REPORT

MEETING ON HEPATITIS B CONTROL THROUGH IMMUNIZATION
Tokyo, Japan, 26-28 June 2002

Manila, Philippines
July 2002
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MEETING ON HEPATITIS B CONTROL THROUGH IMMUNIZATION

Convened by:

WORLD HEALTH ORGANIZATION
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NOTE

The views expressed in this report are those of the participants of the meeting of Technical Experts on Hepatitis B and do not necessarily reflect the policies of the World Health Organization.

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Keywords:

Hepatitis B - prevention and control / Immunization / Japan

This report has been printed by the Regional Office for the Western Pacific of the World Health Organization for the participants in the meeting of Technical Experts on Hepatitis B, which was held in Tokyo, Japan, from 26 to 28 June 2002.
Hepatitis B virus (HBV) infection is an important public health problem, especially in the Western Pacific Region. Current global estimates of measles and HBV-related deaths suggest that both viruses are currently causing about the same number of deaths globally. In the Region, however, there are over 10 times as many deaths from HBV as from measles. Moreover, HBV-related deaths are not as easily recognizable as measles deaths; most occur decades after the initial HBV infection (as a result of chronic HBV infection).

The Western Pacific Regional Office of the World Health Organization (WHO) convened a meeting in Tokyo from 26 to 28 June 2002, to advise on how to improve hepatitis B control through immunization. The meeting discussed a range of issues related to the development of a Regional plan to improve hepatitis B control through immunization as part of the Expanded Programme on Immunization (EPI).

The meeting concluded that:

• universal immunization of infants is the most effective and important strategy to prevent hepatitis B infection and its consequences;

• timely delivery of a birth dose is the preferred immunization strategy for the Region because perinatal infection is common and children who are infected perinatally are likely to become chronically infected;

• as well as monitoring immunization coverage and timeliness of the birth dose, it is important for countries to validate the impact of immunization on disease burden by undertaking at least one serosurvey (for markers of chronic HBV infection) among children born after hepatitis B immunization started (i.e. in cohorts that should have been immunized). Countries should recognize that considerable resources and expertise are needed to assure the validity of such a serosurvey;

• achieving 1% or less chronic HBV infection (in childhood cohorts offered vaccination) is a reasonable standard for all countries in the short to medium term; and

• for those countries that have not yet done so, they should establish a hepatitis B control plan (as part of the national EPI plan) to address the above issues and to fully integrate hepatitis B vaccine as a routine EPI vaccine.
1. INTRODUCTION

A WHO working group meeting on hepatitis B was held at the National Institute of Infectious Diseases (NIID) in Tokyo, Japan from 26 to 28 June 2002. WHO convened the working group, composed of experts and selected country representatives, to discuss various scientific and operational issues related to improving control of hepatitis B virus (HBV) through immunization in the Western Pacific Region. The meeting was intended to provide technical and country input for a Regional plan to improve hepatitis B control and to build on the achievement that since 2001 every country/area in the region has included hepatitis B in their National Immunization Programme (NIP).

1.1 Objectives

The meeting was conducted in Tokyo, Japan from 26 to 28 June 2002 with the following objectives:

(1) to review and make recommendations on the draft Regional plan to improve hepatitis B control in the Western Pacific Region and identify any areas of further work that are needed;

(2) to discuss operational issues to accelerate hepatitis B control in the Region;

(3) to review the current epidemiological situation of hepatitis B in the Region and progress made in its control; and

(4) to review the latest developments in assessing the impact of hepatitis B immunization, including the use of laboratory tests.

1.2 Opening Remarks

Dr Brian Doberstyn, Director of the Combating Communicable Diseases Division of WHO's Western Pacific Regional Office opened the meeting on behalf of the Regional Director, Dr Shigeru Omi. He thanked the participants for taking the time to share their expertise to guide the Region in the development of the Regional plan to improve hepatitis B control through immunization.

Dr Doberstyn noted the importance of hepatitis B and its complications in the Region, which has about a quarter of the world’s population but is estimated to have nearly half of all of those chronically infected with the HBV. Over half of these people die prematurely as a result of infection mainly from hepatocellular carcinoma (HCC) and cirrhosis. The reason for the higher disease burden than infection rate is that people have a relatively long life expectancy in the Region. In the future, children will live hopefully even longer and thus the impact of hepatitis B will be greater. This emphasizes the great importance of preventing infection in the Region’s children.

Dr Doberstyn advised that the meeting’s conclusions and recommendations will guide the development of the regional plan to be reviewed at the meeting of the Technical Advisory Group (TAG) on the Expanded Programme on Immunization (EPI) and Poliomyelitis Eradication. This will be held from 4 to 7 November 2002 after further consultation with experts and those working in the NIP of every country in the Region.
In particular, the experts were asked to advise on:

- the relative importance of the birth dose versus improving coverage, especially for countries where access to health services is very limited;
- how best to help countries fully integrate hepatitis B as a routine EPI vaccine;
- assessing the impact of hepatitis B immunization on disease; and
- setting milestones to measure the control of hepatitis B.

Dr Yoshikura, director of the National Institute for Infectious Diseases (NIID) also welcomed the participants to the institute and was pleased to be able to host the meeting. Having worked for polio eradication, he noted the differences between polio control and hepatitis B control. In addition to the difficulty of monitoring cases because of the increasing primary disease burden after decades of chronic infection, there is also the issue of delivery of an injectable vaccine with its associated logistic, training and injection safety issues. However, a plan to improve hepatitis B control is a timely and appropriate aim, with injection safety an important aspect of the control. [A Regional plan for immunization safety, including injection safety, was prepared by the Regional office in 2001, ¹ and was not discussed at the meeting whose focus was on control through immunization.]

1.3 Appointment of Chair and Rapporteur

Dr Doberstyn proposed the election of officers, and the proposal was approved by the meeting: Dr Tatsuo Miyamura as Chair and Dr David Hipgrave as Rapporteur.

2. PROCEEDINGS

2.1 Issues and options for hepatitis B control

Dr Shaw gave an overview of the issues for HBV control, reminding the audience that it is one of the world's leading causes of mortality with an estimated 750,000 deaths per year and 350 million chronically infected people in the world. The pattern of hepatitis B infection varies around the world with the Western Pacific Region having very high rates that are associated with early age of infection. The importance of injection safety for hepatitis B is highlighted by the estimate that globally about one third of all HBV infections are caused by unsafe injections.

Hepatitis B is unique among blood-borne and sexually transmitted diseases because a very safe and effective vaccine can prevent transmission. Infants and young children are at highest risk of chronic infection. Therefore, routine infant immunization is the best control strategy. The primary aim of hepatitis B control is to prevent chronic HBV infection, which is associated with the major burden of HBV-related disease. The vaccine has been shown not only to prevent infection, but also to reduce rates of chronic infection.
Historically, there have been two main barriers to the introduction of hepatitis B vaccine: lack of appreciation of disease burden and price. Even though the price has continued to decline (from about US$3.00 (1990) to US$0.32 (2002) per dose) the vaccine remains more expensive than other EPI vaccines. The establishment of the Global Alliance for Vaccines and Immunization (GAVI) has dramatically increased access to vaccines for the poorest countries in the world, including Cambodia, China, Lao People’s Democratic Republic, and Viet Nam in the Western Pacific Region. The availability of combination diphtheria-tetanus-pertussis (DTP)-HepB vaccine provides an option to reduce the number of injections (and hence ease logistics and injection safety). However, the combination DTP-HepB vaccine is more expensive (US$1.00 per dose) and cannot be used for the birth dose.

