WORLD HEALTH ORGANIZATION
REGIONAL OFFICE FOR THE WESTERN PACIFIC

REPORT

WORKING GROUP ON HEPATITIS B

Seoul, Republic of Korea
24-26 August 1987

Manila, Philippines
March 1988

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REPORT

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Convened by the

REGIONAL OFFICE FOR THE WESTERN PACIFIC

OF THE

WORLD HEALTH ORGANIZATION

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NOTE

The views expressed in this report are those of the members of the Working Group 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 those who participated in the Working Group on Hepatitis B which was held in Seoul, Republic of Korea, from 24 to 26 August 1987.

CONTENTS

1. INTRODUCTION

A meeting of the Working Group on Hepatitis was convened in Seoul, Republic of Korea, from 24 to 26 August 1987. The members were welcomed by Dr H. Nakajima, Regional Director, WHO Regional Office for the Western Pacific. Dr When Kook Chung was elected Chairman, Dr E.O. Domingo, Vice-Chairman and Dr I. Gust, Rapporteur.

2. OBJECTIVES

The objectives of the Working Group were:

(1) to review the status of the large-scale local production of hepatitis B vaccine and the role of international collaboration in improving HB vaccine supply and distribution;

(2) to consolidate hepatitis B immunization strategies in order to facilitate their integration into the activities of the expanded programme on immunization; and

(3) to review progress in the development of recombinant DNA/HB vaccine.

3. INCREASED AVAILABILITY OF HB VACCINE

In the past four years, increased quantities of hepatitis B vaccine have become available in the Region. In collaboration with WHO and Japan, a technical cooperation scheme for the local production of plasma-derived hepatitis B vaccine in four production centres was developed in China. About 9 million doses were produced in 1986 and 18 million in 1987. In the South Pacific, WHO, in collaboration with Japan, has established a collection system for high titre HBsAg plasma. The plasma is sent to Japan for processing into HB vaccine and the vaccine is returned to the countries. The efforts of local vaccine manufacturers have also resulted in increased production of HB vaccine.

Currently in the Western Pacific Region, plasma-derived vaccines are being produced by four laboratories in China (Beijing, Shanghai, Langzhou and Changchun), three in Japan (Japanese Green Cross, Kitasato Institute, Chemo-serotherapeutic Institute) and two in the Republic of Korea (Korean Green Cross, Cheil Sugar Company). In addition, Singapore produces vaccine locally under licence. Fiji, Samoa and Tonga are included under the WHO and Japan collaborative scheme for the collection and eventual processing of high titre HBsAg plasma into HB vaccine.

At global level, other manufacturers located in Europe and the United States of America are producing plasma-derived hepatitis vaccine.

There is no reason to believe that the expansion of production facilities is complete as at least eight other groups are currently working towards the development and licensing of hepatitis B vaccines produced by recombinant DNA technology in the world. Although some of these are likely to drop out along the way, the Working Group is convinced that with adequate planning, the Western Pacific Region could be self-sufficient in HB vaccine by 1995.

4. DECREASED COST OF HB VACCINE

Perhaps the most significant advance in this field in the last year has been the reduction in cost of the vaccine, particularly when large orders are placed (for public sector programmes) and purchasing involves competitive tendering. At least, two companies are currently planning to supply HB vaccine to the public sector at about US$2.00 a dose ($1.00 per dose for newborn babies).

5. REVISION OF WHO GUIDELINES FOR PRODUCTION OF HB VACCINE

In May 1987, WHO organized a meeting at the National Institute for Biological Standardization in London to review the existing guidelines for production of HB vaccine and determine whether the original criteria should be modified to take into account new knowledge and the excellent safety record of all currently licensed vaccines.

