WORLD HEALTH ORGANIZATION

REGIONAL OFFICE FOR THE WESTERN PACIFIC

REPORT

THIRD MEETING OF THE TASK FORCE ON HEPATITIS B

Nagasaki, Japan

29 September to 2 October 1985

Manila, Philippines

February 1986

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ENGLISH ONLY

REPORT

THIRD MEETING OF THE TASK FORCE ON HEPATITIS B

Convened by the

REGIONAL OFFICE FOR THE WESTERN PACIFIC

OF THE

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Not for Sale

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NOTE

The views expressed in this report are those of the Members of the Task Force on Hepatitis B and do not necessarily reflect the policies of the World Health Organization.

This report has been prepared by the Regional Office for the Western Pacific of the World Health Organization for governments of Member States in the Region and for the Members of the Task Force on Hepatitis B at its third meeting held in Nagasaki, Japan, from 29 September to 2 October 1985.

CONTENTS

1. INTRODUCTION

Hepatitis B virus infection is endemic in the Western Pacific Region and its long-term sequelae such as chronic active hepatitis, cirrhosis and primary hepatocellular carcinoma are common. It has been estimated that there are approximately 160 million carriers of hepatitis B surface antigen in Asia, of whom up to 40% of the men and 15% of the women are likely to die of their long-term sequelae. The development of safe and effective vaccines means that it is now possible to develop strategies for the control and eventual elimination of this disease.

2. BACKGROUND AND OBJECTIVES

Following a meeting of a scientific group on hepatitis B virus and its related liver diseases, held in Nagasaki, Japan from 29 September to 2 October 1982, the WHO Regional Office for the Western Pacific established a Task Force on Hepatitis B to act as coordinating body for WHO's regional programme by:

- collecting and analysing data;
- defining areas requiring future research and assisting in the development of collaborative research proposals;
- closely reviewing progress in vaccine development and its application in the Region, especially in preventing maternal/infant transmission;
- coordinating research in the Region;
- encouraging the sharing of data and effective use of resources.

The Task Force has met on two occasions, in Manila, Philippines, on 8-11 November 1983 and in Sendai, Japan, on 27-30 August 1984 to develop and evaluate strategies for the control of hepatitis B virus infection in the Region. Copies of the reports of these meetings are available from the WHO Regional Office, Manila.[1]

The third meeting of the Task Force was held in Nagasaki from 29 September to 2 October 1985.

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[1]Report of the meeting of the Task Force on Hepatitis B, Manila, Philippines, 8-11 November 1983, published March 1984.

Report of the Second Task Force Meeting on Hepatitis B, Sendai, 27-30 August 1984, published February 1985

The objectives of the meeting were:

(1) to review progress in the development of vaccines to control hepatitis B; and

(2) to prepare guidelines which would enable Member States develop national strategies for control of this infection.

The Agenda and list of participants are found in Annexes 1 and 2.

3. SUMMARY OF PROCEEDINGS

Participants were welcomed by the Regional Director, Dr Hiroshi Nakajima. Dr Nishioka was elected Chairman, Dr Tao Yi-xun, Vice-Chairman and Dr Gust, Rapporteur.

3.1 Progress on the development of hepatitis B vaccines and implementation of control strategies.

(a) Plasma-derived vaccines

The Task Force was encouraged to note that increasing quantities of hepatitis B vaccine are being produced and used in the Region. Vaccine is being manufactured in four centres in China (Beijing, Shanghai, Changchun and Lanzhou). Current targets call for the production of 9 million doses in 1986, 18 million doses in 1987 and more in later years. A two-step programme is being implemented beginning with immunization of babies born to HBsAg carrier mothers. As supplies of vaccine increase, this programme will be extended to susceptible children under the age of 5 years and selected groups of adults at increased risk of infection.

In Japan, three manufacturers have been licensed to produce plasma-derived vaccines. A national control programme has been implementd which seeks to identify HBeAg positive pregnant carrier mothers and administer HBIG and vaccine to their babies after birth. In addition, WHO has commenced a pilot project whereby plasma collected in Fiji, Tonga and Samoa will be processed into vaccine in Japan and returned to these countries for use.

A comprehensive control programme has been initiated in American Samoa. It is hoped to eliminate transmission of infection in this population by immunization of all newborn babies and other susceptible groups in the population. A similar programme is planned for Nauru.

