Third Expert Working Group Meeting on Hepatitis B

Tokyo, Japan
6-7 March 2007

World Health Organization
Western Pacific Region

Meeting Report

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REPORT

THIRD EXPERT WORKING GROUP MEETING ON HEPATITIS B

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NOTE

The views expressed in this report are those of the participants of the Third Expert Working Group Meeting on Hepatitis B in the Western Pacific Region and do not necessarily reflect the policies of the World Health Organization.

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Hepatitis B – drug therapy, prevention and control / Hepatitis B vaccines – standards, therapeutic use / Regional health planning / Practice guidelines / Western Pacific

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CONTENTS

1. INTRODUCTION

The Third Expert Working Group Meeting on Hepatitis B was held at the National Institute of Infectious Diseases (NIID) in Tokyo, Japan, from 6 to 7 March 2007. The WHO Western Pacific Regional Office convened the meeting of the expert working group, composed of hepatitis B experts and selected country representatives. The first and second expert meetings on hepatitis B were organized in 1998 and 2002, respectively, and have guided the expansion of hepatitis B control programmes through vaccination in the Region in the last few years.

1.1 Objectives

(1) To review and make recommendations on the Western Pacific Regional Plan for Hepatitis B Control, developed in 2003, taking into account the recently set time-bound goal set by the Regional Committee during its 56th session and recommendations from the 16th meeting of the Technical Advisory Group (TAG); and

(2) to develop certification guidelines to monitor progress towards the goal and confirmation of its achievement.

1.2 Opening remarks

Dr Yang Baoping, Regional Adviser in the Expanded Programme on Immunization (EPI) of the WHO Western Pacific Regional Office, opened the meeting on behalf of the Regional Director, Dr Shigeru Omi. Dr Omi thanked the participants for taking the time to share their expertise to guide the Region in revising the regional plan to improve hepatitis B control through immunization and in developing the certification guidelines to document the achievement of the regional goal.

Dr Omi noted the public health 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 those chronically infected with the hepatitis B virus (HBV). Over one-quarter of these people die prematurely as a result of infection, mainly from hepatocellular carcinoma (HCC) and cirrhosis. He noted that hepatitis B causes almost the same number of deaths in the Region as tuberculosis.

Considering the public health importance of hepatitis B, and with availability of an effective tool in the form of the hepatitis B vaccine to control and prevent the infection, the Western Pacific Region recently set an ambitious goal for itself: reducing chronic HBV infection rates to less than 2% among children five years of age by 2012, as an interim milestone towards the final goal of less than 1%. The first and second expert working group meetings, held in 1998 and 2002, contributed greatly to the development of the hepatitis B regional plan in 2003 and guided the expansion of hepatitis B vaccination programmes in the Region. However, protocols or guidelines to monitor the impact of hepatitis B vaccination programmes and the progress made towards the goal of reducing the chronic HBV infection rates to less than 2% still need to be developed.

He observed that much progress has been made since 2002, when the last expert meeting was held. He requested the current expert working group to review the technical and programmatic strategies pursued in the Region and to help in refining them further, based on global empirical evidence to guide countries in achieving the goal. Dr Omi noted that, during its third meeting, the expert group was expected to review the regional plan developed in 2003 and help revise it, taking into account the new developments in the field and to align the programmatic strategies outlined in the plan with the set regional goal. It was also expected that the expert group would be able to come out with a set of certification guidelines which can be used to monitor the progress made by Member States in achieving the hepatitis B control goal. In addition, the group would help to resolve any technical and operational issues faced by countries in their efforts in achieving the regional goal.

Dr Tatsuo Miyamura, Director General of the National Institute for Infectious Diseases (NIID), welcomed the participants to the Institute and expressed his pleasure at being able to host the meeting. He noted the changing nature of hepatitis B due to increased migration across countries and the changing distribution of the viral genotype. He said that, by setting a goal to reduce chronic HBV infection rates to less than 2%, the Western Pacific Region is engaging in a kind of historical experiment, and is being watched globally. He stressed the need for strategies informed by scientific evidence to be used to guide the efforts of countries to achieve the regional goal of hepatitis B control.

1.3 Appointment of Chairperson and Rapporteur

The chairperson and rapporteur for each session were approved by the meeting participants. The names of the chairperson and the rapporteur for each session are mentioned before the summary of the proceedings for each session in the next section of this report.

2. PROCEEDINGS

2.1 Session 1: Hepatitis B control in the Western Pacific Region: An overview

Chairperson**:** Dr Takaji Wakita
Rapporteur**:** Dr Stephen Hadler

Dr Yang Baoping opened the technical sessions, summarizing the current recommendations and the status of hepatitis B prevention in the Region. He noted the strong progress throughout the Region, with all countries now providing universal infant immunization as part of EPI. Immunization schedules in all countries now require the first dose of hepatitis B vaccine to be given within 24 hours of birth (referred to as birth dose). However, many countries still face many challenges in achieving high coverage for timely birth dose, including difficulties in providing it for home births.

Many countries that have been able to sustain high coverage of the third dose of hepatitis B vaccine (HepB3) and timely birth dose for many years now seem to be already reaching the regional goal. However, four to six countries will be challenged to reach the goal, still having inadequate routine and timely birth dose coverage. Key challenges are reaching and sustaining high coverage of HepB3; assuring timely delivery of birth doses; assuring financial sustainability; and assuring vaccine potency by preventing freezing. Although great progress has been made in achieving financial sustainability with China, the Philippines, and Viet Nam committing long-term domestic financing, many countries in the Region still remain

dependent on outside funding for procurement of hepatitis B vaccine. In addition, some studies have noted a high incidence of vaccine freezing in some countries, which may reduce the impact of the vaccination programme. Special efforts should be made during training, supervision and vaccine management to minimize the incidence of vaccine freezing. Strengthening routine immunization remains the central strategy to achieving the goal in all countries.

2.2 Session 2: Preventing maternal-to-child transmission

Chairperson**:** Dr. Takaji Wakita
Rapporteur**:** Dr. Stephen Hadler

Dr Andrew Hall summarized data on the effectiveness of hepatitis B vaccine and hepatitis B immunoglobulin (HBIG) in preventing perinatal infection, noting the great effectiveness of hepatitis B vaccine with timely birth doses and the incremental improvement with the addition of hepatitis B immune globulin (HBIG) for infants of hepatitis B carrier mothers (relative risk of 0.52 [0.44-0.63]). The meta-analysis of literature as published by Lee et al (2006)[1] suggest efficacy of vaccine alone and vaccine plus HBIG to be 72% (60% to 80%), and 92% (83% to 97%), respectively. Only one non-randomized study showed no additional benefits from HBIG[2].