The Group noted that plasma-derived hepatitis B vaccines are safe and that no serious side effects have been noted. In particular, no cases of AIDS have been attributed to the vaccine. There are now over 12 licensed manufacturers of plasma-derived hepatitis B vaccines globally. These vaccines have been manufactured, utilizing a variety of biochemical and biophysical procedures for purification and inactivation; but, regardless of procedures utilized, these vaccines have been shown to be highly immunogenic and efficacious. The Group recommended revisions of the current WHO requirements in regard to several important items.

(1) Purity

The Group noted that plasma-derived vaccines should be pure enough to be safe, and that arbitrary specification of degree of purity was no longer appropriate.

(2) Inactivation

The Group noted that the inactivation procedure or procedures utilized should be capable of inactivating agents found in human blood and that arbitrary specification of the nature or number of procedures to be utilized is no longer required.

(3) Chimpanzee safety test

The Group recommended that, after a chimpanzee safety test has been performed on five consecutive lots of a newly developed vaccine, additional chimpanzee safety tests on additional lots are no longer required.

(4) HIV testing

The Group recommended that plasma used as starting material for vaccine production be free of HIV, as determined by an appropriate serological test.

A draft of these revised requirements is now being reviewed, in anticipation of applied adoption by the WHO Expert Committee on Biological Standardization in December 1987.

6. ALTERNATIVE APPROACHES TO THE PRODUCTION OF HB VACCINE

Initial shortages in the supply of HB vaccines and the high cost of the early vaccines, together with concerns about the safety of products derived from human plasma, has led a number of manufacturers to develop HB vaccines using recombinant DNA technology.

HBsAg has been expressed in a number of systems, the most widely used being yeast (S. cerevisiae) and mammalian cells (Chinese hamster ovary) and insect cells. At least two such vaccines (produced in yeast cells) have now been licensed for use in man.

In practice, these vaccines contain a product HBsAg, which is closely related but not identical to the HBsAg particles produced as a result of natural infection. Despite minor biochemical differences, the particles appear to be immunologically indistinguishable and have comparable antigenicity and efficacy to standard plasma-derived vaccines.

Although much attention has been placed on the importance of pre-S proteins in induction of immunity, there is no convincing evidence that vaccines containing this protein are more effective than those that do not have.

Although DNA vaccines were originally considered to offer significant advantages in yield (and, hence, in price), this has not proved to be the case. Expressed HBsAg is found within the transformed cells and associated with cell membranes and can only be recovered after the cells are lyzed and subjected to lengthy and expensive purification procedures.

At the moment, recombinant DNA HB vaccines offer no significant advantages over plasma-derived vaccines. Public health providers should not hesitate to utilize plasma-derived vaccines. All the currently licensed vaccines are safe, antigenic and of proven efficacy.

7. OTHER ISSUES CONCERNED WITH VACCINE PRODUCTION

While there has been marked improvement in the quality of vaccines produced in the Region, some countries require assistance to ensure that their vaccines are produced by internationally accepted codes of good manufacturing practice and to ensure that internal and external quality control programme and licensing practices are strengthened. WHO can play a useful role in this process by the provision of consultants and by developing institutional linkages.

In some countries, the production of the vaccine is considerably less than the capacity of the existing plant. WHO should work with national health authorities to define the limiting factors and make the production process more efficient.

8. DELIVERY OF HB VACCINE

8.1 Immunization schedules

Many different schedules have been studied in the Region. The results of these studies are difficult to compare since they involve vaccines produced by different processes (with varying degrees of purity and content of HBsAg) evaluated under a variety of conditions. A few studies have been undertaken, in which several vaccines are evaluated for antigenicity and efficacy in the same population.

Notwithstanding these limitations, it seems that the most important factor, which determines the efficacy of HB vaccines in preventing transmission of infection from carrier mothers to their newborn babies, is the timing of the first and second doses of the vaccine.

There is considerable evidence to show that the best results are obtained when the first dose of vaccine is given within 24 hours of birth, and the second about a month later. Considerable latitude exists in the timing of the third dose (with some recommending that it be given one month later, others five months later), so that immunization schedules can be adapted to fit in with local delivery systems.

