Hepatitis B control by 2012 in the Western Pacific Region: rationale and implications

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Abstract

In 2005, the WHO Western Pacific Region adopted the hepatitis B control goal of reducing the hepatitis B surface antigen seroprevalence in children at least 5 years of age to less than 2% by 2012. Universal infant immunization with three doses of hepatitis B vaccine, including a timely birth dose, is the key recommended strategy. Measuring seroprevalence in children at least 5 years of age takes into account the period when the risk of acquiring a chronic infection is highest and provides an indicator that can be monitored in the short term, within 5 years of vaccine introduction, and which correlates strongly with the long-term consequences of hepatitis B.

A time-bound supranational hepatitis B control goal was chosen to create a sense of political urgency for strengthening routine immunization services and improving access to delivery care as well as providing resources for hepatitis B vaccination. Consequently, the programme strategies selected are not stand-alone but also contribute to strengthening health systems. Independent certification of achievement of the control goal, hitherto used mainly for eradication goals, is planned for all countries.

Early assessment showed that adopting the regional goal led to greater political commitment, with reduced inequalities in hepatitis B vaccination between and within countries. Previous declining trends in routine immunization coverage also show signs of reversal and there is major progress in providing timely birth doses. A similar approach may be relevant to countries in South Asia and Africa, with high hepatitis B disease burdens, faltering routine immunization and poor access to skilled delivery care.

Introduction
Opinion is divided on the value of international bodies setting time-bound supranational disease-specific goals in an increasingly diversified world with growing inequalities in health and health-care priorities.\textsuperscript{1,2} By 2008, nine disease-specific global goals had been set with definite target dates: the eradication of yaws, malaria, smallpox, polio and guinea worm, and the elimination of lymphatic filariasis, leprosy, maternal and neonatal tetanus and trachoma. Only smallpox eradication has been achieved.\textsuperscript{3} All these goals were set and guided by resolutions of the World Health Assembly, WHO’s key global governing body. In addition, WHO regional committees have set time-bound regional goals; for example, for onchocerciasis elimination in the WHO African Region and Chagas disease elimination in the WHO Region of the Americas.

In September 2005, the WHO Western Pacific Region (WPR), which had a population of 1.8 billion in 2007, became the first WHO region to adopt a regional goal of hepatitis B control, to be met by 2012.\textsuperscript{4} A goal of measles elimination by 2012 was also adopted. This paper describes the scope, rationale and early impact of the hepatitis B control goal in the WPR. In addition, it discusses the implications for health and immunization systems in the region and potential lessons for other WHO regions in controlling hepatitis B in particular and in implementing supranational time-bound disease-specific goals in general.

The regional goal

The hepatitis B control goal is to reduce the prevalence of chronic hepatitis B virus (HBV) infection, as indicated by the seroprevalence of hepatitis B surface antigen (HBsAg), to less than 2% in children at least 5 years of age by 2012.\textsuperscript{4} The persistence of HBsAg in blood beyond 6 months during HBV infection is considered a marker of chronic infection. The point prevalence was used for monitoring the hepatitis B control goal.

The ultimate goal is an HBsAg seroprevalence of less than 1% in children aged 5 years or more, but the target date has not been set. In contrast to disease eradication or elimination, control does not imply the interruption of disease transmission or eradication of the virus from humans. Since the target is a chronic infection, elimination is not achievable, at least in the short term. Instead, the goal is a major reduction in new chronic
HBV infections, which occur predominantly in children under 5 years of age in hyperendemic settings.

The key strategy for achieving the goal is universal infant immunization with three doses of hepatitis B vaccine, with the first dose, hereafter referred to as the birth dose, being given within 24 hours of birth. The interventions must be continued even after the goal has been achieved.

The target HBsAg seroprevalence level of 2% was chosen as representing the best level of improvement that could be expected by 2012 given the performance of routine immunization programmes and access to skilled delivery care in the worst performing countries in the WPR. Any country that had already achieved the HBsAg seroprevalence milestone of <2% was encouraged to strive for the ultimate regional goal or even for a more challenging goal (e.g. the elimination of HBV transmission).

