✓ VRD/FORMS/97.01
Distr.: LIMITED
ENGLISH ONLY

WORLD HEALTH ORGANIZATION

ORGANISATION MONDIALE DE LA SANTE

GLOBAL PROGRAMME FOR VACCINES AND IMMUNIZATION (GPV)
VACCINE RESEARCH AND DEVELOPMENT (VRD)

RESEARCH PRIORITIES - 1998

The Vaccine Research and Development (VRD) component of the WHO Global Programme for Vaccines and Immunization is a goal-orientated Programme which funds research in the following priority areas:

1. DISEASE SPECIFIC VACCINOLOGY

1.1. BACTERIAL AND VIRAL DIARRHOEA VACCINES

In view of the efforts by GPV to facilitate the movement of valuable new vaccines into public health programmes, the Committee has confirmed the need to focus on research projects that will clearly serve this aim.

The committee agreed again that the goal of supported research should be to obtain effective and safe vaccines against enteric diseases, and that research should direct vaccine development toward those candidates that are easy to deliver, that can be delivered in one (or few doses), that can be incorporated into existing schedules of vaccines delivery -- for some of them including EPI—and that are robust enough to retain their protective properties in the adverse conditions likely to be encountered in the developing world.

The committee considers that a critical period has been reached on the way to developing such vaccines. On the one hand several living and non-living vaccine candidates have been developed but on the other, they still require testing in humans. Because only trials evaluating the safety, immunogenicity, transmissibility (for live vaccines), and protectivity of these vaccine candidates according to the standard phase 1-3 evaluative sequence in humans can validate current approaches, such studies are crucial for the committee's research agenda. The committee has therefore confirmed commitment to support Phase 1-3 vaccine trials, and to limit support to the development of new vaccine candidates, unless they represent outstanding approaches that address critical deficits of existing vaccines.

After careful consideration of the current opportunities for moving new vaccines in the public health armentarium against disease presenting the greatest burden, the committee has selected *Shigella*, rotavirus and enterotoxigenic *Escherichia coli* (ETEC) vaccine development and evaluation as having the highest priority. With the expanding use of live vaccines for these and other enteric pathogens, however, attention must be paid in human trials to the potential for *in vivo* genetic instability and reversion.

Priorities of each of the enteric infections considered have been established as follows:

Shigella

- better evaluation of the disease burden – death toll, malnutrition, long-term complications, infection in elderly people
- organization of clinical trials for both non-living and living candidates currently available for testing
- definition of immunological correlates for vaccine protection as a component of such trials
- basic research aimed at identifying the mechanisms of immune protection against shigellosis, and at characterizing *Shigella* virulence properties that may cause adverse clinical reactions to live vaccine candidates.

Rotavirus

Based upon the recent successful trial of the live oral tetravalent rhesus rotavirus vaccine in Venezuela and submission of this vaccine for licensure in the United States, research priorities have recently been reviewed to look at issues related to vaccine introduction.

1. Epidemiologic Surveillance

- initiate surveillance studies to establish the disease burden of rotavirus in countries where vaccines are likely to be introduced early or where vaccine trials are being considered
- encourage regional networks of surveillance for rotavirus morbidity and strain characterization
- develop generic protocols for hospital surveillance, assessment of national disease burden, and routine surveillance for assessment of vaccine impact following an intervention with vaccine
- promote cost-effectiveness/cost-benefit studies to assess need for rotavirus vaccines in a wide diversity of settings.

2. Field trials of Jennerian vaccines in advanced stages of development

- evaluate and optimize ways to boost the immunogenicity of live oral vaccine candidates.
- evaluate the immunogenicity and efficacy of the live reassortant vaccines in at least one country in Africa and Asia where the vaccines have never been tested

- assess the immunogenicity of different regimens of administration (e.g. neonatal dose together with BCG), in tropical settings and in underdeveloped countries where rotavirus infects children earlier during the first year of life

- in settings where the current vaccines have fared poorly when given in low dose (e.g. Brazil, Peru), conduct immunogenicity studies to assess whether vaccine take can be improved with the higher dose currently recommended

- examine whether herd immunity or herd protection can be achieved when environmental levels of rotavirus are decreased through an active program of vaccination

- examine the effectiveness of a rotavirus vaccination program administered as part of the EPI in decreasing hospitalization for diarrhea in young children

- evaluate rotavirus vaccines for efficacy in settings where the current preparations may be severely challenged by unusual serotypes, high incidence of other enteric infections, early childhood infections

- encourage further research to correlate immune markers of infection and protection from disease

- encourage the further testing and expedited evaluation of any new rotavirus candidates that become available.