Although administration of HBIG with hepatitis B vaccine does provide additional protection to infants born to HBsAg positive mothers, compared with hepatitis B vaccine alone, the ,operational and cost issues required for screening of pregnant women for HBsAg and for providing HBIG in addition to vaccine preclude this as a key regional strategy for prevention of perinatal HBV transmission. In addition, there are concerns about the safety of blood products such as HBIG, and the possible reduced immune memory with vaccine in persons who receive HBIG as infants. Dr Hall summarized data from Boxall et al (2004) study[3] that suggested a reduced response to a booster dose of hepatitis B vaccine among children who received HBIG as infants.

Dr Hall reviewed efficacy data for timing of the hepatitis B vaccine birth dose and concluded that available data supports WHO recommendations that the universal birth dose routinely be given within 24 hours. He pointed to the limited data on efficacy for vaccine given after 24 hours (25 hours - seven days) of birth, but noted that conducting randomized studies to assess the effectiveness of a late birth dose would not be feasible ethically. Given this scenario, the only logical recommendation is universal delivery of a timely birth dose for all newborn infants within 24 hours of birth. However, for those infants (especially home births) who cannot be reached within 24 hours of birth, the vaccine should be given at the earliest possible opportunity. He further noted that, if the timing of the first dose of hepatitis B is recorded in a retrievable format, the impact of delayed birth dose delivery may be studied in the future when countries such as Cambodia, the Lao People's Democratic Republic and Viet Nam conduct serosurveys to assess the impact of their immunization programmes.

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[1] Lee *et al*. *British Medical Journal*, 2006, 332:328-336.
[2] Yang *et al*. *Pediatric Infectious Diseases Journal*, 2003, 22:584-588.
[3] Boxall *et al*. *Journal of Infectious Diseases*, 2004, 190:1264-1269.

Finally, Dr Hall presented a brief summary of operational guidelines for the prevention of perinatal infection, developed by the WHO Western Pacific Regional Office.

2.2.1 Experiences in the Republic of Korea

Dr Youngmee Jee presented data showing the excellent progress of the comprehensive hepatitis B prevention and control programme in the Republic of Korea, which includes universal infant vaccination with birth dose within 24 hours of birth and screening of pregnant women, as well as provision of free vaccine and HBIG to infants of HBV carrier mothers since 2002. More than 95% coverage has been maintained for both HepB3 and timely birth dose for almost ten years. The programme has reduced the HBsAg prevalence rate among persons aged 10 to 19 years (born after the start of universal infant immunization) to 0.9%, compared with 3.8% among persons aged 20 to 29 years, as measured by the third Korea National Health and Nutrition Examination Survey (KNANES III) in 2005. Hepatitis B vaccine failures in preventing perinatal infection have been associated with very high HBV deoxyribonucleic acid (DNA) titers > 10^7 /ml.

Sentinel surveillance for viral hepatitis (A,B and C) was started in 2000-2001 to identify high-risk groups for vaccination and for better detection and management of hepatitis B patients. The Republic of Korea hopes to reduce chronic HBV infection rates to less than 2.5% in the general population (all ages) by 2015.

2.2.2 Experiences with delivery of the birth dose in Viet Nam

Dr Manju Rani presented progress in Viet Nam on behalf of Professor Do Si Hien, who could not attend the meeting. Viet Nam is now reporting 98% HepB3 coverage and 64% of children receive timely birth doses (within 24 hours). Viet Nam could successfully expand the timely birth dose for births in public hospitals within a period of two to three years by collaborating with the maternal health department and ensuring vaccine storage in labour rooms. Use of single-dose vaccine vials supplied by the Global Alliance for Vaccines and Immunization (GAVI) has also helped in expanding the coverage with timely birth dose with minimal vaccine wastage. Future emphasis will be on increasing timely birth doses, ideally using locally produced vaccine with vaccine vial monitors (VVMs) out of the cold chain. Currently, there are no VVMs attached to the domestically produced vaccine, but plans are to have vaccine with VVM produced by 2008. Other country issues include alleviating provider concerns about adverse events following immunization (AEFI) when vaccinating newborn infants within six hours of birth, and developing appropriate recommendations for vaccination of low-birth-weight infants.

The discussions touched on several issues:

(1) Copies of the *Operational field guidelines for delivery of the birth dose of hepatitis B vaccine*[4] should be disseminated to all countries to help to ensure that they are being followed, emphasizing the importance of linking maternal and child health (MCH) and antenatal care with EPI in all types of facility.

(2) Tracking timely birth doses to measure progress towards achieving the hepatitis B control goals is very important, especially in countries facing the greatest challenges in

[4] *Preventing mother-to child transmission: Operational field guidelines for delivery of the birth dose of hepatitis B vaccine*. Manila, WHO Western Pacific Regional Office, 2006.

achieving the goal. In addition, the role of private providers in delivering hepatitis B vaccination should be documented.

(3) Some participants noted that despite the strong body of scientific evidence, challenges still exist for using the hepatitis B vaccine out of the cold chain, particularly due to limited national acceptance of this use in some countries without specific vaccine labelling, which does not exist currently for any product. WHO Headquarters and the Western Pacific Regional Office were encouraged to strengthen global recommendations for using hepatitis B vaccine out of the cold chain and to encourage explicit vaccine labelling that would support this use. However, it was noted that off-label use of vaccine is allowed earlier also, for example, in the multi-dose vial policy for liquid vaccines.

(4) Some participants enquired about the rationale for the 2% regional HBsAg goal. It was clarified that this goal was established as an interim goal towards the later goal of reducing the chronic HBV infection rate to less than 1%, and the eventual goal of elimination of HBV transmission. The regional and country plans should reflect this as a stepping-stone, not as the ultimate goal.

(5) Dr Hall suggested the potential usefulness of scientific studies to assess the impact of treating pregnant women with high HBV DNA titers ($> 10^7$/ml) with antiviral drugs to try to further reduce the risk of perinatal transmission in this remaining highest-risk group.