**Why target HBsAg seroprevalence?**
Most deaths due to HBV occur in adults: almost 95% from chronic liver disease such as liver cirrhosis and hepatocellular carcinoma and the remaining 5% from fulminant hepatitis. The main risk factor for chronic HBV-related liver disease is chronic infection acquired at birth or in early childhood when the primary infection is asymptomatic. Treatment has a limited impact on the pool of individuals with asymptomatic persistent chronic HBV infection or symptomatic HBV-related liver disease. Coupled to this, the long time lag between acquiring the infection and developing disease means that the strategy of infant vaccination will have little impact on the incidence of liver cirrhosis or cancer for the next 20–30 years. Monitoring the occurrence of acute hepatitis B will also be of limited value in assessing a strategy aimed at controlling the acquisition of chronic infection during childhood as acute disease occurs mainly in older children and adults. The seroprevalence of HBsAg among children, which serves as a proxy for chronic HBV infection, is the first indicator that will be affected by an infant vaccination programme and can, therefore, be used to monitor the programme’s impact over the short term.

**Why test children at least 5 years of age?**
In the WPR, persistent chronic HBV infection mainly results from either vertical transmission at birth or horizontal transmission in children aged under 5 years. The chance of a child developing a chronic HBV infection is 90% if infected at birth, 30% if infected between 1 and 5 years of age and only 5–10% if infected after the age of 5 years. Moreover, it has been estimated that almost three-quarters of all HBV-related deaths in the WPR occur in individuals infected before the age of 5 years. In the prevaccination era, the seroprevalence of HBsAg increased little after childhood in most countries in the WPR. A national survey conducted in 1979–1980 in China, for example, reported an HBsAg seroprevalence of 3.2% in children aged under 1 year, which increased rapidly to 8.9% in 1–4-year-olds, but changed little thereafter. Similar findings were noted in another survey in China in 1992 and in a survey in Thanh Hoa province in Viet Nam in 1998, in which the HBsAg seroprevalence was 18.4% in 4–6-year-olds and 18.8% in adults.

Consequently, measuring the HBsAg seroprevalence in children at least 5 years of age both takes into account the period when the risk of acquiring a chronic HBV infection is highest and provides a short-term indicator that is strongly linked to the long-term incidence of liver cirrhosis and cancer. There is no upper age limit as the oldest birth cohort involved in hepatitis B vaccination programme could also be tested. However, countries should wait until the first vaccinated cohort reaches 5 years of age before their programmes are evaluated.

Measuring the seroprevalence in children under 5 years of age may underestimate the final seroprevalence as some who currently test negative may subsequently acquire the infection and become carriers. On the other hand, the seroprevalence in older individuals born before universal infant immunization will remain high and not be affected by the control programme.

Fig 1 summarizes the main implications of using the HBsAg seroprevalence in children at least 5 years of age to monitor an infant HBV vaccination programme.

Rationale for a regional goal
One of the key justifications for adopting a hepatitis B control goal was to generate a sense of political urgency for tackling an important public health problem for which a safe and effective solution, namely a vaccine, had been available for many years.

Although the WPR contains only 28% of the global population, it is home to almost half the estimated 350 million people with chronic HBV infections worldwide.\textsuperscript{11} With the exception of Australia, Japan and New Zealand, where the chronic HBV infection rate is under 2%, countries in the region have an estimated chronic infection rate of 8% or more. The rate was as high as 25–30% in many Pacific island nations in the prevaccination era.\textsuperscript{11,12} In the WPR, there are an estimated 160 million people with chronic HBV infections and more than 360,000 HBV-related deaths occur annually.\textsuperscript{5,11,13} This is higher than the number of deaths from tuberculosis, which was 291,240 in 2006.\textsuperscript{14} Liver cancer is the third most common cancer in the WPR, compared with the sixth most common globally, and the WPR accounts for almost 60% of global liver cancer cases. Moreover, liver cancer is the second most common cause of cancer mortality.\textsuperscript{15,16} In China, liver cancer is the fifth most common cause of death, accounting for around 4% of all deaths.\textsuperscript{17}

Nevertheless, uptake of hepatitis B vaccine in the WPR remained slow and uneven until 2000, despite a WHO recommendation for universal infant immunization in 1992.\textsuperscript{18} While high- and high-to-middle-income countries in the region such as Malaysia, the Republic of Korea and Singapore introduced the vaccine within 3–4 years of licensure in the 1980s, vaccine use remained negligible in most low- and low-to-middle-income countries, such as Cambodia, China, the Philippines and Viet Nam.

