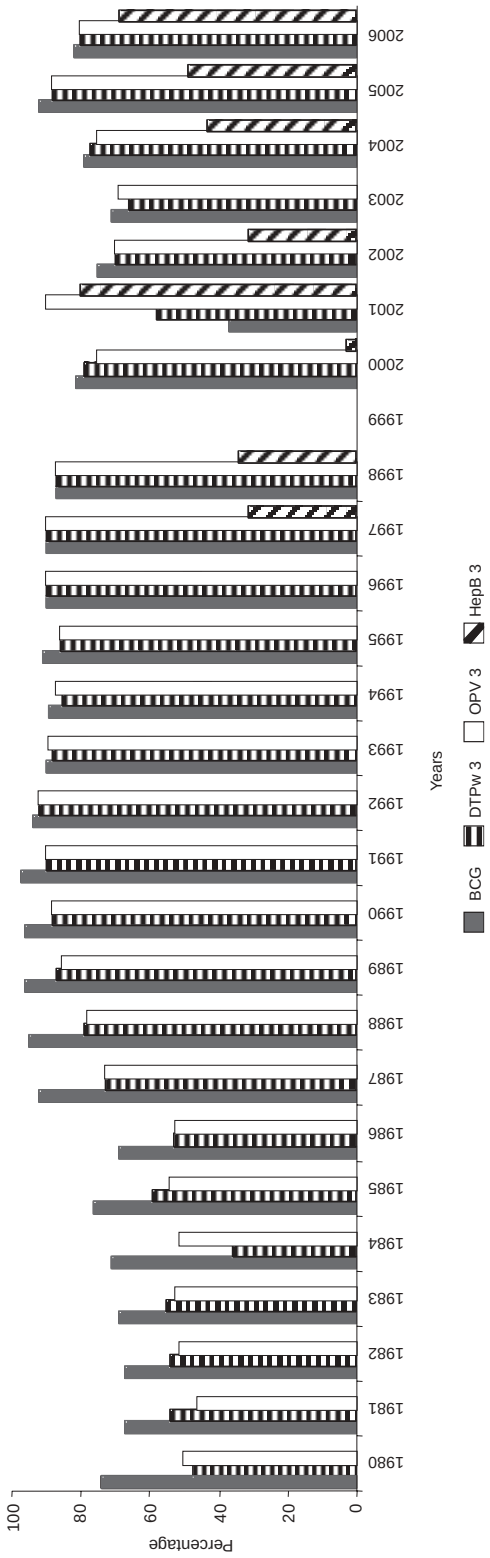

Fig 1–Immunization coverage in the Philippines (1980-2006).

A growing number of private hospitals now have policies for routine HB immunization at birth for newborns. In August 2006, the Philippine Health Insurance Corporation (Philhealth) included first dose HB vaccine at birth in its Newborn Care Benefit Package, available at 1,574 hospitals, 1,100 health centers and 30 ambulatory surgical clinics around the country (Philhealth Circular, 2006).

The most significant development however, in advancing HB control in the Philippines, will hopefully be Administrative Order No. 2006-0015 on "Implementing guidelines on HB immunization for infants" signed by the Secretary of Health, Francisco Duque, on 23 June 2006 (DOH, 2006), which addresses practical measures foreshadowed by Republic Act No. 7846 on "Compulsory hepatitis B immunization among infants and children less than 8 years old". The Order stipulates a program goal aligned with the regional goal, a HBsAg prevalence of less than 1% among 5-year olds born after routine HB immunization at birth has been implemented. It does not specify a target date for achieving this goal, and it regrettably does not specify the interim regional goal of less than 2% HBsAg prevalence in children aged 5 years by 2012. All governments of the Western Pacific Region, including the Philippines, may be assumed to have signed on to this goal. The order does include a number of important policy developments which have the potential to greatly advance HB control in the Philippines, including: The Department of Health (DOH) shall procure 75% of the HB vaccine needs for 2007 and 100% from 2008 onwards to provide three vaccine doses to all infants (including an allowance for 20% vaccine wastage); a HB vaccine birth dose should be given as soon as possible for all newborns, preferably within 24 hours but not later than 7 days after birth, including those born outside

Table 2
Philippines reported immunization coverage 1980-2006.