The birth dose is particularly important in the Region because the high rate of perinatal infection causes an estimated 40% of all chronic infections in China. In addition, comparison of a Chinese to African cohort suggests that those who become chronically infected at birth may have a ten-fold increased risk of developing HCC compared to those who become chronically infected later in life.

A simple static model shows that adding a birth dose has a relatively small impact compared to coverage, but may underestimate the full impact because the model does not incorporate the indirect effect of immunization, nor does it use the relatively high rates of perinatal transmission in this Region. The protection of a child prevents others from acquiring infection from that person. Infection is usually to younger siblings within a household, so this indirect effect of immunization will be primarily on younger cohorts, and has not been quantified. ‘Catastrophic dynamics’ can lead to interruption of transmission at even relatively low rates of coverage because of a ‘virtuous cycle’. Immunization leads to fewer infections, and a higher average age at infection, and so reduces risk of chronic infection. Fewer chronic infections lead to further reduced risk of transmission and hence even fewer infections.

### 2.2 Status of hepatitis B in the Western Pacific Region

Dr Mansoor gave an overview of the status of hepatitis B control in the Western Pacific, one of six WHO regions. The Region is composed of 37 countries and areas with wide variation in size (from China, the most populous, to small Pacific islands), development, and prevalence of chronic HBV infection. However, all but four countries have moderate to high levels of chronic HBV infection (Figure 1).

#### Table 1. Chronic HBV infection before and after immunization programmes

<table>
<thead>
<tr>
<th>Location</th>
<th>Year</th>
<th>Number tested</th>
<th>Age (years)</th>
<th>Immunization coverage (%)</th>
<th>HBsAg+ (%) before</th>
<th>HBsAg+ (%) after</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alaska</td>
<td>1995</td>
<td>268</td>
<td>1-10</td>
<td>96</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Taiwan (China)</td>
<td>1994</td>
<td>424</td>
<td>7-10</td>
<td>73</td>
<td>10</td>
<td>1.1</td>
</tr>
<tr>
<td>Samoa</td>
<td>1996</td>
<td>435</td>
<td>7-8</td>
<td>87</td>
<td>7</td>
<td>0.5</td>
</tr>
<tr>
<td>Lombok</td>
<td>1994</td>
<td>2519</td>
<td>4</td>
<td>&gt;90</td>
<td>6.2</td>
<td>1.9</td>
</tr>
<tr>
<td>Saipan</td>
<td>1994</td>
<td>200</td>
<td>3-4</td>
<td>94</td>
<td>9</td>
<td>0.5</td>
</tr>
<tr>
<td>Ponape</td>
<td>1994</td>
<td>364</td>
<td>3-4</td>
<td>82</td>
<td>NA</td>
<td>1.0</td>
</tr>
<tr>
<td>Micronesia</td>
<td>1992</td>
<td>544</td>
<td>2</td>
<td>40</td>
<td>12</td>
<td>3.0</td>
</tr>
</tbody>
</table>
Estimated Pre-vaccine % HBsAg+

LEGEND:
- > 12% (5)
- 8% - 12% (13)
- 3% - 7% (10)
- 0% - 2% (3)
- No Data (5)

Figure 1. Estimated pre-vaccine prevalence of chronic HBV infection (HBsAg+)

The supply of vaccine has progressively improved in the Region (Figure 2). Since the end of 2001, as a result of the recognized importance of HBV infection in the Region, all countries/areas in the Region have included hepatitis B vaccine in their NIP. However, the integration of hepatitis B vaccine into NIPs is not yet complete and not every child in the Region is being offered immunization:

- Japan has success with a 'high-risk' approach: offering vaccine only to babies of mothers with chronic HBV infection (HBsAg+) and other individuals at increased risk of infection.

- Lao People's Democratic Republic and Cambodia are phasing in combination DTP-HepB vaccine (with GAVI support) from 2001 to be completed in 2004 and 2005, respectively.

- Viet Nam's local vaccine production capacity has been sufficient for only about 15% of births; with GAVI support, vaccine will be provided for all infants by 2003.

- China has had user-fees limiting access; with GAVI support, these fees will be reduced in 2002, with the eventual aim of having the same user-fee as for other EPI vaccines.

- The Philippines has not yet been able to afford to procure vaccine for the entire birth cohort (~80% in 2001).
All countries/areas that have included hepatitis B in their immunization schedule have included a birth dose, with exceptions (Table 2): those that screen pregnant women and only offer vaccine and/or hepatitis B immune globulin (HBIG) (New Caledonia, New Zealand, Wallis and Futuna Islands); and those where access to infants at birth is limited as most births are not attended by a health worker (Cambodia, Lao People's Democratic Republic, the Philippines).

Table 2. Countries with no birth dose in hepatitis B immunization schedule

<table>
<thead>
<tr>
<th>Country</th>
<th>Births in hospital (%)</th>
<th>Births attended by health worker (%)</th>
<th>Birth dose offered (public)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cambodia</td>
<td>6</td>
<td>38</td>
<td>No</td>
</tr>
<tr>
<td>Lao People's Democratic Republic</td>
<td>11</td>
<td>21</td>
<td>No</td>
</tr>
<tr>
<td>New Caledonia</td>
<td>96</td>
<td>96</td>
<td>BCM</td>
</tr>
<tr>
<td>New Zealand</td>
<td>98</td>
<td>99</td>
<td>BCM</td>
</tr>
<tr>
<td>Philippines</td>
<td>34</td>
<td>56</td>
<td>No</td>
</tr>
<tr>
<td>Wallis and Futuna Islands</td>
<td>100</td>
<td>100</td>
<td>BCM (HBIG only)</td>
</tr>
</tbody>
</table>

BCM = offered to babies of carrier mothers

Coverage data show improvements in the third dose of hepatitis B vaccine (HepB3) coverage in infants until 1998, after which the trend is less clear (Figure 3). The reason(s) for the change in trend are not known, but may reflect the need for additional investments for the ‘hard-to-reach’ children in the Region. Most countries/areas do not collect data on timeliness of the birth dose.
Only nine countries/areas in the Region have attempted to assess the impact of hepatitis B immunization on disease. In all these countries the prevalence of chronic infection decreased by 85% or more – with the exception of Mongolia which had only an estimated 50% decline. It has been suggested that this may be the result of vaccine frozen during transport.2

There are also data showing immunization reducing the number of acute hepatitis B cases: about 85% decline in New Zealand and Singapore, 64% in Mongolia, 49% in Macao (China) and 17% in Hong Kong (China). However, Hong Kong (China) data are only available post introduction of universal hepatitis B immunization of infants.

It will take some time to see the impact of hepatitis B on the incidence of cirrhosis and HCC, however, there are data showing a decline in HCC in children aged 6-14 years.3 Some meeting participants suggested that this decline might not be attributable to immunization, given the potential contribution of cofactors such as aflatoxin. However, the majority view was that the decline was primarily the result of immunization because other age groups did not show similar declines, and the data has been accepted internationally as showing that HCC is prevented by immunization.

