DESIGN FOR IMMUNIZATION PROGRAMS IN THE DEVELOPING COUNTRIES • Report of Committee 2

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IX. Summarization

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Introduction

In areas, population groups, or countries where health manpower and material resources are limited, the communicable diseases normally constitute a significant problem and immunization programs are of special importance. Effective, alternative approaches for the prevention of most diseases are not at the moment available or economically possible—for example, the development of safe water supply systems to prevent typhoid. Health personnel and facilities are limited, which necessarily restricts what can be done in the isolation and treatment of patients, procedures that can be of considerable importance in the control of many diseases.

Although programs of immunization represent, by and large, one of the most productive public health investments any country can make to improve the health of its people, in the developing countries such programs have, to date, remained comparatively limited in scope and have generally been restricted to a few antigens. There are many reasons for this, but a few of the major contributing factors should be noted, since they have a bearing on the design of effective programs.

Important factors limiting the development of immunization programs

Relative development of health services

In the developing countries, physicians, and other health personnel are inadequate in number and are often taxed to meet minimum demands of curative services; health centers are widely scattered.

Immunization programs like those in the developed countries, which depend on individuals attending health centers, have generally produced disappointing results. Vaccination coverage, though sometimes satisfactory in the immediate area of a health center, has been found to decline sharply in persons living no more than two to three miles away (*11, 12, 13*).

Facilities for the refrigerated storage of vaccine are usually limited, which makes it difficult to conduct effective programs that employ such thermolabile vaccines as measles, yellow fever, and poliomyelitis.

Costs of vaccines and their application

Vaccine cost is a major concern. Since, in many countries, the expenditure for *all* health programs does not exceed $2.00 per person per year (*2*), it is apparent that, however effective a vaccine, it must be comparatively inexpensive if it is to be widely employed. In general, when vaccine costs more than $.10 per dose, it is beyond the financial resources of most developing countries. Even the less expensive vaccines may be impossible to purchase because of limitations of budget and foreign exchange.

Since vaccine costs a great deal more when packaged in, for example, vials of 2 or 5 doses than in vials of 25 doses or more, many health administrators, in an effort to economize, have purchased the larger containers for use in health centers. Frequently only a few persons are

vaccinated each day in the centers, and, with unsatisfactory facilities for refrigeration, the vaccine deteriorates; the result is that many are vaccinated with ineffective vaccine.

Vaccine quality has been a special problem. Most countries are not able to establish competent independent national testing centers. Many vaccines produced nationally and some that are imported are known to be substandard. On many occasions, considerable expense has been incurred in vaccination programs in which the vaccine used has been impotent.

The cost of instruments to administer vaccines may also be a problem, particularly as buying them usually requires foreign exchange. The cost of disposable syringes and satisfactory, durable jet injectors is so great as to preclude their use in most developing countries. Continuing maintenance of the jet injectors has proved difficult. Single-dose syringes are similarly a luxury that most cannot afford. Multiple-dose syringes, although undesirable because of the intrinsic risk of possible transmission of serum hepatitis, are the only economically practicable instruments for subcutaneous or intramuscular administration of vaccines that are available at this time, although it is to be hoped that less expensive and more durable jet injectors will be developed.

Other difficulties

Transport, whether for the distribution of vaccine or of vaccinators or of vaccinees, is frequently a problem because of lack of vehicles and/or fuel and satisfactory roads. Illiteracy is prevalent and it is difficult to convince the population of the need for vaccination, at least by conventional methods of health education as practiced in the developed countries. The possibilities for publicity through radio and other conventional news media may be more limited and the information provided may not reach beyond the already educated and persuaded. Thus, many techniques and approaches to immunization that are effective in the more developed countries are less applicable to the developing countries.

Design of immunization programs for developing countries

The decision as to which vaccines should be administered, to whom, and according to what schedule must be considered in relation to a number of factors, including the relative importance of the disease; the effectiveness and cost of available vaccines; possibilities for the financing of vaccine purchase or production; resources for testing vaccines to assure purity and potency; the feasibility of vaccine administration by various alternative approaches, such as in health centers, in mass campaigns, or by individual vaccinators; methods for supervision and assessment of programs; the availability of central and peripheral refrigerated storage facilities; and the costs and financing of instruments to administer vaccines.

