

INTERNATIONAL CONFERENCE ON THE  
APPLICATION OF VACCINES AGAINST  
VIRAL, RICKETTSIAL, AND BACTERIAL  
DISEASES OF MAN

WASHINGTON, D.C.  
14-18 DECEMBER 1970



**A SUMMARY**

**PAN AMERICAN HEALTH ORGANIZATION**  
Pan American Sanitary Bureau - Regional Office of the  
**WORLD HEALTH ORGANIZATION**

525 Twenty-third Street, N.W.  
Washington, D.C. 20037

REF: RD 10/1

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SUMMARY\*

In his introductory remarks at the First PAHO/WHO Conference on Live Poliovirus Vaccines, Dr. Abraham Horwitz observed: "In the evolution of ideas in search for those truths which bear on the lives of many people it is indispensable, from time to time, to pause and to analyze what is known, what still remains to be learned and to determine the course which must be followed to reach the original objectives." This theme has served as the guideline to the present Conference, at which, in addition to the vaccines against viral and rickettsial diseases discussed at the previous conference, in 1966, we have dealt with those against diseases of bacterial etiology. During the past four and a half days we have heard papers and discussions dealing with more than 25 separate vaccines - each of which may be administered individually or hopefully as appropriate combinations, with or without adjuvant materials - and broad plans and discussions relevant to the actual implementation and delivery of vaccines to target populations. The breadth of material presented precludes summation by one individual, and so I have relied heavily upon the summaries prepared by the rapporteurs, to whom I am greatly indebted. Before entering upon details relating to specific vaccines, combinations, or approaches to implementation, I should like to consider four broad areas which I have selected to represent an overview of the Conference, with particular emphasis on developments since the first conference held in November 1966.

Goal of vaccine application

In view of the title of the present meeting, it should be re-emphasized that the goal of vaccine application is preventive immunization, and that this is only one approach, though a most important one toward our ultimate goal: The prevention of disease. However, other control

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\*J. P. Sanford for the rapporteurs

measures may be equally or even more effective for many diseases. Several examples of alternatives to immunization have been cited - for example, vector control in the case of arbovirus or rickettsial infections with insect or acarine vectors, though its cost may be prohibitive where such control is merely of a suppressive nature. In contrast, with our present state of knowledge, control of cholera in the Philippines was achieved more effectively and at lower cost through environmental sanitation (construction of pit latrines) than with the application of vaccine.

In other diseases for which immunization is not possible as yet - for example, malaria or leishmaniasis - chemoprophylaxis may be an alternative. Unfortunately, the usefulness of chemoprophylactic regimens appears to be more transient; resistant parasites have been emerging, such as chloroquine-resistant strains of Plasmodium falciparum in many parts of the world, sulfonamide resistance in Neisseria meningitidis, and increased resistance of strains of penumococci to penicillin G in New Guinea in 1969. This last, and very disconcerting, observation, when considered in the context of the gradual but major increase in resistance of Neisseria gonorrhoeae, should turn our attention to other microorganisms that to date have been considered to be uniformly and always susceptible to penicillin G, such as Group B Streptococcus pyogenes and Treponema pallidum. Surveillance programs to confirm susceptibility should be improved and alternatives to prophylaxis or management, including immunization, should receive additional emphasis.

We have heard an updating of the role of chemoprophylaxis against certain viral diseases - an area in which considerable differences of view still persist. In this area, either-or attitudes appear to be too narrow. During periods of high risk, as in smallpox exposure, the thiosemicarbazones enhance the protection of the immunized individual. Against rickettsial diseases such as scrub typhus, combined immunization and chemoprophylaxis is being considered.

Thus, despite our individual interests in the application of vaccines, we need to keep sight of our objective - control of disease - and to evaluate alternative approaches.

Contemporary immunology-microbiology and vaccination practices

The second broad area I should like to consider relates to the phenomenal advances that have occurred in the fields of immunology, molecular biology, and bacterial genetics. While we need not apologize for the past, we must recognize that all too frequently vaccine practices have developed from serendipity and empiricism combined with hard work. From a number of the presentations, it is apparent that current basic information is now being applied toward the solution of problems in immunization. Perhaps it would be advantageous to review several areas that came under consideration.

The existence of at least five classes of immunoglobulin, and subclasses as well, is now recognized, as is the fact that these immunoglobulins differ in function. Unfortunately, we do not know as much about functions, especially in vivo, as about their structure. Complement fixation, bactericidal, and opsonic activity are most marked with IgG; IgM is more efficient in hemagglutination reactions. The question regarding which of these immunoglobulins is more protective in vivo has not been elucidated for most vaccines. Since IgG crosses the human placenta whereas IgM does not, IgG is responsible for the protection of the newborn provided by maternal antibody. Under many circumstances, the antigenic mass is a major factor in determining the class of immunoglobulin produced, with IgM being elicited initially in the sequence of antibody synthesis and with the application of lesser antigenic mass. Thus, natural infection is often associated with IgG (7-S) immunoglobulin. However, some antigens appear only to evoke an IgM response except under extremes of experimental hyperimmunization - for example, typhoid vaccine, both the acetone- and the heat-phenol-inactivated.