2.2.1 Estimating HBV-related disease burden in the Western Pacific Region

Dr Nelson outlined a model developed by WHO headquarters to estimate the global burden of disease, by age and sex, based on the prevalence of chronic HBV infection in different countries (WHO data, 1996) and the age and sex specific mortality from cirrhosis and HCC in those chronically infected (from Gambian data). The Gambian project generated good quality data as it was based upon extensive active surveillance, and very similar estimates were obtained from Taiwan (China). The model can be used to both estimate year 2000 disease burden and the future burden for the cohort born in the year 2000. For the future burden, the model also factors in ‘competing’ background mortality. People with chronic HBV infection who die from other causes should not be included in the overall burden, and should be removed from the at-risk population (see Figure 4).
The model estimates current global burden at 360 million chronically HBV infected people, 5.7 million HBV-related cases, and 520,000 HBV related deaths. Over half of these deaths are in the Western Pacific Region. The relative importance of hepatitis B in the Region, as well as the potential for control, is illustrated by comparing the estimates of 1999 measles deaths. As a result of the Region’s successful immunization programmes, it is estimated that only about 2% of global measles deaths occur in the Region (about 20,000 of the global total of 875,000 measles deaths).

Of the HBV-related deaths, 69% are from HCC (with or without cirrhosis), 21% are from cirrhosis and 10% are from acute hepatitis. In contrast, 92% of the morbidity is from acute hepatitis, 6% from HCC and 2% from cirrhosis.

The estimated future global burden (without immunization) for the cohort born in 2000 is over one million deaths. Vaccinating infants at birth will prevent a large part of this future burden. Assuming that the vaccine protects only the vaccinated person, is about 90% effective and coverage with hepatitis B vaccine is equal to the current reported diphtheria-tetanus-pertussis (DTP3) coverage in each country, then it is estimated that 77% of the future burden in the Region could be prevented. However, preventing a chronic infection in infancy is likely to prevent many other secondary infections, so the potential impact of routine infant immunization is probably even higher.

Source: (WHO 2000)
There are many limitations to the model, including the lack of data on the age- and sex-specific incidence of HBV-related HCC and cirrhosis (current model estimates are based on data from the Gambia and Taiwan (China) only). Another limitation is the failure to account for co-factors associated with HCC and cirrhosis (such as alcohol consumption, aflatoxin, other viral hepatitis infections and occupational, and environmental exposures). The impact of co-factors could be addressed using carefully designed case-control studies in populations with measurable levels of exposure. However, it is unclear whether this would substantially improve the disease burden estimates. Instead, an effort should be made to use WHO’s existing cancer surveillance network to expand the geographical scope of research into HBV’s attributable fraction in cirrhosis and HCC.

The seroprevalence estimates are a key input to the model. Laboratory technique, sampling framework, and other factors can affect the estimates obtained in any seroprevalence study. For example, in Viet Nam HBsAg seroprevalence estimates range from 8% to 18% despite no obvious known biases causing this wide range of variation. In addition there may be important geographical variations sub-nationally (e.g. China) or ethnic variations (e.g. Fiji). Despite these limitations, the model provides a reasonable way of estimating hepatitis B disease burden.

2.3 Country experiences

2.3.1 Singapore

Dr James noted that the importance of hepatitis B was recognized early on and made notifiable in 1976. Immunization started in mid-1983 with immunization for health workers, extended to babies of HBsAg+ mothers from October 1985 (after universal antenatal screening was established), and then to all newborns from September 1987.

Coverage has progressively increased and has reached around 90% in the last few years. An apparent recent decline was due to adjustment of the denominator. The critical success factors for hepatitis B immunization have been the integration into NIP, wide publicity for the vaccine and payment by Medisave (compulsory medical insurance account). Building on these successes, a four-year catch-up programme was started in 2001 for those aged 14 years and older in school and educational institutions as well as for national servicemen. The catch-up programme involves testing prior to immunization: about 0.7% were HBsAg+ and about 40% had antibodies.

The impact of immunization has been shown by a reduction in the number of acute hepatitis B cases and reductions in seroprevalence. However, it appears that seroprevalence was already declining before immunization, presumably as a result of economic development. However, the decline was sharpest for six to 12 year olds (4% in 1987 to 0% in 1994).

The decline in age-standardized incidence of HCC in males from 28 to 29 per 100 000, from 1968 to 1982, to 19 per 100 000 from 1988 to 1997, could only be partly, if at all, attributable to infant immunization.

Singapore has a mature programme that is working well and shows that there is now a low rate of carriage. More effort is needed to document this impact, and a Regional objective is likely to help with national control.
2.3.2 China

Dr Liang advised that hepatitis B vaccine was introduced into the NIP in 1992, but at full cost to parents (including cost of vaccine, distribution charge and administration fee) at an average charge of US$3 for the three-dose series. Thus, a nationwide 1999 coverage survey found an overall 70% coverage for hepatitis B (much lower than for DTP). Coverage depended on income, education and remoteness. The China Foundation for Hepatitis Prevention and Control implemented a demonstration project in 21 rural and poor counties starting from 2000. The vaccine was provided free with a maximum administration fee of US$1.27 for the three doses. There was also supervision and training for health workers and education for the community. Results to date have shown that it was possible to more than double HepB3 coverage (to 94%) and to achieve delivery of timely birth dose (within 24 hours) in 76% of infants.

While user-fees have been a barrier to uptake in poor areas, they enabled hepatitis B vaccine introduction and provided income to health workers delivering vaccine and to health departments. Hepatitis B immunization achieved reasonable coverage (70%) leading to prevention of an estimated seven million chronic infections and 250 000 deaths for each birth cohort. Halving the user fee together with education and training allows the achievement of even better coverage, especially in difficult circumstances. It is not clear what the relative importance of education and training was versus the lower user-fee accounts for the increases in coverage achieved in the demonstration project.

Building on this experience, China has successfully applied to GAVI to assist in reducing user-fees. A new regulation (2001) requires hepatitis B to be fully integrated into the NIP and the vaccine must be provided free of charge like other EPI vaccines. The funding for the 12 Western provinces and poverty counties (about one third of birth cohort) is coming 50% from GAVI with the other 50% from the Government. For the rest of the country it will be the responsibility of the province government as it is for other EPI vaccines. For the GAVI project areas the maximum administration fee will be 3RMB (~US$0.37) per dose (compared to 0.5-1RMB for other EPI vaccines).

Dr Zhuang described a national survey conducted from 1992 to 1995 that tested 67 124 people, including 32 512 males and 34 612 females and found an overall prevalence of 9.7% of HBsAg. The age-specific prevalence showed that nearly all chronic infections have been acquired by the age of five years.

The national survey also estimated the rate of chronic liver disease at 0.8 and 1.6 per 1000 under-15 year olds and total population, respectively, and mortality at 1.4 and 24.9 per 100 000 under-15 year olds and total population, respectively. HCC mortality was 0.8 and 14.8 per 100 000 under-15 year olds and total population, respectively. In a demonstration project in Longan County (where they vaccinated all under-15 year olds) the rate of HCC declined from 5.7 per 100 000 among 10 to 19 year olds to 2.6 between 1986 to 1992, to 0 between 1993 to 1996.

