Eur. J. Epidemiol. 0392-2990
March 1985, p. 1-4

Vol. 1, No. 1

EUROPEAN JOURNAL OF EPIDEMIOLOGY

WHO'S VACCINE DEVELOPMENT PROGRAMME

F. ASSAAD *[1], G. TORRIGIANI **

* *Director Division of Communicable Diseases* - ** *Chief Immunology Unit*
World Health Organization 1211 Geneva 27, Switzerland

Key words: Vaccines - Communicable diseases - Biotechnology.

The World Health Organization is playing a major international role in encouraging, coordinating, and where appropriate commissioning, research and development activities relevant to the control of high priority infectious diseases.

The Expanded Programme on Immunization would be the vehicle for the introduction of new or improved vaccines. In many parts of the developing world the health infrastructure is strained to breaking point by the heavy load of disease. It has failed to make the best use of the already available technology. Immunization provides the simplest, least expensive and most effective intervention technology. Every effort is therefore needed to extend immunization coverage and lighten the burden on the health infrastructure and accelerate the overall development of the vast rural and peri-urban communities in the developing world.

WHO has, on the one hand, to call on the most eminent scientists to give effective and simple interventions, and on the other, on the politicians, social leaders, economic managers, medical profession and all public health workers to build up the infrastructure to put intervention technologies into action.

INTRODUCTION

In developing countries communicable diseases, complicated by malnutrition and other socioeconomic factors, are major contributors to the high levels of mortality, morbidity and disability, particularly in children under five years of age. Malaria affects an estimated 150 million people annually and is responsible for about one million deaths of children in tropical Africa alone. More than 30% of deaths in children under five are due to acute diarrhoea, which is responsible for as many as three to five million deaths. Acute respiratory infections and primary pneumonia are responsible for over two million deaths per year. Tuberculosis and leprosy still remain major public health problems in developing countries.

Sexually transmitted diseases are increasing all over the world and the problem is especially serious in teenagers. So far as blindness is concerned, 80% of the world's estimated 28 million blind people live in developing countries, where the main causes of blindness are mostly avoidable or curable. Diseases resulting from pathogenic protozoa and helminths cause a broad spectrum of diseases of major socioeconomic importance, with 600 million people at risk from schistosomiasis and 200 million from filariasis, including onchocerciasis. There are still real threats of epidemics and pandemics of viral and bacterial origin, made more likely by inadequate epidemiological surveillance, deficient preventive measures and man-made disruptions of the ecological system or other factors. Of increasing concern are acquired microbial resistance to chemotherapeutic agents and vector resistance to chemical pesticides that impede progress in disease reduction and increase costs of control operations. Rapid urbanization and the expansion of travel and population movement and of trade in human and animal foods within and between countries have all increased the risk of introduction of diseases from one country/area to another.

[1] Corresponding author.

TECHNOLOGIES FOR COMMUNICABLE DISEASE PREVENTION AND CONTROL

Measures for the prevention and control of communicable diseases can be grouped as follows:

1) Environmental management, including vector control;
2) Changes in life style/social behavioural attitudes;
3) Chemotherapy;
4) Vaccines.

Environmental management, such as the provision of a safe water supply; the disposal of refuse, waste water and excreta; the securing of adequate housing; etc. would undoubtedly reduce the burden of communicable diseases. However, development of these control measures is, of necessity, a slow process. In urban centres they represent a large capital investment while, in the vast peri-urban and rural areas of the third world, environmental management can only be a part of overall development.

Related to environment is the control of vectors transmitting disease. Chemical control has been used for many years with excellent results and will continue to be used in the future. Owing to the development of resistance to insecticides, vector control is being oriented towards integrated control; involving the use of chemical, biological and environmental measures in optimum combination that can be implemented by the community itself, again as a part of overall development, and of necessity a long-term process.

New drugs and antibiotics for prophylaxis and therapy will, of course, continue to be developed, but many will lose their efficacy as the infecting organisms become resistant.