Immunoglobulin A (IgA) occurs in two forms, as serum 7-S IgA and as secretory or 11-S IgA. Numerous studies have now demonstrated that secretory IgA is the major immunoglobulin in external secretions from the nasal passages, in the gastrointestinal tract, and in breast milk. Secretory IgA has been shown to have viral neutralizing activity. While there is now a consensus that secretory IgA is important in protecting external or mucosal surfaces from viral and probably bacterial invasion, this may pose a dilemma in the oral administration of attenuated vaccines where invasion is desired. The problem of immunization of nursing infants with oral polio vaccine encountered

in some warm climates may well be due to polio antibodies in the secretory IgA in breast milk.

The development of methods that make it possible to stimulate a specific immunoglobulin class might provide solutions to many current problems. For example, would typhoid antigens that stimulated secretory IgA result in "gut immunity," or would typhoid antigens that resulted in circulating IgG antibodies be more protective? Would the stimulation of IgA antibodies in tears protect against trachoma? In this respect, the data suggesting that Adjuvant 65 influenza vaccine is associated with increased anti-influenzal antibody in nasal secretions is of great interest.

Immune interference represents another dilemma in immunization practice. The observation that high levels of IgG antibody will block the initiation of primary antibody synthesis to the specific antigen has resulted in the prevention of Rh hemolytic disease in newborns by administering anti-Rh gamma globulin to mothers at risk. An extension of this concept might be applicable to other diseases, such as schistosomiasis, where the granuloma represents an immune response, although in this disease the granuloma most likely represents a cell-mediated reaction. Despite its practical usefulness in the case of Rh hemolytic disease, immune interference poses many practical problems in other areas; for example, interference with the primary antibody response to vaccine by the simultaneous administration of hyperimmune serum, or the failure of primary measles immunization in the presence of IgG maternal antibody.

The intentional application of cell-mediated immune mechanisms to broad disease control is just in its infancy and could well represent a major area of discussion at the Third Conference. As we have heard, cellular immunity mediated through T-lymphocytes appears to play a major role in host resistance to infection by intracellular parasites - tuberculosis, leprosy, brucellosis, vaccinia. Cellular immunity may also be involved in fungal infections such as coccidioidomycosis. Further understanding in this area may bring about a more rational understanding, control, and evaluation of agents such as BCG, which evokes delayed hypersensitivity and cellular immunity. The control of cancer with vaccines may also involve cellular immunity to a major extent.

Not only has the discipline of immunology contributed to our understanding of immunization practices, but the areas of molecular biology and bacterial genetics are now being applied to the development of better antigens. The use of mutants such as strains of Mycoplasma pneumoniae with sharply limited temperature requirements, or of viral or bacterial hybrids or recombinants in, for example, influenza or shigellosis, provides challenging new horizons.

Clearly, immunization practice constitutes a major area wherein the basic sciences articulate with the meaningful delivery of health care, thus providing us with exciting new approaches but at the same time placing upon us the responsibility for making good use of this knowledge.

#### Keystones in immunization programs

The third broad area or approach to be emphasized consists of the reiteration of four considerations that are basic to any and all immunization programs: The need, efficacy, safety, and ease of administration of the system of immunization. Each of these must be considered in the context of the other, but for discussion purposes they will be considered sequentially.

The needs for control programs depend upon factors such as the incidence of a disease and the associated morbidity and mortality. As smallpox demonstrates, the needs are not necessarily static and periodic re-evaluation is essential.

The minimum vaccine efficacy consistent with the continuation of a program must be considered within the framework of a specific disease; for example, post-exposure antirabies prophylaxis is accepted with limited proof of its efficacy in man, whereas this would be unacceptable for a rhinovirus vaccine.

Provided that the need exists within some defined population group and that a reasonably effective immunizing agent is available, the safety of the agent must be weighed in terms of both need and efficacy. Safety is a broad concept, which should encompass consideration of more than reactions in the recipient. With live attenuated vaccines, the possibility for transmission to secondary contacts, with associated reactions, must be

considered, as was discussed with poliomyelitis, rubella and smallpox immunization programs. Also to be considered is the duration of immunity and nature of the risks if immunity were to lapse within one or fifty years. The exposure of an individual to an antigen may evoke immune reactions other than those desired for protection. The most striking of such responses have been the high fever, atypical rash, edema of the extremities, pneumonitis, and occasionally pleural effusion, and abdominal pain that occurred in recipients of killed measles vaccine in the United States when they were exposed to live measles virus months or years later. The respiratory symptoms observed in infants who had been immunized with inactivated respiratory syncytial virus vaccine were markedly more severe, upon subsequent exposure to wild RS virus than the illness observed in nonimmunized infants. These reactions are felt to represent a form of hypersensitivity (using the term rather loosely). The administration of excessive amounts of tetanus toxoid may result rarely in the late development of both Arthus and anaphylactoid hypersensitivity, the latter presumably related to the final stimulation of antitetanus antibodies in IgE class immunoglobulins.