The national key project undertaken in the cities of six provinces found that immunization led to a reduction in chronic HBV infection of 85%-97%. The chronic infection rate was much lower in Beijing and Shanghai with use of the 20mcg doses (0.3%) than in the other provinces where the dose was 10 mcg (1.1%-1.5%). Up to nine years of follow-up showed that protection was maintained. There were six manufacturers of plasma-derived vaccines in China, but they stopped production since 1998. There are now only two manufacturers producing recombinant vaccine (both are Merck joint venture) and use the standard Merck dose of 5 mcg.
2.3.3 Viet Nam

Dr Cuong explained that hepatitis B immunization had started with using a locally produced vaccine in 1997. However, despite increases in production since then, only enough was produced for about 15% of the birth cohort. Since January 2002, GAVI support has enabled extension of coverage starting with 56% of the districts of 44 provinces (the remaining 17 provinces are using locally produced vaccine). The remaining districts will be covered from 2003.

The first dose is to be given at birth, within 24 hours if the infant is born in a health facility and within three days if born outside. For the first four months of 2002, only 36% of newborns received vaccine within three days, but this should be improved, as vaccine with vaccine vial monitors (VVMs) becomes available allowing for some use outside the cold chain. An important part of the GAVI support was the training for health workers on hepatitis B vaccine, including use of VVMs and auto-disable syringes (ADs). A booklet was prepared and distributed widely, down to the commune level.

There is limited data on the two-month gap between the first dose (birth) and the second dose (given with DTP1) as most studies gave the second dose at one month. In the Gambia, which uses the same schedule, the protection given to babies of HbeAg+ mothers was good. However, there is a need for more observational data.

For Viet Nam the priority is to achieve good coverage and increase the timely delivery of the birth dose. There is also a desire to monitor and evaluate impact.

2.3.4 Cambodia

Dr Soeung advised that there are only limited data on seroprevalence, but Cambodia is in a region that is known to have high rates of infection, and about 10% of blood donors are HBsAg+. Therefore, there was strong support for the introduction of hepatitis B vaccine and this became possible with the availability of GAVI support. Cambodia was successful in the first round of GAVI application in 2000 and received the supplies (as combination DTP-HepB vaccine and ADs) in 2001. The plan is to progressively extend coverage to the entire country by 2005 coupled with the exclusive use of ADs for all EPI vaccines.

A serosurvey was undertaken in 2001 in the pilot district to provide a baseline. In contrast to other data in the region where rates of carriage tend to plateau at about age five (reflecting early transmission), the survey found a continuous increase in prevalence: nine to 17 months: 3%; four to five years: 5%; 13 to 15 years: 8%; and 20 to 35 years: 11%. The reasons for this are unknown but may be due to higher infection rates in earlier cohorts.

It is planned to undertake a survey in 2005 to assess seroprevalence to look at the impact of vaccination, even though there are limited baseline data. A birth dose is being considered, starting with implementation in selected facilities where it can be done safely. Another option for the future is to pilot the feasibility of a monovalent hepatitis B schedule for routine EPI because it is much cheaper than the combination vaccine. (After the five years of GAVI support, Cambodia will need to secure funds to continue vaccine purchase). Also being considered is vaccine for seronegative blood donors in part to provide an incentive for them to donate.

The first priority is to expand coverage of the new vaccine followed by evaluation of the impact. Another priority will be to provide the birth dose.

The main support needs for Cambodia are a sustainable supply of vaccine (including Uniject to help with remote delivery of birth dose if a decision is made to introduce it), and the technical support and resources for the planned 2005 serosurvey.
2.3.5 Japan

Dr Okabe provided the context for hepatitis B immunization in Japan where a 1948 immunization law, amended in 1994, specifies responsibility for immunization being with local government. It also requires informed consent and provides compensation for vaccine reactions. The law specifies two categories of vaccines for routine immunization. Category one is polio (2 doses), DTP (4 doses), diphtheria-tetanus vaccine (DT) (1 dose), measles (1 dose), rubella (1 dose) and Japanese Encephalitis (5 doses). Category two is influenza (for elderly people), Bacillus Calmette-Guérin vaccine (BCG) (under TB prevention law), and hepatitis B only for babies of carrier mothers. Hepatitis B immunization started in Japan in 1986 as a special public health project with free immunization and HBIG for babies of HBeAg+ mothers. Since 1995, the cost has been borne by public health insurance (free of charge) and extended to babies of HBsAg+ mothers. The schedule is for HBIG at birth and again at age one month (second dose of HBIG is optional for babies of HBeAg- mothers). Vaccine is given at ages two months, three months, and five months.

This programme has been found to be very effective at reducing the rate of chronic infection in Japan. However, it does depend on the capacity to test antenatally and to follow-up the babies of HbsAg+ mothers.

Dr Yoshizawa summarized the data showing the effectiveness of Japan’s high-risk approach. In Iwate prefecture, carriage was 0.9% before vaccine introduction compared to 0.03% after the introduction of vaccine. In Shizuoka province carriage was 0.3% in junior high school children before vaccine was introduced compared to 0.03% afterwards. Babies vaccinated at birth have been followed up, and no acute cases have been identified. Similarly, the vaccine has been given in nursing schools, with no cases subsequently identified among those who seroconvert.

Various schedules have been tried and the most effective one to prevent perinatal infection was to give vaccine starting at two months of age with HBIG given at birth.

The overall seroprevalence data of blood donors show a progressive increase up to age 50, and then slight decline in seroprevalence. This suggests a declining rate of chronic infection and that HCC should decrease over time.

In the United States of America, which also is a low-prevalence country, it was found that a high-risk strategy did not work well, so the country adopted universal immunization. Now, in Japan more than 80% of cases in adolescents are sexually transmitted. The main target is prevention of carriage and not prevention of acute infection. For Japanese adolescents, the main risk of infection is in other countries.

There is surveillance data in Japan on acute hepatitis B but only about 10% of cases are reported. However, the surveillance system had identified many small outbreaks, usually they are associated with medical treatment (e.g. dialysis centre). In Japan, about 20% of carriers develop HCC or cirrhosis, with males four times more likely to develop complications than females.

2.4 Advocacy and Mobilization

Mr Milne started his presentation with this challenge: “Given all the information and knowledge about hepatitis B, why are not more children being protected in the Region?”

The role of the advocate is gathering the science and data and then overcoming obstacles. “Do not leave this to your successor” is the message to be given to Governments. The media can be a valuable ally in their thirst for stories.
The challenge for hepatitis B is that the disease does not have the visibility and immediate impact of other vaccine-preventable diseases. Therefore, there is a need for country health officials to be experts who can fully inform the Government, and enthusiastically support the programme. Having incentives helps, and it is useful to think laterally, for example by enlisting the police or military.

Possible key messages include:

“The battle against hepatitis B virus (HBV) is winnable.”

“Every two minutes in our Region, a person is dying from HBV-associated liver disease.”

“In the future, the costs for each country will escalate as treatments become available. Prevention is better than cure.”

“Preventing hepatitis B is as easy as 1-2-3: three doses of a safe, effective vaccine.”

It is also important to emphasize that hepatitis B virus is NOT due to dirt or bad hygiene nor a cause for shame or blame.

Mr Milne suggested these messages for mothers:

“Vaccines to combat hepatitis B are highly protective for babies and very safe. They are among the best vaccines ever produced.”

“Your government will ensure that the vaccine is made available free for every newborn child in your country.”

“It is your duty as a mother to ensure that your baby is vaccinated at birth and receives two further doses as arranged by your health worker.”

“If we work together we will be able to eradicate this disease from our country. This will take many years but we will succeed.”