2.3 Session 3: Review and finalization of draft protocols for conducting serological surveys

Chairman**:** Dr. Andrew Hall
Rapporteur**:** Dr. Susan Wang

Dr Craig Shapiro reviewed the attributes of various methods to evaluate hepatitis B immunization activities: HBsAg serosurveys, vaccine coverage surveys (process indicator), acute disease surveillance, and chronic disease surveillance. He compared the strengths and weaknesses of these methods in terms of accuracy of information, need for ongoing commitment, expenses involved, direct measure of outcome, need for technical inputs (e.g. laboratory), and timeliness of information.

He noted that HBsAg serosurveys have emerged as a crucial tool for measuring the impact of hepatitis B immunization. Undertaking an HBsAg serosurvey requires consideration of technical, ethical and timing issues. Among the technical issues to be addressed are selection of the sampling frame (community-based or school-based), the sampling strategy (stratified, cluster, combination of stratified and cluster, lot quality assurance, convenience sampling), consideration of the sample size (prevalence, level of precision, confidence in estimate, resource limitations) and laboratory testing (quality assurance, external quality assessment, serological markers, use of rapid tests, integration with other assessments).

Ethical considerations for HBsAg serosurvey protocols include the need for the protocols to undergo human subject review, to include informed consent for testing, and to notify the participants of test results. The timing for conducting an HBsAg serosurvey to fit the certification requirements would be five years after implementation of a nationwide vaccination programme with consistent high vaccine coverage levels, as outlined in the certification document.

Dr Shapiro reported that WHO Headquarters has two documents that may be helpful for the Western Pacific Regional Office: (1) a draft report on the general topic of evaluating hepatitis B immunization programmes; and (2) a draft manual of a serosurvey protocol that has been developed to help countries evaluate the impact of hepatitis B immunization programmes, which has been field tested in Oman and Mongolia. These draft documents are being finalized. Additional considerations relating to serosurveys include the need for training for implementation of the surveys, a laboratory manual and funding to conduct the surveys.

2.3.1 Country experiences in conducting serosurveys

Cambodia:

Mr Ork Vichit presented information on the current hepatitis B immunization activities and most recent HBsAg serosurvey performed in Cambodia. Hepatitis B vaccination was introduced as part of EPI in 2001 and expanded nationwide in a phased manner in 2005. Monovalent hepatitis B vaccine is used for the birth dose and tetravalant vaccine (diphtheria-pertussis-tetanus -hepatitis B vaccine [DPT-hepB]) is used for the subsequent three doses of hepatitis B vaccine, administered to infants less than one year of age. In 2006, DPT-HepB3 coverage was 85% and the coverage of the first dose of hepatitis vaccine (HepB1) administered within seven days was 52%. The high proportion of births taking place at home (>85%) is the major challenge for achieving a high rate of timely birth dose coverage.

A national serosurvey was conducted in 2006 to establish a baseline rate of prevalence for HBV infection among five-year-olds. A community-based sample was used: the 24 provinces were divided into three groups by level of development, then each was divided into two groups (urban and rural) for a total of six sub-groups. Based on probability proportionate to size, 60 clusters or communes were allocated to each of the six sub-groups and 26 children were selected from each cluster. The Abbott HBsAg quick-test was used.

Of 1588 five-year-olds, 54 were HBsAg-positive, giving a rate of 3.4% (95% confidence interval: 2.6-4.5%). Although 48 (3.1%) of the children were reported as having received hepatitis B vaccination at a private clinic, only 10 (0.6%) children had hepatitis B vaccine documentation on an immunization card. An accompanying questionnaire administered to the mothers of participant children revealed a low level of knowledge regarding transmission of HBV infection. Factors that contributed to the successful execution of the serosurvey included the involvement and support of local leaders and communities, well coordinated planning at the national and local levels, the use of small gifts for mothers and children, and the ability of surveyors to use the Abbott quick-test successfully and readily. Results were not shared with the participants and their mothers as per the protocol.

The results obtained in this survey of five-year-old children are consistent with another serosurvey carried out in 2001 in one of the provinces—Kampong Chhnang—which observed a seroprevalence rate of 3.4% among children four to five years of age. The same survey observed a rate of 2.7% among children aged 9-17 months and a rate of 11.8% among the adult population from 20 to 35 years of age. These data, if true for Cambodia as a whole, suggest that perinatal transmission accounts for a large share of chronic HBV infections among five-year-olds. Hence, delivering the first hepatitis B vaccine dose within 24 hours of birth, currently a major challenge for Cambodia, will be very important for the country to achieve the goal of a chronic infection rate of less than 2%.

China:

Dr Hui Zhuang presented information on the most recent hepatitis B serosurvey performed in China, in 2006. Prior serosurveys had been conducted in 1979, 1992 and 2002. In China, hepatitis B vaccine was first recommended for routine immunization in 1992, but parents were required to pay for both the vaccine and the service. In 2002, hepatitis B vaccine was fully integrated into the EPI and parents were only required to pay a reduced service fee (approximately US$ 1.00). In March 2005, a new regulation made hepatitis B vaccine administration free of charge. Also in 2005, the Ministry of Health designated hepatitis B as one of the four high priorities for infectious disease control. In 2006, the Ministry published a national hepatitis B control plan for 2006-2010 and identified the goal of achieving less than a 1% HBV carrier rate among children < five years old by 2010.

The objectives of the 2006 serosurvey were: (1) to determine the HBsAg positivity rate by region and by age; (2) to evaluate the hepatitis B immunization coverage for children < 15 yrs old; and (3) to evaluate the impact of integrating the hepatitis B vaccine into routine immunization. It was a community-based survey, using multi-stage cluster sampling. A total of 81 950 persons aged one to 59 years were sampled from 160 disease-surveillance sites in 31 provinces.

The survey also included a questionnaire that collected general information (age, gender, occupation), exposure history (surgery, transfusion, close contact, dental treatment, injections history, etc.), and immunization history, including timing of the first dose of hepatitis B vaccine for the whole sampled population. All the blood specimens were tested for HBsAg using HBV enzyme immunoassay (EIA) kits at the national hepatitis laboratory of the China Center for Disease Control and Prevention (CCDC). Specimens positive for HBsAg were further tested for Hepatitis B 'e' antigen (HBeAg) and anti-HBe. In contrast to Cambodia, test results will be notified to the participants after completion of laboratory testing. Counselling will be provided to HBsAg-positive individuals. If the survey reveals poor vaccination coverage among young children, supplemental hepatitis B immunization will be offered to children born after 2002.

