WHO/EPI/GEN/86/7 REV 1

EXPANDED

PROGRAMME

ON IMMUNIZATION

Immunization Policy

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1. INTRODUCTION

This document is intended as a general review of WHO/EPI immunization policy and therefore immunizations in infants under one year of age will be stressed. Several excellent papers have reviewed EPI vaccines and schedules (1-5) and, although some repetition is unavoidable, this paper will concentrate on positions and topics that are new, have changed or are considered controversial.

No immunization schedule is ideal. The EPI recommends that each country determine its own schedule to best fit its own needs. In developing countries, diseases included within the EPI strike early in life, and it is especially important to protect children through immunization as early as possible. A schedule which will accomplish this, and which the EPI recommends for national consideration, is shown in table 1.

2. DELIVERY OF IMMUNIZATION SERVICES

The immunization schedule shown in table 1 entails five contacts of the infant and his/her mother with the facility providing these services. This schedule allows the health services to provide early protection of the child against vaccine preventable diseases (table 2). No child need be denied polio or BCG immunization because it is too young, and DPT can be provided anytime after six weeks of life. Contacts with the health services which are made for other reasons should be exploited for the purposes of immunization.

The ideal method of health services delivery, given unlimited resources, would be to have a health center offering curative, rehabilitative and preventive services on a daily basis located within easy reach of each family . Resources are, of course, limited, resulting in a number of departures from the ideal. Services at fixed facilities may not be comprehensive, and may be offered on a weekly or monthly basis rather than on a daily basis. In some extreme situations, immunization services may be delivered alone using mobile teams which visit only twice a year.

While recognizing the desirability of providing daily immunization services from fixed facilities, programme managers must adapt the delivery of services to the capacities of the existing health infrastructures while at the same time working to increase those capacities. Where services can be offered as frequently as monthly, the "five contact" immunization schedule cited above can still be used to provide early protection.

Where services are only available less frequently, compromises are required and it may be necessary to make local modifications such as increasing the target age group. The schedules shown in tables 3 and 4 are examples of adaptation for outreach activities where the interval between contact with eligibles is greater than 4 weeks. These schedules do not provide optimal protection, but do provide some protection to infants in areas where target populations cannot be reached more frequently. The major problem with these schedules is that some children may acquire disease before they are adequately immunized.

Other 6 month schedules have been proposed. One is currently being evaluated in West Africa which incorporates a quadrivalent vaccine, DTP-P (Diphtheria, pertussis, tetanus and killed poliomyelitis vaccine). A first dose of DTP-P with BCG is given to infants from 3 to 8 months of age and a second dose of

TABLE 1. EPI antigens, doses and intervals.

ANTIGEN	NUMBER OF DOSES	INTERVALS
BCG	1	At birth
OPV	4	At birth and with each DPT
DPT	3	At 6, 10, and 14 weeks
Measles	1	At first contact after

TABLE 2. Timing of the five contacts.

CONTACT	AGE OF CHILD	VACCINES
1	At birth	BCG and OPV
2	6 weeks	DPT and OPV
3	10 weeks	DPT and OPV
4	14 weeks	DPT and OPV
5	9 months	Measles

DTP-P along with measles vaccine is given to children from 9 to 14 months of age.

Six month schedules have the problem of inadequate protection against pertussis and measles during the first year of life. These schedules should be used only in the most remote areas where it is not feasible to provide more frequent service.

One should be cautious with the notion that immunization schedules which require a reduced number of contacts to provide full protection will result in substantial savings for the health system. The savings result from making services available less frequently, such as only twice a year. But, as noted above, such infrequent services are unsatisfactory for a number of reasons. Costs will increase as the frequency of the service increases. Even if all the EPI vaccines could be administered with a single dose, it would remain desirable to offer immunization and other health services as frequently and as close to families as possible.

Children who are mildly or moderately ill should not have their immunizations postponed. Recent data suggest that the health care setting is a common site for the transmission of measles (6). Immunization status should be determined and whatever vaccines are appropriate should be given to children at every contact with the health services.

In many countries a separation between preventive and curative services exists such that women and children coming for curative services either in clinics or in hospitals are not screened for their vaccine needs. For example, hospitalized infants often have conditions or diseases which predispose them to the more severe consequences of infection with vaccine-preventable diseases. Preventive services should be routinely offered in acute care settings.

Infants in urban settings deserve increased emphasis. In recent years there has been a rapid rise in the numbers of urban poor throughout the world and urban disease rates often exceed those of rural communities. Because of unreliable population and disease surveillance data it has proved difficult to obtain precise incidence data in these populations. When studied, one point has become clear; the urban poor represent a large pool of unvaccinated infants. Methods for local monitoring of EPI diseases need to be improved. The transient nature of many of these populations may require immunization strategies that are different from those used in rural populations. For example, it may be more useful to conduct periodic immunization days in cities or in urban neighborhoods as a supplement to routine services in order to increase coverage rates whereas this might not be efficient in rural areas.