3. Other issues

Research agendas outlined will need to be developed through a network of partners that will include other international and donor agencies, industry, governmental aid groups and foundations. WHO can help provide a guiding role in promoting protocols to make sure that they meet criteria of scientific excellence through a peer review process. Funding to the extent necessary will require partners with similar interests in new vaccines, immunization, and child survival efforts.

ETEC

- better definition of the human immune response against ETEC antigens

- definition, development, validation and standardization of immunological correlates of vaccine protection in human trials

- development and clinical testing of new living and non-living candidates

- increase of the protective coverage of currently available vaccine candidates.

Cholera

- development and testing of formulations of existing new vaccine candidates that increase the ease of vaccine administration and/or resistance to adverse environmental conditions

- evaluation of locally-produced cholera vaccine candidates that offer potential advantages in term of low costs

- development and testing of bivalent vaccine against O1 and O139 cholera

- development, standardization and validation of immunological correlates of vaccine protection, both in human challenge trials and in trials conducted in areas with endemic cholera.

Typhoid fever

- clinical evaluation of existing new vaccine candidates

- development of new parenteral or oral vaccines that can be effective after one dose and that can be incorporated into the existing EPI schedule of vaccine delivery

- definition of immunological correlates of vaccine protection.

1.2. MYCOBACTERIA (TUBERCULOSIS AND LEPROSY)

Overall objectives:

- to develop new and more efficient vaccines
- to translate progress in fundamental research into new tools for detection and prevention of tuberculosis, which will complement current control strategies
- to develop research tools and methods to support the implementation of TB control strategies

TB Vaccines Candidates:

- to develop subunit vaccine candidates
- to develop vaccine candidates by rational attenuation of the *M. tuberculosis*
- to develop live-vectored vaccine candidates ("improved BCG")
- to develop nucleic acid vaccines

Animal Models:

- to develop and standardize protocols to test the protective capacity of vaccine candidates in appropriate animal models.

Correlates of Protection:

- to identify immunological parameters which correlate with protective immunity against tuberculosis in humans.

Immunopathology:

- to develop strategies to predict and modulate immunopathology of leprosy, with particular reference to reactions and nerve damage.

Diagnostic and Epidemiological Tools:

- to develop new delayed-type-hypersensitivity (DTH)-inducing (skin test) reagents that allow differentiation between BCG vaccination and TB infection.
- to develop new skin test reagents with improved specificity/sensitivity for leprosy.

Genome structure:

- to co-ordinate and optimize the use of information which will soon result from efforts to sequence the genomes in relation to all the above-mentioned priority areas of mycobacterial research.

1.3. MENINGOCOCCAL AND PNEUMOCOCCAL DISEASES VACCINES

Overall objectives

To facilitate the development and provision of vaccines against the main bacterial causes of meningitis and pneumonia, *Streptococcus pneumoniae* (pneumococcus), *Neisseria meningitidis* (meningococcus) and *Haemophilus influenzae* type b (Hib).

Pneumococcus

There are three families of pneumococcal vaccines - the 23 valent polysaccharide vaccine (covering 23 of the possible 90 serotypes; currently used for adults in many parts of the world), the 9-11 valent protein-polysaccharide conjugate vaccines (which are just entering phase 3 trials in infants), and vaccines based on common protein epitopes (one of which has entered a phase 1 trial).

VRD's priorities for research are as follows:

- support for and co-ordination between phase 3 trials of pneumococcal conjugate vaccines
- evaluation of maternal immunization with pneumococcal polysaccharide vaccine
- evaluation of alternative regimens for the use of pneumococcal conjugate vaccines in infants
- support for the further development of common protein pneumococcal vaccines
- evaluation of the role of conjugate and polysaccharide vaccines in infants at high risk of pneumococcal disease

Meningococcus

In use around the world is a polysaccharide vaccine covering the two important serotypes causing epidemic meningococcal meningitis, Groups A and C, with or without two less common serotypes. Group C vaccine is not suitable for young infants and controversy surrounds the use of the AC polysaccharide vaccine in the "meningitis belt" of Africa. Conjugate vaccines against Groups A and C are currently under development. Protein vaccines against Group B, the main cause of endemic meningococcal disease around the world, have shown variable efficacy due to variable serotype specificity, and new approaches for this organism are under evaluation.

VRD priorities

- support for phase 2 and 3 evaluation of meningococcal AC conjugate vaccines
- support for further development and evaluation of newer meningococcal B vaccines
- support (in collaboration with EMC) for further evaluation of the role of meningococcal A polysaccharide vaccine in badly affected areas

Hib vaccines

Hib conjugate vaccines are in routine use in most parts of the industrialised world where they have virtually eliminated invasive Hib disease and reduced the rate of Hib carriage. However their use in developing countries is limited by lack of understanding of the epidemiology of Hib disease, particularly in Asia, and the high cost of the vaccine.