2.5 Options for vaccine use in National Immunization Programmes

2.5.1 Vaccine supply and security

Ms Molari reviewed the situation of the hepatitis B vaccine supply in the context of the overall vaccine supply situation. The United Nations Children's Fund (UNICEF) procures vaccines for 100 countries (the 76 poorest and 24 middle-income countries) totalling over 2.8 billion doses in 2002 or 40% of the world’s children. This contribution is only 8% of the global vaccine market value. There is now an increasing divergence between vaccines used in poor and rich countries (e.g. measles-mumps-rubella (MMR) versus measles, inactivated versus oral polio vaccine, acellular pertussis versus whole cell, and combination vaccines). As a result, there is a shortage of traditional EPI vaccines. However, for monovalent hepatitis B vaccine there is an adequate supply, with an increasing number of producers entering the market. As a result, price decreases can be expected in the future. A long term stable price that allows adequate profits for the vaccine manufacturers is not certain. However, there is only a single supplier of combination DTP-HepB vaccine and very limited supplies. It is unlikely that the combination DTP-HepB vaccine can be offered to any additional countries before 2005.

In order to secure a long term supply of vaccine it is important to have a healthy, thriving vaccine industry with a variety of manufacturers in both industrialized and developing countries. To help achieve that, it is important to provide the industry with guaranteed procurement based on accurate and reliable forecasts. In addition to working with
countries to improve the quality of their forecasting it is important to also secure the funding for the vaccines.

UNICEF will be undertaking its tender for 2004 to 2006 at the end of 2002. It is therefore important to start preparing the vaccine forecasts of country demand.

From 2002 all the UNICEF supplied monovalent hepatitis B vaccines have VVMs – except for the six-dose vial.

2.5.2 Vaccine history, safety, and efficacy

Dr Kim reviewed the history, safety and efficacy of vaccines. Hepatitis B vaccines are composed of highly purified preparations of HBsAg bound to an aluminium salt to enhance the immune response. The first vaccine, licensed in 1982, used HBsAg from the blood of chronically infected people (plasma-derived). Recombinant vaccine (first licensed in 1986) is prepared from genetically modified cells (plasmid containing HBsAg gene inserted into yeast or mammalian cell).

Despite extensive safety precautions and the evidence of safety, there continue to be unfounded fears about plasma-derived vaccine. Partly because of these fears, but mainly because of the limited source material and the relatively high cost of production, plasma-derived vaccines are little used now and are no longer procured by UNICEF.

The HBsAg in recombinant and plasma-derived vaccines is morphologically and antigenically similar. However, the recombinant vaccine is entirely non-glycosylated whereas the plasma-derived vaccine is 70% to 80% non-glycosylated.

Several combination vaccines containing hepatitis B vaccine, are available: diphtheria-tetanus-pertussis-hepatitis B (DTP-HepB), diphtheria-tetanus-acellular pertussis-hepatitis B (DTaP-HepB); diphtheria-tetanus-pertussis-hepatitis B- haemophilus influenzae type b (DTP-HepB-Hib); diphtheria-tetanus-pertussis-hepatitis B-haemophilus influenzae type b-inactivated polio vaccine (DTP-HepB-Hib-IPV); haemophilus influenzae type b-hepatitis B (Hib-HepB); hepatitis A-hepatitis B (HepA-HepB). At present there is only one manufacturer of DTP-HepB because of the technical difficulty in overcoming interference with the combination.

Hepatitis B is one of the safest vaccines available in the world. The only known serious adverse event, after 20 years of increasing worldwide use, is anaphylaxis estimated at one in 600 000 doses. Minor reactions such as fever (1% to 6%), pain at injection site (6% to 29%), and local reaction (10% to 29%) occur less often than with traditional EPI vaccines. Non-specific, systemic symptoms also occur after immunization in up to 15%. These may be unrelated as are more serious events that have been reported after immunization. Recently, there were concerns that hepatitis B vaccine caused multiple sclerosis and demyelinating diseases based on reports of these events happening after immunization. However, assessment of available data have shown that these are coincidental events and not caused by immunization.

The vaccine (with HBIG) has been 79% to 98% effective in preventing perinatal transmission in babies of HBeAg+ mothers. The vaccine alone appears to be practically as effective as vaccine with HBIG as long the vaccine given is not of very low dose.

In addition to the data on individual protection, there are data on reduction of carriage rates in populations that have been vaccinated. For example, in Korea the carriage rate in young children is now less than 1%. In 1980, seven-year old children had a carriage rate of 7.5%, but by 1995 it was 0.38%.
The vaccine has been shown to be immunogenic in a variety of schedules. Those who develop an antibody level of at least 10 IU/L have been found to be 100% protected against chronic infection. Boosters are not needed despite the decline in antibody levels - protection appears to be maintained.

Injection of the vaccine in the buttock has been shown to lead to lower rates of seroconversion in adults and is not recommended. In infants the thigh is the recommended site, while the deltoid is recommended for older children and adults.

There are several factors that are known to affect seroconversion: smoking, obesity, HIV infection, chronic disease and age. However, there do not appear to be any important differences in the efficacy of the range of available vaccines.

The vaccine is very sensitive to freezing because it separates the aluminium adjuvant. However, there are no data on the immunogenicity of vaccine that has been frozen.

In Fiji, antibody levels following immunization were three times higher in Fijian Indians than in Melanesians, suggesting the possibility of ethnic differences in response. However, the seroconversion rates were similar, and there are no data suggesting that the vaccine is less efficacious in specific ethnic groups.

2.5.3 Mathematical modelling to assess impact

Dr Wilson explained that mathematical models have been extensively used to provide a quantitative understanding of biological processes. In vaccination, it has been possible to model the phenomena of priming and boosting, where priming is the generation of an ability to produce antibody and boosting is the actual production of these antibodies. The model was used in a meta-analysis of empirical data. Specifically, 10,815 antibodies to HBsAg (anti-HBs) measurements from 1,923 individuals from trials with eight different hepatitis B vaccines in six countries were analyzed. The results suggested that the first vaccine dose successfully primes immune memory that then expands over one to six months depending on the vaccine. The second and third doses lead to greater antibody production but do not affect the time over which this immune memory develops. Therefore, according to this model, protection (i.e. sufficient priming to be able to produce 10 IU/L) can be achieved with a single dose. Given the adequacy of a single dose for priming, it is to be expected that a wide range of schedules will lead to seroconversion, as indeed has been found to be the case.

There is some empirical evidence for complete protection from carriage with schedules of fewer than three doses: three randomized controlled studies (involving 124,255 and 318 individuals) found no cases of chronic infection in groups vaccinated with one or two doses. These studies involved between nine and 12 years of follow-up and took place in high-risk populations in Zambia and in children and infants in Italy and Hong Kong (China). However, there was a consensus that these data are currently insufficient to change the recommended number of doses for neonates as there have been no protective efficacy studies using fewer than three doses specifically in newborns. Neonates are susceptible to perinatal transmission and Professor Hall presented some data suggesting a delay between the birth and second dose of vaccine may be associated with reduced protection.