In the Republic of Korea, plasma-derived vaccines are now being produced by two manufacturers.

(b) Vaccines produced by recombinant DNA technology

The Task Force was pleased to receive reports on progress in the development and testing of vaccines produced by recombinant DNA technology. Nine international companies are involved in the production of hepatitis B vaccine from yeast and four from mammalian cells. Two of these manufacturers are in the Western Pacific Region. Preliminary studies of one yeast derived vaccine suggest that it is safe and antigenic in man. Efficacy studies are under way. Clinical studies of other manufacturers' vaccines are in their early stages or about to commence.

Plans to produce vaccines using this type of technology are being made in China, Japan and the Republic of Korea and are under consideration in Singapore. A set of draft requirements has been prepared by WHO and will be submitted to the Expert Committee in Biological Standards in November 1985 for provisional endorsement.

3.2 Diagnostic reagents

The Task Force was pleased to note that the range of diagnostic reagents being produced in the Region is increasing, that WHO has continued to support the training of scientists to undertake activities, and that reagents produced in the Region are being evaluated in WHO collaborating centres.

4. GUIDELINES FOR HEPATITIS B CONTROL PROGRAMMES AND IMMUNIZATION STRATEGIES

4.1 Control programme elements

A number of separate components are needed in a comprehensive hepatitis B control programme. These include:

(a) Prevention of post transfusion hepatitis B

The availability of sensitive and specific diagnostic tests for HBsAg allows the blood transfusion services to screen potential donors and avoid transfusion of HBsAg positive units. In countries in which comprehensive testing programmes have been introduced, post-transfusion hepatitis B has been virtually eliminated.

While several WHO expert committees have recommended the universal introduction of screening programmes, lack of laboratory facilities and the high cost of reagents has often prevented implementation of these recommendations.

National health authorities should assess the priority of this approach in their own countries. In countries where hepatitis B infection is uncommon, most adults are susceptible to infection, consequently routine screening of blood donors is likely to have a high priority. In some countries where hepatitis B is highly endemic, infection occurs in infancy and childhood, and thus the majority of the adult population are immune to hepatitis B. In these countries, prevention of post-transfusion hepatitis is likely to receive a lower priority than other control measures.

b) Prevention of dialysis associated hepatitis B

In some countries it has been possible to reduce or eliminate the occurrence of dialysis-associated hepatitis B by separating susceptible patients and staff from those who are HBsAg positive. These programmes require routine testing of staff and patients for HBV markers and use of separate equipment for infected patients. The relative contribution of these programmes to the control of hepatitis B in most countries is small, especially for countries of high HBV endemicity, where dialysis programmes are either modest or nonexistent.

(c) Prevention of injection-associated hepatitis

The re-use of unsterile needles for injection, blood collection tattooing or acupuncture carries a risk of transmitting blood-borne infections such as hepatitis B. This practice should be strongly discouraged. Acceptable alternatives include use of disposable equipment, boiling the needles, or use of pressure cookers.

(d) Hepatitis B immunoglobulins

The use of immunoglobulins with a high titre of antiHBs (hepatitis B immunoglobulin, HBIG) can reduce the incidence of hepatitis B virus infection in health care workers who have been accidentally exposed to HB virus and the risk of infants born to HBsAg positive mothers becoming chronic carriers by about 75%. When deciding whether to use HBIG, national authorities must take into account several factors. First, many countries do not have facilities for plasmaphoresis and do not produce blood products such as HBIG. Second, commercially derived HBIG (prepared by Cohn fractionation of human plasma) is costly and in short supply. Third, the availability of hepatitis B vaccine has reduced the importance of HBIG in control programmmes.

While it is unlikely that any country will use HBIG prophylaxis unless an immunization programme is also in place, some countries may introduce hepatitis B immunization programmes without the supporting use of HBIG.

Any person who is a candidate for post-exposure prophylaxis with HBIG should also receive hepatitis B vaccine.

There are now good data to show that a single inoculation of hepatitis B vaccine in babies born to HBV carrier mothers can reduce their risk of becoming chronic HBV carriers by at least 75% and that the combined use of HBIG and hepatitis B vaccine can increase this to about 95%.

National authorities must decide whether the additional efficacy provided by double therapy is justified, in view of the increased cost and complexity of such programmes. In hyperendemic countries, where HBIG is neither locally produced nor available and where the infrastructure for vaccine delivery is less sophisticated, the use of HBIG is likely to be a low priority in control programmes.