Efforts by WHO and other international partners in the late 1990s highlighted the issue and helped to build a regional consensus but failed to inspire a sense of political urgency in developing countries. By 2001, Cambodia, China, the Lao People's Democratic Republic, the Philippines and Viet Nam, which together account for more than 85% of the regional population, were still not providing universal infant hepatitis B vaccination in their national immunization programmes. Moreover, routine immunization services were faltering in many developing countries and the 1990s saw little improvement in skilled attendant coverage at childbirth (Fig. 2 and Fig. 3).
Sustaining infant hepatitis B immunization remained a concern because donor support was time-limited and there was an uncertain political commitment in some countries (e.g. Cambodia, China, the Lao People’s Democratic Republic and Viet Nam) that expanded or introduced hepatitis B vaccination with the GAVI Alliance between 2001 and 2003. In addition, the Philippines, which was ineligible for GAVI assistance, was still procuring only 40% of its vaccine needs in 2004.

In addition, simply making hepatitis B vaccination available would not have ensured disease control. Coverage with the three doses of hepatitis B vaccine remained low or was even declining in some countries and little or no effort was being made to interrupt mother-to-child transmission, which accounted for 30–40% of all chronic HBV infections.

Overall, efforts to control hepatitis B in the WPR remained suboptimal. Political commitment had been lacklustre and there was no sense of urgency. The supranational time-bound goal of achieving hepatitis B control by 2012 was intended to spur political leaders to commit resources for hepatitis B vaccination and to provide a specific outcome for policy-makers to focus on.

**Monitoring routine immunization services**

Although hepatitis B is of immense public health importance in the WPR, the motivation for setting a regional hepatitis B control goal goes beyond the control of hepatitis B.\textsuperscript{19} When the WPR was certified poliomyelitis-free in 2000 and measles mortality declined by more than 99%,\textsuperscript{20} an urgent need was felt to strengthen routine immunization services to maintain past gains and to increase the public health impact of current and new vaccines. However, as the saying goes, “what gets monitored is what gets done”: an indicator was needed to measure the performance of routine immunization services. Since the inception of WHO’s Extended Programme on Immunization (EPI) in 1974, coverage with the three doses of diphtheria, pertussis and tetanus vaccine has been used to monitor immunization programmes. However, due to difficulties in instituting high-quality surveillance for diphtheria and pertussis, vaccination coverage became an end in itself and it was not possible to evaluate the quality of immunization services.
The proposed hepatitis B control goal provides an outcome indicator for monitoring both the quantity (i.e. coverage) and quality of routine immunization services. While coverage with the three doses of hepatitis B vaccine will serve as the intermediate process indicator, documented reductions in the HBsAg seroprevalence rate will link the outcome to coverage and the quality of the immunization services. Hepatitis B vaccine coverage can be linked to the reduction in HBsAg seroprevalence using specially developed mathematical models.\textsuperscript{5} Hence, data from serosurveys could both validate official immunization coverage estimates and confirm the quality of vaccination. For example, a hepatitis B serosurvey carried out in Mongolia in 2002 found a much higher HBsAg seroprevalence rate among children than anticipated from the reported vaccination coverage.\textsuperscript{21} This prompted a review of immunization quality, including the timing of the birth dose and the incidence of vaccine freezing, which may render the vaccine impotent.

**Maintaining routine immunization services**

The WPR has also adopted the goal of eliminating measles by 2012. The strategy is to achieve greater than 95% coverage with two doses of measles vaccine through routine immunization systems. However, it is recommended that the second dose is given through routine immunization services only if coverage with the first dose is 80% or higher for three consecutive years. Otherwise, broad age-group measles immunization campaigns should be carried out every 3–4 years to rapidly fill gaps in population immunity. Hence, with the measles elimination initiative, there is a risk that countries will bypass routine systems in favour of conducting periodic immunization campaigns. It is anticipated, though, that setting the hepatitis B control goal along with the measles elimination goal pre-empt this risk because achieving the hepatitis B control goal will depend solely on routine immunization services providing hepatitis B vaccination at birth and during infancy. Nevertheless, catch-up campaigns may be useful for extending protection for some children later on, but they will not help countries, especially hyperendemic countries, to achieve the HBsAg seroprevalence goal of less than 2% as most children might have been infected before the campaign is organized. It was envisaged that setting the same target date for both measles elimination and the hepatitis B control goal would ensure that immunization services had sufficient resources and were
flexible enough to carry out high-quality supplementary immunization activities without losing their focus on routine immunization. Otherwise, countries would risk achieving one goal at the expense of another.