On the other hand, vaccines are amongst the most potent weapons ever devised against communicable diseases and provide the greatest hope for an almost immediate reduction in the toll of these diseases.

New biotechnologies, including the production of microbial antigens by recombinant DNA technology and peptide synthesis, and monoclonal antibody techniques, now provide enormous potential for the development of new or improved vaccines for the control of communicable diseases. In addition, there is much new information on the functioning of the immune system which provides a basis for rational vaccine design. Mankind is on the threshold of a new era in the technology of vaccine development and production.

CONVENTIONAL VACCINES

The effective prevention and control of several infectious diseases of major importance is being achieved in the developed countries and in a number of countries in the third world by the wide use of conventional vaccines. Vaccines available today could prevent five million deaths per year and prevent serious disability in a similar number of children. The WHO Expanded Programme on Immunization aims at extending these benefits to the developing world. Among virus diseases, measles and poliomyelitis are well controlled by vaccines whilst immunization with bacterial toxoids has eliminated diphtheria and tetanus as major threats and bacterial polysaccharide vaccines have repeatedly shown their effectiveness in containing outbreaks of meningitis and pneumonia. Smallpox is unique in that is has been eradicated by a combination of an efficient vaccine and rigorous public health measures.

Classical immunoprophylaxis of bacterial and viral diseases may make use of inactivated vaccines or their products, or live attenuated vaccine. Inactivated vaccines consist of organisms or their toxins, treated physically or chemically to abolish infectivity or toxicity. Such vaccines have been successful against tetanus, diphtheria, pertussis, rabies, influenza, tick-borne encephalitis, Japanese encephalitis, and — more recently — meningococcal infections. In this case, the polysaccharides of the bacteria have been used.

The efficient production of an inactivated vaccine generally requires, first, that it should be possible to cultivate the organism *in vitro* so as to produce immunogenic quantities of the antigen; secondly, that an available inactivation procedure will destroy infectivity and/or toxicity but retain antigenicity; thirdly, that the antigen can be suitably purified; and, finally, that the end product should elicit an immune state in man.

A unique case is hepatitis B vaccines. So far the only hepatitis B vaccines available are based on hepatitis B surface antigen (HBsAg), the viral surface antigen is obtained from infected human plasma which is treated to remove unwanted plasma components and to inactivate other possible infectious agents.

The use of live, attenuated organisms as vaccines has the potential advantage that the immune response generated is likely to resemble more closely that induced by natural infection, in contrast to the responses to inactivated vaccines. It is thought too that a live vaccine will stimulate a longer immunity. Live vaccines against tuberculosis, poliomyelitis, measles, rubella, mumps and yellow fever are widely used. Live attenuated influenza vaccines are potentially valuable, but further research is required to establish their safety and efficacy.

A live, attenuated vaccine must not induce significant disease, but it must replicate and induce an immune state. Further, attenuated vaccines must be genetically stable, since the appearance of genetic revertants of the original vaccine strain during production or in the vaccinee is cle-

arly undesirable. Such an event has never yet been documented, but it should be emphasized that no live vaccine can be regarded as being absolutely safe. The degree of risk involved in the use of such a vaccine, however, is very much less than that arising from the disease it prevents. For live polio vaccines, a single case of vaccine-associated paralytic illness appears on average once every three million doses of vaccine administered.

Inactivated and live vaccines are prepared in batches using established seed strains of the organisms, and in-process control tests on the final product must be rigorously applied to ensure the safety and efficacy of the product. The World Health Organization has formulated specific requirements for virtually all vaccines in regular use.

Although great progress has been made in the prevention and control of viral and bacterial diseases by the approaches described above, certain limitations are apparent. Some organisms do not grow *in vitro* or produce only small amounts of antigen. For example, the only source of hepatitis B antigen is human plasma from chronically infected persons. The production of the vaccine is technically complex and the yield is small. For products derived from human plasma there is a risk of contamination with pathogens present in donors.