(e) Hepatitis B vaccine

The most important method of preventing infections with HB virus is active immunization. Immunization is the single most important factor in any national control strategy and if properly used has the potential to eradicate hepatitis B in man.

Several sub-unit vaccines have been prepared from the plasma of chronic carriers of HBsAg and these have been shown to be safe, immunogenic and highly effective. When given prior to exposure, hepatitis B vaccines are more than 95% effective in preventing infection, and when given immediately after exposure, at least 75% effective in preventing disease of or development of the chronic HBV carrier state, even in babies born to HBeAg positive mothers. At least 2 million people have now received vaccines produced by manufacturers in several countries. The imminent licensure of additional plasma-derived vaccines and vaccines prepared by DNA recombinant technologies suggests that HB vaccine will be available more readily and at lower cost within the next few years.

Countries in the Region considering vaccination programmes need to take a number of matters into consideration, especially: the source of vaccines, the choice of vaccine starting material, and the quality control procedures available.

(i) Source of vaccine

The initial choice facing national authorities is whether to import vaccine, to commence local production, enter into an agreement with a foreign manufacturer to supply starting plasma and receive the finished product or to produce the manufacturer's product locally under licence.

While decisions of this importance require an evaluation of national economic and technical structures and priorities, certain principles are clear. In order to produce vaccine, a sophisticated facility capable of producing complex biological products must be available, and a national control authority (capable of measuring lot-to-lot variation in vaccine potency and immunogenicity and ensuring adequate production standards)

must be present Countries wishing to evaluate their ability to manufacture vaccine locally should refer to the WHO document - "Requirements for hepatitis B vaccine prepared from human plasma".[1]

Countries which are not able to manufacture hepatitis B vaccine may wish to consider alternatives such as importation of bulk vaccine for local packaging and distribution, or export of local plasma for processing and return for local use.

(ii) Choice of vaccine starting material

While currently licensed hepatitis B vaccines are manufactured from human plasma, alternative vaccines produced by DNA recombinant technology (either in yeast or in continuous mammalian cell lines) will be available in the next few years. Some countries have delayed the introduction of hepatitis B control programmes until these newer vaccines become available, on the grounds that they wish to utilize the most modern technology available. WHO has recommended that hepatitis B control programmes utilizing plasma-derived vaccines should proceed as rapidly as possible. Even though they will ultimately be replaced by vaccine produced by other techniques, this is likely to be a gradual process. Plasma-derived vaccines are likely to continue to provide a reliable source of product for the next decade. Concurrent use of plasma vaccines and recombinant vaccines is likely over the next few years.

(iii) Quality control assurances

Countries, whether importing vaccine from abroad, or engaged in local manufacture, must ensure (through their national licensing authorities) that hepatitis B vaccines utilized are of appropriate quality. A set of WHO requirements is published in the "Thirty-fifth report of the WHO Expert Committee on Biological Standardization".[2]

4.2 Immunization strategies

Strategies for use of hepatitis B vaccine must take into consideration differing patterns of hepatitis B prevalence which occur in individual countries and among different groups in the same country in the Region (see Tables below.)

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[1] WHO Technical Report Series, No. 725, 1985 (WHO Expert Committee on Biological Standardization: thirty-fifth report), Annex 3, page 70.

[2] Ibid.

Table 1 Patterns of hepatitis B prevalence

Low	Intermediate	High
HBsAg, 0.2-0.5%	HBsAg, 2-7%	HBsAg, 8-20%[a]
Anti-HBs, 4-6%	Anti-HBs, 20-55%	Anti-HBs, 70-95%
Childhood infection infrequent	Childhood infection frequent, neonatal infection frequent	Childhood infection highly frequent, neonatal infection highly frequent
Australia, Central Europe, North America	Eastern Europe, Japan, Mediterranean, south-west Asia, USSR	Some parts of China, southern Asia, tropical Africa

[a] Prevalences up to 50% have been identified in some isolated Pacific islands.

Table 2 Recommendations for hepatitis B vaccine prophylaxis according to prevalence of HBV

Low prevalence		Intermediate or high prevalence	
Pre-exposure	Post-exposure	Pre-exposure[a]	Post exposure[a]
High risk groups (health care personnel, dialysis patients, institutionalized patients, drug addicts, male homosexuals, military recruits)	Accidental percutaneous exposure, infants of HBsAg positive mothers, sexual contacts of acute cases, and carriers	All infants or selected groups at increased risk	Infants of HBsAg-positive mothers

[a] Depending on availability of vaccine.