	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
BCG (Bacillus Calmette - Guérin vaccine)	74	67	67	69	71	76	69	92	95	96	96	97	94	90	89	91	90	90	87	–	81	37	75	71	79	92	82
DTP1 (First dose of diphtheria toxoid, tetanus toxoid and pertussis vaccine)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	81	58	75	67	81	92	82
DTP3 (Third dose of diphtheria toxoid, tetanus toxoid and pertussis vaccine)	47	54	54	55	36	59	53	73	79	87	88	90	92	88	85	86	90	90	87	–	79	58	70	66	77	88	80
HepB3 (Third dose of hepatitis B vaccine)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	31	34	–	3	80	31		43	49	69
MCV (Measles-containing vaccine)			9	27	44	49	51	68	77	83	85	88	90	87	86	86	90	90	87	–	80	75	73	55	81	93	83
MCV2 (Measles-containing vaccine 2nd dose)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Pol3 (Third dose of polio vaccine)	50	46	51	52	51	54	52	73	78	85	88	90	92	89	87	86	90	90	87	–	75	90	70	69	75	88	80
TT2+ (Second and subsequent doses of tetanus toxoid) for pregnant women	9	13	14	20	16	22	24	31	37	44	47	54	70	68	36	48	43	53	–	–	58	60	45	27	52	46	42
VAD1 (Vitamin A doses (VAD1) by 12 months)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	74	83	93	55	89	88	85

[a] Source: WHO 2007a; [b] 2006 data are provisional; [c] Updated 28 June 2007

Table 3
Key data from the Philippines 2003 National Demographic and Health Survey on place and assistance during delivery and place and timing of postnatal checks.

Antenatal care provider (%) *N*=4,802	Doctor: 38
	Nurse/midwife: 50
	TBA : 7
Place of delivery (%) *N*=6,954	Government hospital: 23
	Government health center: 1
	Private health facility: 14
	Home: 61
Delivery assistance (%) *N*=6,954	Doctor: 34
	Midwife: 25
	Nurse: 1
	TBA: 37
Delivery assistance by place of birth (%) *N*=6,954	Home: TBA 61, midwife 34
	Government hospital: doctor 92
	Government health center: midwife 76, doctor 21
	Private health facility: doctor 89, midwife 10
Timing of first postnatal check (%) *N*=2,874	Within 2 days of birth: 34
	3-6 days after birth: 17
	7-41 days after birth: 15
	None or after 41 days: 34
Place of postnatal check (%) *N*=3,451	Home: 46
	Public health facility: 35
	Private health facility: 19

[a] Source: NSO, 2004

hospitals and other healthcare facilities (with subsequent doses at 6 and 14 weeks). Standing orders for all medically stable infants weighing 2,000 g or more should reflect this; children with a birth weight lower than 2,000 g or having pre-maturity are not contraindications to HB immunization, but such infants should receive a birth dose and three subsequent doses (*ie* an additional dose). In regard to recommendations for delivery of HB vaccine birth dose for infants born outside healthcare facilities, facilitated by the presence of a Vaccine Vial Monitor (VVM) on all HB vaccines supplied by DOH, midwives should carry the HB vaccine as part of their midwifery kit to administer a birth dose to infants they deliver, and can carry the vaccine outside the cold chain for as long as the VVM is not past the discard point. For births attended by TBAs, the parents should either bring the newborn to a health facility within 7 days of delivery, or the TBA or parents should notify the nearest health facility to enable a midwife to visit the home to administer the first dose within 7 days.

While HB vaccines are not strictly comparable by dose, as the immunogenicity of the surface protein relates not only to its mass but its tertiary folding and epitope presentation, the Order's specification of recombinant vaccines containing 10 μg of HBsAg protein for the birth dose is appropriate, as recombinant vaccines containing more than

Table 4
Priorities for hepatitis B control in the Philippines.