The production of inactivated vaccines against highly pathogenic agents, such as those of African haemorrhagic fevers, may be hazardous to those engaged in this work.

As knowledge of the genetic basis of attenuation is meagre, vaccine strains have to be selected on arbitrary criteria. Live vaccine strains may have the potential to revert to virulence or to lose immunogenic activity.

Some viruses are associated with cellular transformation and, potentially, with the induction of malignancy. This is true of certain herpes viruses. Attenuated vaccines against these agents therefore call for rigorous safety tests.

Owing mainly to the complexity of the etiological agents, little progress has been achieved in the control of parasitic diseases using conventionally produced vaccines.

VACCINE DEVELOPMENT - BIOTECHNOLOGY

In recent years, the biomedical sciences have progressed substantially and some of these technologies can now be applied for the production of vaccines of public health importance.

While in the past vaccines were produced mainly using an empirical approach, it is now possible to design vaccines which will be safe and effective.

The improved understanding of the immunological system together with our increased knowledge of the immunological mechanisms involved in protection should allow us to construct vaccines that will maximize the stimulation of a protective immune response and minimize side effects (immunopathology).

On the other hand, thanks to monoclonal antibodies, it is now possible to identify protective epitopes (epitopes which can stimulate a protective immunoresponse) and obtain them in large quantities in the laboratory either by chemical synthesis or by DNA technology.

In spite of all this, much remains to be done. It will be especially important to know for each disease which arm of the immune response is important for protection (humoral or cell-mediated immunity). Once this is know, we will have to find out if the desired immune response can be stimulated by the antigen alone or whether an adjuvant is needed. With synthetic antigens we may also need to couple the antigen to a carrier molecule as, usually, small antigens are poor immunogenes.

During the present decade a major burden of responsibility falls on WHO to ensure that the prospects for very material improvements in infectious disease control provided by the present biotechnological revolution are vigorously exploited. With the WHO's high priority Expanded Programme on Immunization providing the delivery system within primary health care, the Organization has established an accelerated programme of Vaccine Development, under the guidance of a Scientific Advisory Group of Experts (SAGE) and five Steering Committees. SAGE is composed of a number of eminent scientists in appropriate aspects of virology, bacteriology, immunology, etc. Each of the Steering Committees oversees one of the areas where novel or improved vaccines can have a major impact on the control of the disease: viral respiratory diseases of children, bacterial meningitis and pneumonia, dengue haemorrhagic fever, hepatitis A and tuberculosis.

Within the WHO Expanded Programme on Immunization the conventional pertussis vaccine which has been in use for a long time has recently attracted criticism; its replacement by a more effective and less reactogenic vaccine would certainly be welcomed. The efficacy of the conventional pertussis vaccine varies considerably with the different methods of production; there is no reliable laboratory method to measure the protective effect of the vaccine and the side-effects, though rare, have attracted public attention. However, since the introduction in Japan of acellular vaccine composed of the two haemagglutinin proteins, leukocytosis promoting factor and filamentous haemagglutinin, there has been a resurgence of interest among well-established laboratories. WHO's role in this area has been to coordinate collaborative studies on the acellular vaccine in the laboratory and the test of their efficacy in humans.

The Organization is playing a coordinating role in the development of hepatitis B vaccine in yeast. On the other hand WHO has played a leading role in the study of the molecular biology of the polioviruses, including the genetic basis of virulence leading eventually to a novel vaccine.

The Diarrhoeal Diseases Control programme is actively pursuing the development and testing of rotaviruses, *Salmonella typhi* and cholera vaccines. The Special Programme for Research and Training in Tropical Diseases is pursuing the development of vaccines for the diseases included in their programme, e.g.: malaria, schistosomiasis, filariasis, African and American trypanosomiases, leishmaniasis and leprosy. At the moment, encouraging data have been obtained for malaria and leprosy.