With successful programs, side effects become more apparent and safety of more concern as the apparent need for immunization diminishes. Smallpox vaccination, poliomyelitis vaccine, tetanus toxoid, and pertussis vaccine provide examples.

An additional potential problem that at least needs to be considered is that of alterations in microbial ecology in response to the elimination of one or more members. Adenovirus type 7 came to the fore when type 4 live attenuated vaccine was given to a population in which both types of adenovirus were endemic. The administration of group C meningococcal polysaccharide vaccine led to increased nasopharyngeal colonization with meningococci of other serogroups. The same phenomenon may occur with pertussis and polioviruses and perhaps is more prevalent than has been recognized.

From the standpoint of ease of administration, considerations must include the entire system of delivery: The route of administration; the schedule of primary, reinforcement, and booster doses; the stability, the cost effectiveness, public acceptance and many other factors.



Strategy for immunization programs

The last area I should like to stress is the need to define and develop a logical strategy for immunization programs. Classically, immunization has been designed to provide direct protection to the vaccinee. In other circumstances, immunization programs may be designed to provide indirect protection to a susceptible host; the immunization of a woman in the childbearing age with tetanus toxoid protects her newborn against tetanus neonatorum. Protection to individuals within a group may be provided either through herd immunity or through the establishment of an epidemiological shield. This latter principle is being applied in the United States in the rubella vaccine program: immunizing children, the major source to interrupt the transmission of the disease to pregnant women. If man is the only reservoir and provided that "immune carriers" are either nonexistent or rare, immunization should be able to eradicate a disease, as is the goal of the smallpox program. Finally, immunization of nonhuman hosts may protect humans as in the case of urban rabies and Venezuelan equine encephalitis.

As a preamble to a summary of the discussions of specific diseases and programs let me reiterate:

1. Immunization is only one approach to the control of disease.
2. Immunization practice represents a major area where advances in immunology, molecular biology and bacterial genetics can be applied.
3. In design of immunization programs, need, efficacy, safety, and ease of administration should be considered.
4. Strategies of immunization differ, and care should be taken to choose the most appropriate.

Arbovirus diseases

Live attenuated yellow fever vaccines have been administered to many millions. The Dakar strain is no longer recommended and 17-D is used almost exclusively, though it is not entirely free from complications. Of current antiviral vaccines, it is probably the most effective and elicits the longest-lasting immunity. However, yellow fever vaccine has usually contained fowl leukosis virus derived from its egg substrate, and although this extraneous agent is apparently harmless to man, it must be eliminated, not only because it has now been recognized, but also because of its theoretical hazards. Seed virus has now been freed from fowl leukosis virus and a limited amount of "clean" vaccine can be produced from available "clean" eggs. The poor stability of this vaccine in shipping and storing, particularly in the tropics, is a serious handicap, and methods to improve it are being actively investigated.

Yellow fever control in Africa appears to be almost entirely dependent on vaccine, vector control not being practicable at present. In South America, vaccine alone is applicable to jungle and to many other nonurban areas, but urban areas depend largely on Aedes aegypti eradication for control. Urban epidemics are now rare. Jungle reservoirs and insidious outbreaks in man persist. Unfortunately, many circumstances militate against attaining complete vaccination of the population. Despite the wave of yellow fever that swept over Central America in the 1950's, endemicity does not and apparently cannot persist in southern South America, northern Panama, and Central America. However, without continuous, vigilant surveillance and control efforts, outbreaks in man can be expected to occur repeatedly.

Combinations of yellow fever vaccine with other live vaccines such as smallpox, measles, and BCG are being investigated. Some have already been found satisfactory, and obviously are advantageous; others require further study.

Many other arboviruses (about 90) produce human disease, some serious, but most are recognized only in limited areas. The development of vaccines against these agents holds no promise of monetary gain from sales, and unless subsidized by government, or otherwise, such potential vaccines will not be

suitably tested, manufactured, or used. A number have been developed already and have not come into use. A few viruses are so widespread and dangerous that vaccines have been developed and have survived this economic hurdle. However, many areas of the world will remain undeveloped or seriously handicapped unless vaccines are both developed and used.

Vector control, although frequently recommended, may well cost more than vaccine, is entirely impractical in some places, and once started must be continued (though this last is also true of vaccine).

Both live and inactivated vaccines have been used, and both are currently under investigation. Each has advantages and disadvantages, and opinion differs as to where the highest priority should be placed. Inactivated vaccines in general are safer and are quicker and easier to develop and test, but may not be as effective or result in such long-lasting protection.

A real potential exists for the development of polyvalent arbovirus vaccines consisting of several viruses within the same immunological group. Other areas recommended for investigation include definition of the kinetics of the immune response, particularly the rapidity with which immunity develops, and determination of whether or not it is safe or effective to use live arbovirus vaccines when exposure to natural infection might be more or less simultaneous.