2.5.4 Options for the birth dose

Dr Hipgrave outlined the rationale for the birth dose of hepatitis B vaccine, particularly for this Region. The key fact is that 25% to 50% of all chronic infections in Asia result from perinatal infections (compared to 10%-20% in Africa) because of the relatively high rate of HbeAg+ in pregnant women. In China, the best estimate is that 40% of chronic infections are perinatally acquired. In addition, the infants who acquire perinatal infection are more likely to become chronically infected, are likely to be important in spreading infection to others and appear to be at increased risk of developing HCC.
The protective efficacy (PE) of hepatitis B vaccine in preventing perinatal transmission is variable and depends on: the antigenicity (dose is used as a proxy but is not equivalent); degree of exposure (HBeAg is used as proxy for the viral load; HBV DNA would be a better indicator but is not widely available); and timing of the dose and possibly the timing of the exposure. The addition of HBIG only adds marginal PE to immunization as long as a low dose vaccine is not used.

Receipt of the first dose (less than seven days after birth) amongst infants of highly infectious mothers (HBeAg positive) in four studies gave higher PE (70% to 95%) than if given after one week in four other studies (50% to 57%). But none of these studies differentiated infants who received vaccine very early from those receiving it later in the first week, and an exception was the protective efficacy of 75% found in one group of infants of HbeAg+ mothers who received the vaccine alone in week two.

Therefore, WHO recommends that the birth dose should ideally be given within 24 hours of birth. However, it is also important to emphasize that it is never too late for a birth dose, and that it needs to be given as soon as possible. There are also inadequate data on the effect of the timing of the second dose on PE, but it is generally recommended within two months of the birth dose.

The heat stability of the HBsAg protein allows use of the vaccine outside the cold chain to facilitate timely delivery of a birth dose in areas with no functioning cold chain. The addition of VVMs now allows assurance that there has not been sufficient cumulative heat exposure to inactivate the vaccine. However, the cold chain also protects vaccine from freezing, which is a risk in some areas.

At present WHO does not yet recommend the use of hepatitis B vaccine outside of the cold chain, because of the need for more field data on efficacy outside the cold chain. Dr Hipgrave presented some additional information on the efficacy in a trial in Viet Nam. The study also showed the importance of education and training as well as incentives for harder-to-reach communities.

The Uniject also aids delivery of the birth dose by the birth attendants who may not normally deliver immunizations. This was shown by the trial in Indonesia that was very positively evaluated both by the midwives and community, and is now leading to a (GAVI-supported) national introduction of Uniject for the birth dose of hepatitis B.

For most countries, the additional costs of screening and HBIG are not justifiable given the likely higher programme efficacy of a timely birth dose delivered to all newborns. However, as many births are not attended, countries will need to develop locally appropriate strategies to reach as many newborns as possible, as fast as possible. Monitoring the delivery of the proportion of birth doses given within 24 hours of birth will be an important management tool to improve timely delivery.
2.6 Laboratory tests

Dr Yano described the different hepatitis B antigens and antibodies, and their use for laboratory diagnosis:

- **HBsAg**
  - **HBeAg**
  - **HBV-DNA**
  - **anti-HBc**
  - **anti-HBs**

There are a range of different laboratory assays that are used in Japan for detecting HBsAg that vary in their sensitivity (0.2 to 20 ng/ml) and price (US$1.10 to US$3.40). The choice of assay used depends on their purpose. The cost of antibody to HBsAg is similar.

HBV genotyping is also routinely undertaken, with HBV subtype C being the predominant type in all areas except Okinawa. As Okinawa has a relatively low rate of HCC despite high rates of HBV carriage, subtype C appears to be more likely to cause HCC than subtype B. An association has also been found between the clinical features of acute hepatitis and the pre-core and specific genotypes.

The actual performance of tests, and hence the results, are dependent on the quality of laboratory procedures as shown in Kenya by a large increase in seroprevalence following training.

2.6.1 Laboratory test results in China

Dr Zhuang described the laboratory tests used in China. China has more than 40 producers of HBV assays, mostly ELISA. The cost for HBsAg and anti-HBs is about US$0.10 per test, and for IgM anti-HBc is slightly higher at about US$0.14 per test. A gel gold strip was developed in 1999 that cost US$0.20 per dose that provides a visual result (line) in 10 minutes. It was designed for field use.

The National Institute for the Control of Pharmaceutical and Biological Products is responsible for the establishment of reference panels and evaluation of test kits.

In China, the genotype of HBV is predominantly subtype C (50%–73%), followed by subtype B (30%). There are reports of up to 30% escape mutants in some series, but this does not match the approximately 90% reduction in chronic infection seen with immunization.
2.7 Monitoring the impact of hepatitis B immunization

2.7.1 Framework for assessing impact

Dr Shapiro presented a framework for assessing the impact of hepatitis B immunization, pointing out the purpose of evaluation in terms of monitoring progress (and “what gets measured gets done”), to identify and fix problems, and perhaps most importantly to advocate. Unlike other vaccine-preventable diseases, monitoring of acute cases may not demonstrate the impact for many years, and even then only partially as the main burden arises from chronic infection.

**Objectives of monitoring**

<table>
<thead>
<tr>
<th>Objective</th>
<th>Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provide hepatitis B vaccine to all infants</td>
<td>Routine reports of coverage</td>
</tr>
<tr>
<td></td>
<td>(administrative)</td>
</tr>
<tr>
<td></td>
<td>Coverage surveys</td>
</tr>
<tr>
<td>Prevent/eliminate new HBV infections</td>
<td>Surveillance for acute hepatitis B</td>
</tr>
<tr>
<td>Prevent/eliminate chronic HBV infection</td>
<td>Serologic surveys (serosurveillance)</td>
</tr>
<tr>
<td>Prevent long term sequelae of hepatitis B</td>
<td>Surveillance for HBV-related mortality</td>
</tr>
</tbody>
</table>

Administrative coverage data is readily available in most countries, and must provide the base information for programme management. However, the accuracy and completeness of numerator and denominator data are important issues. Additionally, there is a need for an indicator on timeliness of first dose. The main concern is that coverage may not be the same as effectiveness, for example because of frozen vaccine, late delivery of birth dose and other programme failures.

A coverage survey can validate administrative data and provide additional information on reasons for not receiving or late receipt of vaccines. However, it requires expertise in sampling, survey and interview methods, is relatively labour intensive, and it is difficult to ensure representation of the samples and obtaining reliable immunization histories. A coverage survey for Hepatitis B would need additional information on timeliness of birth dose.

Acute hepatitis B surveillance has historically not been used because most cases in children are asymptomatic. However, it is possible (e.g. Singapore) to monitor impact of immunization. It does require sufficient childhood case and laboratory capacity for diagnosis, and ongoing resources for maintenance (minimum would be IgM HAV, IgM anti-HBc and HBsAg). Sentinel surveillance is more likely to be better undertaken than national surveillance.

Serosurveys aim to compare chronic infection before and after immunization. They require a representative population and laboratory capacity. As prevalence varies by age, geography and risk group, it is important to ensure the sample selected is representative. Adding anti-hepatitis B core (anti-HBc) can be useful, but maternally derived anti-HBc can be present in infants for up to 18 months after delivery and thus may interfere with measurement of this marker. (However, this was not a problem in the Gambia.) Anti-HBs can be used to demonstrate immunity, but there is waning of antibodies in those who remain protected.
A serosurvey can be undertaken by taking blood as part of a coverage survey or part of another survey. Rapid tests for HBsAg may provide the ability to undertake serosurveys even in countries with limited capacity to test for hepatitis B. Field evaluation of these tests is needed, especially in areas with malaria because of the potential for higher rates of false positives.