Selection of vaccines for immunization programs

Taking into account the various factors mentioned above, the available vaccines may be considered in four general categories. The rationale for the assignment of vaccines to each of these groups is set forth in Annex I.

1. Vaccines recommended for general use in developing countries:
   - Smallpox
   - BCG
   - Diphtheria, pertussis, tetanus, typhoid
   - Measles (rubeola; assuming substantial reductions in cost or provision through international assistance).
2. Vaccines recommended for general use in some countries or areas:
   - Poliomyelitis
   - Yellow fever
3. Vaccines *not* recommended for routine use in the developing countries:
   - Mumps
   - Rubella (German measles)
   - Influenza and other respirovirus vaccines
   - Cholera
5. Vaccines in the developmental stage that may in the future be applicable for use among populations at special risk:
   - Arboviruses
   - Rickettsiae
   - Trachoma
   - Meningococci
   - Shigella

Procurement of vaccine

Vaccine cost is a particularly important consideration in the developing countries, a con-

sideration frequently complicated by restrictions in the availability of foreign exchange. These problems may be overcome in part if vaccines can be inexpensively produced locally or, better, on some sort of cooperative regional basis. The production of bacterial vaccines (diphtheria, pertussis, tetanus, typhoid) involves a less complex technology than live virus vaccines such as poliomyelitis and measles. They could be produced relatively inexpensively in moderately well-equipped and staffed laboratories in developing countries. Smallpox vaccine is now produced in several developing countries and is available to most others through donations made to WHO or through bilateral assistance; BCG vaccine is being supplied to many countries through UNICEF. Yellow fever vaccine is required for general use by comparatively few countries, and regional production centers in the developing countries now supply most of the requirements at comparatively low cost.

The production of poliomyelitis and measles vaccines is technically far more difficult and is not practicable in the developing countries, except in a few special cases. To reduce costs and foreign exchange requirements, a very few large regional production centers might be considered. Alternatively, both of these vaccines and others as well might be purchased in bulk from major producers and packaged locally.

Quality control of vaccine

The effectiveness of any immunization program depends first and foremost on the quality of the vaccines used. Thus, provision must be made for routine testing of all vaccines at a competent independent national testing center or at an international center. The importance of quality control is illustrated by the fact that, at the beginning of the global smallpox eradication program, not more than 10 to 15 per cent of the vaccine in use in endemic countries met WHO recommended standards. The present status with respect to other vaccines in routine use in developing countries may not be different.

Plans and methods for the development of national biological control laboratories were recently described by a WHO Expert Committee (*23*).

Packaging of vaccine

It is commonly believed that supplying vaccine in single-dose containers for use in health centers, hospitals, and other institutions might sharply reduce vaccine waste. Although this might in fact occur, it is considerably costlier to prepare vaccine in, for example, 1-, 2-, or 5-dose containers than in 10-, 20-, or 100-dose containers. This fact alone recommends the design of immunization programs that permit the use of larger multiple-dose containers of vaccine.

Administration of vaccine

With the exception of smallpox vaccine, which is administered by the bifurcated needle, and polio vaccine, which is administered by mouth, all vaccines in routine use are administered by the syringe and needle or the jet injector. The currently available jet injectors are not fully satisfactory—they are expensive and difficult to maintain and repair, and several are not sufficiently sturdy for routine field use. To use them efficiently, large numbers of persons must be immunized each day. Single-dose glass or plastic disposable syringes are usually employed in the developed countries to ensure particularly that the virus of serum hepatitis is not by chance transmitted from one to the next. While this approach is technically sound, its cost has precluded its use in many developing countries. Until a more effective and inexpensive means of vaccine administration can be found, the use of 5- or 10-dose glass or nylon syringes with separate needles for each recipient would seem at this point to be the only economically practical means of vaccine administration in many developing countries.

