Reviews Analyses

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The efficacy of DPT and oral poliomyelitis immunization schedules initiated from birth to 12 weeks of age

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Infants should receive live trivalent oral poliovirus vaccine (TOPV) and DPT immunization as early in life as possible in order to minimize the time that they are at risk of contracting these vaccine-preventable diseases. Passively acquired circulating maternal antibodies provide protection in the first few weeks or months of life. Although these antibodies may modify or block the serum immune response during the first few weeks of life, the first or priming dose of DPT can be given effectively after four weeks of age.

TOPV administered to infants during the first week of life results in intestinal infections and local immune responses in 50-100% of infants and serum antibody responses in 30-70% of infants. The serum antibody response following TOPV administration at 4-8 weeks of age is as effective as vaccine administered to older infants.

The WHO Programme on Immunization recommends initiating DPT and TOPV schedules at 6 weeks of age. In countries where poliomyelitis has not been controlled, TOPV should be given at birth, or at first contact with the health services, then at 6 weeks of age, followed by two additional doses 4 weeks apart.

INTRODUCTION

Infants should receive immunization as early in life as possible in order to be protected against the natural diseases prior to the highest risk periods. Infants born to immune women receive maternal antibodies which protect them for variable periods of time. Ideally, immunizations should induce an active immune response before the infant loses this passive protection so that there will be continuous protection from birth without any gap in immunity to natural diseases. However, the presence of maternal antibodies can modify or suppress the infant's response to immunization, especially if the vaccine preparations are of low potency. Several investigators during the 1940s and 1950s noted lower antibody titres following one or two doses of diphtheria toxoid and pertussis vaccine administered to infants under 2 or 3 months of age, compared with the response in older infants (*36*, *133*). They, therefore, often recommended postponing immunizations until after the age of 3 or 6 months, when the modifying effect of the maternal antibodies had disappeared.

In 1977, when the original guidelines for the Expanded Programme on Immunization were formulated, a starting age of 3 months was chosen for the routine schedule in order to be consistent with the recommended guidelines used in western Europe.

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However, several authors have recommended beginning DPT and OPV (oral poliovirus) immunizations at younger ages, and many countries have carried out successful immunization studies and programmes beginning at 6–8 weeks of age (*5*, *13*, *14*, *24*, *38*, *56*, *64–66*, *119*, *130*, *140*). These recommendations were based on observations that young infants do respond to immunization with potent vaccines and toxoids even in the presence of low to moderate levels of maternal antibodies.

In the light of these findings, the Global Advisory Group of the Expanded Programme on Immunization noted in its recommendations in 1983 and 1984 that DPT and trivalent oral poliovirus vaccine (TOPV) can be safely and effectively administered as early as 6 weeks after birth (*47*, *48*). The present review provides further support for this statement, based on the available literature on the efficacy of early immunization with these vaccines.

This paper does not deal with the question of the earliest age to administer measles vaccine, BCG, or killed poliovirus vaccines. The optimum age to administer measles vaccine has been reviewed in recent publications (*60*, *149*). BCG immunization of neonates has been accepted by most countries and the majority of investigations reveal that it is effective at this age (*77*, *138*, *147*). Data are currently being generated on the response of infants in the first three months of life to immunization with the new generation of inactivated polio vaccines. The present review has, therefore, been limited to OPV and DPT.

ORAL POLIOVIRUS VACCINE ADMINISTERED FROM BIRTH TO 12 WEEKS OF AGE

Evaluation of the immune response to OPV in early infancy

Live oral polio vaccine virus probably infects intestinal epithelial cells. After replication, the virus is transported to Peyer's patches where a secondary multiplication with subsequent viraemia occurs. The virus spreads to other areas of the body resulting in the production of circulating antibodies. Intestinal infection also stimulates the production of IgA secretory antibody which provides protection against subsequent challenge with wild-type or vaccine viruses (*75*, *102*).

The protective effect of OPV can be measured by five methods: (1) measurement of serum antibodies following immunization; (2) measurement of secretory antibodies in intestinal secretions; (3) detection of viral multiplication in the intestinal tract following immunization; (4) prevention of intestinal viral multiplication in previously immunized individuals following challenge with wild-type virus or subsequent doses of vaccine; and (5) prevention of paralytic disease in immunized persons as compared to unimmunized persons in exposed populations.

All of these techniques have been used by investigators evaluating poliomyelitis vaccines. However, the most practical and widely used techniques for evaluating the response to immunization are measurement of increased levels of circulating antibody and measurements of viral excretion in stool. During the first few months of life, most infants have circulating antibodies derived from their mother before birth. There are no practical techniques to distinguish these passively acquired antibodies from antibodies that the infant has made in response to immunization. Therefore, most investigators have measured cord blood or venous blood antibodies prior to immunization and compared the results with the venous blood titres observed after immunization. Based on an estimated half-life of approximately 30 days (range, 21–45 days), the expected level of passively acquired antibody was determined. If the results obtained were fourfold or greater than the expected results, these investigators concluded that the infant had responded to the vaccine.

Although this technique was used in most of the investigations summarized in Table 1, this method almost certainly results in an underestimate of the host's serological response to immunization. The presence of maternal antibodies probably prevents the detection of low-level active antibody responses in the first few weeks of life. Since no techniques have been developed to separate maternal from infant antibodies, many investigators have had to assume that no response occurred in infants with low levels of antibody. By waiting until 5–6 months of age to measure antibody, other investigators observed higher response rates following immunization in the first few weeks of life even though similar vaccines were utilized (*62*, *91*, *117*). One author underevaluated the response rates by counting only the absolute increase in antibody titres following immunization (*49*). In this instance, the published results allowed for the calculation of response rates by the usual criteria (Table 1).

Several published studies have probably underestimated the response following immunization because suboptimal procedures were utilized for measuring antibodies. Albrecht has shown that laboratories measuring identical serum specimens obtained results that varied more than tenfold (*3*). Some laboratories measured antibody at 1:10 dilutions or greater, but others measured titres as low as 1:2. Sabin has also shown that unless proper techniques are followed, the sensitivity of the tests is suboptimal (*127*). These methodological problems help explain the variation

Table 1. Serum antibody response and viral excretion rates following OPV in the first week of life