There are also important ethical considerations for blood testing in relation to the advice for and treatment of those found to be infected.

Most countries in the Region do not have the laboratory capacity for routine serologic testing for hepatitis cases. The experiences in establishing the polio laboratory network, and now the measles laboratory network, could be used to establish laboratory capacity since tests for measles serology and hepatitis serology use similar methodology (e.g. ELISA). However, establishing a laboratory network for hepatitis would require considerable resources and technical input. Although not feasible at this time, it might be considered in selected areas if resources become available.

2.7.2 Experience in assessing impact

Professor Hall described experience in the field in measuring impact. A sophisticated laboratory is needed to produce reliable, consistent results. The availability of baseline data is very helpful, and if possible the same group should be used to assess impact. The age group to be assessed can be restricted to those aged from one to five years to assess the impact on chronic carriage or it can be extended to the entire target age group that has received vaccine. Older children (i.e. non-vaccinated) can be included to show impact, but some of them will have been indirectly protected.

The presence of HBsAg (which usually represents chronic infection) is the most important endpoint for assessing impact. However, this requires a sample of at least 1000 children. Using infection as an indicator (anti-HBc) allows a smaller sample. An even smaller sample (about 100 children) is needed for evaluating immunogenicity (anti-HBs). The advantage of testing for immunogenicity is that it provides immediate feedback on any problems with the programme.

In Colombia a sample of 3573 children aged under 11 years (vaccinated group) were randomly selected, with both mother and child tested. The health workers were interviewed for their knowledge about hepatitis B and the vaccine. The importance of coverage included maternal income and education and also health worker knowledge. HBsAg seroprevalence increased with longer intervals between birth and the first dose and with longer intervals between the first and second dose of the vaccine.

In Yemen, the sample included older children to assess the pre-vaccine rate. The sample size calculations used a pre-vaccine estimate that was much too high because of previous laboratory errors, highlighting the importance of a reliable laboratory.

Serosurveys are probably the best way to capture useful data and are not to be undertaken lightly. At minimum there is the need for one epidemiologist and one laboratory expert to undertake a serosurvey. The survey should use a representative rather than a convenience sample, as disease rates are much higher in the poor areas, even in areas that appear homogenous, leading to important biases in hospital-based studies.

2.7.3 Modelling impact

Dr Wilson explained how modelling can be used to make an economic evaluation of the impact of different vaccination strategies. Data on the age-specific seroprevalence of HBV markers in different countries in the region would allow the amount of perinatal transmission (especially from the sub-group of HbeAg+ mothers) and the rate of horizontal transmission in older age groups to be quantified. These data, together with specific
demographic data, could be used to model the impact of different vaccination strategies in different countries. However, there is currently uncertainty as to the efficacy of preventing perinatal transmission when the first dose is given at different times soon after birth. Hence an economic assessment of the cost-effectiveness of a birth dose could not easily be made.

The prevention of the long term sequelae of chronic HBV infection can be predicted and costed. An economic assessment would then involve subtracting the costs of each programme from these savings generated by vaccination. This gives a cost per death prevented or other health outcome gained, e.g. disability adjusted life year (DALY).

For hepatitis B discounting future costs and benefits (i.e. valuing short-term costs and benefits more highly than long term ones) has a major impact because of the delayed consequences of infection. Programmes generally become more cost-effective over time for the same reason, but also need to be maintained for many decades.

It was noted that an economic assessment for the UK had suggested that supporting hepatitis B immunization in the countries where immigrants are coming to Britain would be more cost-effective than vaccinating within the country. Similar arguments may apply to low-prevalence countries in the Region (i.e. Australia, Japan, New Zealand).

2.8 Setting a Regional objective

An objective must be scientific, enable monitoring and evaluation, and be a tool for advocacy and resource mobilization. Setting a disease control objective for hepatitis B is not straightforward because of the nature of the disease, and the need to have objectives that can be met in a five to 10 year timeframe and require baseline data that do not exist for most countries. The full impact of hepatitis B immunization programmes of today will not be seen for 30 to 40 years.

The consensus was that a Regional objective should be based on the seroprevalence of HBsAg (as the measure of chronic HBV infection) in vaccinated cohorts. As part of the aim of monitoring impact is to identify and fix problems, the measurement of carriage should be undertaken in one year olds. However, as there may be continuing horizontal transmission, seroprevalence also needs to be assessed at around five years of age. (Few chronic infections result from exposure over the age of five years).

It was noted that milestones would be more appropriate than objectives. In addition, given the limited capacity in some countries there may be some conflict between achieving coverage (and birth dose) and monitoring impact.

China’s national plan has three indicators, coverage, first dose coverage and seroprevalence. By end of 2005 coverage in urban areas is expected to be 90%, in rural areas 80%, and in remote areas 70%. Also by the end of 2005, first dose coverage within 24 hours is expected to be 80% in urban areas, 70% in rural areas and 50% in remote areas; seroprevalence is expected to be 1% in urban areas, 3% in rural areas and 5% in remote areas.

Given the importance of health worker’s functional knowledge about hepatitis B adding an indicator to monitor and improve that aspect was felt to be important.
3. CONCLUSIONS AND RECOMMENDATIONS

3.1 Conclusions

3.1.1 Disease burden and vaccine

- HBV is an important cause of clinical disease and death in the world, and even more so in the Western Pacific Region with over half of the global burden and only one quarter of the global population. A safe and effective vaccine is available. Through immunization the disease can be controlled and perhaps even eradicated after some generations.

- There has already been considerable progress in the Region in protecting a large proportion of children through immunization. In addition, several countries/areas in the Region have shown the impact in reduced rates of disease and chronic infection and, in one area, even liver cancer. The full impact of immunization on liver cancer will not be seen for several decades because of the delayed consequences of chronic infection.

- There is extensive data on the safety, effectiveness and impact for hepatitis B vaccine. In addition, effectiveness has been shown for a range of different schedules, given at the same time or in combination with other vaccines. Even though antibody levels are higher if there is a longer gap between second and third dose, the protection is the same. Therefore, hepatitis B vaccine may be delivered at the same time, but at different sites, as other EPI vaccines. Usually BCG is given at the same time as the birth dose, and DTP at the same time as subsequent doses (or as combination DTP-HepB vaccine).

3.1.2 Immunization strategies

- There is the potential to improve programmes in the Region (i.e. schedule, monitoring, using data to improve programme, safe injection and disposal). Experience from other accelerated disease control programmes should be used in the control of hepatitis B infection.

- Effectiveness of control is intimately related to quality of routine immunization services, especially coverage and injection safety. Hence, the most important aspect of improving hepatitis B control is to improve routine immunization services.

- Universal infant immunization is the most effective and efficient way to reduce hepatitis B disease burden. Achieving and maintaining high immunization coverage in infants is the most important strategy for the control of hepatitis B.

- A high-risk approach that focuses on protecting the babies of carrier mothers and others at increased risk of infection has not been found to work elsewhere in the world, but appears to be successful in Japan, where meticulous detection and follow up of carrier mothers and their vaccinated infants has been possible.