Possible schedules of immunization

In the developed countries, model vaccination schedules call for vaccination on as many as 10 to 15 different occasions between birth and 5 or 10 years. This is not reasonable in the developing countries, where visits to health centers are sporadic and touring vaccinators or vaccination teams may reach villages or towns not more than once in one or two years. Simultaneous administration of several antigens may help to reduce the number of visits required. A considerable

number of studies have now been done that indicate no impairment in vaccine efficacy and no increased risk of adverse effects when a number of different inactivated and live antigens are administered simultaneously.

Reduction in the usually recommended number of injections of the killed antigens, such as diphtheria, pertussis, tetanus, and typhoid, constitutes a second approach that may permit a reduction in the number of required visits. In the developed countries, 4, 5, or 6 injections of the inactivated antigens are usually recommended. However, each additional inoculation after the second or third improves only fractionally the level of protection. Where the cost of vaccine and vaccine administration is a minor consideration, such additional inoculations may be justified. In the developing countries, however, the cost of each additional inoculation must be carefully weighed in terms of the additional protection conferred.

Finally, the inactivated vaccines (diphtheria, pertussis, tetanus, typhoid) may be combined in a single preparation, thus reducing the costs of administration and of instruments (5). In most immunization programs, this single combined product could be administered to all children. However, other mixtures of vaccines, such as smallpox-measles, have proved to be of limited value in routine programs. In a program administering measles and smallpox vaccines, for example, smallpox vaccine as a separate preparation is needed for vaccinating those younger than nine months and older than four years. Having the mixture available adds very little since, in any case, two preparations are required and the added cost of preparation of the combined vaccine is not justified by other savings. Similar problems affect other mixtures of live virus preparations; in fact, a mixture of yellow fever and smallpox vaccines results in a lower proportion of seroconversions to the yellow fever vaccine (*14, 15*), although administration at the same time but at different sites produces a satisfactory response.

A virtually infinite number of vaccination schedules could be prepared, each with its relative merits and demerits. Taking into account the various factors bearing on the optimum time for vaccination, the relative risks of the diseases at various ages (Annex II), and the costs and benefits of multiple inoculations, three schedules are set forth below as illustrative of simplifications that might be achieved.

In Schedule A, quite acceptable levels of protection could be afforded against the seven diseases in Group I in four immunization sessions, one of which is timed to coincide with school entry.

Schedule B might be considered for a program of immunization in which mobile vaccination teams were able to visit each area only once in two years. It is recognized that protection against diphtheria, pertussis, and tetanus would not approach satisfactory levels until after the second session and that protection against poliomyelitis and, in some, against measles would not be optimum. However, such a program would in fact confer substantial protection to a considerable proportion of the children.

For countries where smallpox is not endemic and thus where early vaccination is less critical, a simplified program, Schedule C, is suggested. The BCG vaccination scar could be used as one "marker" to indicate that a group of antigens had been given, and the smallpox vaccination scar to indicate that the second group of antigens had been administered. The scars could serve effectively as vaccination certificates for administrative and assessment purposes. As in Schedule B, the protection afforded is not optimum, although a very substantial reduction in the incidence of each of the diseases might be anticipated.

Prevention of neonatal tetanus

Because of the importance of neonatal tetanus in all developing countries and the fact that it is averted if the mother has been protected by at least two injections of tetanus toxoid, special provisions should be made for administering tetanus toxoid to adolescent girls and women of childbearing age.

Place of vaccination

Although vaccination in the developed countries is usually performed in a clinic or physician's office, in the developing countries satisfactory coverage is impossible if vaccination is restricted to existing health installations. As has been shown in several studies, vaccination cov-

SCHEDULE A

Vaccines	1–3 months	4–8 months	9–12 months	5–6 years
Group I	DPT[1]-typhoid Smallpox[2] BCG[2]	DPT[1]-typhoid	Measles	DPT[1]-typhoid Smallpox
Group II	Polio[3]	Polio[3]	Polio[3] Yellow fever	

SCHEDULE B

Vaccines	0–24 months	2–3 years	4–5 years
Group I	DPT[1]-typhoid Smallpox[2] BCG[2] Measles (if 9 months or older)	DPT[1]-typhoid	DPT[1]-typhoid Smallpox
Group II	Polio[3] Yellow fever (if 9 months or older)	Polio[3]	