The national survey had multiple data quality safeguards (interviewer training, double data entry, data audits and reviews, etc.) and laboratory quality controls. In addition, five domestic HBV EIA test kits were evaluated with Abbott EIA test kits, using reference sera. The two domestic HBV EIA kits with the highest sensitivity and specificity, produced by Xinchuang and Kehua ,were used.

The survey was reviewed and approved by the CCDC Ethics Committee. The preliminary results in 2006 suggest less than 2% HBsAg prevalence among children one to four years of age compared to 3.1% in 2002 and 9.7% in 1992 in the same age group.

School-based surveys in the Western Pacific Region:

Dr Manju Rani briefly described three school-based serosurveys, since the Cambodia and China examples were both household-based serosurveys. A 2003 survey in Macao was done using a census of students who were six to 15 years of age and born between 1997 and 1988 as the sampling frame. Students were randomly selected from the list and invited, with their parents, to go to a designated health facility on a designated date for testing. In Macao, the school enrolment rate is more than 99%, ensuring that the sample was the representative. However, the serosurvey response rate was only 76.3%, mainly because parents were invited to go to the health facility rather than surveyors accessing the children in school or at home.

In American Samoa, the individual classroom was used as a cluster for sampling purposes, with probability sampling proportional to size. All the sampled children were contacted with the help of village, health department and school officials. In Mongolia, a stratified cluster survey was done, using a sampling of classrooms in selected subnational levels. Questionnaires were administered and blood specimens obtained at the schools on designated days. The response rate was more than 90%, relatively higher than that obtained in Macao, where the parents were asked to bring the students to the health centre on a designated day.

2.3.2 Key discussion points:

Laboratories:

It was noted that currently there is no formal viral hepatitis laboratory network. Countries have blood banks that perform viral hepatitis testing; however, laboratories that perform serosurveys and laboratories that perform blood banking may be different and the standards for these two types of laboratory may also differ. It was suggested that a national laboratory should be designated for conducting tests for a national serosurvey and that there will be a need for external and internal quality control of such a laboratory. Unlike the laboratory situation for measles and poliomyelitis, where there is a constant flow of specimens, testing for hepatitis B would likely be only episodic.

Rapid testing:

Using rapid tests for serosurveys was felt to be acceptable provided they had been reviewed and approved by WHO. However, it was noted that, in a population with low HBV prevalence, the positive predictive value of the tests would be lower. In such situations, rapid test results may be acceptable for a population survey, but would not be adequate for notification of individuals regarding their HBV infection status. It was noted that some investigators use the rapid test to determine those who are negative for HBsAg, and that for those who are HBsAg positive on the rapid test, a venous sample is obtained and tested in a reference laboratory.

Serological markers needed for serosurveys:

The single necessary test for serosurveys is an HBsAg test. If additional blood, financial and technical resources are available, it would be useful to do additional serological markers to confirm results and provide additional epidemiological information. Others noted that sometimes additional testing can cause confusion.

Ethical review of serosurvey protocols and notification of participants of test results:

It was agreed that serosurvey protocols should undergo ethical review. Ethical issues have become even more important with the availability of antiviral treatments for HBV infection. It was also felt that persons with positive HBsAg test results should be notified of the results and counselled for further evaluation to the extent possible; however, this will remain a country decision depending upon the resources and facilities available for treatment and counselling, as well as the legal situation. WHO documents should emphasize that persons with HBV infection should not be discriminated against.

Timing of a serosurvey:

Countries with low vaccine coverage levels should not perform large-scale national serosurveys, but rather should first devote their limited resources to increasing vaccine coverage levels. National serosurveys should ideally be conducted several years after high birth-dose coverage has been achieved with both HepB3 and timely birth dose.

Approach to sampling:

Either school-based or community-based sampling is satisfactory provided that an adequate response is achieved. The sample size required will be dependent on the precision desired and the requirements of the certification document. Ideally, 95% confidence intervals should be achieved.

2.4 Session 4: Monitoring the achievement of the regional goal: Certification process

Chairperson**:** Dr Andrew Hall
Rapporteur**:** Dr Craig Shapiro

Dr Rani gave a presentation on the draft *Guidelines for Certification of the Western Pacific Regional Hepatitis B Control Goal*. The draft guidelines propose vaccine coverage levels (HepB3 and timely birth dose) and HBsAg seroprevalence as two basic indicators for certification. Vaccine coverage thresholds for certification are proposed as HepB3 $\geq$85% and timely birth dose tcoverage of $\geq$65% in countries with HBsAg prevalence rate of about 8% in the adult population. These estimates are based on a mathematical model developed to calculate the coverage levels required to achieve an HBsAg seroprevalence rate of less than 2% among five-year-old children. The model takes into account the risk of HBV transmission from mother to infant, and the efficacy of hepatitis B vaccine in prevention of infection following perinatal and horizontal exposure.

The second key indicator is HBsAg seroprevalence among five-year-old children. The guidelines suggest that a seroprevalence of 2%±0.25% should be taken as evidence for achievement of the less–than-2% goal, or in other words, the seroprevalence point estimate for seroprevalence does not have to be exactly less than 2%, just the lower confidence interval. In addition, the guidelines propose that seroprevalence may be from age groups of less than five years, but a lower criterion for HBsAg prevalence should be used in that case. The guidelines touch upon the issue of acceptability of rapid/quick tests to determine HBsAg seroprevalence. It is proposed that a lower HBsAg prevalence criterion should be used in countries that use these tests because of the lower sensitivity of rapid tests compared with standard enzyme-linked immunosorbent assay (ELISA) HBsAg tests. In addition, the presenter discussed whether the criteria should be met at the sub-national levels or only at the national level.

Besides presenting the certification indicators and thresholds, the current guidelines described the procedure for certification, which borrows elements from both the certification process used for poliomyelitis and the validation process used for maternal and neonatal tetanus elimination. They propose constitution of expert resource panels and certification panels (the latter to be drawn from the expert resource panels). Details were presented about the process by which the certification procedure would be initiated (at the request of the country to the WHO Western Pacific Regional Office, with submission of required documents). It was proposed to report the certification results yearly, in the annual session of the Regional Committee, and in the Weekly Epidemiological Record.

Key discussion points:

(1) Thresholds for vaccine coverage levels: The issue of certification indicators was discussed in detail, especially use of vaccine coverage as a criterion for certification. There was consensus that HBsAg seroprevalence should be the main criterion for certification. However, while vaccine coverage information should be considered to determine the sustainability of the control efforts, it should not be used as a criterion for certification. As an indication of a country's efforts in controlling hepatitis B, there was consensus that part of the certification review should include presentation by countries of plans for accelerating hepatitis B control to meet the next goal of HBsAg seroprevalence of less than 1% among five-year-old children.