The Western Pacific Region contains countries with a variety of patterns. While Australia is a country of low prevalence and Japan and Malaysia fall within the intermediate prevalance category, many countries such as China, the Philippines, Viet Nam and many smaller South Pacific island nations have a high prevalence of infection. Immunization strategies adopted by national health authorities are likely to vary, as shown in Tables 1 and 2, from limited administration to specific high risk groups (in low prevalence countries) to widespread immunization in infancy and early childhood (in countries of intermediate and high prevalance). In many countries in which hepatitis B is hyperendemic the most effective way of controlling HB virus infection (and the development of long-term sequelae) is by immunization of all babies at birth or as soon as possible after birth. Implementation of this strategy requires access to all pregnant women.

(a) Selection of alternative strategies

Data which health authorities require in order to develop a rational immunization strategy include the prevalence of hepatitis B infection in the community (especially the prevalence of HBsAg among women of child-bearing age and patients with acute and chronic hepatitis, cirrhosis and hepatocellular carcinoma) and among different groups who may be at increased risk of infection; an estimate of mortality rates for cirrhosis and hepatocellular carcinoma; the number of births per year and the proportion which occurs in medical facilities; and the status of current infant immunization programmes and the efficiency of coverage under the expanded programme on immunization.

(b) Requirements for strategy implementation

To implement an effective control programme, a health care system capable of delivering vaccines and diagnostic services to the populations and recording and monitoring their effects is required.

The following components are considered desirable: a national disease surveillance system capable of monitoring the incidence of acute hepatitis B and chronic sequelae such as chronic active hepatitis, cirrhosis and liver cancer in the population; access to a laboratory capable of evaluating immune responses and persistence of immunity in populations undergoing immunization and an adequate vaccine delivery system capable of efficient immunization of infants in those countries where mass infant immunization is undertaken. In these countries hepatitis B vaccine should be delivered as part of the vaccines utilized in EPI programmes.

5. DIAGNOSTIC REAGENTS

5.1. Need

A supply of high quality reagents is essential for any country seeking to collect reliable data on the prevalence of hepatitis infection, to study the epidemiology and mode of spread of the diseases, and to develop and monitor its own control programmes.

5.1.1 Diagnosis of patients with acute viral hepatitis

At least three distinct forms of viral hepatitis are recognized: hepatitis A (HA), hepatitis B (HB) and hepatitis non-A non-B (HNANB). In general it is impossible to distinguish the cause of a patient's illness on the basis of particular clinical or epidemiological features. Accurate diagnoses are possible only if specific laboratory tests for infection with hepatitis A virus (HAV) or hepatitis B virus (HBV) are available.

While a number of serological tests are available for establishing a diagnosis of hepatitis A or hepatitis B, the diagnosis of hepatitis non-A, non-B remains one of exclusion.

(1) Laboratory diagnosis of hepatitis A

The typical course of virus excretion and the development of specific antibody are shown in Figure 1.