Priority	Comments
1. High 3 dose infant coverage	Current HB3 coverage is unacceptably low because overall immunization coverage is insufficient and because of inadequate and erratic supply of HB vaccine. An interim target of 90% coverage for each annual cohort of infants, and a final target of 95%, are appropriate and have been achieved in a number of countries.
	HB doses given at the same time as DTP can most optimally be delivered using a combination vaccine, ideally including DTP, HB and Hib.
	There are possible advantages and no disadvantages for an infant receiving 4 rather than 3 doses of HB *eg* allowing the same combination to be used for each of the 3 primary DTP doses.
2. High birth dose coverage	Birth dose should be given as soon as practicable, target within first 24 hours, and preferably within 7 days of birth.
	Proceed from easy to difficult: coverage of all 60% of deliveries currently attended by a health professional should be rapidly achievable.
	Prioritize trained delivery care for HB birth dose administration for infants currently delivered without professional care.
	Birth notification and active outreach visits by health staff to deliver a package of postnatal maternal and child care, including HB birth dose, for infants born without trained care.
	Utilize heat stability of HB vaccine and VVMs to facilitate birth dose delivery.
	Health staff should be trained and supported to take HB vaccine outside the cold chain for births they assist where there is no cold chain capacity, and for postnatal outreach visits.
	Train and support TBAs to deliver HB vaccine with *Uniject* outside the cold chain for the birth dose in remote areas where midwife or nurse access is not feasible or too slow.
3. Catch-up immunization for children and adolescents who have missed out on completing a course of HB vaccine	Prioritize younger children especially under 5 years.
4. Immunization of high-risk adolescents and adults	Especially healthcare workers, but also public safety workers with potential exposure to blood or blood-contaminated body substances, household contacts and sexual partners of persons with chronic HB infection, injecting drug users, those with multiple sex partners or STIs, persons with chronic liver disease not due to HB, clotting factor recipients, chronic dialysis patients, clients and staff of institutions for the developmentally disabled (CDC, 2006).
	Post-immunization testing is useful where feasible for those at occupational risk such as healthcare workers; pre-immunization testing can also be used to identify those already infected or immune.
5. Advocacy and social mobilization	Particularly directed to increase parental awareness of the benefits of HB immunization and the importance of a timely birth dose in order to increase demand for HB immunization.
6. Monitor HB control	HB control should be fully integrated in planning, delivery and monitoring of immunization, maternal and child health, and primary healthcare services.
	Monitoring HB control requires population-based serological data, periodic national serosurveys should be planned to monitor progress towards the regional targets of less than 2% HBsAg prevalence in 5 year-olds by 2012 and the final target of less than 1% in 5 year-olds.

a few μg of HBsAg have been shown to be most efficacious in preventing mother-to-infant transmission (Andre and Zuckerman, 1994).

The government's commitment to fund sufficient vaccines for all Filipino children is particularly important given the low level of government expenditure on health. The major source of healthcare financing (around 60% in 2003) is out-of-pocket payments (WHO, 2006c). Population coverage of health insurance is also relatively low, 64% in 2005 (WHO, 2006c). In the absence of assured government funding for HB immunization for all infants, access to this essential and highly cost-effective basic primary healthcare service would continue to be inequitable and inconsistent, disproportionately disadvantaging the poorest, largely rural, children who are also at highest risk for HB infection (Lansang, 1996).

What is now needed from all Filipino healthcare professionals, immunization staff and program managers is a concerted and focused effort to hold their government to account to deliver on the important new policies reflected in Secretary Duque's Administrative Order and to exert their best efforts to ensure their effective implementation. Pediatricians continue to have a critical role to play in this effort as care providers, teachers, researchers, leaders and expert advocates for children.

Reaching all infants

The Philippines has the second largest birth cohort in the Western Pacific region, estimated at 2.03 million in 2005 (WHO, 2006a). The most authoritative available data regarding delivery place and assistance and source of postnatal care are likely to be from the National Demographic and Health Survey (DHS), most recently undertaken in 2003, which provides data regarding births which took place between 1998 and 2003 (Table 3) (NSO and ORC Macro, 2004). The proportion of births attended by a health professional increased only minimally from 56% in the 1998 survey to 60% in the 2003 survey, well short of the 80% target for 2004 set by the Department of Health (NSO and ORC Macro, 2004). For the 60% of infants whose delivery was assisted by a trained healthcare worker, delivery of the birth dose of vaccine should be relatively easily achievable with minimal or no additional staff cost. However, the challenge is significantly greater for the 40% of infants whose births were not attended by a health professional able to give injections. The great majority of these births (37% of all births) were attended by a TBA.

An additional challenge relates to the timing of the first post-natal health check: these checks took place within 2 days of delivery for 34% of mothers and infants, and up to 6 days after delivery in 51% (Table 3) (NSO and ORC Macro, 2004) *i.e.* 49% occurred 7 or more days after birth.