Investigator, year, and reference	Country	Vaccine type[a]	No. of infants	Age (days)	Percentage with antibody response[b]			Percentage with viral excretion[c]		
					I	II	III	I	II	III
Krugman, 1961 (*79*)[d]	USA	I	109	0–2	23–37			50–90		
		I,II,III	115	0–2	4–10	30–58	8–18	(----------56–90----------)		
Lepow, 1961 (*83*)[e,f]	USA	I	144	0	>50			71–87		
Lepow, 1961 (*84*)[d,g]	USA	I	272	0–5				29–57		
Pagano, 1961 (*105*)[h]	USA	I	15–25	0–7	47			88		
Holguin, 1962 (*63*)[i]	USA	I	80	0–4				68–91		
Sabin, 1963 (*128*)[e,g]	USA	I	109	0–2	32			44–88		
Warren, 1964 (*145*)[g,i]	USA	II,III	9–35	0					65–68	33–89
		II,III	11–36	3					45–96	69–94
Katz, 1968 (*73*)[j]	USA	I	28	0–7				60–100		
Katz, 1968 (*74*)	Uganda	I	32	0				53		
Farmer, 1969 (*49*)[k]	New Zealand	TOPV	22	0–3	27	36	45			
Banfi, 1974 (*7*)[j]	Chile	I	110	0	44–67					
Ordonez, 1966 (*104*)	Mexico	I	268	0–7	37					
De-Xiang, 1984 (*37*)[l]	China	TOPV	108	3	30	30	18	41	41	27
Gelfand, 1960 (*54*)	USA	I,II,III	21–26	2–3				85	95	77
Pagano, 1962 (*106*)[m]	USA	I	64	3	37			92		
Ganzaga, 1963 (*58*)[n]	USA	I	32	3					100	
Plotkin, 1966 (*115*)[g,i]	Uganda	I	60	3				57		
Levine, 1961 (*85*)	Israel	TOPV	53	3–5				70	0	70
Prem, 1960 (*117*)[o,p]	USA	TOPV	62–73	5–7	70	18	85			

[a] I, II,III indicate monovalent preparations; TOPV = trivalent oral poliomyelitis vaccine. Data from preparations with $\geq 10^{4.5}$ $TCID_{50}$ included in Table.

[b] Antibody response based on increased levels above that expected from the decline in maternal antibody (see text).

[c] Presence of type-specific poliovirus in stool 3–15 days after immunization.

[d] Multiple immunization schedules and variables evaluated data are summarized in this publication.

[e] Sixty-nine infants were tested for antibody.

[f] Interference noted with mixed monovalent vaccines. Percentage reported is for one or more types when mixed.

[g] Lower percentages noted for breast-fed infants.

[h] Lower response rates in infants who received low-titre vaccine.

[i] Suppressive effect of high maternal antibody titres noted.

[j] Infants fed high-titre monkey antisera with OPV not reported here.

[k] Author concluded lower response rates with OPV (see text).

[l] Response rate determined by increased percentage of immunized subjects with antibody compared with unimmunized group. The actual response rate was higher.

[m] Premature infants.

[n] Infants fed colostrum from unimmunized cows. Only 27% of infants fed colostrum from immunized cows responded.

[o] Response defined as percentage with antibody at six months of age.

[p] Some mothers received OPV during pregnancy. High antibody titres did not prevent infant's response.

in results reported by different authors in Tables 1-3.

Infants fed OPV may briefly excrete low titres ($< 10^2$ $TCID_{50}$ per gram) of vaccine virus in the stool during the subsequent 48 hours. This probably represents passive transfer of the vaccine virus through the intestinal tract. However, when vaccine virus has been detected three or more days after immunization with OPV, it usually is present in much higher titres (10^3–10^7 $TCID_{50}$) and undoubtedly represents multiplication of the virus in the intestinal tract (*79*). This multiplication results in the production of local immunity as manifested by the development of intestinal secretory IgA antibodies which correlate with protection against rechallenge with the same virus strain (*75*, *129*). Although circulating passive antibodies may suppress or block the viraemia following immunization and the infant's serum antibody response (*63*, *105*), only very high serum titres appear to affect the development of intestinal infection following OPV (*115*, *128*, *145*). As a result, the percentage of infants responding with viral excretion following monovalent OPV or TOPV immunization in the first week of life is almost always higher than the percentage developing a serum antibody response (Table 1, Fig. 1). This was effectively demonstrated

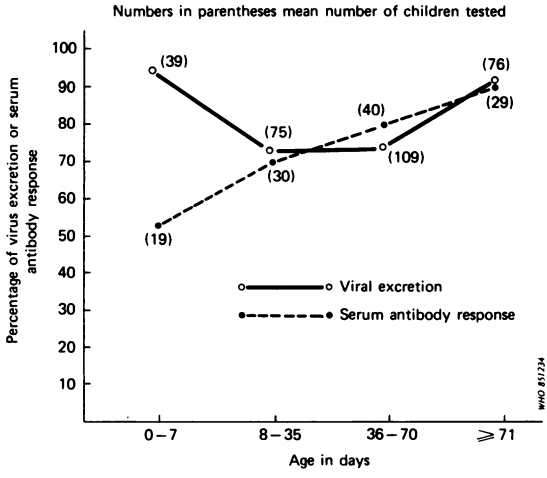

Fig. 1. Viral excretion and serum antibody response following one dose of type I, II or II monovalent poliovirus vaccine by age (data adapted from Plotkin et al. (*114*)).

by Plotkin (*114*) (Fig. 1). After the first week of life, the serum antibody response improved and usually coincided with the viral excretion rates. The explanation for the apparent decrease in viral excretion rates after the first week of life is unknown, but this has been observed by other investigators (T. J. John, personal communication, 1984).

Infants who excreted virus following OPV but did not develop an increase in serum antibodies do develop an intestinal immune response to poliomyelitis. Sabin demonstrated that these infants often develop a secondary type of circulating antibody response when challenged with killed poliovirus vaccine at 3 months of age and that they have lower viral excretion rates following rechallenge with the same vaccine type (*129*). Keller et al. demonstrated the development of intestinal IgA antibodies in infants who shed virus following TOPV immunization but who did not develop serum IgG antibodies (*75*). Pre-immunization passive neutralizing antibody titres of more than 1:128 appeared to correlate with a blunted infant serum antibody response to TOPV.

Keller also found maternal IgG in the intestinal secretions of infants born to women with high levels of IgG serum antibodies. This finding may help explain the lower rates of virus excretion in immunized infants born to highly immune mothers (*63*, *84*, *115*, *145*). Other studies have demonstrated a weak correlation between pre-immunization infant serum antibody titres and the excretion of polio virus following immunization (*74*, *106*). The viral excretion data in Table 1 reflect studies where viral cultures were positive three or more days after feeding of OPV. Some of the variability in the results may have been caused by differences in study methodology. Some investigators cultured the stool daily and others obtained only single stool specimens (usually 4–8 days after feeding).

The efficacy of TOPV given from birth to 12 weeks of age

The efficacy of live oral poliovirus vaccines in the first week of life is shown in Table 1. The serological

Table 2. Serum antibody response following one dose of OPV or TOPV at 1–12 weeks of life

Investigator, year, and reference	Country	Vaccine type[a]	No. of infants	Age at immunization (weeks)	Percentage with antibody response[b]		
					I[a]	II	III
Plotkin, 1959 (*116*)	USA	I,III	10–17	<4	77		80
		I,III	10–18	4–8	83		60
		I,II,III	11–18	>8	100	89	100
Pagano, 1961 (*105*)	USA	I	30	1–5	67		
		II,III	9–22	5–10		78	77
Batson, 1962 (*12*)	USA	TOPV	16	6	44	81	50
		TOPV	13	12	54	100	54
		TOPV	16	18	44	94	50
John, 1976 (*69*)	India	TOPV[c]	26	6–41	42	85	31
		I, II, III[c]	14	6–41	89	93	76
McBean, 1984 (*91*)	USA	TOPV	187	6–13	85[d]	87[d]	83[d]

[a] I, II,III indicate monovalent vaccines. TOPV indicates trivalent oral poliomyelitis vaccine.