3. IMMUNIZATION SCHEDULES

A guiding strategic principle of any immunization programme is that protection must be achieved prior to the time infants are at high risk from a disease. For example, from one quarter to one half of all new poliomyelitis cases occur in infants from 6 to 12 months of age with some cases occurring in those as young as 3 months. Infants are susceptible to pertussis soon after birth and one half of all deaths from pertussis occur during the first year of life.

The perfect immunization schedule would consist of a single vaccine given at birth which would offer life-long protection against all EPI diseases. This ideal is not

TABLE 3. Sample immunization schedule for visits at intervals from 4 weeks to 4 months.

Age of child	Antigens
Less than 6 weeks	BCG and OPV
Above 6 weeks	BCG, if not given previously OPV (3 doses) DPT (3 doses)
Above 9 months	Measles

TABLE 4. Sample immunization schedule for visits every 6 months

Age of child	Antigens
Less than 3 years	OPV irrespective of total doses received.
Less than 3 years	DPT to a total of 3 doses; BCG (single dose).
From 6 months to 3 years	Measles to a total of 2 doses if the first dose given below 9 months; single dose if given after 9 months.

yet attainable and any immunization schedule represents compromises. The most important compromise is that of obtaining protection at as young an age as possible while acknowledging that seroconversion with some EPI antigens is age-dependent.

In recent years, increased emphasis has been placed on early immunization. One example is giving oral poliomyelitis vaccine (OPV) at birth. Reasons for encouraging this have recently been published (7) and are summarized below:

- OPV induces intestinal infection in 50-100 percent of newborns with virus excretion lasting about four weeks. Twenty to forty percent of these infants will also mount an antibody response.

- No harmful effects have been noted after neonatal OPV administration. Specifically, infants who did not demonstrate a serologic response at birth had normal responses to vaccine given later.

A recent Chinese study of neonatal OPV administration has provided good data to support a firm recommendation to give OPV at birth (8). Some 100 infants were given OPV at 3, 60, 90 and 120 days while a control group of equal numbers received OPV at 60, 90 and 120 days. Viral excretion and seroconversion after immunization were studied. In infants given OPV at three days the gradual fall in polio virus antibody levels, characteristic of passively transferred maternal antibodies, was not seen; titers either stayed at a plateau or increased. Intestinal infection with OPV strains was common with over 80 percent of infants given OPV at 3 days excreting polio virus at one week. Post immunization titers in both study groups were identical at four months. Hence adding a dose of OPV at 3 days increased early protection and would, of course, have even more importance in the situation where later OPV doses might be delayed or missed for whatever reason.

Injection associated poliomyelitis provides an additional incentive for a dose of OPV at birth and for working towards early completion of an immunization series. Injections are known to predispose infants to paralytic poliomyelitis in the extremity which has received the injection. Most infants in developing countries are protected from poliomyelitis during the first few months of age by maternal antibody. As antibody titers wane, susceptibility increases. Hence it is desirable to complete a primary series of DPT/OPV immunizations by 4 months of age during which time the risk of post injection poliomyelitis is extremely low.

4. INTERVALS BETWEEN DPT IMMUNIZATIONS

Response to whole cell pertussis vaccine is age-dependent. Efficacy studies of the pertussis component of DPT show that better than 80 percent protection can be expected after 3 doses of whole cell pertussis vaccine if the first dose is given after 4 weeks (9). A first dose of DPT is now recommended at 6 weeks with subsequent doses at 10 and 14 weeks. In general, higher antibody titers against pertussis are noted if intervals of at least two months separate DPT injections. However, it has not been possible to correlate these higher antibody levels with improved protection from pertussis. In addition, studies of D and T indicate that the higher antibody levels achieved with longer intervals are temporary with no significant differences between titers one year after completion of the primary DPT series administered at monthly intervals when compared to a bimonthly schedule (10).

5. INTERRUPTED IMMUNIZATIONS

Interrupted immunizations need not be restarted, i.e., the remaining dose or doses should be given as if the prolonged interval had not occurred (11). For all practical purposes there is no maximum interval between doses of DPT or polio vaccine (11).

6. CONTRAINDICATIONS TO IMMUNIZATION

Fever, respiratory tract infection, diarrhea, and malnutrition should not be considered as contraindications to immunization. In fact because of the severity of measles in malnourished children presence of malnutrition should constitute a prime indication for immunization with measles vaccine. A useful general rule is to give routine immunizations unless the infant is felt to be sick enough to warrant hospitalization (5). Children who have diarrhoea should be given OPV. This dose should not be counted.

No restrictions on breast-feeding are necessary for the administration of OPV.

Considerable data exist as regards the safety and efficacy of measles vaccine given to hospitalized children; an important point because of the constant threat of nosocomial measles. Children with a wide range of acute and chronic conditions which necessitated hospital admission have been included in these studies. Measles immunization did not adversely affect the course of the children's illness and the risk of measles cross-infection was considerably diminished in the pediatric wards which had adopted this policy (5).