- A timely birth dose (preferably within 24 hours of birth) is needed to prevent perinatal transmission, which is known to be a major source of chronic infection in this Region and may be responsible for a higher proportion of long term complications of infection. Ideally, the second dose should be given not later than two months after the birth dose and ideally at the same time as DTP is administered.
• For reaching children in remote areas where there is no cold chain, the addition of VVMs on hepatitis B vaccine (available for most UNICEF-procured vaccines from 2002) provides a new opportunity to use the vaccine beyond the cold chain. This may be especially useful for the timely provision of a birth dose, but caution will be needed to ensure that messages about the importance of the cold chain are not diluted by such practices.

• There are some data, primarily in adults, suggesting that one dose of hepatitis B vaccine may be sufficient to prime immune memory enabling rapid production of antibodies in the event of future exposure. However, most of the existing data on immunogenicity and protective efficacy among infants is based on the use of three doses. Therefore three doses for infants should continue to be the standard until such time as more evidence for reducing the number of doses is available.

3.1.3 Monitoring impact

• Coverage is the best way to monitor programs of vaccination against hepatitis B. The impact of immunization on disease cannot be measured in the same way as other vaccine-preventable diseases because of the long time lag before complications develop from chronic infection and because those complications are not exclusively caused by HBV.

• Measuring the prevalence of chronic infection can be effectively done using serosurveys for HBsAg. A range of serological tests can be used to measure HBsAg, possibly including rapid strip tests that can be used in places without existing laboratory facilities. Quality assurance programmes are an essential part of laboratory testing. Ethical considerations should be taken into account in the planning of serology surveys.

• The impact of immunization may also be observed by monitoring acute infections and liver cancer rates, but these have important limitations and considerable resources to establish these would be required. Therefore, measurement of the seroprevalence of chronic infection and coverage surveys is the primary way to measure the impact of immunization.

• In addition to serosurveys, an assessment of immunogenicity may be useful to assess the programme, especially if there is doubt about the cold chain or other aspect of the programme.

3.1.4 Advocacy and social mobilization

• The nature of hepatitis B means that special advocacy and social mobilization efforts are needed, as the impact of the disease burden has poor visibility and vaccinating newborn infants may be difficult in some societies. This includes ensuring that health workers are fully informed as to the importance of hepatitis B immunization.

3.2 Recommendations

3.2.1 Regional objectives/milestones

The following milestones should be used to monitor country and Regional progress to improve hepatitis B control:

a) include receipt of three doses of hepatitis B for a child to be ‘fully immunized’;

b) achieve full immunization of at least 80%, and ideally 95%, of each birth cohort;
c) establish a system to monitor timeliness of birth dose (within 24 hours of birth) and a target appropriate to the country by 2004;

d) achieve HBsAg prevalence of <1% in those born after routine vaccination started; and

e) establish a national hepatitis B control plan (as part of overall EPI plan) that includes a protocol to monitor health worker knowledge as an indicator of overall EPI practice.

3.2.2 Immunization strategies

• Each country should have a national plan of action for hepatitis B control that addresses issues of coverage (including timely birth dose), implementation and monitoring. That plan is likely to be most effective and appropriate as part of the overall EPI plan, as the basic strategy is to strengthen routine EPI services, with an additional focus on the timeliness (or delivery) of a birth dose and the monitoring of impact. The plan also needs to include a special focus on advocacy and social mobilization for hepatitis B as part of the overall EPI.

• For countries that have not yet done so, hepatitis B vaccine should be fully integrated into the EPI by rationalizing schedules, including hepatitis B in the definition of the fully immunized child, and ensuring coverage matches that of DTP. Although the priority should be to establish routine immunization of infants at high levels of coverage, countries introducing the vaccine are encouraged to consider catch-up immunization of all children under five years and other high-risk groups, to accelerate disease control.

• Protecting children against perinatal infection is a high priority in this Region. Accordingly, delivery of a birth dose of hepatitis B vaccine for all children is the preferred strategy. The alternative strategy of testing pregnant women and following up their infants is impracticable for most countries in the Region. This means that timely delivery of a birth dose and a second dose within two months for all children is the ideal. For children whose birth is not attended by a health worker, hepatitis B vaccine should be administered as soon as possible after birth.

• Ideally there should be no out-of-pocket expenses for immunization because of its positive externality (i.e. benefit to others of an individual’s immunization) and public good. User-fees worsen health equity and discourage uptake. However, where user fees exist, any charge for hepatitis B vaccine should be the same as for other EPI vaccines.

• Care should also be taken at all levels of distribution to avoid freezing of the vaccine, which may decrease its effectiveness.

3.2.3 Monitoring impact

• The primary method for countries to evaluate their programme is through monitoring immunization coverage. For the purposes of monitoring impact, this should be supplemented by at least one serosurvey to validate that the impact on carriage correlates with coverage data.

• Countries must monitor the programme with reliable data on the number and percentage of infants that complete the course of hepatitis B immunization by the age of one year. Coverage monitoring should also include the timeliness of the birth dose, access, dropout and comparison with other vaccines. It should be done regularly (at least quarterly) and down to district level.
• Every country should undertake at least one survey of HBsAg prevalence in vaccinated cohorts, supported by WHO as needed, within five years after introduction of the vaccine. Children at age one year should be sampled to measure impact and at age five years to assess horizontal transmission (after at least five years of immunization). The sample size should be adequate to show with 95% confidence HBsAg prevalence of <1%. WHO should prepare technical guidelines to assist with all aspects of serosurveys. Ideally, such a survey should be population-based, to facilitate interpretation and increase generalizability.

• Acute hepatitis B surveillance, especially in sentinel sites, may be considered as an additional means to monitor impact if a system can be established within available resources.

4. ACKNOWLEDGMENT

Dr Brian Doberstyn closed the meeting by thanking the participants for their special efforts to participate in this important meeting, which is likely to be seen as a historic milestone for hepatitis B control in the Region. He especially thanked the participants for their intensive participation in the discussion and the efforts of the Chair and Rapporteur. Based on the recommendations of the meeting, the WHO Regional Office for the Western Pacific will change the draft Regional plan for hepatitis B, and that will then be submitted for review and endorsement by the TAG at their next meeting, 4 to 7 November 2002. The Australian Agency for International Development (AusAID) was also cited for their role in providing financial support for this meeting.

REFERENCES
2 Edstam JS et al. Comparison of hepatitis B vaccine coverage and effectiveness among urban and rural Mongolian two-year-olds, Preventive Medicine. 2002; 34(2): 207-14
ANNEX 1

Meeting Agenda

1. Opening ceremony
2. Hepatitis B control: issues and options
3. Hepatitis B immunization in the Western Pacific Region (WPR)
4. Hepatitis B disease burden in WPR
5. Country Experiences
   a) Singapore
   b) China
   c) Viet Nam
   d) Cambodia
   e) Japan
6. High risk approach
7. Advocacy and social mobilization
8. Roundtable discussion: Setting a regional objective and meeting country needs
9. Vaccine supply and price
10. Vaccine safety and efficacy
11. Vaccines schedule options
12. Birth dose delivery
13. Roundtable discussion: Options for vaccine use
14. Laboratory tests for Hepatitis B
15. Laboratory monitoring in China
16. Assessing impact of vaccine: framework and methods
17. Field experience of assessing impact
18. Mathematical models
19. Roundtable discussion: Priority strategies for monitoring impact
20. Review and discussion of the draft EPI Regional Plan to Improve Hepatitis B Control
21. Conclusions and recommendations: presentation and discussion
22. Closing ceremony
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