VRD priorities

- to investigate the burden of Hib disease in those parts of the world where this is not well documented
- to investigate lower cost regimens for Hib vaccination

1.4. MEASLES VACCINES

Strategic plan for accelerated control and elimination of measles.

Overall objectives

- Develop the technology for monophasic measles vaccine delivery as a liquid, powder, capsule or tablet.

- Develop reliable tests for measles diagnosis in the field and for laboratory confirmation.

Specific issues concerning measles eradication

(a) Develop simple tests for rapid diagnosis of measles infection, that can be used in a primary health care setting and distinguish measles from a number of other rash diseases, and implement laboratory tests for confirmation, that can be integrated in WHO diagnostic network.

(b) Create a system for the molecular typing of measles virus isolates which may distinguish viruses from different geographical areas.

(c) Explore alternative routes of immunization with existing vaccines, including mucosal routes.

(d) Explore the potential of existing and new devices for safe administration of measles vaccines.

(e) Periodically evaluate cost and benefit of alternative approaches for measles vaccination.

Research priorities

- Characterize the immunobiology of measles virus infection and immunization.

  (a) Identify the protective immune responses, including the study of humoral and cell-mediated immunity, in animals and man. Identify the B- and T-cell epitopes on the MV protective antigens. Study the immune response and characteristics of infection during natural MV infection and immunization.

  (b) Develop animal models, including transgenic mice, to study: (i) molecular pathogenesis of MV infection; (ii) immunobiology of MV infection; (iii) immunopathology of MV infection or immunization including immunosuppression; (iv) safety, immunogenicity, and efficacy of new formulations of MV vaccine; (v) atypical disease during MV infection of vaccinees previously immunized with inactivated virus.

- Apply the infectious clone technology of measles virus rescue to study viral pathogenesis

1.5. DENGUE AND JAPANESE ENCEPHALITIS VACCINES

The long-term goal is to obtain affordable, safe vaccines that induce life-long protection to the four serotypes of dengue, or to Japanese encephalitis viruses.

Current priorities are:

- Identification of the virulence determinants and protective epitopes at the sequence level.
- Use of infectious clone technology to study viral pathogenesis and immunity, and to construct mutant viruses as potential vaccines.
- Exploration of the value of live vectors of proteins of dengue and Japanese encephalitis viruses for protection against these viral infections, with special reference to recombinant vaccinia-vectored antigens and baculovirus-expressed truncated E protein.
- Investigation of alternative biotechnological approaches (Nucleic Acid Vaccines) for the development of dengue and Japanese encephalitis candidate vaccines.
- Research aimed at evaluating, comparing and then optimizing the protective effect of candidate vaccines in current or newly developed animal model systems.
- Research on the clinical evaluation of safety, immunogenicity and efficacy of candidate vaccines.

Research aimed at improving the existing formulations, optimization of manufacturing conditions, and development of novel vaccine delivery methods, including oral and combination vaccines.

Development of pilot studies to investigate diagnostic reagents useful for evaluation of safety and efficacy of DEN, JE and yellow fever vaccines.

Epidemiology of Japanese Encephalitis.

2. NEW VACCINATION APPROACHES AND NEW DELIVERY SYSTEMS

2.1. NEW IMMUNIZATION APPROACHES

Objective:

Define immunization approaches more efficient than existing ones that are applicable both to existing vaccines and to diseases for which no suitable vaccine yet exists. The interaction with other Steering Committees is essential.

Sub-objectives:

1. **DNA vaccines**

- measure **correlates of protection** for DNA vaccines as compared to conventional ones, using appropriate challenge models
- assess the potential of the **mucosal** route for DNA immunization for induction of local and systemic immunity; delivery systems
- assess the ability of DNA vaccines to raise immune responses in the **newborn**
- evaluate the use of DNA vaccines for **priming** in combination with other modalities of vaccination for boosting.

2.[1] **Mucosal immunization**

- assess **mucosal adjuvants** for local and systemic immunization; different formulations for oral and nasal delivery; safety aspects
- emphasis should be placed in their evaluation through **human trials** and determining correlates of protection.

3. **Neonatal/infant vaccination**

- circumvent the inhibition of immune responses by **maternal antibodies**
- determine the induction of **appropriate immune responses** (T helper 1, T helper 2 and B cell responses) in a relatively immature immune system, both at the systemic and mucosal level, emphasis on B cell responses to polysaccharide vaccines
- assess the quality of these responses to existing vaccines in **humans**.

4. **Combined vaccines**

- evaluate interactions between protein and polysaccharide vaccines.

5. **Therapeutic vaccines**

- Explore their use for the treatment of **chronic** infectious diseases.