**Integrating health-care services**

One of the prerequisites for achieving hepatitis B control is to interrupt mother-to-child transmission by giving a birth dose. This depends on personnel competent enough to administer an injection being present at the birth. Consequently, EPI managers may be forced to develop links with neonatal and maternity services. In addition, it is anticipated that this focus on providing birth doses could highlight the issue of having skilled attendants at deliveries, thereby promoting another major health-system goal, which is one of the key indicators for monitoring progress towards UN Millennium Development Goal 5.

To conclude, the strategies recommended for achieving the hepatitis B control goal do not involve additional or intensified special time-limited activities, such as vaccination campaigns specifically for hepatitis B. Instead, they are intended to inject a sense of urgency into improving routine immunization and maternity services, which are long-standing, cherished, health-system goals, as well as into committing resources for hepatitis B vaccination.

**Monitoring the hepatitis B control goal**

In 2007, certification guidelines were developed to define the procedures and criteria to be used in each country for independently validating the achievement of the hepatitis B control goal. Certification will be based on measuring the HBsAg seroprevalence using a nationally representative serosurvey in children at least 5 years of age who were born after the start of the nationwide infant vaccination programme. However, the guidelines recommend that the serosurvey should be conducted only after vaccination coverage with three doses of hepatitis B vaccine, including a timely birth dose, has been high enough for at least 5 years. While the serosurvey in children at least 5 years of age will document the impact of the vaccination coverage achieved 4 to 5 years earlier, subsequently the hepatitis B control certification status will be assessed by regular monitoring of vaccine coverage data.
**Early impact on health-care systems**

Adoption of the hepatitis B control goal in the WPR mobilized a long overdue political commitment to controlling the disease, especially in the poorest countries. Almost all countries set a national goal based on the regional goal, with some setting even more ambitious goals. Box 1 summarizes the early impact on political commitment, national policy and inequalities between and within countries.

Momentum was generated to increase coverage of a timely birth dose. As summarized in Box 1, many countries reviewed and changed their birth-dose vaccination policy. In addition, in 2006 the WHO Regional Office for the Western Pacific developed operational guidelines for preventing mother-to-child transmission. China, Papua New Guinea and Viet Nam organized pilot projects aimed at increasing coverage of a timely birth dose for home births in remote areas. Cambodia and the Lao People's Democratic Republic started to provide birth doses in hospitals for the first time.

Setting the regional goal also motivated many countries to evaluate their vaccination programmes for the first time by conducting serosurveys and assessing the timeliness of the birth dose. In addition, a sense of urgency for improving routine immunization services developed and new strategies were implemented to counteract the declining trend in routine coverage in some countries, though countries such as the Lao People's Democratic Republic and Papua New Guinea are still struggling.

Though it is too early to quantify the impact on the development of partnerships between EPI and maternal and neonatal health services, EPI programme managers have started to supply vaccine to delivery rooms, to educate obstetricians about mother-to-child transmission of hepatitis B, and to develop joint strategies for providing skilled care at home births.

The attendance of skilled personnel at births has increased substantially in some countries (e.g. China and Viet Nam), though whether or not this is related to the hepatitis B control goal is difficult to establish. However, the goal is unlikely to have decreased the attendance of skilled personnel at births.

**Discussion**
To date, most supranational time-bound disease-specific goals have focused on eradicable diseases and were driven by the cost savings that could be achieved after eradication. The example of the regional hepatitis B control goal in the WPR shows that setting a supranational time-bound disease control goal can help generate a sense of political urgency and accelerate efforts to control diseases that pose important public health problems but are not necessarily eradicable. Whereas for disease eradication, the target date relates to the time needed to implement a large-scale intervention involving immunization or drug treatment to wipe out a pathogen, the target date for disease control relates to the time needed to bring the programme performance up to a desirable level.