(2) HBsAg point estimates and confidence interval: The proposal in the certification guidelines that countries with HBsAg prevalence point estimates up to 2.25% provided the lower confidence interval was less than 2% should be certified as having achieved the goal, was debated in great detail. There was consensus that the criterion for certification should be an HBsAg seroprevalence of <2.0%. If the point estimate is 2% or more than 2%, then the country should be deemed as not having achieved the goal.

(3) The expert working group concluded that a confidence interval of 0.5% is appropriate, but further analysis based upon the results of the development of the protocol at WHO Headquarters and the implications for sample size requirements may mean that the confidence interval would need to be re-evaluated.

(4) Measurement at national and/or subnational level: The main measure should be at the national level. However, if resources were sufficient, sub-national level data, perhaps of less precision, would be helpful.

(5) Constitution/selection of the expert resource panel and certification panels*:* The process for selecting these panels, as described in the draft certification guidelines, is appropriate, and that it is not necessary to convene an independent certification panel.

(6) Certification plan for countries that seem to have already achieved the goal: The certification panel should accept pre-existing data to certify countries.

(7) Steps after certification: The need for countries to increase and monitor their vaccine coverage data regularly after being certified as having achieved the <2.0% goal was discussed. There was agreement that serosurveys will eventually need to be repeated to determine if countries have met the 1% seroprevalence goal. After achieving the less <1% seroprevalence goal, countries may have to use alternative data, rather than seroprevalence data, to guide their hepatitis B control efforts (e.g. acute hepatitis surveillance data).

(8) Resources to implement the process: Working group members felt that efforts need to be made to mobilize resources through international organizations and domestic sources to support the certification process.

(9) Communications plan: It would be beneficial to develop a communications plan for disseminating the results of the certification, both within and outside the Region.

2.5 Session 5: Hepatitis B surveillance

Chairman**:** Dr John Ward
Rapporteur**:** Dr Susan Wang

Dr Stephen Hadler reviewed key features of HBV transmission, information on age at HBV acquisition in different settings, and the rationale for acute hepatitis surveillance. He noted that acute hepatitis surveillance is one of several tools to evaluate disease burden and monitor the effectiveness of prevention programmes. Acute viral hepatitis surveillance data can also help to define the need and target groups for hepatitis B vaccination programmes in older age groups. He noted that in the Western Pacific Region, as infant immunization programmes become successful, the remaining disease burden will be in older age groups and acute viral hepatitis surveillance would be a tool to identify the need to vaccinate older populations, to identify outbreaks, and to enhance disease prevention for the control of other bloodborne and sexually transmitted infections.

For Western Pacific Region countries with successful perinatal infection prevention programmes and advanced infant vaccination programmes, Dr Hadler proposed that enhanced acute viral hepatitis B surveillance be established using sentinel or population-based sites. In surveillance sites, all acute viral hepatitis cases should be identified, followed by laboratory confirmation and case investigation.

2.5.1 Country experience: Japan

Dr Masashi Mizokami reviewed the changing HBV genotypes of acute HBV infection in Japan. He noted that the clinical manifestations of HBV infection vary worldwide due to different host characteristics and the different genotypes causing infection in different geographic regions. He noted that there have been increased population movements and that, in Japan, half of the acute HBV genotypes are imported. Dr Mizokami felt that a universal hepatitis B vaccination policy needed to be discussed in Japan but noted that the media and others in Japan had many concerns about vaccine side-effects. He also raised the issue of the doubtful protection offered by the existing hepatitis B vaccine against escape mutants.

2.5.2 Key discussion points

(1) Acute viral hepatitis B surveillance: It was noted that it could be quite challenging to identify acute hepatitis B cases; symptomatic patients would need multiple tests, asymptomatic patients might not be identified, it is hard to distinguish between acute HBV infection and an exacerbation of chronic HBV infection, etc. The resources needed for such surveillance are not insignificant; laboratory and epidemiological resources and funds would be needed. The Western Pacific Region is already very aware of the HBV disease burden, so acute surveillance data are not so necessary for advocacy purposes. It may be appropriate only for countries that have achieved success with their infant vaccination programmes and that have the resources to undertake acute viral hepatitis surveillance.

(2) Vaccine efficacy and side-effects: It was noted that vaccine efficacy is very high and that there has been no evidence to date that transmission of escape mutants is an issue for a vaccinated population. WHO and CDC have convened meetings and shared reports regarding the safety of hepatitis B vaccine.

2.6 Session 6: Finalizing the recommendations for vaccination for groups other than infants

Chairman**:** Dr Youngmee Jee
Rapporteur**:** Dr Craig Shapiro

Dr John Ward summarized the rationale and evolution of hepatitis B vaccination recommendations in the United States of America over the past two decades. During the 1980s, hepatitis B vaccine was initially only recommended for adult high-risk groups. However, the limited coverage achieved in adult high-risk groups, with little impact observed on acute hepatitis B incidence, along with recognition of the contribution of perinatal and early childhood infection to chronic HBV infection, led to a change in immunization policies. Since the 1990s, universal infant immunization, and more recently, universal birth dose administration have been the mainstay of hepatitis B control. Nevertheless, catch-up vaccination, including routine adolescent (recommended since 1995) and high-risk adult immunization, remain important components of the comprehensive immunization strategy to eliminate HBV transmission in the United States of America. Routine adolescent immunization is being promoted through the concept of the routine adolescent health visit and the middle-school entry laws. Currently, 37 out of 50 states in the United States have middle-school entry laws for vaccination.

Dr Ward commented that an important lesson learnt from the United States experience that is relevant to the Western Pacific Region is that catch-up immunization strategies can prevent infections later in life and are an important supplement to infant immunization. However, infant immunization is the first priority; health worker vaccination may begin at the same time as infants. Catch-up vaccination of older children (with the emphasis on children less than five years of age because of the higher risk of chronic infection after acute infection) and vaccination of adults at high risk should follow the establishment of a mature infant immunization programme.