SCHEDULE C

Vaccines	3–9 months	9 months - 2 years
Group I	DPT[1]-typhoid BCG (marker)	DPT[1]-typhoid Smallpox (marker) Measles
Group II	Polio[3]	Polio[3] Yellow fever

[1] Diphtheria-pertussis-tetanus, with adjuvant.
[2] May be given from birth onward.
[3] Oral trivalent.

erage rapidly diminished among persons living more than 2 to 3 miles from a vaccination center. Even those health units which have been established frequently do not have refrigeration and thus cannot serve as immunization centers for other than very thermostable vaccines. Further, even in developed countries, experience has shown that the immunization coverage of children in lower socioeconomic levels is generally inadequate unless immunization programs are extended into the communities themselves.

In the developing countries, a dual approach to vaccination would seem most practicable: (1) vaccination in existing health centers that are equipped for it; and (2) vaccination by special vaccinators or vaccination teams moving from village to village, performing vaccinations at collecting points or on a house-to-house basis. Such an approach serves to strengthen the role and importance of the health centers for their over-all programs of health care while ensuring adequate coverage by means of the special vaccination units, which might perhaps use the health centers as bases.

Health centers that serve as vaccination centers should be equipped with the necessary refrigeration and the staff should be properly trained in vaccination technique. Since some vaccines (BCG, smallpox, measles, yellow fever) are freeze-dried in multiple-dose containers that must be discarded at the end of the day on which they are reconstituted, vaccination programs should be designed to ensure that at least 25 to 50 persons (depending on the size of the vaccine container) are available for vaccination in order to avoid waste. In some areas this has been achieved by designating one day in the week as "vaccination day." Attendance may sometimes be improved by offering powdered milk or other foods at this time.

The schedules of the vaccinators or vaccina-

tion teams must similarly be arranged and proper supervision be provided to ensure that large amounts of vaccine are not wasted through failure to vaccinate a sufficient number of persons each day. Experience in smallpox and BCG vaccination programs has shown that upwards of 100 persons per day can readily be vaccinated daily by a single vaccinator even under very difficult circumstances of travel and terrain. Vaccination may sometimes be conducted at "collecting points" in villages; in other circumstances, house-to-house vaccination has produced better results. When thermolabile vaccines are employed, particularly careful planning is required in regard to refrigeration to ensure that the vaccine is still potent when it is administered.

Recording and registration of vaccinees

Experience has shown that most immunization programs, at their inception, have endeavored to keep far too complex and elaborate records, which almost inevitably have had to be abandoned as serving no useful purpose. Efforts to maintain complete registers of eligible children in a community have almost invariably failed except in isolated instances when very small numbers have been involved.

For programs in which only BCG or smallpox vaccine is administered, the vaccination scar provides an indication of vaccination status. In the case of BCG, however, this is subject to some error because inactivated BCG vaccine may induce the development of a small scar. Simple survey methods have been developed that make possible, with minimal effort, an estimate of the immunity level of a village, a city, or a very large area.

For other vaccines, the problem is more difficult. The most workable system has involved a simple tabulation, by age, of the numbers vaccinated by vaccinators and at health centers and, at the same time, the issuance of a simple vaccination card which is retained by the vaccinee. An immediate report is thus available as to the numbers of vaccinations being performed; coverage is determined by a sample survey in which vaccination cards are checked. Although it has often been assumed that the vaccination cards would be easily lost, experience in several African and Asian countries has shown that a large proportion of the vaccinees keep their cards. Instead of a card, a metal disc to be hung around the neck has been proposed by some.

Program execution and assessment

A very great deal could be and has been written regarding various administrative aspects of importance to the execution of immunization programs. To discuss in detail the various approaches and contingencies in terms of different health service systems, resources, and objectives is beyond the scope of these recommendations. Reference may be made to the papers of a number of authors who have discussed this subject at some length (*8, 10, 16, 21, 22*).