Immunizations ought not be refused on the basis of vaccine wastage, i.e., opening a 10 dose vial of measles vaccine to immunize a single child is reasonable because (1) the cost of the vaccine is a small fraction of the total expense of providing vaccine and (2) the social and medical costs of a case of measles outweigh any potential savings in vaccine.

Multiple antigens such as BCG, DPT, polio and measles vaccines can be given simultaneously. Neither their safety nor their efficacy is compromised (56).

7. IMMUNIZATION AND AIDS

In countries where human immunodeficiency virus (HIV) infections are considered a problem, individuals should be immunized with the EPI antigens according to standard schedules. This also applies to individuals with asymptomatic HIV infection. Unimmunized individuals with clinical (symptomatic) AIDS in countries where the EPI target diseases remain serious risks should not receive BCG, but should receive the other vaccines (Table 5).

In general, live vaccines are not given to immunocompromized individuals, but in developing countries, the risk of measles and poliomyelitis in unimmunized infants is high and the risk from these vaccines, even in the presence of symptomatic HIV infection, appears to be low (52,53)

TABLE 5.

Recommendations on the use of EPI antigens in HIV-infected individuals in countries where the EPI target diseases remain important causes of morbidity

	Vaccine	Asymptomatic	Clinical AIDS
Infants	BCG	yes	no
	DPT	yes	yes
	OPV	yes	yes
	IPV	yes	yes
	Measles	yes	yes
Women	Tetanus toxoid	yes	yes

8. INJECTION EQUIPMENT AND STERILIZATION PRACTICES

Since the possibility exists that unsterile needles and unsterile syringes can transmit not only the AIDS-related HIV, but also other infectious agents including hepatitis viruses, immunization programmes have the obligation to ensure that a sterile syringe and a sterile needle are used with each injection (2).

Countries which for many years have tolerated the use of unsterile techniques for immunization and other injections are now faced with rising concerns about the risks which such practices entail. The WHO/UNICEF joint guidelines (52,54) recommend the following:

- A single sterile needle and a single sterile syringe should be used with each injection.

- Reusable needles and syringes are recommended for use in developing countries. They should be steam-sterilized between uses. Boiling is an acceptable alternative procedure until steam sterilization is available. The number of reusable needles and syringes, and sterilizers, should be adequate to ensure that operations are not impeded by sterilization requirements. The low cost of the new plastic syringes now makes this possible.

- Disposable needles and syringes should only be used if it can be assured that they will actually be destroyed after a single use.

- Disease transmission by use of jet injectors is theoretically possible and has been demonstrated in humans in a single situation (55). bntil further studies clarify the risks of disease transmission with different types of jet injectors, their use should be restricted to special circumstances where large numbers of persons need to be immunized within a short period of time.

9. BOOSTER DOSES OF EPI ANTIGENS

A booster dose is defined as a reinforcement dose of an antigen to boost an antibody level that has waned and may not be protective. Booster doses are part of many immunization calenders, particularly in developed countries, but for the most part the need for these supplemental doses has not been rigorously proven.

Efforts to provide supplementary doses of EPI antigens ought to be a secondary priority of any immunization programme. The first priority is ensuring that infants are completely immunized against target diseases at the youngest age possible. It is suggested that resources not be invested in providing booster doses until coverage levels for fully immunized infants are above 80 per cent.

Antigens which provide life-long immunity do not require reinforcing doses. For example, seroconversion following measles vaccine or OPV is thought to confer protection for life. The rationale for providing several doses of OPV is to assure initial seroconversion against all types of polio virus, not to boost waning immunity. Since wild polio viruses circulate freely in most developing countries infection occurs at a young age. Thus, an appropriate strategy for the prevention of poliomyelitis is giving 4 doses of OPV by 14 weeks of age as previously outlined. The decision to give further doses of OPV should depend on documentation of poor seroconversion rates after 4 doses. If necessary, a fifth dose could be given at the time of measles immunization (at 9 months of age).

Measles vaccine is another vaccine believed to confer life-long immunity after seroconversion, and no booster dose for this vaccine is recommended. At least one industrialized country currently uses a two dose schedule for measles immunization, the second dose (given at the age of 20-24 months) being given in order to achieve seroconversion in those few children not responding to the first dose rather than to boost antibody titers.

Many immunization schedules call for a booster dose of DPT one year following the primary series. Such a dose increases antibody titers such that good protection against all three diseases can be expected. Yet this is of limited significance, as the major risk from pertussis has already passed, and the protection conferred against diphtheria and tetanus by the primary series is already excellent. Where pertussis remains a common disease, contact with the organism will boost the immunity conferred by immunization. Programmes which have decided to give a fourth dose of DPT should consider timing it so as not to require an additional visit to a health provider. For example, it could be given at the time of measles immunization. Some countries prescribe even a fifth dose of DPT in their immunization schedule.

Children who have received a primary series would benefit from at least one additional dose of DT vaccine prior to school leaving. In order to minimize reactions the so-called "adult" dose of diphtheria toxoid or Td in combination with tetanus toxoid should be used.