2.6.1 Lessons from countries

Malaysia:

Dr Nor Zahrin bt Hasran gave a presentation on the rationale and decision-making process for hepatitis B immunization in Malaysia. The prevalence of HBsAg among the general population in the country is 3%-10%, and an estimated 0.8 to 1.7 million people are infected. HBV is a major cause of liver cancer and cirrhosis. Surveillance data show that most acute hepatitis B cases are among adults, and that major risk factors are sexual transmission, injecting drug use and blood transfusion. Hepatitis B vaccine has been recommended since 1989 as a routine infant immunization and reported HepB3 coverage has been high (>90%) for many years. Adults at high risk (e.g. health care workers, haemodialysis patients, injecting drugs users) are also recommended for vaccination.

Studies have shown that risk factors (e.g. unsafe sexual activities) for HBV transmission are prevalent among adolescents. In 2006, therefore, a catch-up vaccination programme for adolescents (up to grade 6) was initiated, and coverage for dose 1 and dose 2 has reached 86%. Emphasis is also being placed on promotion of healthy lifestyle practices among adolescents. In addition, the Government recognizes the need for and is developing a comprehensive control programme for hepatitis B, to take into account all modes of HBV transmission.

Japan:

Dr Takaji Wakita gave a presentation on experiences with high-risk group vaccination in Japan. Hepatitis B vaccination targets infants born to HBV carrier mothers and to health care workers. Both programmes are covered by health insurance. Infants born to HBsAg-positive, HBeAg-positive mothers receive HBIG at birth and two months of age, and hepatitis B vaccine at two, three and five months. Infants born to HBsAg-positive, HBeAg-negative mothers, receive HBIG at birth, and hepatitis B vaccine at two, three and five months. Follow-up testing is conducted at six months. Based on data from Shizuoka, only 4% of children born to HBeAg-positive mothers become chronically HBV infected. Seroprevalence studies among children attending elementary, junior and high schools show that the HBsAg seroprevalence rate has decreased dramatically over the past two decades. Coverage data for hepatitis B vaccine among health care workers are not available.

2.6.2 Key discussion points

(1) During the discussion, it was mentioned that the previous Western Pacific regional plan (2003) is silent regarding catch-up or adolescent immunization, but now, with many countries having adopted infant immunization, there is an opportunity for the recommendations to address vaccination of groups other than infants. In fact, 11 countries currently recommend vaccination of older children and adolescents and 10 countries recommend routine immunization of health care workers. Catch-up vaccination of older children and adolescents has been accomplished either at the same time as the introduction of the vaccination into the infant programme, or after introduction has been completed. In general, countries that have undertaken catch-up immunization are those that have more mature infant immunization programmes and have higher capacity and greater resources. Hence, most of the participants agreed that vaccination of older age groups can be considered if resources allow. The emphasis for vaccination of older age groups should be those under five years of age. However, vaccination of children and adolescents older than five years can also be considered, and countries should have the flexibility to consider which age groups to target, based upon local epidemiology, school attendance and other factors. In addition, different strategies for vaccination of older children (e.g. catch-up or patch-up) may be taken up, depending on the country context.

(2) The issue of vaccinating health care workers was discussed extensively, as well as pre- or post-vaccination screening and discrimination as regards employment. It was agreed that the vaccination of health workers should be undertaken, but should be implemented as part of a more comprehensive training programme regarding principles of injection safety and infection control. Stigma and discrimination against chronically infected persons are potential problems in some Western Pacific Region countries. Screening activities undertaken as part of vaccination programmes may identify persons who are chronically infected. Therefore, efforts (e.g. development of anti-discrimination laws) should be taken to ensure that the rights of such persons are protected.

(3) Vaccination of other high-risk groups should be considered, with the understanding that in some countries' experiences, high coverage levels among these groups have been difficult to achieve.

(4) Some participants remarked that economic analyses looking at various options for vaccination of groups other than infants can be helpful for countries in determining the optimal strategies to undertake.

2.7 Session 7: Finalization of the regional plan for hepatitis B control

Chairman**:** Dr Ernesto Domingo
Rapporteur**:** Dr Steve Hadler

Dr Manju Rani summarized the updated draft regional plan of action. The key areas of her presentation focused on: defining why the regional goal should be measured in five-year-old children; the eight fundamental strategies proposed in the new plan to reach the regional goal; recommended approaches for monitoring progress towards the regional goal; and evaluating the impact of overall hepatitis B control efforts.

Participants agreed with the key strategies and elements of monitoring and evaluation outlined the plan. Subsequent discussion focused on clarifying issues in several areas. For strategy 2, participants appreciated the development and dissemination of the *Operational Field Guidelines for Delivery of the Birth Dose of Hepatitis B Vaccine*, and urged incorporation of these guidelines more directly into the regional plan. All participants agreed that for catch-up vaccination of older children (strategy 3) the priority should be children up to and including age five years, who have the highest risk of becoming HBV carriers if infected.

Strategy 4, vaccination of high-risk groups, was discussed extensively, particularly vaccination of health care workers. The group agreed that the guidelines should recommend that hepatitis B vaccine should be offered to all health care workers free of charge at entry into training or health care work, and should be offered to all current health care workers. Some participants did not agree that vaccination should be "mandatory", preferring the wording "all health workers should be provided with hepatitis B vaccine free of charge". Dr Ward emphasized that hepatitis B vaccination should be linked to education of workers on prevention of all bloodborne infections in the health care setting. Regarding pre-vaccination screening, it was pointed out that, with lower vaccine costs, this is unlikely to be cost-effective. Dr Hall suggested that post-vaccination testing may be useful for those at high risk of non-response (e.g. > age 40 years). All agreed that recommendations regarding screening should be simple and generally agreed with the scope of the current wording in the draft regional plan. Three country experts (Cambodia, China and the Republic of Korea) agreed with these recommendations and stated that they were feasible in their countries, although Cambodia raised the issue of resources for vaccination of health care workers. All agreed that household (and sexual) contacts of HBV-positive persons should also be high priority for vaccination, acknowledging that these contacts are not always easily accessible.

Participants agreed that strategy 5, promoting self-reliance for hepatitis B vaccine financing, is important. Dr Domingo pointed out that this is an ongoing issue in the Philippines (although the Government has promised funding through 2010), and Dr Rani noted this would also continue to be a challenge for several other countries in the Region, particularly Cambodia and the Lao People's Democratic Republic. These latter countries may continue to be supported by GAVI for the present, but need to think of long-term financing plans after that support ends.

The importance of health education and advocacy was also emphasized, particularly the need to educate health workers about the lack of contraindications to hepatitis B vaccine. The participants also discussed need for school-based education efforts. Some countries such as Korea (measles only); Cambodia (but has problems with retention of immunization cards) and China, are using school entry check for vaccination status.