2.2. NEW DELIVERY SYSTEMS

Objective:

Promote the development of vaccines simpler to deliver than existing ones with particular emphasis on reducing the number of doses needed to induce long-lasting protection.

Sub-objectives:

1. **Controlled-release vaccines**

- continue the development of a **single-dose tetanus vaccine** as a model vaccine including initial clinical studies
- assess **potential application** to other vaccines (diphtheria, pertussis, Hib, HB, DNA) including the oral delivery
- assess the potential of **nanospheres** technology.

2. **Subunit vaccines**

- identify new carriers for peptide or oligosaccharide vaccines; evaluation of the effects of **pre-existing immunity** to the same carrier.

3. **Live vectors**

- evaluate **prime-boosting** strategies involving live vectors
- **clinical aspects**, emphasis on safety.

4. **Transgenic plants as edible vaccines**

- vaccinology aspects: assessment of the **induction** of immune responses, including tolerance.

---

[1] Commissioned research will be supported only for two sub-sections: mucosal immunization and delivery of vaccines in a dry form and one section: HIV/AIDS vaccines

5.[1] **Delivery of vaccines in a dry form**

- recommended possible antigens are Vi polysaccharide, measles, diphtheria, influenza.

There is a strong recommendation to apply any of these approaches to antigens of diseases relevant to GPV. In addition, a given approach and individual projects are to be supported only if they have a transdisease nature. Phase I protocols will be systematically reviewed by external bodies

2.3.[1] HIV/AIDS VACCINES

- Use of BCG as a vector:

  - Explore its potential to induce neutralizing antibodies against clinical isolates
  - Explore its capacity to accommodate large and multiple epitoper, particularly CTL epitopes

- Identification of CTL epitopes and HLA restrictions in clades other than B
- Mucosal delivery of HIV/AIDS vaccines
- Generation of clade A SHIVs.

3. EPIDEMIOLOGY AND FIELD RESEARCH

3.1. Disease Epidemiology: Develop standard methodologies that allow the evaluation of the local burden of specific diseases. Validate methods and conduct selected demonstration studies.

- Respiratory syncytial virus (RSV): Support disease burden studies based on a WHO Generic Protocol. Provide training to local investigators.

- Haemophilus influenzae type b (Hib): Continued support to Hib disease-burden studies based on a WHO Generic Protocol.

- Rubella and congenital rubella syndrome (CRS): Develop new tools to document the regional burden due to congenital rubella syndrome.

3.2. Approaches that aim at improving quality and management of immunization programmes and campaigns.

- Rubella modelling: Through mathematical modelling, assess the impact of private sector vaccination on CRS.

- Private sector immunization: Assess approaches to include the private sector into national vaccine-preventable diseases surveillance and/or in other components of the immunization programme.

- Measles modelling: Development and validation of mathematical models that predict optimal schedules for mass immunization campaigns

- Tetanus: Assess the operational utility of tetanus antitoxin serosurveys for neonatal tetanus elimination strategies. Facilitate the development of a rapid diagnostic test for tetanus antitoxin antibodies.

4. COORDINATED RESEARCH ON POLIO AND RESPIRATORY VIRUSES

4.1. POLIOVIRUS VACCINES

Research in the following areas will be considered, provided it is relevant to the initiative for the global eradication of poliomyelitis by the year 2000.

- Development of alternative models for safety testing of OPV.

- Development of rapid and accurate methodology for identifying wild type poliovirus in clinical specimens and environmental samples.

4.2. ACUTE VIRAL RESPIRATORY DISEASES OF CHILDHOOD: VACCINES FOR RSV AND PIV3

The priority is the development of vaccines that protect against disease without potentiating disease.

The aim is to globally control the acute respiratory diseases of infancy and early childhood which are due predominantly to infection by respiratory syncytial (RS) virus and parainfluenza type 3 (PIV3) virus, and to a lesser extent by other parainfluenza viruses.

Since several subunits and live attenuated RSV and PIV3 vaccines have entered into clinical testing, the Steering Committee will closely follow and evaluate the data generated. Special attention will be given to exploring the possibility of vaccination in women at childbearing age.

Furthermore, ongoing clinical studies of passive immunization in young infants against RSV will be followed closely.

Requests for information should be addressed to:

Vaccine Research and Development
WHO Global Programme for Vaccines and Immunization
World Health Organization
20, Avenue Appia
1211 Geneva 27
Switzerland

Facsimile numbers:

WHO general: (41-22) 791 0746
GPV/VRD direct: (41-22) 791 48 60
Email: eidm@who.ch
Internet: in the section "What's available"/Vaccine Research on World Wide Web site at
http://www.who.ch/programmes/gpv/gpv_home.htm