If these many important diseases are to be controlled, vaccines will be necessary for most of them.

### Rabies

Rabies vaccines for man are used principally after exposure in an attempt to prevent an otherwise fatal disease. The methods used at present throughout most of the world employ crude, relatively dangerous central nervous system products, administered either alone or in conjunction with a crude hyperimmune animal serum that is also associated with many reactions. Attempts to improve these products (the use of suckling animal brain, chemical treatment to remove myelin, passage on duck embryo) have not to date yielded any remarkable results with respect to effectiveness or freedom from reactions.

The immunization regimen that will ultimately be developed will quite certainly be based upon a radically different product, probably a highly purified and concentrated cell-culture inactivated virus given in fewer doses. Encouraging experimental results are being obtained in animals. Concomitantly, research has led to questioning the effectiveness and perhaps even the safety of some antisera under certain circumstances and of whether neutralizing antibody is related to protection, a currently accepted concept.

Another encouraging area of investigation is related to the role of interferon and its induction for postexposure protection. Chemoprophylaxis may also play a role eventually.

Pre-exposure immunization is proving to be highly effective and should be more widely employed. Some of the safer, newer vaccines (duck embryo) are proving to be adequately effective for this, and the cruder preparations with greater potential for adverse neuroparalytic effects need not be employed.

#### Respiratory virus diseases

The overall public health importance of the 119 currently known viruses that cause respiratory disease in man is as difficult to quantify as their incidence. In the developed countries, respiratory viruses are the most common cause of acute minor illnesses that disrupt optimal function and are frequently primary or contributory causes of death. While less emphasis has been placed on respiratory viruses in the developing countries, they are just as important as causes of ill health in these areas. Influenza viruses are more dramatic than rhinoviruses in their measurable impact, but which cause more total damage to the health of the public? Are the respiratory syncytial viruses, because of their threat to the young infant or elderly patient with chronic obstructive airways, more or less important to public health than either the influenza viruses or rhinoviruses? The answers to such questions are not available, but it is within this framework of cost-benefit that efficacy, safety, and ease of administration must be considered.

Turning initially to the most dramatic of the respiratory viral illnesses, influenza, the WHO program of a system of laboratories to forewarn of coming epidemics was felt to have functioned well with regard to the pandemic of A<sub>2</sub>/Hong Kong influenza that broke out in 1968. Large amounts of vaccine were produced, but utilization was suboptimal. During the 1968-1969 pandemic, total excess mortality for 122 U.S. cities was estimated at 19,500, and the situation in Europe in 1969-1970 was much the same. Does this 1968-1969 experience in the United States represent failure of antigens or failure of the strategy of immunization? It was unanimously agreed that the answer is not either-or. In a report on the absence of influenza in U.S. military populations, which are uniformly vaccinated, and the higher incidence in civilian populations, which are not vaccinated, the opinion was expressed that it is unnecessary to change vaccine composition during the period when one influenza family is prevalent, but only if the vaccine currently available is well used and reaches the target population. Evidence was presented from retrospective studies in Northern Australia to support the idea that community immunization programs could limit the spread of the virus (A<sub>2</sub>/Hong Kong).

In the United Kingdom, work has continued on the development and testing of live attenuated influenza A<sub>2</sub> strains for intranasal administration. In the USSR, 20 to 30 million doses annually of live influenza vaccine are administered by the intranasal route. Efforts at selecting optimal vaccine strains continue, and in recent trials the oral route of administration appears to be effective. Enteroviruses have been found to be effective interferon inducers; in field trials, the incidence of influenza was reduced 3.4-fold in groups that had received oral type 1 poliovirus vaccine.

The Conference did not provide either new data or analysis from which an informed consensus could be reached or far-reaching recommendations drawn.

Less time was devoted to other respiratory viral vaccines than at the 1966 conference because of the phenomenal advances in other areas, such as smallpox, measles, and rubella, and because of the frustrations encountered with respirovirus vaccines. The importance of local nasal antibody in resistance to RS virus, rhinovirus, and parainfluenza viruses was stressed.

Yet the administration by mouth of live attenuated adenovirus types 4 and 7 vaccines to U.S. military recruits has led consistently, since 1966, to a 75 per cent reduction in overall hospitalizations for acute respiratory disease and a 90 per cent reduction in type-specific illness, although these vaccines have not evoked local nasal antibody.

The experience with an inactivated Mycoplasma pneumoniae vaccine in U.S. military trainees demonstrated immunogenicity and approximately a 50 per cent reduction in illness. Further refinements in killed vaccine preparation and efforts to develop modified strains for immunization suggest that another immunoprophylactic tool will be available in the future.