[b] Percentage with higher than expected titres based on pre-immunization antibody titres.

[c] High-titre vaccines.

[d] Percentage with antibody at 5–6 months of age.

Table 3. Serum antibody response following two or three doses of TOPV initiated at approximately 6–8 weeks of life

Investigator, year, and reference	Country	No. of doses[a]	No. of infants	Percentage with antibody at 5–6 months of age		
				I	II	III
Murphy, 1967 (*99*)	USA	2	134	98	100	100
McBean, 1984 (*91*)	USA	2	189	93	99	95
Hardy, 1970 (*62*)	USA	2	110	92	99	90
		3	103	93	100	91
Batson, 1962 (*12*)	USA	3	16	88	100	81
Oduntan, 1978 (*101*)	Nigeria	3	56	48	92	52
Dong De-Xiang, 1984 (*37*)	China	3	109	100	98	99

[a] Separated by 4–8-week intervals.

response from single doses of TOPV are shown in Table 2 and the responses following two or three doses beginning at 6–8 weeks of age are shown in Table 3. Although the methods and results of reported investigations have varied, the following general conclusions can be drawn from the available data.

(*a*) No differences in the effectiveness of TOPV have been demonstrated for two- or three-dose primary series starting at 4–6 weeks of age, compared with starting at older ages. Specifically, there is no reason to delay initiating immunization with TOPV until 3 months of age as is commonly practised in many countries (*63*).

(*b*) Live oral poliovirus vaccine effectively induces infections in infants of all ages including the newborn period. Although very high levels of passively acquired maternal antibodies may modify or block the mucosal response, infections were induced in 50–100% of infants in most studies. Most infants excrete the virus for less than four weeks. Therefore, the administration of a single dose of TOPV at birth should not interfere with the immune response to vaccine at 4–6 weeks of age.

(*c*) The serological response following immunization is affected by maternal antibodies during the first few weeks of life. High titres of these passively acquired antibodies may block the infant's serological response by preventing entry of the virus to the bloodstream.

(*d*) The beneficial effect of a dose of TOPV given at birth has been demonstrated most clearly in studies recently completed in China (*37*, *46*) (Fig. 2). Although the final antibody titres at 4 months of age were identical, a higher percentage of infants fed a dose at birth had antibodies against all three types of poliovirus at younger ages. Thus, immunization at birth assured higher levels of protection at earlier ages against wild-type polioviruses. In another recent study carried out in India, the serological response was as good in infants beginning immunization at 1–4 weeks of age as in older children (Table 4) (*72*).

(*e*) No harmful effects have been observed from the early administration of live oral poliomyelitis vaccines. Specifically, there is no evidence of immune "tolerance" induced by early immunization. Infants who fail to respond with serum antibodies following immunization in the neonatal period respond normally to subsequent doses of vaccine. In some instances, a transient but mild increase in frequency of loose stools has been noted (*37*).

(*f*) TOPV administered to breast-fed infants during the first three days of life may be somewhat less effective than immunization of older breast-fed infants or non-breast-fed infants (*63*, *73*, *74*, *83*, *115*, *145*). However, 30–80% of breast-fed infants excreted virus when fed in the first three days and 20–40% developed antibody responses (*63*, *84*, *115*, *128*, *145*). There is no significant effect of breast-feeding on older infants (*32*, *70*). The explanation for these apparently discrepant findings is that colostrum produced in the first three days after childbirth contained four times the secretary IgA antibody concentration of breast milk obtained after the fourth day (*115*). These lower levels of antibody are less likely to prevent virus multiplication. Thus, there is no reason to withhold breast milk from infants who receive OPV at or after six weeks of life (*32*, *70*, *76*, *111*).

FACTORS AFFECTING THE RESPONSE TO DIPHTHERIA AND TETANUS TOXOIDS AND PERTUSSIS VACCINE

There are at least eight variables that have been demonstrated to affect the reported serum antibody responses following DPT immunization: (1) the quantity or potency of the antigen administered; (2) the presence and effectiveness of adjuvants; (3) the

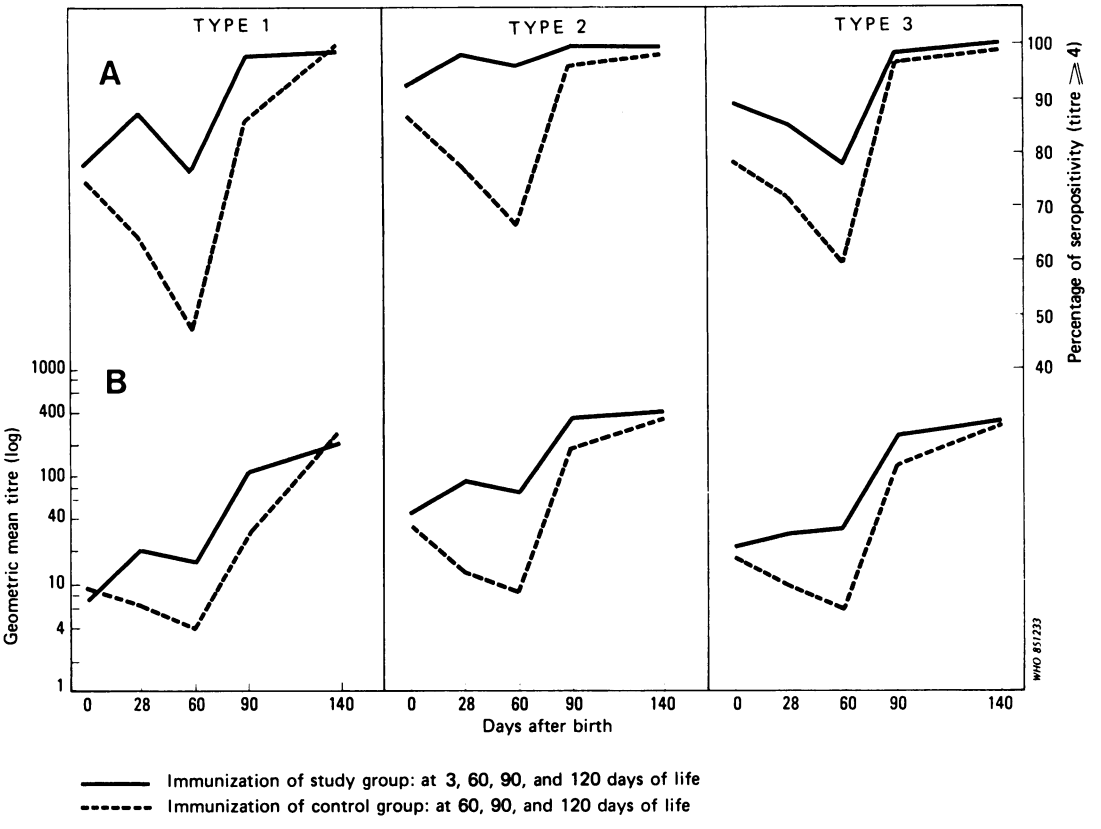

Fig. 2. Comparison of seropositivity (A) and of geometric mean titres of polio neutralizing antibodies (B) against 3 types of poliovirus: control and study groups, China, 1982 (*46*).