Primary issues raised concerning monitoring and evaluation included the challenge to document that vaccine is actually being given in some areas (the issue of falsified records). The group noted that the regional plan should state that countries 'should be encouraged' to establish acute hepatitis B surveillance, with laboratory confirmation and case investigation in sentinel or population-based sites, particularly countries with mature infant hepatitis B vaccination programmes. Guidelines should include quality assurance for laboratory testing, but should be kept simple for the present, utilizing available guidelines, such as those published by WHO.

The group also recommended that the WHO Western Pacific Regional Office should designate one or more regional hepatitis reference laboratories or collaborating centres to provide laboratory expertise throughout the Region for conducting serosurveys.

2.8 Closing session

Dr Yang Baoping thanked the participants for making a special effort to participate in the important meeting, which is likely to be seen as an historic milestone for hepatitis B control in the Region. He especially thanked the participants for their intensive participation in the discussions and also acknowledged the efforts of the Chairperson and the Rapporteur. Based on the recommendations of the meeting, the WHO Western Pacific Regional Office will modify the draft regional plan for hepatitis B, which will then be submitted for review and endorsement by the Technical Advisory Group at their next meeting, to be held from 27 to 29 June 2007.

3. CONCLUSIONS AND RECOMMENDATIONS

3.1 Conclusions

The conclusions of the meeting were as follows:

3.1.1 Preventing perinatal transmission

The group strongly endorsed the *Operational Field Guidelines for Delivery of the Birth Dose of Hepatitis B Vaccine* published by the WHO Western Pacific Regional Office and strongly encouraged that they be implemented further in the Region's weakest countries. Different countries and areas in the Region are at different stages in terms of antenatal care coverage, capacity and resources to carry out antenatal screening and provide HBIG to HBsAg-positive mothers. The literature review suggests that HBIG does provide some additional protection above that conferred by hepatitis B vaccine alone. However, issues related to the prenatal screening and the cost and potential safety issues of HBIG preclude routine prenatal screening and administration of HBIG to infants born to HBsAg positive mothers. There is not much empirical evidence on vaccine efficacy in preventing perinatal infection if hepatitis B vaccine is given later, after 24 hours of birth. Randomized prospective studies to answer this question are not ethically possible. However, the efficacy of vaccine in preventing perinatal infection if given with 24 hours of birth is well documented.

3.1.2 Review and finalization of draft protocols for conducting serological surveys

Countries with low vaccination coverage should devote their limited resources to raising vaccine coverage and should undertake national serosurveys only after achieving sustained high vaccine coverage, including birth-dose coverage, for at least four to five years. The choice between school-based or household-based serosurveys will depend on the country context, including the school enrolment rates. The sample size needed is dependent on the precision desired. Ideally 95% confidence intervals should be the aim. The protocols for serosurveys should undergo review by countries' ethical review boards, and the decision to communicate HBsAg results will be taken by countries based on their local situations (e.g. ability and resources to provide counselling and antiviral treatment). The single necessary test for serosurveys is HBsAg testing, but additional tests (anti-HBs and anti-HBc) can be undertaken depending on the resources available. Rapid tests with documented sensitivities and specificity may be used in serosurveys.

3.1.3 Monitoring and achievement of the regional goal: certification process

While an HBsAg seroprevalence rate <2.0% (with a confidence interval of preferably 0.5%) at national level should be the main criterion for certification, vaccine coverage data will be used to determine the sustainability of control efforts. If a country were certified as having a rate lower than the 2% milestone at the first attempt, a second serosurvey would be needed to determine the achievement of less than the 1% seroprevalence goal. After certification, vaccine coverage data will be used to monitor the maintenance of control status.

3.1.4 Acute hepatitis B surveillance

Acute hepatitis surveillance allows a country to identify risk factors for HBV transmission in various age groups and may be useful to document the impact of vaccination programmes targeting other than infants. However, it has limited usefulness for evaluating the impact of infant vaccination programmes. In addition, it does require a very well functioning surveillance system and a high level of laboratory and epidemiological resources. Thus it is only appropriate for countries with more mature infant vaccination programmes that are ready to start addressing the need to vaccinate older age groups.

3.1.5 Vaccination of groups other than infants

Achieving high vaccination HepB3 coverage among infants, including a timely birth dose, remains the first priority. Countries that are yet to achieve sufficient coverage for infants should makes this the highest priority. However, countries with mature infant vaccination programmes should consider catch-up or patch-up immunization strategies for older children, prioritizing children up to five years of age first, followed by children of six to 15 years. In addition, vaccination for health care workers may be prioritized along with infant vaccination programmes.

3.1.6 Finalization of the regional hepatitis B plan 2007

The regional plan developed in 2003 needs to be revised to reflect the regional goal set up in 2005 and the progress made by countries since then. The two key strategies remain the same—high infant vaccination coverage with three doses of hepatitis B vaccine by age one and with a timely birth dose within 24 hours for all newborn infants. However, it was concluded, that the scope of regional plan should be expanded to include more explicitly the strategies for countries that have more mature infant immunization programmes and that are already near to or have achieved the regional goal. Hence, those countries with more resources and with mature

infant hepatitis B programmes may consider providing HBIG in addition to vaccine at birth, to vaccinate older children and adolescents, and to set up acute hepatitis B surveillance systems. In addition, vaccination for health care workers should be prioritized along with infant vaccination in all the countries.

3.2 Recommendations

The working group made the following recommendations:

3.2.1 Preventing perinatal infection

(1) Universal provision of a birth dose of hepatitis B vaccine within 24 hours of birth should be the key regional strategy to prevent perinatal transmission. In addition, high coverage with HepB3 by age one needs to be achieved for both prevention of perinatal transmission and horizontal transmission.

(2) Countries with high coverage of antenatal care and the resources to provide antenatal screening and HBIG, might also consider providing HBIG in addition to the vaccine at the time of birth.

(3) WHO Headquarters and the Western Pacific Regional Office should provide strong guidance for using hepatitis B vaccine out of the cold chain with proper VVMs and should work with manufacturers towards appropriate labelling of such vaccines for use out of the cold chain. However, use of vaccine out of the cold chain should be recommended strongly and encouraged where it is needed to increase coverage with the timely birth dose and where it is acceptable to countries while waiting for specific labelling of the vaccine by manufacturers for out-of-cold-chain use.

(4) Studies on the impact of antiviral drugs on prevention of perinatal infection, especially among pregnant women with high HBV DNA titers, should be encouraged where resources allow.