### Smallpox

The extraordinary progress of the WHO eradication program was reviewed. In 1967, when fewer than 5 per cent of the cases were reported, 131,000 cases were recorded. In 1970 there will be fewer than 30,000 cases despite an improvement in case reporting to 20 per cent. Only 21 countries still harbor smallpox. In South America, it remains endemic only in Brazil, but over 75 million of the 95 million population have now been vaccinated. In Africa, it is endemic in only four countries - Sudan, Ethiopia, Burundi, and the Democratic Republic of Congo. Indonesia, Pakistan, and India have made enormous gains in the past few years.

In 1967 not more than 15 per cent of the vaccines used in endemic countries met WHO standards. Currently only freeze-dried vaccines are used and all conform to WHO standards. The eradication campaign has been facilitated by a number of technical developments: freeze-dried vaccine, jet injectors for mass campaigns, the bifurcated needle, and the abandonment of skin preparation.

The strategy of epidemiological control that has been employed against importations into nonendemic areas - finding outbreaks, delimiting the boundaries both in time and in space, and then vaccinating all persons at immediate risk - has been used for the past four years in endemic areas. In 1967 it made possible the elimination of smallpox from an endemic area of 10 million people in five months. In 1968 this approach was employed

in all the remaining endemic countries of West Africa, and within twelve months all but one was smallpox-free, even with less than half of the population being vaccinated. The lesson to be learned is that precise application of vaccine to selected populations may at times be more important than mass vaccination.

Although the goal of smallpox eradication appears to be within sights, it has not yet been achieved. Now that most countries are free of the disease, however, attention is being concentrated on untoward reactions associated with the administration of vaccinia. In the United States in 1968 there were 153 severe or significant complications from smallpox vaccination of which 9 were fatal: 137 cases of eczema vaccinatum (126 cases, 1 death) or vaccinia necrosum (11 cases, 4 deaths) and 16 cases of postvaccinal central nervous system syndromes ("encephalitis"). The first two complications should be reducible to minimal incidence. Postvaccinal encephalitis is poorly understood and is the least predictable. There was no major disagreement with the statement that current programs for childhood vaccination in the United States should not yet be abandoned but that recommendations should be interpreted more flexibly and contraindications scrupulously observed. In contrast, some felt that in endemic countries there are no absolute contraindications to vaccination and that vaccination at birth should be routine. Neither pregnancy nor acute or chronic illness should preclude vaccination or revaccination when efforts are being made toward eradication.

Experience with allantoic-membrane-adapted vaccinia strain CVI-78 in 2,500 vaccinations was reviewed. The attenuated strain was used for primary vaccination of 1,400 children suffering from eczema. CVI-78 would appear to be a safe, attenuated strain for the eczema patient who requires vaccination. Concern was expressed about the neurotropism of CVI-78 for mice, but a similar strain of virus was accompanied by a lower rate of postvaccinal encephalitis than that usually encountered in the Netherlands. Further efforts toward the development of more acceptable vaccinia virus vaccine, perhaps through recombinants or temperature-sensitive mutants, are still needed.

### Poliomyelitis

The availability and extensive use of poliovaccines have eliminated the problem of paralytic poliomyelitis in many countries of the world. The incidence of the disease has declined to insignificant levels in the United States, Canada, Europe, and Australia. In contrast, in many countries of Central and South America, Africa, and Asia, poliomyelitis continues to be endemic and sporadically epidemic. Moreover, the incidence of paralytic disease appears to be increasing.

The problems of poliomyelitis in certain developing areas of the world are compounded by various factors: (1) failure to use the vaccine for oncoming generations of infants, (2) unsatisfactory refrigeration, (3) interference from other enteroviruses, (4) the suppressive effect of antipoliomyelitis antibody that may be present in breast milk, and (5) unknown factors.

### Measles

The extraordinary progress and the problems associated with the widespread use of various measles vaccines were highlighted. Live measles vaccine has been well tolerated and is highly immunogenic. The use of more than 40 million doses in the United States since the vaccine was licensed in 1963 has produced a dramatic decline in the incidence of measles and encephalitis, with no apparent increase in reported cases of subacute sclerosing panencephalitis that might have been vaccine-associated. The extensive use of measles vaccine in Chile since 1964 has had a profound effect on the mortality from measles in that country: a reduction approximating 90 per cent, from an average of 2,000 to 3,000 a year to 335.

The use of over 20 million doses of measles vaccine in various African countries was followed by a 60 per cent decline in the reported incidence of the disease for the first year after immunization. Most noteworthy has been its virtual eradication from the Gambia since mid-1968.

The occurrence of measles in previously vaccinated children has been attributed to various factors, including (1) inadequate refrigeration



of vaccine, (2) excessive exposure of diluted vaccine to light, (3) use of the wrong vaccine diluent, (4) suppression of antibody by transplacentally acquired antibody during the first year of life, and (5) unknown factors. Currently licensed live measles vaccines have elicited seroconversion rates of approximately 98 per cent. Consequently, it is not unreasonable to anticipate a 2 per cent attack rate in children who have been inoculated but not immunized with measles vaccine. This has been the general frequency of "vaccine failure" in previously vaccinated children.

