VACCINE DEVELOPMENT
AND CONTROL OF COMMUNICABLE DISEASES
BY IMMUNIZATION

The World Health Assembly in May 1986 adopted resolution WHA39.30 urging Member States to commit themselves fully to achieving the 1990 immunization goal. At this stage in the expansion of immunization coverage, it is necessary to promote the acceptability of vaccines and reduce the drop-out rate due to vaccine reactogenicity by improving the quality of existing vaccines. Advances in biotechnology have made it possible to improve the quality of some of the existing vaccines, and accelerate the development of new, effective and inexpensive vaccines such as those for viral hepatitis B and Japanese encephalitis. The possibility of including hepatitis B and Japanese encephalitis vaccines in the immunization programme should be considered in areas where such infections are highly prevalent.
1. INTRODUCTION

Communicable diseases continue to be of major concern and are posing problems which still have to be overcome. Following the eradication of smallpox, the expanded programme on immunization (EPI) was established in the Region in 1976. Developed countries have maintained high coverage (over 80%) against the six target diseases - diphtheria, pertussis, tetanus, poliomyelitis, measles and tuberculosis whereas the developing countries have only reached about 50 percent coverage during the last decade. The impediments to achieving higher coverage are still ignorance of and indifference to the benefits of immunization, the reactogenicity of pertussis vaccine, and an underdeveloped infrastructure for delivering vaccines without delay. Remoteness is particularly a problem where three doses are needed, as in the case of diphtheria, pertussis and tetanus (DPT) and the trivalent oral poliovaccine (TOPV).

To promote the acceptability and increase the coverage of immunization so as to control these diseases, not only health education is needed but a reduction in side reactions, particularly in the case of pertussis vaccine. This will encourage mothers to bring their children for second and third doses of DPT which will reduce the drop-out rate for both DPT and TOPV.

As immunization against poliomyelitis is increasing, there is also a concern about the appearance of vaccine-associated paralysis and the occurrence of minor epidemics of type 1 and type 3 in immunized children, particularly in the tropics. This suggests that there is a reversal of attenuated vaccine strain to virulent type and that inadequate immunity is conferred by conventional oral poliovaccine. Therefore, further improvement of the vaccine is necessary to prevent these two complications.

Other communicable diseases which are of particular importance in the Western Pacific Region, because of high endemicity are hepatitis B, Japanese encephalitis, dengue, dengue haemorrhagic fever and haemorrhagic fever with renal syndrome. Since immunization is one of the effective ways to prevent and control these diseases, the development and provision of vaccine against them is of the utmost importance to WHO.

Hepatitis B is endemic in almost all countries and areas of this region and it is estimated that there are over 100 million carriers here out of approximately 280 million in the world.

The hepatitis B carrier rate in the Region ranges from 0.1% in Australia, through 11% in the Philippines to 20% in some of the Pacific island countries.

Regional guidelines for hepatitis B control and immunization strategies were formulated in 1985 and consolidated in 1987. They emphasize immunization of all newborn babies in hyperendemic countries.

Several countries of the Region have initiated the use of hepatitis B vaccine to prevent infection and reduce both carrier rates and ill effects, which include chronic hepatitis, cirrhosis and hepatocellular carcinoma.

Japanese encephalitis is caused by an arthropod-borne virus belonging to the flavivirus group. It is endemic in many countries of South-East Asia and Eastern Asia, including Burma, China, India, Indonesia, Japan, the Philippines, the Republic of Korea, Sri Lanka and Viet Nam.
use of it for the prevention and control of hepatitis B in many developing countries. Two models making the vaccine available in developing countries have been developed in the Region. One involves producing it locally, and the other involves the collection of HBsAg positive plasma to be used as a source of the vaccine.

Technical support has been provided to China since 1983 for the development of large-scale plasma-derived hepatitis B vaccine production. Nine million doses of the vaccine were produced in China in 1986, and over 15 million in 1987. Efforts to increase vaccine production will continue in order to achieve the immunization target of 85% of newborns by 1995. The vaccine is now produced in three countries of the Region: China, Japan and the Republic of Korea.

A system has been established for the collection of high-titre HBsAg plasma, which is then processed into hepatitis B vaccine in Japan and subsequently returned to the countries in which the plasma was originally collected. The plasma collection system has been developed in Fiji, Papua New Guinea, Samoa and Tonga. In September 1987, approximately 20 kg. of concentrated high-titre HBsAg plasma was sent to Japan from Fiji and Tonga. It is expected that these countries will obtain hepatitis B vaccine and start immunization of newborns in 1988. Technical support will be provided to other countries wishing to join this scheme.

2.3.2 Recombinant DNA hepatitis B vaccine

Recombinant DNA hepatitis B vaccine prepared in yeast cell has recently become available. Efficacy of the vaccine is almost the same as that of plasma-derived vaccine. In this region the vaccine is produced in Japan and the Republic of Korea.