Immunity induced by BCG given to newborns wanes such that re-immunization at school age is recommended in many countries (13). There is no universal agreement that re-immunization (or even first immunization) at this age is useful. If the risk of tuberculosis is very high re-immunization or initial immunization at school entrance may be justified as many infections will take place during the first years at school. A school based BCG immunization programme could be integrated into an effort to provide diphtheria and tetanus toxoid immunization to those children who have not received a primary immunization series.

10. STANDARD EPI ANTIGENS

This section will update new developments or highlight controversies in the use of the standard six antigens used in EPI. General information on these antigens is available in review articles published by the WHO/Geneva (4,5,13).

10.1. Polio vaccines

OPV continues to be the vaccine on which the majority of countries base the control of poliomyelitis. OPV has eliminated wild polio virus from large geographic areas and recent data from West Africa suggest that OPV can significantly decrease the number of cases of poliomyelitis with coverage rates of less than 60 percent (14). The Brazilian OPV mass immunization programme achieved a dramatic effect and has served as a strong impetus for a poliomyelitis elimination programme in the Americas (15). A major reason for the success of OPV is its community effect, that is, enteric multiplication of vaccine virus leads to its dissemination beyond the individual being immunized. This community dissemination of vaccine virus probably accounts for the rather dramatic effect OPV coverage rates of 50 to 60 percent have had on lowering the incidence of poliomyelitis beyond what would have been expected from coverage data.

Unresolved questions associated with OPV use remain. Perhaps the most important of these are the geographic differences in seroconversion rates. In temperate climates seroconversion rates to all three polio serotypes after three OPV doses is about 95 percent whereas similar studies, most notably those from India, have documented seroconversion rates as low as 50 to 60 percent (16). Five doses of OPV are required to get to 90 to 95 percent seroconversion rates (17). The precise cause for these lower seroconversion rates has not been identified. Breast feeding has been shown to inhibit OPV takes in neonates but prospective and retrospective studies have shown that breast-fed and bottle-fed infants had no differences in seroconversion rates when given OPV at 2, 4 and 6 months (18, 19). Viral interference has also been postulated as an important cause for poor seroconversion rates after OPV although several negative studies have been published (16,20). These issues, while interesting, have not had a major public health impact since OPV in tropical countries, including India, has been shown to be effective (21,22).

Poliomyelitis cases in immunized persons are a continuing concern. Vaccine failure can be caused by breakdown of the cold chain. But as

TABLE 6. Vaccine efficacy formula.

$$\text{Vaccine efficacy} = \frac{\text{Attack rate unimmunized} - \text{Attack rate immunized}}{\text{Attack rate unimmunized}} \times 100$$

the efficacy of the oral vaccine is not 100%, even with potent vaccines which are properly administered, some cases may occur. As immunization coverage rates increase, although total cases will decrease, a higher proportion of the remaining cases can be expected to occur in vaccinees. This can raise concerns that vaccine efficacy has diminished. An excellent example of this type of problem has been described from Bombay where immunized persons had risen from 5 percent of all polio cases in 1975 to 15 percent in 1981 (23). Calculation of vaccine efficacy using the formula in table 6 shows that the vaccine had an efficacy of 82 to 88 percent from 1979 to 1981 and that the increase in poliomyelitis cases among immunized persons as a proportion of total cases reflected increases in immunization coverage.

The point that requires emphasis is that the proportion of total polio cases who are immunized cannot be used as an index of vaccine efficacy since it varies according to immunization coverage. For example, when vaccine coverage reaches 95 percent, the proportion of total cases who are fully immunized is expected to be about 50 percent even when using vaccine with 95 percent efficacy (24). This applies to all vaccines, not only to polio vaccine.

The debate on the role of inactivated poliomyelitis vaccine (IPV) in EPI has been vigorous and more intense in recent years because of (1) more attention being paid to vaccine associated cases of poliomyelitis in countries with high OPV coverage rates and (2) the development of a more potent killed vaccine.

Several field trials of the new more potent IPV have shown that seroconversion rates approaching 100 percent against all three serotypes are possible after two doses. Preliminary results from a recent epidemic investigation suggest that clinical protection from IPV may be less than indicated by the antibody studies, however. Optimally the first dose should be given after 3 months of age with the second about 6 months later. Some programmes have given the first dose at 2 months of age with a second after a two months interval. IPV can be combined with DPT although care must be taken that preservatives in the DPT do not adversely affect other antigens. Such a schedule is being used in remote areas in some West African countries as part of a two dose EPI schedule as previously discussed. There is no question that use of this new IPV can reduce cases of poliomyelitis but the vaccine is currently expensive; two doses of IPV/DPT cost some ten times more than three doses of DPT and four doses of OPV.

Just where the new killed polio vaccine will fit into EPI is still unclear. Questions remain concerning the total number and timing of doses required to provide initial protection and concerning the need for booster doses. There is increased interest in using IPV and OPV in combination, especially in those countries for whom the cost of IPV is not considered a constraint.

WHO continues to recommend OPV as the standard EPI antigen for the control of poliomyelitis because of its low cost, its dissemination within a community and its record of efficacy. Further research with IPV and with combinations of IPV and OPV are encouraged.