Inactivated measles vaccine has been responsible for sensitizing children, who subsequently developed clinical manifestations of delayed hypersensitivity after exposure to wild measles virus.

Evidence presented by various groups indicated that the currently licensed measles vaccines should provide long-lasting immunity.

#### Mumps

Live attenuated mumps vaccine has been shown to be well tolerated, immunogenic, and protective against the clinical disease in the USSR and during the three-year period following its use in the United States. Studies have demonstrated the persistence of antibody in serum for as long as five years. The major question relates to the priority this vaccine should receive in vaccination programs. If additional experience continues to prove effective, it should be most useful when combined with other immunizing agents, such as measles and rubella vaccines. It is essential to continue surveillance to confirm that childhood vaccinees are not left as susceptible adults.

#### Rubella

The serious consequences of congenital rubella as a cause of death and disability were described in detail. The development of various live attenuated vaccines has provided immunizing agents that will be useful for the control of congenital rubella. The potential problems of adverse clinical reactions, communicability, reinfection, and duration of immunity were discussed in detail. The available evidence indicates that the

vaccines are well tolerated, highly immunogenic, and not communicable and that immunity has persisted for four to five years. The strategy for the use of rubella vaccine will vary from country to country, depending upon local epidemiological circumstances and other factors.

#### Rickettsial and bacterial diseases and vaccines

Despite the prevalence of rickettsioses throughout the world, interest in and support for the development and improvement of rickettsial vaccines remains insufficient. Typhus vaccine prepared from the live attenuated E strain of R. prowazekii shows great promise, having afforded a high degree of protection in the field trial in Burundi in 1969.

With respect to trachoma, epidemiological, clinical, microbiological, and serological evidence is being accumulated to show that active immunity is induced both in man and in animals by infection and by inactivated vaccines. These data justify further efforts to produce a vaccine.

Diphtheria and tetanus toxoids are still two of the most effective antigens and may be used in combination, principally for infant and childhood immunization; tetanus toxoid may be used alone to induce immunity in specific groups, such as women at or near childbearing age in developing countries to prevent neonatal tetanus. Preparations that can induce lasting immunity after one or two doses require further study. Properly prepared pertussis vaccine has markedly reduced morbidity and mortality from whooping cough, but preparations of pertussis antigen of high antigenicity and low reactivity are urgently needed.

Although typhoid vaccines for parenteral use have proved effective in field trials and may be used in combined vaccines, the high reactivity of current preparations is still a disadvantage. A living vaccine given orally was reported effective against challenge in volunteers. The multiplication of infecting organisms was limited, so that only 33 per cent of the vaccinated subjects had positive stool cultures and there were no relapses in contrast to 76 per cent positive stool cultures in the controls. This living vaccine seems worthy of larger-scale clinical trials.

The oral administration of hybrid organisms derived from Escherichia coli and shigella induced resistance against dysentery following challenge of volunteers. Confirmation and extension of these observations are eagerly anticipated.

While cholera vaccine may give a degree of short-lived protection to the individual, its use for mass vaccination in an attempt to control the disease is probably not justified, and existing better means of control should be employed. Several approaches to the preparation of a better vaccine are being investigated.

The world-wide importance of tuberculosis as a continuing public health problem is reflected in the mortality statistics of all but a few countries. So much was generally agreed, but major differences arose over the strategy for control. In developing countries, the definition of target populations and the administration of BCG vaccine appears to be the most feasible approach. In developed countries, the controversy between advocates of BCG and of isonicotinic acid hydrazide (INH), either in chemoprophylaxis or through epidemiologic control, could not be settled because of differences in definition of the problem, baseline data, demographic characteristics of the population at risk, variability in vaccines, and the occurrence of cross-reacting mycobacterioses in some areas. The need for improved standardization and quality control of BCG and for the acceleration of research into newer methods of immunoprophylaxis and alternative methods of control is most pressing. A multiplication of production laboratories is not encouraged.

Increased concern about meningococcal, pneumococcal, and hemophilus influenzae infections has resulted in the development of purified antigens for active immunization. Clinical trials of these vaccines are in progress. The field studies of Group C meningococcal polysaccharide antigens are more advanced and demonstrate a high level of protection against Group C meningococcal disease.

#### Vaccine combinations

The rapidly growing number of accepted and approved vaccines has

added a new dimension to the problem of the organization of immunization programs. Sequential inoculations of one agent after the other - the "disease-a-month" approach - are hardly practicable, are unnecessarily costly, and are not well accepted by the public. The use of combined vaccines offers a solution to this problem.

It was reported that various combinations of live measles, mumps, rubella, and smallpox vaccines, when tested in seronegative children, have given seroconversion rates comparable to those obtained with each individual preparation. No untoward reactions have been observed in several hundred children so tested. Combined inactivated vaccines containing DPT plus triple polio or polio and measles components are already routinely used in several countries. The possibility of combining live with inactivated preparations was also considered. Small trials with vaccinia + measles + tetanus, or BCG + tetanus have produced encouraging results. There may, however, exist an increased risk of sensitization when measles is given together with alum-adsorbed toxoids. It was suggested that notoriously reactogenic vaccines such as pertussis and typhoid should preferably not be included in mixed preparations, since this might discourage their use.