The two broad challenges in delivering a timely birth dose of HB vaccine are: ensuring timely contact occurs between a healthcare provider who is able to give injections, and newborns, preferably within 24 hours and at least within 7 days of birth; and ensuring access to potent vaccines at each of these contacts.

The best strategy to ensure early contact with newborns is for health workers to conduct outreach visits, utilizing a reliable and timely system of birth notification, rather than for parents to bring their newborn to a health facility soon after delivery (WHO, 2006a). Birth notification can be provided by TBAs, community health workers, village leaders or parents (Ruff *et al*, 1995). However, the main emphasis in provision of a timely birth dose of HB vaccine should be to increase the proportion of births attended by a trained health worker (WHO,

2006a). This is because immediately after birth is the optimal time to provide the birth dose, and because provision of trained delivery care is a synergistic approach that has many other benefits for the mother and child. Trained delivery care is central to progress towards the Millennium Development Goal 4 to reduce by two-thirds the mortality rate of children under 5 years, and Goal 5 to reduce maternal mortality by three-quarters between 1990 and 2015. Though infant mortality is declining in the Philippines, it is still high compared with neighboring countries and more than half (59%) of infant deaths in the Philippines occur in the neonatal period (WHO, 2006c). The Philippines continues to have one of the highest maternal mortality rates in Asia, and this rate has improved minimally from 1970 (190 per 100,000 live births) to 1998 (172 per 100,000 live births) (WHO, 2006c). As previously noted, attendance of a trained health worker at, or at least shortly after, delivery can provide a timely opportunity to deliver a package of postnatal care interventions for both mother and infant; and HB birth dose coverage can provide an indicator of coverage of trained delivery care (WHO, 2006a).

The heat stability of the HB vaccine, the ability to procure HB vaccine in *Uniject*™, including through UNICEF, and the presence of VVMs attached to all HB vaccines are features which can greatly facilitate delivery of a timely birth dose of HB vaccine for all newborns, including those born in the community. While attendance of a trained professional at all births should be a priority goal, past experience in the Philippines, with 37% of births between 1998 and 2003 attended by a TBA, and the proportion of births attended by a trained carer having risen only 4% between 1998 and 2003 (NSO and ORC Macro, 2004), suggests achieving this goal is unlikely to be rapid. This makes the possibility of HB vaccine in *Uniject*™ being added to TBA birthing kits worthy of consideration as a fallback option in areas where expanding the reach of midwives attending deliveries will be slow. TBAs in Bolivia, Mali and Afghanistan have been successfully trained to administer immunization injections (tetanus toxoid for women) with *Uniject*™ (Quiroga *et al*, 1998; Levin *et al*, 2005).

The authors support the priorities for HB control recommended by the WHO (WHO, 2007a) summarized and adapted in Table 4.

CONCLUSION

HB is a major public health problem in the Philippines and unlike other vaccine-preventable diseases targeted in early childhood, the primary purpose of immunization is to prevent the sequelae of chronic infection, which occur largely among adults. Because the risk of chronic infection is high in the perinatal and early childhood the protective benefit of HB immunization can be substantially enhanced by commencing immunization very soon preferably within 24 hours, of birth. The HB vaccine is the only childhood vaccine where the timing of the first dose is critical.

It is now 28 years since HB vaccines were first licensed. Progress in HB control in the Philippines has been slow, erratic and to date inadequate, compounded by a high proportion of births not attended by a trained professional and inadequate immunization coverage. There have been welcome changes in policy in the past few years, most importantly a 2006 Administrative Order by Health Secretary Duque which stipulates a vaccine dose at birth for all infants, government funding for sufficient vaccine to provide 3 doses for 75% of infants in 2007 and 100% in 2008, and a recommendation midwives carry HB vaccine outside the cold

chain to facilitate administration of a dose at birth for all newborns. The means to enable all Filipino infants to be protected against HB from birth are now available: the recent policy changes and funding commitments, the heat stability of HB vaccines, allowing them to be taken beyond the cold chain if required, and their potency verified at the time of vaccine administration through VVMs attached to all HB vaccine vials.

Obstetricians, pediatricians, midwives, and all other health personnel involved in the care of infants have a major role to play to protect current and future generations of Filipinos from the scourge of HB by exerting their best efforts to ensure successful implementation of universal HB immunization without further delay, commencing with a birth dose for all infants, wherever they are born. This dose should be administered as early as feasible: if possible within 24 hours of birth, at least within 7 days.

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