TABLE 7. Relationship between doses of tetanus toxoid and duration of protection.

Dose	Minimum interval	Percent protected	Duration of protection
TT 1	-	0	0
TT 2	4 weeks	80 (60-90)	3 years
TT 3	6 months	95	5 years
TT 4	1 year	99	10 years
TT 5	1 year	99	life long

10.2. DIPHTHERIA AND TETANUS TOXOIDS

Little has changed in recent years regarding these vaccines. They are superb antigens with low toxicity and their regular use prevents these diseases.

The most important development in recent years is the recognition of the major toll being taken by neonatal tetanus in many countries. Survey techniques have been developed and should be used more extensively to give countries a clear idea of the magnitude of neonatal tetanus incidence. At the root of the problem is, of course, low tetanus toxoid immunization rates in women of child bearing age. A major immediate goal of EPI is to encourage tetanus immunization in all women of child bearing age using all contacts that women have with health services to accomplish this goal. This strategy leaves out younger girls who may not have received a primary immunization series and who are in need of protection. School based tetanus-diphtheria immunization programmes should be encouraged since they aim at immunizing a largely unprotected group (both boys and girls) and are inexpensive. Success of this strategy depends upon the level of school enrollment which is limited in many developing countries.

Training of birth attendants is a complementary strategy and use of these two approaches can result in a major decrease in the incidence of neonatal tetanus as has been well documented in Sri Lanka (25).

In Table 7 the relationship between tetanus toxoid doses and duration of protection is summarized (51).

10.3. PERTUSSIS

The current pertussis vaccine was shown to be effective in large well conducted field trials in the 1940's and 1950's. Concern over the toxicity of the vaccine has recently limited use in some developed countries but decreased use has resulted in a resurgence of pertussis cases (26,27). Fever and mild local reactions after pertussis immunization are common. A severe neurologic event with permanent sequelae occurs once in every 300 000 doses.

Young infants are not protected at birth by maternal antibodies and are at risk soon after birth. Therefore it is important to complete pertussis immunization at as young an age as possible. A review of published studies shows that an immunization schedule that begins at six weeks with three doses provided at four week intervals provides good seroconversion rates and disease protection. Beginning pertussis vaccine at birth has not proven to be feasible because of interfering maternal antibodies. Three doses of pertussis vaccine given at monthly intervals beginning at 1 week were less immunogenic than a similar regimen beginning at 6 or 8 weeks (3,7).

A great deal of interest has been expressed over the possibility of using a two dose pertussis schedule. Such a schedule would simplify vaccination activities particularly in areas where access is difficult. The trials of two dose schedules that have been most positive have used 6 month intervals between first and second doses and herein lies the problem (3). The long interval that is necessary in a two dose schedule would leave a child unprotected until after the second dose is given. A two dose schedule should be considered only for those areas where services cannot be provided more frequently than twice a year.

To further confound the issue some investigators have suggested that a two dose pertussis schedule results in milder cases when they occur, a point which is difficult to prove. This and other questions pertaining to whole cell pertussis vaccine are likely to remain unanswered as emphasis shifts to the new acellular vaccines.

In the interest of decreasing the side effects inherent in the whole cell vaccine new acellular pertussis vaccines have been developed and have been tested. The largest experience with acellular vaccines which contain Filamentous Haemagglutinin (FHA) and Lymphocytosis Promoting Factor (LPF) has been in Japan where equivalent protection was shown in children 2 years and older between the standard whole cell vaccines and acellular vaccines in a non-randomized trial (28). An effective acellular pertussis vaccine which would presumably not have the toxic side effects inherent in the whole cell vaccine would be welcome. Nonetheless, programmes ought not lose sight of the fact that the current vaccine is very effective if given properly and that new vaccines are likely to be several years away and more expensive.

10.4. BCG

One of the main issues with the use of BCG has been the vexing problem of efficacy. The question as to the efficacy of BCG in adults is far from being settled with well controlled studies showing protection ranging from 0 to 80 percent. There has long been the feeling among epidemiologists and phthisiologists that BCG was particularly effective in decreasing the number of cases of miliary tuberculosis and tuberculous meningitis in infants but the data for this assertion were predominantly anecdotal rather than statistical. This point is now on stronger footing as a result of new studies from several countries which indicate that BCG is quite effective in infants (29).

Case-control and contact study techniques were used in these studies. In the case-control method, BCG coverage was determined in patients and matching controls so that the relative risk of contracting tuberculosis could be estimated. The contact method determined relative risk from the incidence of tuberculosis in immunized and non-immunized contacts of newly diagnosed patients with infectious tuberculosis. Results of these studies are summarized in table 8.

TABLE 8. Summary of studies on the efficacy of BCG in infants.