Combined vaccines will be of particular value in developing countries, but can also facilitate the immunization of hard-to-reach disadvantaged groups in developed nations.

### Adjuvants

A review and updating of information on the efficacy and safety of the use of adjuvants with inactivated vaccines led to a continuation of the controversy as to potential oncogenicity and the relevance of animal models. With the development of Adjuvant 65, which is metabolizable, some of the concern regarding mineral oil adjuvants has been dispelled, but Adjuvant 65 still contains Arlacel A. The advantages - enhanced antibody response, longer persistence of antibody, broadened antibody response, spacing of antigen requirements, and diminution of early reactions - were again reviewed.

Recent data were presented that suggested that the intramuscular injection of influenza vaccine (A<sub>2</sub>/Aichi 2/68 - 400CCA) in this adjuvant was associated with an enhanced stimulation of anti-influenzal antibodies in nasal secretions (presumably IgA). The potential for oncogenicity was suggested from a series of experiments in Swiss Webster strain mice in which Arlacel A was associated with a significantly higher incidence of tumors in male mice than in control male mice. Increased tumor incidence was also observed when known carcinogens were suspended in Arlacel A than when other excipients were used. Contrasting experiments by another group, also using male Swiss Webster strain mice, revealed a higher tumor rate in mice injected with alum-adsorbed diphtheria-tetanus-pertussis vaccine than with Arlacel A. The tumor rate with Arlacel A approximated that in control mice inoculated with aqueous influenza vaccine or isotonic saline solution. Long-term follow-up of humans who had received mineral oil adjuvant vaccines has shown no evidence of oncogenesis.

Thus, the advantages of adjuvants must be weighed against conflicting animal data and apparent safety with some antigens in man. Further review of the data would seem necessary, and the case for or against Adjuvant 65 should not be closed.

#### Quality and safety control

For obvious reasons a satisfactory control of vaccine quality is of the utmost importance. Generally the emphasis is on safety, but potency is equally essential. Efforts should be made to maintain consistency in production - by the use of seed lots, for example. To exclude extraneous agents from tissue cultures as far as possible, the establishment of controlled animal donor colonies must be encouraged. However, even greater safety might be achieved by using strictly monitored diploid cell lines of human or animal origin.

Potency should be assayed with the aid of dose-response curves in comparison with standard reference preparations. Measurements should be made in the region of maximum slope of the curve. Since suitable challenge tests are generally not available, it is important that efficacy be controlled

in clinical trials and by continuous surveillance.

The principles for evaluating vaccine safety and efficacy formulated for the 1954 trial of inactivated polio vaccine in the United States have been further developed as new experience has been gained. It was stressed that the reporting system must permit immediate identification of untoward events, and that the reliability of the results is determined by the quality of the primary data.

Long-term evaluation will necessitate more sophisticated methods. The introduction of mathematical models seems to afford new opportunities and to permit the development of rational monitoring methods. For these purposes automatic data processing and direct linkage systems will be needed. For a complete surveillance, three sets of records are essential: those of the manufacturer, the vaccinator, and the vaccinee.

The approval and licensing of vaccines should be based on (1) complete information on the biological properties of the agent used, (2) records of animal studies of the agent and of vaccines prepared therefrom, and (3) records of clinical trials. Requirements for production and control must be formulated at an early stage. The characteristics to be assessed include the safety, purity, potency, and stability of the product under the conditions of actual use in the field. It is important that agencies concerned with decisions in these matters be provided with resources for independent research.

All vaccines carry potential hazards. What to do with persons who may suffer damages in connection with recommended or enforced immunization is a problem that must be solved. In Europe, some governments have recognized the problem and others are beginning to do so to the extent that they will probably assume the responsibility for indemnifying such persons.

#### Vaccination programs and their implementation

The development of new and the improvement of existing vaccines is a responsibility of laboratory scientists and epidemiologists. However, the practical application of a new or improved product in a formal vaccination program is the responsibility of a health administrator, who

is everywhere faced with a shortage of funds and who has to compete for his share.

Under these circumstances, vaccination programs must be appropriately planned to meet the needs and resources of the area and subjected to continual review of effectiveness. More and more it will be necessary to provide the greatest benefit for the greatest number of people at the most reasonable cost. Recent developments in the combining and simultaneous administration of vaccines and the use of jet injectors are therefore very timely and should be encouraged. Increasingly, the more conventional epidemiological statistical techniques of the health planner are being supplemented by the techniques of the health economist. Cost-benefit analysis is a useful tool that makes possible the selection of appropriate immunization or alternative programs according to the resources required and the benefits provided; it also gives an administrator the opportunity to improve programs so as to achieve better results for less cost. This form of analysis should be a continuous process or, at least, should be used periodically to adjust programs to existing local conditions. The techniques available range from simple nomograms to sophisticated mathematical models.