Certain principles in the development of an immunization program should, however, be noted. The need for detailed planning prior to its inception cannot be overemphasized; objectives must be established, specific time targets set, the methodology of execution determined, lines of authority clearly demarcated, logistics of supply and transport elaborated, personnel recruited and trained, mechanisms for publicity and public education decided upon, and so on.

Finally, methods for assessing the success of the program must be decided upon and incorporated from the very beginning. Two general methods of assessment have proved most valuable: (1) appraisal by independent assessment teams of the extent of vaccination coverage and (2) surveillance for disease occurrence. In the past, most programs have appraised the success of their efforts by comparing the number vaccinated with the population in the area. Though this approach may be useful, it has often proved unsatisfactory and sometimes misleading. Health centers and vaccinators alike have frequently exaggerated or grossly overestimated the numbers of vaccinations performed; census data have frequently proved to be highly unreliable. This problem may be countered by having trained independent assessment teams conduct regular sample surveys of the population to determine the extent of coverage. Such teams serve most effectively to provide the necessary quality control for a program. Experience has shown, in fact, that vaccinators and health centers alike are more productive when they know that such a continuing assessment is being carried out.

Since the objective of an immunization program is to control disease incidence, the ultimate test of the program is whether or not a decrease occurs in the incidence of the disease for which vaccination is being given. Surprisingly, this—the most important and helpful component in the evaluation of immunization programs—has been the most neglected. For example, the persistence of disease in one area or segment of the population suggests the need for more intensive efforts in this area; the occurrence of cases of the disease in supposedly vaccinated persons raises questions as to the efficacy of the vaccine and/or technique of administration. By closely following disease occurrence, the over-all program may be monitored and appropriate adjustments made as required.

ANNEX 1

VACCINE CATEGORIES: RATIONALE

Vaccines recommended for general use in developing countries

Smallpox
BCG
Diphtheria, pertussis, tetanus, typhoid (preferably as a combined vaccine)
Measles (rubeola; assuming substantial reductions in cost or provision through international assistance)

For each of the diseases noted, vaccination is, in general, the preventive procedure of choice, taking into account the economic costs of possible alternative preventive measures such as water supply development in the prevention of typhoid or case-finding and treatment in the instance of tuberculosis.

Tuberculosis, tetanus, pertussis, and measles are generally acknowledged to be significant public health problems of real concern in all developing countries. Diphtheria is a problem in urban areas but is less serious in rural areas, perhaps because of the frequency with which immunity develops as a result of cutaneous infection. Because diphtheria toxoid can be readily and inexpensively combined with pertussis and typhoid vaccines and tetanus toxoid and administered at essentially no additional cost, diphtheria toxoid is included in the "recommended" group. The extent and severity of typhoid infections is incompletely documented, although in most areas where detailed studies of enteric infections have been conducted, it has been found to be a significant problem. Lastly, the ever-present threat of smallpox has, for a century or more, made smallpox vaccination a primary component of public health programs throughout the world.

Each of the vaccines induces effective and durable protection in a high proportion of recipients after not more than two or three injections. Two injections of diphtheria or tetanus toxoid, administered at intervals of two months or more, will produce satisfactory immunity in 80 per cent or more of recipients and a third injection will increase the efficacy to more than 90 per cent. Effective protection against the disease itself may extend for a decade or more and protection against a fatal outcome for an even longer period. Pertussis vaccine, although usually regarded as a comparatively poor antigen, appears to induce a significant "herd immunity" when used on a community-wide basis even when fewer than the "optimum" number of doses are administered (*17, 20*).

In studies in endemic areas, acetone-killed and dried typhoid vaccines have been found to provide protection for more than 7 years to more than 90 per cent after two injections and considerable protection even after a single injection. Typhoid vaccine prepared by other means has been almost as effective (*9*). BCG vaccine is generally acknowledged to afford substantial and durable protection, particularly against the disseminated miliary and meningeal forms of the disease. Primary smallpox vaccination provides protection to more than 95 per cent for more than 5 years; a single revaccination is believed to extend the duration of protection for at least two decades, with only gradually waning immunity thereafter. Measles vaccine provides very long-term if not actually lifetime immunity.