(a) CASE CONTROL STUDIES (less than 5 years of age)

Country	Matching basis	Cases			Controls			Protective effic. (%)
		Total	+BCG	%	Total	+BCG	%	
Brazil	Meningitis	73	38	52	514	463	90	90
Burma	All cases	311	162	52	1555	995	64	39
Argent.	All cases	175	51	29	875	516	59	74

(b) CONTACT STUDIES (less than 6 years of age)

Country	Total exposed	Immunized with BCG			NOT immunized with BCG			Protective effic. (%)
		Total	+TBC	%	Total	+TBC	%	
Thailand	1507	1253	158	13	253	60	24	53
Togo	1421	875	62	7	546	113	21	80

Protection ranging from 40 to 90 percent was demonstrated in each of the studies. In the Burma study all clinical cases of tuberculosis in children under five years were used as index cases and when a separate analysis of those infants with disseminated tuberculosis was done protection increased to about 80 percent.

These are important new data. In view of the importance of intra-familial spread of tuberculosis, immunization of infants with BCG as early as possible continues to be a strong recommendation of EPI. Some protection against all forms of tuberculosis can be expected but especially so for the more serious forms such as tuberculous meningitis.

BCG immunization at school-entering age is performed in many countries, but there is no universal agreement that re-immunization (or even first immunization) at this age is useful. Policies in individual countries should be determined by the tuberculosis control programme at national level, based on the epidemiology of the disease in each country.

10.5. MEASLES

The timing of measles immunization remains a common question for health staff. The problem is two-fold. On the one hand, in countries where measles remains a problem for children in their first year of life (the situation in most developing countries, at present), WHO/EPI recommends a single dose of measles vaccines as soon as possible after nine months (270 days) of life (30). This contrasts with the situation in most industrialized countries where measles occurs later, and immunization is recommended only at 12-15 months of age.

On the other hand, because measles does strike so early in many developing countries, cases not infrequently occur before the age of nine months, raising questions as to whether to immunize earlier. Unfortunately, measles vaccine rapidly diminishes in effectiveness, owing to the interference from maternal antibodies, as the age of immunization is decreased below nine months, becoming only about 50% effective at the age of six months.

One solution, where resources permit and measles under 9 months is a major problem, is a two-dose schedule. The first is administered at six months, the second at nine months. This approach has not worked in the past, however. In several programmes in Africa which instituted this as general national policy, low coverage was achieved with the first dose, and few infants receiving the first dose were ever returned for a second. This resulted in many children immunized at six months remaining susceptible to measles. Interest is now being rekindled in two-dose strategies, especially in dense urban settings where measles strikes particularly early and in remote rural areas where services can only be provided twice a year. More evaluation of the impact of such strategies is needed. Past experience suggests that where this policy is tried, it should be highly selective within programmes, and should be accompanied by close supervision to assure that children immunized before the age of nine months do in fact receive a second dose at nine months.

Studies in the Gambia by Whittle and co-workers may resolve the problem of measles in children below the age of nine months (31). They have used an attenuated Edmonston-Zagreb strain passed in human diploid cells to immunize small numbers of infants from 4 to 6 months of age. Large doses (11 400 to 39 800 PFU) of this vaccine were administered either intradermally or subcutaneously. Vaccine recipients were bled before and 16-24 weeks after immunization and were visited weekly for 1 to 2 years by a health worker to document episodes of measles. All infants immunized with this schedule increased their antibody titers and no child had an HI titer of less than 1:4 after 16 to 24 weeks after immunization. None of the 42 children given the vaccine developed measles during the next one and one-half to two years of surveillance despite measles cases in the village. Corroborative studies are underway and if successful would provide the basis for a major breakthrough: the importance of being able to offer effective measles immunization to children under 6 months of age can hardly be overstated.

11. ANTIGEN MIXTURES

Some EPI antigens such as DPT and DPT/IPV are given as mixtures. These combinations have been tested to ensure that the antigens do not interfere either chemically or immunologically with each other (32). Recently in an effort to simplify vaccine logistics DPT/IPV has been suggested as a diluent for measles vaccine. Laboratory studies by John have shown that such a mixture remained stable for four hours at 33°C, but showed a significant decline in vaccine virus titer after four hours (33). While such mixtures are of interest they must be fully evaluated and tested before being considered acceptable.

12. OTHER ANTIGENS WHICH CAN BE OFFERED AS PART OF EPI

In this section several vaccines are discussed which may be of interest to managers of immunization programmes. They are not yet recommended for global use. Some of the vaccines have been shown to be effective but the diseases they prevent are only of local significance. In such settings cost effectiveness should determine whether these vaccines should be included in a national EPI. Other vaccines are not in general use because of high cost, questions on efficacy when used in infants or because further development work is required.

12.1. HEPATITIS B VACCINE

There are an estimated 200 million carriers of hepatitis B virus (HBV) in the world. This group represents the reservoir for continued transmission of the agent. Mother to infant transmission (vertical transmission) is the most important reason for high carriage rates. Mothers who are carriers of hepatitis B surface antigen (HBsAg), especially those whose sera are positive for the e antigen of HBV, are highly infectious and are responsible for a large proportion of infections. The chance that infection will result in persistent antigenemia is inversely related to age at the time of infection.