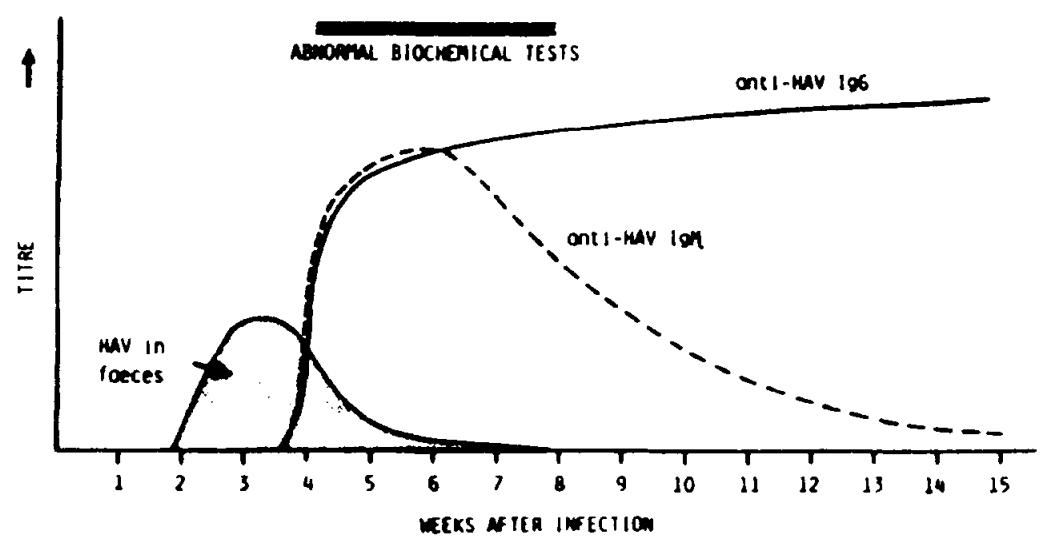

Fig. 1. Typical course of hepatitis A

While a specific diagnosis of hepatitis A can be confirmed by a demonstration of the virus in faeces or demonstrating a rise in anti-HAV titre, the most useful single test is the detection of the presence of anti-HAV of IgM class. This is the test of choice for diagnosis of hepatitis A and enables a diagnosis to be made within 24 hours of the patient seeking medical attention.

(2) Laboratory diagnosis of hepatitis B

The HBV has three major antigens known as HBsAg, HBcAg and HBeAg, each of which stimulates a specific antibody response. In addition, the genetic material of the virus (double stranded DNA) and a unique viral enzyme (HBV specific DNA polymerase) may be found in the blood, making the serology of this disease quite complex. The typical course of detection of these factors in patients with acute or chronic infection are shown in Figures 2 and 3.

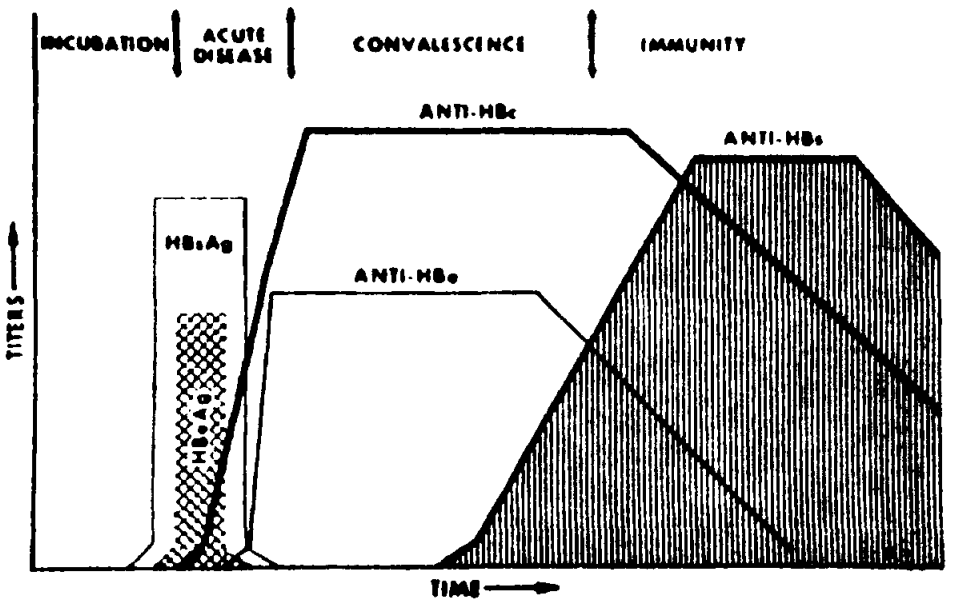

Figure 2. Typical course of hepatitis B

A specific diagnosis of the acute transient type of hepatitis B can be made by detecting (i) the transient presence of HBsAg, (ii) a rising titre of anti-HBc or (iii) the presence of anti-HBc of the IgM class. The value of these tests varies according to the prevalence of HB virus infection in the community being tested, e.g. while the presence of HBsAg in the serum of an Australian patient with hepatitis is strong evidence of a diagnosis of hepatitis B, it is less relevant in a Pacific islander or a Chinese patient because of the high background level of HBsAg in these groups.

(3) Laboratory diagnosis of acute hepatitis A, hepatitis B and hepatitis non-A,non-B

The simplest combination of tests which will enable all three forms of the disease to be defined is

- anti-HAV IgM
- HBsAg
- and anti-HBc IgM.