Table 4. Serum antibody response in neonates and infants to three doses of TOPV according to age at which immunization was started[a]

Age at which the first dose was given (weeks)	No. of children studied	Percentage with antibody response[b]		
		I	II	III
1	23	83	83	78
2	30	80	90	70
3	25	64	96	56
4	26	90	95	65
5	19	47	68	42
6	16	69	81	63
1–6	139	73	87	63
6–20[c]	86	72	88	79
6–51[d]	61	66	95	72

[a] According to T.J. John (*72*).
[b] Antibody response based on increased levels above that expected from the decline in maternal antibody.
[c] Infants with maternal antibody, according to T.J. John et al. (*70*).
[d] Infants without maternal antibody, according to T.J. John et al. (*70*).

age at immunization; (4) the number of doses administered; (5) the interval between doses; (6) the time interval between the last dose and serum antibody testing; (7) the presence or absence of passively acquired antibodies; and (8) the sensitivity and reliability of the antibody assays.

The purpose of the present review is to evaluate only one of these variables — age of administration of the first dose of DPT. Since other variables may have affected the results of studies reviewed here, they will be reviewed briefly and dealt with in the individual sections where appropriate. Whenever possible, data relevant to these variables have been included in the Tables and graphs.

Potency or amount of antigen administered

Data from studies where unsatisfactory quantities or impotent vaccines and toxoids were utilized have not been included in this review. The results from some otherwise excellent field trials have not been useful because impotent pertussis vaccines were utilized (*18*). The need for standardization of vaccine and toxoid potency testing has been reviewed in detail elsewhere (*23*, *123*). Unfortunately, many of the studies reviewed here were performed prior to international standardization of procedures and preparations. Also, several investigators utilized preparations of greater than normal quantity or potency. However, these investigators frequently tested the response of infants immunized at different ages, thus allowing for the evaluation of age as a variable. Therefore, their data have been included in the Tables.

Adjuvants and passive antibodies

Fluid or plain toxoids and pertussis vaccines are much less effective than adjuvant preparations, especially for primary immunization. The most effective and widely used adjuvants have been aluminium hydroxide and aluminium phosphate (*6*). Calcium phosphate has been widely used in France (*125*). Although different investigators have argued for the use of one adjuvant over the others, the published data have not shown a consistent superiority of a particular preparation (*56*, *100*). The variable results can probably be explained by differences in the degree of adsorption due to suboptimal techniques in the manufacturing process (*6*). All three of the above adjuvants are acceptable for routine use with DPT. Preparations without an adjuvant are affected by passively acquired antibodies to a much greater extent that adjuvant preparations. An analogous situation of possible interference between passive and active immunity is the use of tetanus toxoid simultaneously with tetanus antitoxin or tetanus immune globulin for tetanus prophylaxis following injuries. Interference did occur between passive and active immunity when fluid toxoids or large doses of antitoxin were used (*29*), and some authors did not recommend simultaneous use of toxoid and antitoxin (*107*). However, at present there is a general agreement that active–passive immunization may be an effective procedure when potent, absorbed toxoids are used, when toxoid and antitoxin are injected at separate sites, and when a standard antitoxin dose is used and subsequent doses of tetanus toxoid are given after 4–6 weeks and 6–12 months (*40*, *41*, *50*, *126*, *134*, *138*). A similar situation occurs in young infants who have passively acquired antibodies from their mothers. Adjuvant diphtheria and pertussis preparations have been shown to be significantly more effective than plain preparations in infants with passive antibodies at the time of immunization (*20*, *87*, *95*, *119*, *130*, *144*). Since WHO recommends that only adjuvant DPT preparations be utilized in immunization programmes, the data from fluid (or plain) preparations have been omitted from the Tables and figures presented here.

The interval between doses and the total number of immunizations administered

Data regarding the interval between DPT injections and the effectiveness of each dose have been summarized in a recent publication (*103*). In general, higher antibody titres against all three components of DPT vaccine are observed following primary immunization with longer intervals between doses. However, the effect is temporary. No significant differences in the percentage of individuals protected or in mean antibody titres one year after completion of the primary series administered at monthly and bimonthly schedules were noted by Brown et al. (*18*). The first dose of standard potency preparations provides little or no protection against disease. Two doses of tetanus toxoid induce protective levels of antibody in almost 100% of infants and two doses of adsorbed diphtheria toxoid induce protective levels of antibody in 70–100% of infants. One investigation revealed that two doses of standard DPT vaccine administered at an interval of two months resulted in pertussis agglutinin levels similar to those achieved following three doses given at approximately monthly intervals. This study was, however, marred by the use of pertussis vaccines of widely varying potency (*148*). In other studies two doses of a vaccine of higher than standard potency, administered at a six-month interval, resulted in a satisfactory agglutinin response that was similar to the response observed following three doses given at three-month intervals (*89*, *98*). However, the antibodies waned more rapidly in the two-dose group, the difference between the groups becom-

ing statistically significant after an interval of two years (*98*). One DPT preparation did not produce satisfactory results even when two doses of a vaccine were administered at a six-month interval (*90*).

Clinical efficacy studies evaluating the use of two doses of DPT vaccine are rare and the results are not consistent. Although the reported protection following pertussis immunization has been highly variable, two doses of DPT resulted in more than 80% protection in an outbreak of whooping cough in a rural area of Indonesia (*45*). In another investigation of household exposures, the estimated vaccine efficacy for two doses of DPT vaccine was only 59% (*44*). These topics will not be discussed in detail in this review.

The effect of age and passive antibody

There is an age-related host response to immunization with most antigens. The most significant factor influencing the age-related response to antigens is the modifying effect of passively acquired maternal antibodies in young infants. Vahlquist, Di Sant Agnese and other investigators have demonstrated that infants without maternal antibodies respond almost as well as older children following immunization with diphtheria toxoid (*21*, *27*, *34*, *36*, *141*, *142*). Similarly, infants born to mothers with low levels of antitetanus antibodies respond to adsorbed tetanus toxoid at one week of age almost as well as older children (*33–35*). The higher the level of passive diphtheria antibody at birth and subsequently at the time of immunization, the more difficult it is to induce active immunity by giving diphtheria toxoid.

One study showed that the average diphtheria antitoxin content in the serum of 1-day-old infants was about 60% of that in cord blood. Subsequently, the infants lose their passively acquired immunity to diphtheria at a steady rate; one half of the 1-day-old infants' antibody content was lost every 4½ weeks (*9*).

Several studies have shown that levels of passive antibody below 0.1 IU/ml had a minimal effect on immunization in the first few weeks of life. However, levels above 0.1 IU/ml may temporarily interfere with immunization and levels above 1 IU/ml may result in blocking the response to two doses of diphtheria toxoid (*21*, *27*, *34*, *141*).

In areas where cutaneous diphtheria is common, a high percentage of adults have natural immunity to the disease. Mothers in these areas often have high antibody titres. Workers in Mali found that 87% of the samples of cord blood contained antibody levels of more than 0.1 IU/ml and half of them had at least 1.0 IU/ml (*4*). In other tropical countries nearly all persons acquired natural immunity to diphtheria by the age of 15–20 years. On the other hand, in areas where the reservoir of *Corynebacterium diphtheriae* is reduced, mothers are less likely to have immunity and their babies seldom acquire passive protection.[a] In the studies reviewed in this paper, 30–50% of infants had some passive antibody present at one to six weeks of age. Only 7% of infants in Christie's study had levels greater than 1.0 IU/ml at six weeks of age (*27*).