Hepatitis B vaccine is prepared from the plasma of HBV carriers. The vaccine is highly immunogenic and in well controlled trials has been shown to be very effective in the prevention of hepatitis B. Hepatitis B vaccine is very immunogenic in newborns. In well controlled studies from Senegal and Taiwan, seroconversion rates in newborns given hepatitis B vaccine at birth, 30 days and at 6 months have given seroconversion rates greater than 90 percent (34,35). Studies of clinical protection have yielded comparable results. Results of these studies have shown protection rates in the 90 percent range in neonates at risk of acquisition of HBV from carrier mothers (36,37). Thus an effective vaccine can now be given at birth which could break the most important chain of transmission of HBV. Beneficial results of such a programme in countries with high HBV carrier rates could be significant since it is estimated that about one quarter of all hepatitis B carriers die from either cirrhosis or hepatocellular carcinoma induced by HBV infection. A recent WHO Scientific Group meeting affirmed that immunization with hepatitis B vaccine could prevent 80 percent of the 250 000 annual cases of hepatocellular carcinoma which occur globally (38).

Introduction of hepatitis B vaccine into an EPI should be an important priority for any country with carrier rates of HBsAg greater than 10 percent (39). The vaccine is expensive and its widespread use cannot be expected to take place until its price dramatically decreases. More efficient preparation of HBV vaccine from plasma and/or so called "second generation" hepatitis B vaccines developed through genetic engineering may provide the necessary source of inexpensive antigen required for implementation of a global immunization programme. The need for the vaccine is clear and in anticipation of its availability countries should initiate epidemiologic and serologic studies to define the extent of hepatitis B infection in their population.

12.2. YELLOW FEVER VACCINE

Yellow fever is a major epidemic threat particularly in Africa. Epidemics involving forest mosquito vectors affect tens of thousands of persons at intervals of a few years but few cases are reported. Major outbreaks in recent years have occurred in Burkina Faso, Gambia, Ghana, Nigeria and Senegal. The age specific attack rate is such that most cases occur in the young with a case fatality rate of about 25 percent. The situation in South America is quite different where most of the 200 to 400 annual cases occur among persons with occupational exposures in forested areas.

Yellow fever vaccine is a live attenuated virus preparation made from the 17D yellow fever virus strain. The vaccine is extremely safe and effective. Immunity after a single dose may be lifelong. Given the severity of yellow fever and its unpredictability, yellow fever vaccine should be considered for incorporation in routine EPI activities in any country falling in the endemic-epidemic African belt. Regular immunization of all infants with yellow fever vaccine would over time lead to an ever increasing pool of immune individuals. Yellow fever vaccine can be given at 6 months of age or with measles vaccine at 9 months.

12.3. TYPHOID VACCINE

Most clinical disease due to **Salmonella typhi** occurs in the 5 to 30 year age group. Typical typhoid fever is unusual in preschool children. The incidence of atypical infection is probably higher than appreciated, but still less than in school age children.

Killed typhoid vaccines have been in use for almost 100 years. However it was not until the WHO sponsored controlled trials carried out in the 1950s and 1960s that a clear idea of the protective value of these vaccines became known. In school children acetone precipitated vaccine gave 80 to 90 percent protection when compared to placebo. The vaccine has significant side effects and its efficacy in young children has never been shown in controlled trials. Hence killed vaccine cannot be recommended as part of an EPI.

In recent years interest has focused on a live oral vaccine against S.typhi. Egyptian school children were given strain Ty21a with sodium bicarbonate in three doses and three years of surveillance in this group showed a 96 percent efficacy (40). Follow up studies using enteric coated capsules of Ty21a have not been as dramatically successful but these studies are continuing. To date no data have been published on the use of this new oral vaccine in infants. Therefore the attenuated S.typhi oral vaccine cannot be recommended as an EPI antigen unless typhoid in 1-3 year olds proves a greater problem than it seems and protection from immunization extends well into school age or is easily boosted on school entry. None of these questions is answered at present.

12.4. ROTAVIRUS VACCINE

Infection with rotaviruses is one of the most important causes of severe diarrhea in children under 5 years of age and addition of an effective oral vaccine against rotavirus would be a major addition to an EPI. Over the last 5 years major strides have been taken in the development of an effective vaccine. Attenuated animal rotavirus strains have been the most thoroughly studied. One or two doses of this vaccine provided 80-90 percent protection in Finnish infants over 6 months of age. However, the vaccine has not been shown to be effective in field trials done in developing countries (41). Reasons for the failure of the vaccine are not yet known but may reflect over-attenuation of the vaccine virus. Field trials using a low passage Rhesus rotavirus are underway in several countries. This vaccine appears to be considerably more immunogenic than earlier vaccines but did cause occasional fever and mild diarrhea.

12.5. PNEUMOCOCCAL VACCINE

A 23-valent pneumococcal vaccine has been licensed and is in clinical use in several countries. Unfortunately children under age 2 generally have an unsatisfactory serological response to pneumococcal vaccine hence it may not be of value in an immunization programme that focuses on infants under one year.