5.1.2 Determining immunity to HAV and HBV

The presence of anti-HAV and anti-HBs in the serum indicates that the person has recovered from infection with HAV and HBV and is now immune to reinfection. Anti-HAV may be transiently detected as a result of passive immunization. Anti-HAV may also be produced by administration of hyperimmune globulin or by active immunization.

5.1.3 Studying the etiology of chronic liver disease

The existence of specific laboratory tests makes it possible to determine the contribution that infection with HAV, HBV, HNANB and the HBV-associated delta agent make to the development of chronic liver disease. Evidence now exists that chronic infection with HBV is associated with an increased frequency of chronic active hepatitis, cirrhosis and primary hepatocellular carcinoma, that superinfection of carriers of HBV with the delta agent may be associated with severe hepatitis and the development of chronic hepatitis, and that some forms of HNANB are likely to lead to the development of chronic active hepatitis.

5.1.4 Studying the epidemiology and mode of spread of the disease

Specific diagnostic tests are essential to study the natural history of HA, HB and HNANB, and to determine how they are spread. This information is essential for planning preventive strategies and monitoring their efficacy.

5.2. Availability of specific diagnostic tests

A variety of assays for detecting infection with HAV, HBV and the delta agent are now available commercially, the major manufacturers being located in Europe, Japan, United Kingdom and the USA. Details of the assays available and their approximate cost can be obtained from the manufacturers or from one of the WHO collaborating centres for viral hepatitis (see Appendix A).

While the costs of these tests are relatively modest (50 cents to $2.50) they are beyond the reach of most countries in the Western Pacific Region. For this reason, WHO has encouraged Member States which wish to develop hepatitis control programmes to develop the capacity to produce their own reagents.

5.3 Choice of assays

When introducing diagnostic tests for hepatitis, laboratory directors and public health officials must first decide in favour of importation or local manufacture, then determine the group of tests to be used and finally select the type of test system WHO can assist in this process.

Over the last decade a wide range of assays has been developed for detecting hepatitis antigens and antibodies, of which the most widely used are reverse passive haemagglutination (RPHA), passive haemagglutination (PHA), enzyme-linked immunosorbent assay (ELISA) and solid phase radioimmunoassay (SPRIA). Provided reagents are carefully prepared and there is consistency of materials and production protocols, each of these assays is sensitive and specific, ELISA and SPRIA being somewhat more sensitive than red cell agglutination procedures.

Choice of a particular system will be guided by factors such as the availability of good quality plastics, difficulties of disposing radioisotopes and preferences of local laboratory workers.

The test chosen should be sensitive, specific, simple and cheap and capable of being performed by laboratory workers with limited training and facilities. While the most widely used test is ELISA, other tests such as RPHA and PHA can be used.

If a country elects to produce its own reagents, their quality should be checked by collaborative studies organized through the WHO network. Local quality control programmes should also be established to ensure that the tests continue to be of a high standard and are performed accurately throughout the country.

5.4 Priorities in diagnostic test development

WHO gives the highest priority to reagents for the detection of acute or chronic infection and immunity to HBV. The single most important test within this context is the test for detection of HBsAg, followed by anti-HBs and anti-HBcIgM. The next priority is assays for anti-HAV IgM for the diagnosis of acute hepatitis A.

5.5 WHO support in the production of diagnostic tests

The key to WHO's role in this area is the development of national self-reliance. While the WHO Regional Office for the Western Pacific is unable to provide bulk supplies of reagents to Member States, it has provided and will continue to provide funds to train laboratory workers, to arrange visits of consultants to laboratories in the Region as well as support from the network of WHO collaborating centres, to arrange national or regional training programmes and to collaborate in the acquisition and supply of training materials. The Regional Office can also support national laboratories in obtaining reference reagents from WHO Headquarters.

It is important for laboratory workers who are not employed by WHO collaborating centres to ensure that requests for cooperation are channelled through their respective ministries of health.

Details of future training programmes and information on how to apply for support from WHO can be obtained from the WHO Regional Office.

5.6 Training courses

In recent years the WHO Regional Office for the Western Pacific has organized a number of courses to train laboratory workers in the production of diagnostic reagents. Courses have been conducted in Beijing, Shanghai, Nagasaki, Tokyo and Melbourne and have usually been of two weeks' duration. Special training manuals were developed for each of these courses, copies of which are available from the WHO Regional Office for the Western Pacific, United Nations Avenue, Manila, Philippines.