In most investigations less than 10–20% of infants had any antitetanus antibody prior to immunization at one or more weeks of age. These antibodies did not significantly alter the effect of immunization with adsorbed toxoids (*10*, *11*, *33*, *34*, *113*). However, it is likely that mothers immunized with tetanus toxoid during pregnancy will transmit higher titres to their infants which could modify their response to immunization in the first few weeks of life (*61*, *80*). However, Gill et al. observed minimal differences in the IgG antitetanus response in infants whose mothers had received tetanus toxoid in pregnancy, compared with control infants following immunization with DPT at 2, 4 and 6 months of age (*55*). The investigators believe that the infants were primed immunologically while *in utero* when their mothers received tetanus toxoid. However, their presentations of the data were incomplete and their argument was not convincing. The important conclusion from the available data is that DPT immunization at 6–8 weeks of life is highly effective in infants regardless of the presence of low levels of maternal antibody.

For some non-protein immunizing agents, there is a well-described maturational effect on the immune response. This has been best described for bacterial polysaccharide vaccines (*57*, *110*). Although the results vary for individual preparations, most infants fail to develop a satisfactory response until 18 months of age or older. The response continues to improve with increasing age until after 8 to 10 years of age. These polysaccharide antigens are T-cell-independent antigens. However, most of the available data suggest that passively acquired maternal antibodies are the primary factors influencing the age-related response to the DPT antigens.

Breast-feeding at the time of the first dose of DP vaccine, given at two months of age, had no impact on the results of the Schick test (*13*). No significant differences were found in the tetanus antibody response following DPT immunization in breast- and bottle-fed children (*136*). Based on our knowledge of the immune response, we believe that breast-feeding should not have any effect on the antibody response to any of the components of DPT vaccine.

[a] HALSEY, N. & GALAZKA, A. *The effectiveness of DPT and oral poliomyelitis immunization schedules initiated from birth to 12 weeks of age*. Unpublished WHO document EPI/GEN/84.8/Rev.1.

Antibody assays

The response to immunization with toxoids has usually been measured by detecting toxin-neutralizing antibodies utilizing mice or guinea-pigs for tetanus antibodies and guinea-pigs or rabbits for diphtheria antibodies. Although there have been some differences in the methods employed in these assays, the results in most laboratories have been satisfactory and within reasonable limits of variability (*26*, *52*, *109*). Other *in vitro* tests to measure antibody responses without utilizing animals have been developed. The indirect haemagglutination test, ELISA and radioimmunoassay (RIA) tests are simple, economical and sensitive procedures. The results generally parallel those obtained with the neutralization tests, but antibody activity as determined by *in vitro* methods may be influenced by the class, affinity or valency of the antibody tested. Tetanus antibody unitage as determined by the indirect haemagglutination test was often 5 to 10 times higher than the neutralization test results, especially at low antibody levels (*52*, *53*). Therefore, any *in vitro* technique should be validated by comparing its results with those obtained with the *in vitro* neutralization method which is the method of reference. The "protective" level of antitoxin antibodies for diphtheria and tetanus is generally believed to be 0.01 neutralizing units per ml. The term "protective level" was often overused in studies where 0.01 haemagglutinating units or ELISA or RIA units were automatically assumed to be an equivalent of the same level of neutralizing units (*31*, *108*). Lower levels of maternal antibody may provide some protection against neonatal tetanus (*88*). As in other immunological situations, protection is dose-dependent and not an all-or-none phenomenon. Rarely, mild cases of tetanus have been observed in individuals with a history of immunization or persons with 0.01 neutralizing antibody units (*15*, *42*).

The primary antigens in whole-cell pertussis vaccines responsible for inducing protection against disease were unknown until recently. Most investigators have utilized the serum agglutinin response to evaluate the effect of vaccines. Agglutinins are not the protective antibody, but the results have correlated with protection in most studies (*92*, *130*). Sako and Miller demonstrated that levels of 1:80 were associated with partial protection, but complete protection was not observed until titres of 1:320 or greater (*96*, *130*). However, the degree of protection afforded by different vaccines was not always related to their ability to produce agglutinin in children. A vaccine containing disrupted *Bordetella pertussis* organisms gave good protection in children although it stimulated an agglutinin response which was less than those produced by whole bacteria vaccines with equally good protective properties (*93*). Table 5 summarizes the available data regarding the proportion of infants developing titres greater than 1:320 in immunization schedules beginning prior to 3 months of age. Since lower titres may be associated with partial protection, geometric mean titres (GMT) were calculated from the author's published tables when possible. In addition, the results obtained in different laboratories have varied because the type of organism utilized for the agglutination test influences the outcome of the laboratory test. The types of organisms utilized for vaccine production and for laboratory testing have varied (*81*, *86*).

A subcomponent (acellular) pertussis vaccine has been developed recently and is currently undergoing field and laboratory evaluations (*132*).[b] The protective antigens in the vaccine are appropriately detoxified lymphocytosis-promoting factor (LPF) and purified filamentous haemagglutinin (FHA). There are, however, some other potentially important protective antigens which require further studies. The precise methods for determining safety and potency of acellular vaccines are still under investigation. The development of an ELISA technique may facilitate studies on the response to LPF and FHA following immunization and natural infection (*8*, *19*, *59*, *81*, *94*, *143*). Baraff et al. measured serum agglutinins and the response to FHA and LPT with an ELISA technique in infants who received whole-cell pertussis vaccines (*8*). The response to these antigens in the new acellular vaccine appears to be as good as the response with whole-cell vaccines, and the acellular vaccines were more effective at inducing protection in mice. Other studies do not show this enhanced effect of cellular vaccines convincingly (*124*).[b] Furthermore, Baraff et al. demonstrated good anti-LPF and anti-FHA responses with whole-cell vaccines despite the induction of relatively low (105–200) agglutinin titres (*8*). They also demonstrated that maternal antibodies may modify the response in very young infants. When the acellular vaccines become available it will be important to evaluate their efficacy in infants at four weeks or more of age. It is possible that they could be used effectively at even younger ages when diphtheria and tetanus toxoids also have some beneficial effect.

THE EFFICACY OF IMMUNIZATION WITH TETANUS TOXOID BEGINNING AT 1–12 WEEKS OF AGE

Tetanus toxoid is the most effective immunizing agent available for routine use today. The results of

[b] *Report of the meeting on the results of the WHO collaborative study on the acellular DPT vaccine, Geneva, 28–30 May, 1984.* Unpublished document WHO/BVI/PERT/84.1.