At present the cost of recombinant DNA hepatitis B vaccine is not lower than that of plasma-derived hepatitis B vaccine. However, preparation of recombinant DNA hepatitis B vaccine using different cells has been progressing, and the recombinant DNA hepatitis B vaccine prepared in mammalian cell line will become available in the near future. Further progress in this field is expected to provide a low-cost hepatitis B vaccine.

2.4 Japanese encephalitis vaccines

2.4.1 Inactivated Japanese encephalitis vaccine

Inactivated Japanese encephalitis vaccine has been produced in China, Japan and the Republic of Korea, and has been demonstrated to be effective. Technical support has been provided to China and the Republic of Korea to upgrade its quality. The working group on Japanese encephalitis vaccines, held in Osaka, Japan, in February 1987, formulated draft WHO requirements for inactivated Japanese encephalitis vaccine with a view to developing international collaboration in promoting its wide use. The WHO requirements were published in December 1987 by WHO Headquarters. However, use of this vaccine in developing countries where large outbreaks continue to occur, is still limited because of its high cost.
Epidemics are associated with the increase in the number of *Culex* mosquitos, usually in areas of rice culture and where there are large numbers of pigs, which act as amplifying hosts. Inactivated vaccine is used routinely to control Japanese encephalitis in China, Japan and the Republic of Korea.

2. VACCINE DEVELOPMENT

Advances in biotechnology have provided the opportunity to upgrade the quality of existing vaccines by minimizing their reactogenicity, improving their heat stability, maintaining their genetic stability and increasing their efficacy. In addition, they have made possible the preparation of new vaccines against infectious diseases which continue to be major causes of morbidity and mortality. The eventual inclusion of these new vaccines in the immunization programme needs to be considered.

2.1 Pertussis vaccine

The major effort in pertussis vaccine research has been directed towards reducing the endotoxin content of the vaccine through the development of an acellular vaccine consisting of filamentous haemagglutinin (FHA) and a lymphocytosis-promoting factor (LPF) of the organism. The best characterized acellular vaccine has been developed in Japan, which has one-tenth of the endotoxin content found in the conventional whole-cell vaccine. It has been used since the autumn of 1981 in conjunction with diphtheria and tetanus toxoids in the mass immunization mainly of 24-month-old children in Japan, where its efficacy and reduced reactogenicity have been reported in the field trials. The large-scale field trial has been completed in Sweden, and is currently being evaluated. Preliminary reports indicate that the efficacy is similar to that of conventional pertussis vaccine but with significantly reduced reactogenicity.

2.2 Poliomyelitis vaccine

Two excellent poliomyelitis vaccines, one oral (Sabin) and the other injectable inactivated (Salk), are available and both are highly effective. Almost all countries or areas in the Region are using Sabin oral vaccine, but some concern has been expressed about the reversion of attenuated virus types 2 and 3 to wild type, resulting in vaccine-induced paralysis (one per 3 million doses used). Further research is therefore being conducted to improve this oral vaccine. Since the Sabin 1 (type 1) vaccine is genetically more stable than Sabin 2 (type 2) and Sabin 3 (type 3) vaccines, recombinant attenuated poliomyelitis vaccines (type 2 and type 3) were recently constructed in vitro by the replacement of only the gene encoding the antigenic determinants of the Sabin 1 (type 1) by the corresponding gene of type 2 and type 3. These candidate vaccines showed biochemical and biological properties that are indistinguishable from the parent virus strains. Further tests will be conducted to determine their efficacy.

2.3 Hepatitis B vaccine

2.3.1 Plasma-derived hepatitis B vaccine

During the past several years, millions of doses of plasma-derived hepatitis B vaccine have been administered and it has been demonstrated that the vaccine, which meets WHO requirements, is effective and safe. However, the high cost of this vaccine has prohibited wide
2.4.2 Recombinant DNA Japanese encephalitis vaccine

Progress has been made, in Japan and the United States of America, in the determination of the total nucleotide sequence of the Japanese encephalitis virus. Another development is the collaborative research being conducted by China and Japan on infectious cDNA clones of live attenuated Japanese encephalitis vaccine strain, with the aim of preparing genetically stable live attenuated vaccine.

3. FUTURE DIRECTIONS

3.1 An effective but less reactogenic acellular pertussis vaccine has been developed and is being tested, and is likely to be accepted for wide coverage.

3.2 Further improvement of the poliomyelitis vaccine is necessary to prevent the reversal of the attenuated vaccine strain to the virulent wild type and to replace the inadequate immunity conferred by conventional polio vaccine. The recombinant attenuated poliomyelitis vaccine was recently produced in vitro and further tests will be conducted to determine its efficacy.

3.3 Effective vaccines against hepatitis B and Japanese encephalitis have been developed. Where feasible, local production of these vaccines through technology transfer should be promoted in large developing countries where these diseases are endemic. These countries should be urged to increase their production so as to meet the needs of small countries and areas in the Region as well.

3.4 The possibility of including hepatitis B and Japanese encephalitis vaccines in the immunization programme should be considered in areas where such infections are highly prevalent.