Currently, much work is being undertaken to devise ways in which the HB vaccine can be integrated into the expanded programme on immunization without the need for additional contacts with the child. Further work needs to be done to determine whether it is possible to combine several vaccines (e.g., DPT, hepatitis B), in a single vial, thus reducing the number of injections needed to deliver each vaccine.

To promote acceptance of the value of immunization, particularly by women who have no formal education, practical health education measures designed to change their behaviour need be devised.

8.2 Delivery systems

The Working Group considered that, in the near future, access to low-priced HBV vaccine may no longer be the major factor limiting the development of hepatitis B control programmes in the Region, and that Member States should begin to focus their attention on developing adequate delivery systems.

They noted that, while a few countries are now producing several million doses of the vaccine per year, distribution is not being undertaken on the basis of the greatest need. The Group urged Member States to review their policies covering the distribution of the vaccine and to ensure that, where supplies are limited, the vaccine is used where it will be of greatest benefit.

The Group believes that the major challenge for WHO and its Member States is to develop efficient systems of vaccine delivery, and, in particular, to integrate them with the expanded programme on immunization. It is important to address such issues as stability of HB vaccine under field conditions or to work with manufacturers to develop and field test vaccines which will withstand extremes of temperature.

It is important to address such issues as the stability of the HB vaccine, particularly its ability to withstand extremes of temperature under field conditions. It is also essential to work with local health workers and vaccinators not only to develop more effective ways of vaccine delivery but also to improve their performance in this regard.

The Group suggested that these issues can best be addressed by model immunization projects in selected sites, such as in the southern provinces of China, where HB infection is hyperendemic and the incidence of long-term sequelae is well documented.

9. RECOMMENDATIONS

The Group made the following recommendations:

(1) WHO should encourage Member States to review the use of HB vaccine in their countries to ensure that it is consistent with their own policies and the WHO strategy for control of hepatitis B.

(2) In most countries the most cost-effective manner of reducing HB infection is immunization of newborn babies; immunization should be extended to older children where appropriate.

(3) WHO should support Member States to define the problems which limit current production processes. In order to overcome these barriers:

(a) Studies should continue to determine the optimal dose and schedule of immunization, the stability of vaccines and duration of immunity under field conditions.

(b) Greater emphasis should be placed on establishing efficient delivery systems and integrating hepatitis B vaccine into the expanded programme on immunization (EPI). In particular, pilot vaccination projects should be undertaken in several countries to evaluate alternative systems for efficient vaccine delivery in both rural and urban populations. These studies should include populations in which the majority of children are born at home.

(c) Only one sterile syringe and needle should be used for each injection. Safe storage should be made available and instructions provided in the proper disposal of needles and injection equipment.

(d) Screening of blood donors of HBsAg (and anti-HB) should be encouraged as blood transfusion is an important means of transmission of infection in some endemic areas.

(e) Some latitude may exist in the timing of the second and subsequent doses provided the first dose is administered as soon as possible after birth.

(f) The schedule used in any country should be based on experience with the particular vaccine and in general should be the least costly regimen which induces acceptable levels of anti-HBs in the target population.

(4) Member States are urged to strengthen efforts to educate policy-makers, the medical profession and the public on the importance of HB infection, its mode of transmission and the opportunity for control, stressing in particular, the importance of immunization in infancy.

ANNEX 1

AGENDA

1. Registration
2. Opening Ceremony
3. Large-scale local production of hepatitis B vaccine in China
4. Immunization against hepatitis B in Long Ahn County
5. High-titre HBsAg plasma collection in Fiji and Tonga
6. Hepatitis immunization strategies
7. Overview of the development of recombinant DNA/HB vaccine
8. Drafting of recommendations
9. Finalization of recommendations
10. Closing Ceremony

ANNEX 2

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