Table 5. Serum agglutinin response following immunization with adsorbed pertussis vaccine schedules initiated from one day to three months of age

Investigator, year, and reference	Vaccine type	Potency in units per single dose	Amount of organisms $\times 10^9$ per single dose	No. of infants	Age at immunization (weeks or days, when specified)		Age at antibody testing (months)	Percentage with agglutinins	
					1st dose	2nd/3rd doses		⩾1:320	GMT
Provenzano, 1965 (*118*)	DPT	7	10,10,10	8	1 day	1,2	3	25	48
Barrett, 1962 (*11*)[a,b,c]	DPT	NA		49	1-2 days	4-8,8-13	3-4		(50)
				33	4-8	8-13,13-16	4-5		(100)
Baraff, 1984 (*8*)	DPT	NA		10	3.5 days	8,18,26	9		105
				13	8	18,26	9		200
Pstragowska, 1966 (*121*)	DPT	NA		103	6 days	5,9	NA	23	62
Di Sant Agnese,									
1949 (*33*)[d]	DPT		10,20,20	125	1	5,9	3.5	54	260
1950 (*36*)			10,20,20	108	1	5,9	6	33	126
			10,20,20	47	1	5,9	12	34	118
Gaisford, 1960 (*51*)[e]	DPT	NA		31	1	5,9	3.5	19	47
Butler, 1962 (*20*)	P		10,10,20	121	1	6,13	4		131
Miller, 1949 (*95*)	P		16,24,40	115	6	10,14	4.5	63	259
Waddell, 1946 (*144*)[f]	P		40,80,80	50	1	4,9	6	90	1432
			40,80,80	43	8	13,17	6	95	1740
Goerke, 1958 (*56*)[g]	DPT		30,30,30	80	<2	6,10	3.5	12	34
Adams, 1947 (*2*)	P		20,40,40	21	1	2,3	1	NA	160
				19	4	8,12	4-5	NA	80
Dupan, 1958 (*38*)[d]	DPT	NA			0-2	4-8,8-12	3		320
					4-8	8-12,12-17	4		450
Sako, 1947 (*130*)[h]	P	NA	8,12,20	1007	4-8	8-12,12-16	6-8	51	131
	DPT	NA	10,20,20	1294	4-8	8-12,12-16	6-8	28	71
Lippset, 1953 (*87*)	P		20,30,30	22	4	8,12	6	82	1280
Provenzano, 1959 (*119*)[h]	DPT	7	10,10,10	7	4	8,12	6		120
		7	10,10,10	25	4-12	8-16,12-20	6-8		92
Peterson, 1951 (*112*)[h,i]	DPT		20,40,40	289	6	12,18	7.5	71	642
Murphy, 1984 (*100*)[j]	DPT	8.5-11.5U		23	8-12	12-16,16-22	6-9		214
	DPText[k]	4-5.5 U		19	8-12	12-16,16-22	6-9		118
Weihl, 1963 (*146*)[l,m]	DPT	⩾4 NIH		67	6-12	10-18,14-24	?	(85)	
	DPText.	⩾4 NIH		31	6-12	10-18,14-24	?	(97)	
Swartz, 1984 (*137*)[n]	DPT	NA		14	8	14	4.5		363
	DPT	NA		44	8	12,26	7		258

[a] Median values, not GMT
[b] Pertussis vaccines have lost potency (or been of low potency).
[c] Median titres of 250 for schedules beginning over three months of age.
[d] Higher response in infants immunized beginning >6 months of age.
[e] Titres ⩾1:256.
[f] The unusually high titres may have been an artifact of the test procedure.
[g] Aluminium phosphate adjuvant produced higher titres than aluminium bydroxide.
[h] No difference in antibody titres for infants immunized beginning after three months of age.
[i] Titres ⩾1:400.
[j] Titres lower with aluminium phosphate than with alum.
[k] Extract of pertussis vaccine.
[l] Extract of vaccine much more effective at inducing mouse protective antibody (97% vs 54%).
[m] Percentage with agglutinins, not protective titres.
[n] Quadruple vaccine: DPT + inactivated poliovirus vaccine.

the studies summarized in Table 6 reveal that either two- or three-dose regimens induce protective levels of antibody in almost 100% of infants. Immunization as early as one to two days of age is effective when adsorbed preparations are utilized. The titres were higher following three-dose regimens and presumably could lead to a longer duration of immunity (see above for further discussion).

THE EFFICACY OF IMMUNIZATION WITH DIPHTHERIA TOXOID BEGINNING AT 1-12 WEEKS OF AGE

The results of studies evaluating two- and three-dose regimens of diphtheria toxoid are shown in Table 7. Immunization beginning as early as one week of life has been shown to be effective at inducing protective antibody levels. Three-dose schedules result in

Table 6. Serum antibody response following two or three doses of tetanus toxoid in immunization schedules initiated from birth to three months of age

Investigator, year, and reference	No. of infants	No. of doses of DPT[a]	Age at immunization (weeks)		Age at antibody testing (months)	Percentage with >0.01 IU/ml[b]
			First dose	2nd/3rd doses		
Cooke, 1948 (*30*)	73	2	4–12	12–20	4–6	100
Peterson, 1951 (*113*)	284	2	6	18	7.5	99
Barrett, 1962 (*11*)[c, d]	47	3	1–2 days	4–8, 8–12	3–4	100
	35	3	4–8	8–12, 12–16	4–5	100
Di Sant Agnese,						
1949 (*33, 35*)	128	3	1	5, 9	3.5	100
1950 (*36*)	63	3	1	5, 9	12	100
Gaisford, 1960 (*51*)[e]	31	3	1	5, 9	3.5	100
Barr, 1955 (*10*)[e, f]	61	3	1	6, 14	6.5	100
Bradford, 1949 (*17*)[g]	38	3	6	10, 14	6	100
	45	3	6	10, 14	9	100

[a] Cooke used DT and Peterson used DPT + typhoid. No information available from most studies on potency or amount of toxoid per dose. Barr's contained 6 Lf, Di Sant Agnese and Peterson reported 1055 MLD per dose.

[b] Some authors reported antitoxin units, AU/ml.

[c] Data reported by percentiles; ≥90% of infants had titres >1.0 IU/ml (100% response).

[d] Median titres 1 IU/ml, lower than titre for infants immunized at 3–4 months and 5–6 months (10 IU/ml).

[e] All titres >0.10 IU/ml.

[f] At 12 months of age, 100% had >0.1 IU/ml.

[g] All titres >0.05 IU/ml.

Table 7. Serum antibody response following two or three doses of diphtheria toxoid in schedules initiated from birth to three months of age

Investigator, year and reference	Toxoid amount in Lf units[a]	No. of doses	No. of infants	Age at immunization (weeks)		Age at antibody testing (months)	Percentage with ≥0.01 IU/ml
				1st dose	2nd/3rd doses		
Christie, 1951 (*27*)[b]	35	2	274	6	18	7.5	69
Cooke, 1948 (*30*)[b]	NA	2	75	4–12	12–20	4–6	77
Butler, 1954 (*21*)[b, c]	72.5	2	61	1	14	6	98
		3	86	1	6, 14	3	97
		3	86	1	6, 14	6	95
Barrett, 1962 (*11*)[d]	NA	3	47	1–2 days	4–8, 8–12	3–4	75
		3	35	4–8	8–12, 12–16	4–5	100
Di Sant Agnese,							
1949 (*33–35*)[e]	15–30	3	123	1	5, 9	3.5	85
1950 (*36*)	15–30	3	103	1	5, 9	6	72
	15–30	3	57	1	5, 9		77
Gaisford, 1960 (*51*)	NA	3	31	1	5, 9	3.5	100
Barr, 1955 (*10*)[b, e]	30	3	61	1	6, 14	6	100
	30	3	56	1	6, 14	12	93
Goerke, 1958 (*56*)	NA	3	88	<2	4–6, 8–10	3.5	100
	NA	3	54	<2	4–6, 8–10	12	100
Bradford, 1949 (*17*)[f]	NA	3	38	6	10, 14	6	97
	NA	3	45	6	10, 14	9	100

[a] DPT or DPT + polio except in Butler (D), Cooke (DT), and Christie (DPT + typhoid).