3.2.2 Review and finalization of draft protocols for conducting serological surveys

(5) The WHO Western Pacific Regional Office should develop a WHO regional collaborating laboratory network to provide technical support for countries performing serosurveys.

(6) Countries should conduct representative serosurveys, either household-based or school-based surveys sampling children of at least five years of age and using laboratory tests with documented sensitivity and specificity, measuring at least HBsAg and aiming at 95% confidence intervals.

3.2.3 Monitoring and achievement of the regional goal: certification process

(7) An expert resource panel may be set up and should, in turn, be used to draw members for a certification panel as and when a request is received from a country. The serosurvey data documenting HBsAg levels of less than 2% at national level, preferably with 95% confidence, will be the mainstay for certification, and vaccination coverage data will be used to monitor the sustainability of control efforts. As an indication of their continued efforts in controlling hepatitis B, countries should present plans for accelerating hepatitis B control to meet the next goal of HBsAg prevalence of 1% at the

time of certification for the less than 2% goal. The current certification guidelines developed by the WHO Western Pacific Regional Office may be modified accordingly.

3.2.4 Hepatitis B surveillance

(8) Countries with mature infant hepatitis B programmes and with adequate resources may be encouraged to consider establishing acute hepatitis B surveillance, with laboratory confirmation and case investigation in sentinel or population-based sites, to guide their programmes at advanced stages of hepatitis B control.

3.2.5 Vaccination of groups other than infants

(9) Countries should aim to provide free vaccination for all health workers at the time of entry into training schools or at job entry, as well as for all health workers currently on the job, prioritizing it along with infant immunization.

(10) Immunization of older children (first priority - children through five years of age, and second priority- children six to 15 years of age) should be instituted in countries with mature infant immunization programs and additional resources. Either a catch-up or patch-up or a combination of both may be used depending upon the local context of a country.

3.2.6 Regional plan for 2007

(11) The eight key strategies presented in the draft regional plan 2007, along with the monitoring and evaluation framework, are endorsed, with recommendations for a few modifications as described under Section 2. The two key strategies will be achieving and maintaining high coverage with HepB3 and timely delivery of the birth dose within 24 hours of birth for all infants. Under the monitoring and evaluation framework, it is recommended that the WHO Western Pacific Regional Office should designate one or more regional hepatitis reference laboratories or collaborating centres to provide laboratory expertise throughout the Region.

4. ACKNOWLEDGMENTS

The WHO Western Pacific Regional Office gratefully acknowledges the excellent facilities and administration support provided by NIID in organizing this meeting. The Regional Office is extremely grateful to all the NIID staff, especially, Ms Mizoguchi Tomoko, Dr Koji Ishii and Dr Hiromu Yoshida, who provided almost full-time support to the meeting in addition to their normal duties at NIID. We also thank all participants for their intensive participation and open discussion, which greatly contributed to making the meeting a success. Special thanks are due to participants who acted as Chairpersons and Rapporteurs in the various sessions.

3rd EXPERT WORKING GROUP MEETING ON HEPATITIS B
6-7 MARCH 2007
Tokyo, Japan

TENTATIVE ANNOTATED AGENDA
(8 February 2007)

Day 1, Tuesday, 6 March

Time	Event	Tentative Speaker
0930-0945	Registration	Secretariat
	Session 1: Opening and Overview	
0945-1000	1 Opening remarks Welcome remarks by NIID (followed by photo session)	Dr Yang Baoping Dr Tatsuo Miyamura
1000-1045	2. Hepatitis B control in Western Pacific: current status, goal and strategies (30 mins presentation: 15 mins Q & A)	Dr Yang Baoping
1045-1100	Coffee Break	
	Session 2: Finalizing recommendations on perinatal transmission in the WPR	Chair: Dr T. Wakita Rap: Dr. S. Hadler
1100-1130	Current recommendations on preventing perinatal transmission	Dr A. Hall
1130-1200	Experiences in the Republic of Korea	Dr Youngmee Jee
1200-1230	Experiences in Viet Nam	Prof Do Si Hien
1230-1300	Discussion and finalization of the recommendations for WPR	
	Session 3: Review and finalization of draft protocols for conducting serological surveys	Chair: Dr A. Hall Rep: Dr S. Wang
1345-1415	Presentation on the draft protocols developed by WHO	Dr C. Shapiro
1415-1500	The experiences in WPR in conducting serosurveys i) Cambodia ii) China iii) Experience with school-based serosurveys in WPR	 Dr Ork Vichit Dr Hui Zhuang General discussion
1500-1530	Round table discussion and finalization of the survey protocols	
1530-1545	Coffee break	
	Session 4: Monitoring the achievement of Regional goal: certification process	Chair:Prof Do Si Hien Rep: Craig Shapiro
1545-1630	Certification for hepatitis B goals: indicators, threshold and procedures (30 mins presentation + 15 mins Q & A)	Dr M. Rani
1630-1730	Round table discussion and finalization of certification indicators, thresholds and procedures	
1730	Close of Day 1	
1800	RD's reception	

Day 2, Wednesday, 7 March

	Session 5: Hepatitis B surveillance	Chair: Dr. John Ward Rap: Dr. Susan Wang
0930-1015	Hepatitis B surveillance: guidelines and role (30 mins presentations: 15 mins Q & A)	Dr S. Hadler
1015-1100	Country experiences: Japan and round table discussion to finalize the recommendations for hepatitis B surveillance in WPR	Dr M. Mizokami
1100-1115	Coffee Break	
	Session 6: Finalizing the recommendations for vaccination for groups other than infants	Chair: Dr Youngmee Jee Rap: Dr Craig Shapiro
1115-1200	Role and strategies for older group immunization in hepatitis B control	Dr John Ward
1200-1245	i) The rationale and decision-making in Malaysia ii) The experiences with high-risk group vaccination in Japan iii) The current status of older age group vaccination in WPR	Dr Nor Zahrin Bt Hasran Dr T. Wakita
1245-1330	Round table discussion and finalization of recommendations for older age group and high-risk group vaccination in WPR	
1330-1415	Lunch Break	
	Session 7: Finalization of Regional Plan	Chair: Dr E. Domingo Rap: Dr S. Hadler
1415-1500	Presentation of draft regional plan for hepatitis B	
1530-1630	Round table discussion on draft regional plan to finalize it	
1630-1700	Closing ceremony	Dr Yang Baoping Dr Tatsuo MIyamura

ANNEX 2

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