Except for measles vaccine, all of these vaccines are comparatively stable and their costs are comparatively low. Most could be produced in reasonably well-equipped national laboratories or may be obtained through international donation (BCG and smallpox vaccines, for example).

Measles vaccine constitutes a special problem. While this disease is recognized as one of the

most serious health problems in infants and young children in all developing countries, the vaccine has two major drawbacks. It is much more thermolabile and light-sensitive than the other vaccines in this recommended group and its cost is probably from 10 to 100 times higher than that of any of the others. The timing of immunization constitutes an additional problem. Because of the presence of maternal antibody, the vaccine is ineffective if administered before the sixth month and has somewhat diminished efficacy if administered before the ninth. Since measles generally afflicts children at an earlier age in the developing countries, it must be administered before the third year of life if it is to be effective. The problem is to execute an immunization program that assures vaccination in the comparatively narrow span between 6 or 9 months and 24 months of age.

The relative expense of a measles program is illustrated by the experience of one African country (*19*) where a highly effective measles vaccination program was conducted at the same time as a smallpox program. Three fourths of the *additional* cost in the measles vaccination program was for the vaccine itself, which at that time cost 44 cents per dose, not appreciably more than at present. The cost to prevent one measles case was calculated to be $3.69; to prevent one measles death, $73.85.

To reduce costs, some have advocated the administration of measles vaccine diluted two- or threefold and have shown that a high proportion of those given the diluted vaccine exhibit satisfactory serological responses. Unfortunately, this is an unsatisfactory and hazardous approach. It is noted that standards for all live virus vaccines require that they contain substantially more than the minimum infective virus titer. Since all such vaccines lose titer in the process of normal storage and handling, an excess of virus is normally incorporated to assure that at the time of immunization the vaccine titer is sufficient to induce immunity. Additionally, diluted measles vaccine will indu e a significantly lower proportion of seroconversions in children under one year of age. In most developing countries, measles is a particularly serious problem in this age group and thus it is this group specifically that is of priority concern. Under optimum study conditions and in children more than one year of age, dilution of measles vaccine is satisfactory; under conditions of routine field use, it is a hazardous procedure, particularly with the currently available thermolabile and light-sensitive vaccines.

Until the costs of measles vaccine are substantially reduced, most developing countries cannot consider its routine use without international assistance to defray costs for vaccine and special refrigeration facilities.

Vaccines recommended for general use in some countries or areas

Poliomyelitis
Yellow fever

Yellow fever vaccine. The considerable threat posed by yellow fever has generally recommended the use of this vaccine in threatened populations. While the vaccine is highly efficacious and affords very long-term protection after a single injection, it has the disadvantage of being very thermolabile, relatively expensive, and impracticable to produce in most countries. The risk of the disease to particular populations during specific periods generally overrides other considerations and dictates the general use of this vaccine.

Poliomyelitis vaccine. In recent years poliomyelitis has become an increasingly serious problem in a number of the developing countries, although far more complete reporting is required to assess fully the magnitude and extent of the problem. Naturally acquired subclinical infection used to protect most children at an early age, but today more cases of paralytic disease are being observed in many of the developing countries. The situation, however, appears to differ from one country to another.

The variable efficacy of the vaccine when used in tropical countries constitutes an as yet unresolved problem. Interfering enteroviruses not infrequently prevent the necessary growth of the vaccine virus in the intestine. This makes it difficult at present to appraise the probable benefits of a vaccination program.

While some developing countries will wish to include polio vaccination in routine programs of immunization, some may wish to restrict vaccination to urban areas, where the costs of administration can be held to a minimum, and

to provide vaccination to other areas only when outbreaks occur. In other countries, the problem may be so slight as to make routine vaccination unnecessary.

Vaccines not recommended for routine use in the developing countries

Mumps
Rubella
Cholera
Influenza and other respirovirus vaccines

Mumps vaccine. Mumps is normally a mild disease with only rare and usually not severe complications; the vaccine is very expensive. Even if it were available at very low cost, the costs of administration of this very heat-labile vaccine would preclude its routine use in the developing countries.