[b] Some suppression with high titres of maternal antibody.

[c] Lower mean titres after two doses, then three doses.

[d] Data reported by percentiles. Over 75% of infants had >0.1 IU/ml, the lowest tested.

[e] Titres ≥0.03.

[f] 97% ≥0.1 IU/ml, the lowest titre tested.

close to 100% protection. Two doses in most studies resulted in 70–98% of the infants developing antibody levels of at least 0.01 IU/ml. However, some of these studies were performed with higher than normal concentrations of toxoids and the antibody titres in all studies decreased after 6–12 months. Therefore, three doses should be considered optimal for primary immunization. A booster dose of toxoids should be administered 6–18 months after the primary series or upon entrance to school at four to six years of age in order to assure the persistence of antibody (*103*).

Passively acquired maternal antibodies modify the response to immunization in young infants (see above, section on effect of age and passive antibody). However, the response to three doses of diphtheria toxoid given at 4–8 week intervals has resulted in satisfactory responses when started at one to eight weeks of life, even when some passive antibody was present at the time of the initial immunization.

PERTUSSIS VACCINE ADMINISTERED FROM BIRTH TO 12 MONTHS OF AGE

Evaluation of the efficacy of pertussis vaccine has been more difficult than any of the other antigens discussed in this paper. The lack of a simple laboratory test that measures protective antibodies has made field testing and standardization of vaccines very difficult. As a result, a wide variety of vaccines of variable efficacy have been utilized in field trials and in general immunization programmes. Some of the problems with the agglutinin test were discussed above. However, some conclusions can be drawn regarding the age of immunization from the data on agglutinin titres. The most useful studies compared the agglutinin response at different ages using the same vaccine preparations and laboratory techniques.

Whole-cell pertussis vaccine is a less effective antigen than diphtheria and tetanus toxoids. This difference is most clearly noted when immunization was begun in very young infants. The results from the well-designed studies by Di Sant Agnese demonstrate this point most clearly (*33*).

Immunization beginning at one week of age with pertussis vaccine is less likely to result in "protective" antibody levels than it is with diphtheria and tetanus toxoids. The GMT of serum agglutinins observed, following immunization in the first week of life, was much lower than immunization beginning at older ages. Other studies showed that only 12–23% of infants who received the first dose of DPT vaccine within the first two weeks of life responded with agglutinin titres of 1:320 or more. Similar results were obtained by Barrett (*11*), Provenzano (*118*, *119*), and Baraff et al. (*8*). Baraff's study demonstrated that infants immunized at two, four and six months of age with whole-cell pertussis vaccine developed antibodies to LPF and FHA (see above), in spite of only a moderate agglutinin response. They also demonstrated that an additional dose of DPT at 3½ days of age was not beneficial in producing long-lasting immunity against pertussis. The infants who received the early dose developed lower agglutinin titres and lower IgG anti-LPF titres. This effect was most noted in infants with low cord-blood titres. Therefore, the decreased response was not entirely due to interference (or blocking) by maternal antibodies.

Most studies revealed that immunization initiated after one week of age resulted in reasonable agglutinin titres. The response to immunization beginning at four or more weeks of age was better in most studies and almost as good as the results obtained after eight or more weeks. The few studies that evaluated protective efficacy following immunization of young infants suggest that the vaccine is effective. Butler et al. found a 64% protective efficacy in infants who had received three doses of adsorbed pertussis vaccine at 1, 9 and 13 weeks of age, even though the geometric mean antibody titre for agglutinins was only modest (*20*). Sako et al. found that the protection against disease correlated with the serum agglutinin titres but immunized infants without detectable agglutinins also had some protection against disease (*130*, *131*). Overall, there was an 87% reduction of disease in infants who had received three doses of DPT beginning at 4–8 weeks of age. Also, Abayomi et al. appeared to improve the protection against pertussis in a Nigerian village by lowering the age of the first dose of DPT to one month (*1*). Therefore, immunization with whole-cell pertussis vaccine, beginning after four weeks of age, should result in a satisfactory antibody response and protection against disease. Although the agglutinin titres induced by immunization at older ages might be somewhat higher, there is no evidence that this would result in increased protection against the disease.

THE NEED FOR COMPLETING THE PRIMARY IMMUNIZATION SCHEDULE AS EARLY IN LIFE AS POSSIBLE

The objective of immunization programmes is to prevent disease. In order to be most effective, primary immunization must be completed before the age when infants are at high risk for contracting these diseases. Although passively acquired maternal antibodies provide temporary protection, most infants are susceptible to pertussis prior to two months of age

and to poliomyelitis prior to six months of age. Before the widespread use of immunizations in developed countries, 50–67% of all deaths from pertussis occurred in infants under six months of age (*38*, *131*). Limited data from developing countries reveal a similar high mortality in young infants (*22*, *28*, *39*, *97*). Although the age-specific attack rates are higher for children from one to four years of age, the case fatality rate has been highest in infants in all countries. Since satisfactory protection against pertussis is not achieved until after the third dose, primary immunization should be completed as early in life as possible.

Lameness surveys have revealed that the prevalence of paralysis from poliomyelitis is much higher than was known 10 years ago (*16*, *82*). The highest risk period for acquiring paralytic poliomyelitis is from six months to two years of age. Therefore, immunization against polio should be completed prior to six months of age. Although the protection achieved by two doses of TOPV in industrialized countries appears to be adequate (*62*), lower response rates have been observed in tropical countries (*25*, *67*, *71*). Therefore, the partial protection achieved by two doses of TOPV should not be depended on too heavily. John has shown that the infants' response rates may be improved with multiple doses of vaccines (*68*). Since immunization in the neonatal period has been demonstrated to have a beneficial effect in all studies to date, this neonatal dose should be added to the primary regimen in all countries where polio has not been adequately controlled.

An additional reason for completing the primary immunization schedule with DPT and TOPV prior to six months of age is the occasional case of injection-associated paralysis when infants who are incubating wild-type polio infections receive intramuscular immunizations. If the primary series is completed prior to six months, then infants will be protected against wild-type polio by TOPV and they will not be receiving DPT injections during the highest period of exposure to polio.

Mothers are most likely to seek preventive services and routine health care interventions in the first few months of their children's life. This can be seen most clearly in immunization programmes by examining the data on completion of a three-dose series of DPT or TOPV. In a one-year time period, the number of infants receiving their third dose of vaccine should be approximately the same as the number receiving their first dose minus the expected mortality. However, in almost all countries where these data have been examined, a significantly lower percentage of infants complete the schedule than receive the first dose.