However, as the manuals are designed to complement the instruction programme and practical demonstrations, they are of little use alone. They may be of considerable value to national reference laboratories which have a core of well trained personnel, a high level of skill in reagent production and wish to run training courses for other laboratories in their country.

As a result of their involvement over a number of years, several institutions in the Region (and adjacent regions) have developed a high level of expertise in the diagnosis of viral hepatitis, in training visiting scientists and running training courses in the field. A list of WHO collaborating centre experts in these fields is found in Annex 3.

5.7 Existing network of WHO laboratories

WHO has a three-tiered system of laboratories serving interregional, regional and national needs.

(a) Collaborating centres for viral hepatitis (see Appendix A) are responsible for the development, evaluation and distribution of reference reagents, developing standard methods of detecting hepatitis B infection and preparing training programmes and training manuals, and transferring these skills to regional laboratories.

(b) In each Region, appropriate WHO collaborating centres are responsible for the transfer of these skills to national laboratories, the distribution of reference and working reagents and the development of regional control programmes.

(c) National laboratories are responsible for the development of training and quality control programmes and the production of working reagents on a national basis.

6. RECOMMENDATIONS

The Task Force made the following recommendations:

(1) The Regional Director should continue to implement the major recommendations of previous task force meetings;

(2) The Regional Director should prepare guidelines to support countries in developing strategies for the control of hepatitis B infection. Such guidelines should be made widely available and published in a WHO journal.

(3) The next Task Force meeting should be called at an appropriate time to review progress towards the implementation of these recommendations.

ANNEX 1

AGENDA

Sunday, 29 September	Nagasaki Chuo National Hospital (Omura)	
1400	Registration	
1530	Opening ceremony	
1600	Special lecture by Professor K. Matsubara	
1800	Welcome party	
1930	Transfer to Parkside Hotel (Nagasaki)	
Monday, 30 September	Parkside Hotel	
0900	1. Production of HBV vaccine and diagnostic reagents and formulation of a vaccination programme	
	1.1 Global over-view	Dr F. Assaad
	1.2 Country report	
	China	
	National over-view	Dr Li He-min
	Beijing Institute	Dr Zhao Kai
	Shanghai Institute	Dr Guo Shengqi
1030	Coffee break	
1045	Changchun Institute	Dr Zhang Quanyi
	Lanzhou	Dr Yin Suiya
	Republic of Korea	Dr W.K. Chung

Annex 1

1200	Lunch break	
1330	1.2 Country report (cont'd.)	
	Japan	Dr H. Shimojo Dr M. Yano
	Malaysia	Dr C.G. Lopez
	Philippines	Dr E. Domingo
	Singapore	Prof. C.J.Oon
1500	Coffee break	
1530	Phase I Hepatitis B Eradication Project in American Samoa	Dr J. Maynard

Tuesday, 1 October

0900	2. New vaccine development	
	Global over-view	Dr F. Assaad
	Japan	Dr H. Shimojo Dr N. Ohtomo Dr M. Nishida
1030	Coffee break	
1100	China	Dr Li He-min
	USA	Dr R. Gerety
1200	Lunch break	
1330	3. Formulation of regional guidelines for diagnostic reagents and vaccination strategy	
	Diagnostic methods	Dr I.D. Gust
	Vaccination strategy	Dr J. Maynard
1500	Coffee break	
1530	4. Drafting of recommendations	

Annex 1

Wednesday, 2 October

0900	Finalization of recommendations
1200	Closing ceremony

ANNEX 2

FINAL LIST OF MEMBERS, CONSULTANTS, OBSERVERS AND SECRETARIAT

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ANNEX 3

LIST OF WHO COLLABORATING CENTRES FOR REFERENCE AND RESEARCH ON VIRAL HEPATITIS AND THEIR RESPECTIVE DIRECTORS

London School of Hygiene
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Keppel Street (Gower Street)
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Pettenkoferstrasse 9A
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Federal Republic of Germany — (Dr F. Deinhardt)

Nagasaki Chuo National Hospital
Omura City
Nagasaki Prefecture
Japan — (Dr M. Yano)

Clinical Research Institute
Catholic Medical College
Seoul
Republic of Korea — (Dr W.K. Chung)

Institute of Poliomyelitis
and Virus Encephalitis
P.O. Institute of Poliomyelitis
Moscow Oblast 142 178
U.S.S.R — (Dr S.G. Drozdov)

Division of Viral Diseases
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Annex 3

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