If a supranational goal is to achieve its intended impact, it should be based on technical evidence and have clearly defined programme strategies, process indicators and a measurable outcome goal, and there should be a definite time-line for achieving the goal. Equal emphasis needs to be placed on the final outcome and the process used to achieve it. The proposal that achievement of the hepatitis B control goal should be independently certified using well-defined criteria is innovative, and has previously been applied only to disease-eradication goals. The independent certification process will involve few additional costs and regular reporting of results will maintain both a sense of urgency and pressure to improve performance.

Many disease- or programme-specific initiatives, such as the GAVI Alliance and the Global Fund to Fight AIDS, Tuberculosis and Malaria, mention health-system strengthening as a complement to their disease-specific focus. However, few describe what the strengthening of health system actually means or how it can be measured within the disease-control programme. Health-system strengthening must be linked to visible health outcomes. A disease with a very high perceived disease burden could provide an ideal indicator for monitoring health-system strengthening, provided the disease itself can be easily and reliably monitored and the processes used to control it reinforce the routine functioning of the health system. It is important that the process is not ignored in an attempt to achieve the final goals rapidly through short-sighted, stand-alone strategies. International agencies, including WHO, and national governments must ensure that the hepatitis B control goal does not become simply a disease-specific goal, but remains, as
intended, also a measure of the performance of both immunization services and health systems.

Many countries in South Asia and Africa have yet to introduce the hepatitis B vaccine, despite having a high disease burden. The hepatitis B control goal may be useful in these countries where routine immunization systems are faltering and access to skilled delivery care is very poor. Particularly in countries that are still struggling to eradicate polio through immunization campaigns, setting a hepatitis B control goal may help to focus attention on routine immunization services and to achieve the eradication of polio.

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Box 1. Impact of setting a time-bound goal for hepatitis B control in the WHO Western Pacific Region on political commitment and national policy

*Increased political commitment:*

- In 2005, China recognized hepatitis B as one of four priority communicable diseases, along with HIV/AIDS, schistosomiasis and tuberculosis
- China issued a national hepatitis B control plan in 2006 and adopted the more ambitious target of reducing the HBsAg seroprevalence to less than 1% among 5-year-old children by 2010
- The Governments of China and Viet Nam started fully financing hepatitis B vaccines after the end of GAVI Alliance support in 2006 and 2007, respectively
- In 2006, the Philippines made a commitment to provide 100% funding for hepatitis B vaccination for the first time

*Greater equality within and between countries:*

- In 2005, China passed a law abolishing user fees for all immunizations offered as part of EPI, thereby increasing access to hepatitis B vaccine among poor population groups
- With committed financing in developing countries, such as Cambodia, China, the Philippines and Viet Nam, the gap between developed and developing countries has closed

*Change in national policy:*

- In 2005, Mongolia started providing the birth dose of the hepatitis B vaccine within 24 hours of birth, replacing its earlier policy of giving it within 24–48 hours
- The Philippines changed its hepatitis B immunization schedule so that the first hepatitis B vaccine dose is administered within 24 hours of birth rather than at 6 weeks of age
- In 2006, Viet Nam changed the schedule for the first dose of hepatitis B vaccine from within 7 days of birth to within 24 hours

HBsAg, hepatitis B surface antigen; EPI, WHO’s Expanded Programme for Immunization.
Fig. 1. **The main implications of using the HBsAg seroprevalence in children at least 5 years of age to monitor an infant HBV vaccination programme**

**The goal:** to reduce the HBsAg seroprevalence to under 2% in children aged 5 years or older

**Short-term indicator:** reduction in the prevalence of chronic HBV infection measured in children at least 5 years of age

**Key programme strategy:** universal HBV vaccination at birth and in infancy

**Key aim:** to prevent the development of chronic HBV infection in newborns and children aged under 5 years born after the start of the vaccination programme

**No impact on:**
- existing population with asymptomatic chronic HBV infections
- existing population with symptomatic chronic liver disease

**Long-term indicator:** reduction in chronic liver disease in birth cohorts born after the start of vaccination

HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen.
Fig. 2. Routine immunization coverage of children aged 12–23 months with three doses of diphtheria, pertussis and tetanus vaccine in WHO Western Pacific Region countries between 1996 and 2006


Fig. 3. Percentage of births with skilled attendants present in WHO Western Pacific Region countries between 1996 and 2006