Moreover, most infants do not receive their first, second and third doses of vaccine at the recommended ages. When a specific age is recommended for the first dose of DPT and TOPV, infants are often seen four to eight weeks later than the scheduled visit. In developing countries, the problems of vaccine delivery are compounded and few infants receive immunizations at the scheduled times. If six weeks is recommended as the age for the first dose of DPT, most infants will receive their first dose of vaccine at an older age. For example, in India, Paul et al. intended to start immunizations at three months of age, but only 6 out of 80 infants started at this age; 66 infants were older than six months when they received their first dose of vaccine (*108*). Also, in Lesotho, only 45% of infants received their first dose of oral polio vaccine within two months of the recommended age of three months.[c] This percentage had decreased to 31% for infants who received the third dose within two months of the recommended seven months of age (the immunization schedule for Lesotho has recently been revised). Although other factors undoubtedly contribute to the failure to receive all of the recommended immunizations, the available data suggest that completing the schedule early in infancy would improve coverage rates.

CONCLUSIONS AND RECOMMENDATIONS

Immunization of newborns with TOPV is a safe and effective means of improving protection against disease and OPV may be administered simultaneously with BCG vaccine (*104*). Although the serological response in the first week is less than that observed from immunization of older infants, 50–100% of neonates benefit by developing active infections and local immunity in the intestinal tract. In addition, 30–50% of the infants develop serum antibodies to one or more poliovirus types. Many of the remaining infants have been immunologically primed and they respond promptly to additional doses later in life.

For the 10–40% of infants in many countries whose only encounter with preventive services is at the time of birth, this single dose of vaccine will offer some protection against disease and they will be less likely to be a source of transmission of wild polioviruses during infancy and childhood. For the 20–40% of infants who receive only one or two additional doses of poliovirus vaccine, the initial dose at birth will help ensure higher levels of immunity against poliomyelitis.

Immunization with tetanus toxoid is highly effective in the first week of life and diphtheria toxoid

[c] KINGDOM OF LESOTHO, MINISTRY OF HEALTH. *Report on a joint mission to evaluate the Lesotho Expanded Programme on Immunization*, Ministry of Health, Save the Children Fund, UNICEF/WHO, Lesotho, 1982.

only slightly less effective. However, pertussis vaccine is less effective in the first week of life and some data suggest that a dose in the first week may result in lower antibody titres after subsequent immunizations. The administration of three or more doses of adsorbed pertussis vaccine has been demonstrated to induce protection against disease when the first dose was given after one week of age. Immunization with DPT beginning in the first three weeks of life results in lower antibody titres than immunization beginning at older ages. The final titres achieved with schedules beginning at four to eight weeks of life are somewhat lower than immunization beginning at three to six months of age. However, when potent, adsorbed preparations are used, the percentage of infants with protective levels of antibody are not improved by waiting until an older age.

Beginning immunizations early in infancy will result in early protection against diphtheria, tetanus, pertussis and poliomyelitis. Additional benefits may be improved compliance and higher completion rates for the primary series prior to six months of age when infants are at highest risk of contracting severe pertussis and poliomyelitis.

Specific recommendations

(1) Routine immunization with DPT and TOPV can be safely and effectively initiated at six weeks of age in all countries.

(2) In countries where poliomyelitis has not been controlled, TOPV should be given at birth or at first contact with health services, and then at six weeks of age followed by two additional doses four weeks apart.

RÉSUMÉ

VACCINS DTC ET ANTIPOLIOMYÉLITIQUE BUCCAL (VPO): EFFICACITÉ DES SCHÉMAS DE VACCINATION COMMENÇANT ENTRE LA NAISSANCE ET L'ÂGE DE 12 SEMAINES

Il convient de vacciner les nourrissons dès que possible pour les protéger contre les maladies naturelles avant qu'ils n'atteignent l'âge où les risques sont les plus grands. Les nourrissons nés de mères immunisées reçoivent passivement des anticorps qui les protègent pour des périodes plus ou moins durables. Dans l'idéal, les vaccinations devraient susciter une réponse immunitaire active avant que l'enfant ne perde la protection passive que lui confèrent les anticorps maternels, ce qui leur assurerait une protection continue depuis la naissance sans qu'à aucun moment ils ne deviennent sensibles aux maladies naturelles.

Toutefois, les anticorps maternels peuvent modifier ou supprimer la réponse du nourrisson à la suite de la vaccination, surtout si la préparation est peu active.

En 1977, date où les premières directives du Programme élargi de vaccination ont été formulées, on a décidé de commencer l'administration systématique à l'âge de trois mois par souci d'uniformité avec les directives suivies dans certains pays industrialisés.

Plusieurs auteurs ont néanmoins recommandé de commencer l'administration des vaccins DTC et VPO plus tôt et de nombreux pays ont mené à bien des études et des programmes de vaccination entrepris dès l'âge de six à huit semaines.

Ces recommandations ont été formulées après qu'on eut observé une réponse immunitaire chez des jeunes nourrissons auxquels on avait administré des vaccins et des anatoxines actifs malgré un taux d'anticorps maternels faible à modéré.

A la lumière de ces observations, le Groupe consultatif mondial du Programme élargi de vaccination a noté dans ses recommandations en 1983 et 1984 que le DTC et le VPO trivalent pouvaient être administrés efficacement et sans risque dès l'âge de six semaines. Le présent article fournit des arguments supplémentaires dans ce sens et passe en revue la littérature existante sur l'efficacité de l'administration précoce de ces vaccins.

Le vaccin antipoliomyélitique buccal (VPO) trivalent vivant administré à des nourrissons au cours de leur première semaine provoque des infections intestinales et des réponses immunitaires locales chez 50 à 100% des nourrissons et des réponses en anticorps sériques chez 30 à 70% des nourrissons. La réponse en anticorps sériques après l'administration du vaccin antipoliomyélitique buccal trivalent à l'âge de quatre à huit semaines est aussi efficace que lorsque le vaccin est administré à un âge plus avancé.

La concentration définitive d'anticorps conférée par les vaccins antitétanique et antidiphtérique et par le vaccin anticoquelucheux lorsque la vaccination DTC est entreprise dès l'âge de quatre à huit semaines est quelque peu inférieure à celle qui est obtenue lorsque la vaccination est entreprise à l'âge de trois à six mois. Toutefois, lorsqu'on utilise des préparations actives adsorbées, le pourcentage des nourrissons qui acquièrent un taux d'anticorps suffisant pour être protégés n'augmente guère si la vaccination est effectuée plus tard.

En commençant à administrer les vaccins dès la petite enfance on conférera une protection précoce contre la diphtérie, le tétanos, la coqueluche et la poliomyélite. Cela aura en outre l'avantage d'accroître le nombre des enfants entièrement couverts par les primovaccinations avant l'âge de six mois, lorsque les nourrissons sont le plus exposés au risque de contracter une coqueluche grave ou la poliomyélite.

Le Programme élargi de vaccination de l'OMS recommande que l'administration du DTC et du VPO trivalent commence dès l'âge de six semaines. Dans les pays où la poliomyélite n'a pas été jugulée, le VPO trivalent devrait être administré à la naissance ou lors du premier contact avec les services de santé, puis à l'âge de six semaines, deux doses supplémentaires étant ensuite administrées à quatre semaines d'intervalle.

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