Rubella vaccine. Although a small number of rubella-induced malformations undoubtedly occur in all countries, the incidence even in the developed countries is comparatively low. The use of this expensive, heat-labile vaccine is certainly not warranted.

Influenza and other available respirovirus vaccines. While extensive morbidity occurs in all countries as a result of infection with influenza and other respiroviruses, the available vaccines confer only very transient, partial protection. None can be recommended at this time for immunization programs in the developing countries.

Cholera vaccine. While cholera is a serious disease in a number of endemic areas, the currently available vaccines are regrettably unsatisfactory. One injection of vaccine provides, at best, equivocal protection; two injections, given a month or so apart, may protect perhaps 50 to 55 per cent for a period of 3 to 6 months (*1*, 7). Repeat inoculations every 6 months are required to assure continuing protection. The costs of conducting repeat programs of mass vaccination every 6 months are far too great for most countries. It is believed that comparable expenditures diverted to the treatment and isolation of patients and contacts (*18*) and to the control of waste disposal and water supplies (*6*), where possible, would produce more satisfactory results at far less cost.

Vaccines in the developmental stage that may, in the future, be applicable for general use among populations at special risk

Arboviruses
Rickettsiae
Trachoma
Shigella
Meningococci

All these vaccines are considered to be in the "developmental" stage, with as yet uncertain or unsatisfactory levels of protection and durations of immunity. None can be recommended for routine use at this time. However, the primary diseases against which they provide protection constitute major health problems in some areas. When these vaccines have been further developed, their possible use would have to be weighed in regard to the cost of the vaccine, the duration and degree of protection afforded, the extent and severity of the disease problem itself, and the problems of administration to large populations.

ANNEX II

VACCINATION SCHEDULES: PERTINENT CONSIDERATIONS

Smallpox

Vaccination from the time of birth has been shown to be safe and effective. Revaccination at about the time of school entry should provide reasonably complete protection for several decades.

BCG

Vaccination from the time of birth (without antecedent tuberculin testing) has been shown to be safe and effective.

Diphtheria-pertussis-tetanus-typhoid

A vaccine combining these four antigens has been shown to be effective. An adjuvant preparation induces more effective antibody responses. Immunization before one month of age may be less effective in the instance of diphtheria and pertussis vaccines because of maternal immunity, and immunization at birth is therefore not recommended. The most effective antibody responses are induced if 2 to 3 months or more are allowed to elapse between inoculations. However long the interval between inoculations, second and subsequent inoculations produce a booster response. As few as two inoculations spaced 2 or more months apart is believed to provide protection against diphtheria and tetanus to more than 80 per cent of vaccinees for periods of more than 5 years. A third inoculation should provide 90 per cent or more protection for at least 10 years. In respect to typhoid, the vaccine has been found to confer protection to 90 per cent for 7 years and perhaps longer after two inoculations (9).

Polio

Vaccine given before one week of age is frequently ineffective in breastfed infants. If the vaccine is to be used, at least two and preferably three feedings, at least one month apart, are recommended. No statement about the efficacy of the vaccine can be made, because in the developing countries other viruses in the intestinal tract frequently interfere with the growth of the poliovirus. As poliomyelitis in developing countries is a disease of children under 4 to 5 years, the feeding of vaccine to older children is *not* recommended.

Measles

A single injection of vaccine confers long-lasting, perhaps lifetime immunity. Diluting the vaccine before administration, although recommended by some, is not advised since the vaccine is very thermolabile; the excess titer in the vaccine as originally prepared only serves to ensure that the requisite minimum titer is present in the vaccine at the time of administration. Vaccine given before 9 months of age is ineffective because of interference by maternal antibody. The administration of vaccine to those older than 4 to 5 years is not recommended, since in most areas natural infection rarely occurs beyond this age.

Yellow fever

A single injection confers immunity for at least 10 to 20 years, perhaps longer. Vaccine may be administered to those 9 months of age or older. Maternal antibody may interfere with a successful response if the vaccine is administered at an earlier age.

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