In view of the particular problems in many of the heavily populated developing countries, especially where distances are considerable, the procedures being adopted in the Republic of Cameroon will be followed with interest. There, as recommended by the Organization for the Coordination of the Fight Against Endemic Diseases in Central Africa (OCEAC), priority is given to protection against measles, smallpox, yellow fever, and tuberculosis by means of special teams that travel through the country every two years and vaccinate various age groups from six months of age upwards, using combined products and simultaneous administration of vaccines.

#### Local, national, and international involvement

In the implementation of immunization programs it is essential to take into consideration the human sociological and cultural factors involved. To reach the "hard-to-reach" population groups, it is necessary to realize

their physical and emotional needs and to demonstrate to them in understandable ways that the benefits of immunization are worth the often great effort it requires of them. Services must be made as convenient as possible. Facilities should be attractive and recipients must be treated with dignity, respect, and compassion. Health education approaches must be made in the local idiom and be directed toward encouraging a climate of acceptance.

Legal compulsion is of limited value; relying too much on force leads to resentment and apathy. The participation and support of local community leaders, village officials, and medical practitioners from the area greatly facilitates community response. In developing countries, the provision of nutritional supplements, such as powdered milk for infants, provides an inducement and prevents weight loss in babies on marginal diets.

The effect of immunization on the explosive growth of population has been substantial, although it is but a small factor in the total population increase. Present methods of contraception and post-conception control are now sufficient to bring the birth rate into balance with the death rate, although even when this has been achieved there will still be a large further increase in total population because of the tremendous number of young persons in the world. The basic problem is to persuade people to practice family limitation, and this can only be achieved when they perceive that their babies have a reasonable chance of survival. Any program of family planning and population control must therefore be undertaken in close collaboration with effective programs of maternal and child health. The birth rate and the death rate must be brought into a balance at a low level by a true partnership effort.

Cost-benefit studies show that the gains from immunization procedures are among the greatest to be achieved by existing public health procedures. Continued support for research is vital to continued progress.

#### The present and future of immunization

In recent years great progress has been made in the control of infectious diseases, particularly certain viral infections. This is



especially true in developed countries, but notable success has been achieved also in developing countries.

While no disease has yet been eradicated throughout the world, the indigenous dissemination of certain viruses, such as smallpox, has been stopped completely in large areas. "Area eradication" is coming close for polio also, in many areas, and should be attainable for measles. The same concept may be applicable to other infections, provided that they are caused by viruses that are obligate human parasites, that vaccination is effective not only against the clinical manifestations but also against the spread of the agent, and that the public considers the effort worthwhile.

In contrast to these successes in the control of acute infectious diseases, the control of chronic degenerative diseases such as those caused by "slow viruses" and hypothetical human cancer viruses still remains on the horizon. Both complex immunological mechanisms, as yet only poorly understood, and defective intracellular virus replication may play an important role in the pathogenesis of slow virus disease such as subacute sclerosing panencephalitis (SSPE). Other chronic infections such as kuru and the Creutzfeldt-Jakob type of presenile dementia, for which the etiological viruses have been isolated, produce no recognizable immune response in the host, and it has thus far been impossible to induce immune responses in susceptible animal hosts to virulent scrapie viruses.

Although no single human cancer virus has yet been definitely recognized, the possibility is great that several different viruses may be responsible for cancers in man. The control of virus-induced tumors in man will probably require approaches differing from those employed with conventional virus vaccines, including perhaps immunization against virus-induced transplantation antigens, interference with the enzyme polymerase, the use of gene repressors, or interference with natural derepressors. Recent studies, however, provide optimism for the prevention of at least some cancers in man.

In recent years considerable effort has been made to develop effective chemotherapeutic agents for the therapy and prevention of viral illness. Herpetic infections, particularly keratitis, have been treated

successfully with iododeoxyuridine (IDU). Thiosemicarbazone has proved effective in the treatment of eczema vaccinatum and vaccinia gangrenosum. The present antiviral chemotherapeutics are not well suited for long-term protection, but some - such as thiosemicarbazone with smallpox and amantadine with influenza - have proved of value in the protection of susceptibles during periods of high risk.

Chemical compounds that induce the release of autologous interferon would seem to hold great promise, especially for the control of upper respiratory and other viral infections caused by a multiplicity of sero-specific strains that make the production of vaccine impossible or impractical.

It was recommended that collaborative studies be initiated to assess the therapeutic efficacy of antiviral drugs, particularly in instances where cases may be sporadic in occurrence, such as IDU in herpes simplex encephalitis.

In summary, during this long and full week, the Conference has provided an opportunity to discuss many important areas that, let us hope, will aid in determining the course toward our ultimate objective - disease control and the establishment and maintenance of health.

PAHO/WHO INTERNATIONAL CONFERENCE ON  
THE APPLICATION OF VACCINES AGAINST VIRAL, RICKETTSIAL,  
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