U.S. and Finnish investigators have collaborated on a study of the effect of pneumococcal vaccine on the incidence of pneumococcal otitis in infants from 6 months to two years of age. A decrease in the the number of infections due to serotypes present in the vaccine was noted. However the reduction in episodes of acute otitis media was not sufficient to alter the experience of children with middle ear infection or the duration of middle ear effusion (42).

12.6. MENINGOCOCCAL VACCINE

Meningococcal disease is an important epidemic and endemic cause of morbidity and mortality particularly in the subSahelian meningitis belt in Africa (43). Attack rates of greater than 500 cases per 100,000 population are not unusual. The age distribution of these cases is biphasic with about half of all cases occurring in the 0-4 age group.

Over the last 20 years polysaccharide vaccines have been developed against meningococcal serogroups A, C, Y and W135. These vaccines have been used predominantly as a control measure against meningococcal meningitis and excellent evidence exists for the role of meningococcal vaccine in that setting (44,45).

The major problem with meningococcal vaccine and a difficulty shared by all polysaccharide vaccines is the difficulty in immunizing infants under two years of age (46). For example a single dose of group A vaccine given to persons over age 2 will protect for 1-3 years. However, protection from vaccine given to children under 24 months was short lived, lasting for a single year. A sequential case control study monitored protection of a single dose of Group A meningococcal vaccine by age. While vaccine efficacy remained high for three years after immunization of children greater than 4 years of age it decreased dramatically to 52 and 8 percent 2 and 3 years after immunization in children who were less than 4 years of age when they received the vaccine (47).

A vaccine for prevention of group B meningococcal disease is not currently available, as the group B polysaccharide induces an IgM response, which is short-lived, in all age groups. A type 2 outer membrane protein - B polysaccharide vaccine has shown immunogenicity in children and is being evaluated for clinical protection (48).

At present it is not possible to recommend meningococcal vaccine as an integral part of any infant immunization schedule. Published data are consistent with the policy of the use of meningococcal vaccine as an essential component of epidemic control. A major research effort needs to concentrate on the development of new polysaccharide vaccines which can be used in infants under three months of age.

12.7. HAEMOPHILUS INFLUENZAE TYPE B VACCINE

Haemophilus influenzae type B (Hib) is the most common cause of non-epidemic meningitis and systemic infection in young infants. A vaccine composed of purified capsular polysaccharide has been prepared and antibodies against this capsular material are correlated with disease protection. As with other polysaccharide vaccines the antibody response is directly related to the age of the patient. Infants under 18 months respond poorly; infants between 18 and 24 months respond somewhat but not as well as those 2 years or older.

A randomized controlled trial of Hib vaccine was done in Finland in 1974 which suggested that the vaccine was effective in preventing meningitis in children above 23 months of age (49). A long term follow up of this group showed that protection continued in the age group above 23 months. Efficacy in children 18-23 months of age could not be demonstrated (50). Hib vaccine has been introduced at 24 months of age in some national immunization programs but should not be included in any immunization schedule for infants under one year.

12.8. JAPANESE B ENCEPHALITIS VACCINE

Japanese B encephalitis virus is an arbovirus which is a major cause of encephalitis in the Indian subcontinent and in other countries in South East Asia. The disease has a predilection for the young with the main risk occurring in the 2 to 4 year age group. The disease presents as a classical encephalitis with fever, progressive obtundation, coma and convulsions. The illness is a severe one; about 20 percent of cases die and another one third have some neurologic residual. The majority of infections are asymptomatic and serologic studies suggest progressive exposure to the agent with increasing age such that seropositivity increases from about 35 percent in 15 year olds to 75 percent in adults in their fifth decade.

Formalin inactivated vaccines against Japanese B encephalitis have been manufactured and used in Japan and China for several years. The Japanese vaccine is made from a purified mouse brain preparation which has been inactivated with formalin. No international requirements for the vaccine currently exist. Vaccine efficacy studies in Japan and Taiwan suggest that the vaccine is effective at the 80 percent level. Reactions to the vaccine are relatively minor. Because of the presence of some brain tissue in the vaccine the possibility of allergic encephalomyelitis as a complication of the vaccine is real. Careful follow up studies of vaccinated persons in Taiwan did not uncover any cases and if the complication does occur it is estimated to be in the range of one case per 1 million inoculations.

Japanese B encephalitis vaccine is part of the Korean EPI and is widely used in China. Given the severity of the disease particularly in young children and the effectiveness of the current vaccine that is available, countries with an endemic problem with Japanese B encephalitis ought to consider its inclusion into their immunization programmes. There are no data on whether Japanese B encephalitis vaccine can be given simultaneously with measles or other vaccines.

Much more work needs to be done on the control of Japanese B encephalitis but its relative severity particularly in young infants makes it a high priority area for more investigation. Issues that need to be resolved soon include (1) the optimal earliest age of immunization; (2) the need for a booster dose and if so the optimal time for this booster dose and (3) whether Japanese B encephalitis vaccine can be given simultaneously with other EPI antigens.

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