

Immunization of neonates with trivalent oral poliomyelitis vaccine (Sabin)

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A study was carried out between November 1981 and April 1982 on the immunological effect of administering trivalent live, oral polio vaccine to 200 mature healthy neonates from Henan Province, China. The initial dose of vaccine was given at 3 days of age, and 2 months thereafter antibodies to poliovirus types 1, 2, and 3, respectively, were detected in 46.7%, 60.7% and 48.6% of the neonates; after the second dose, the levels were 86.9%, 95.3%, and 97.2%, with geometric mean titres of 1:106.2, 1:349.8, and 1:232.5. Almost 100% of neonates exhibited antibodies after the fourth dose of vaccine. Eighty-two percent of the neonates excreted poliovirus for at least a week after the initial dose of vaccine, and this increased to 99% after the second dose. Seroconversion at 4 months of age was similar to that of a group of controls who received their initial dose of vaccine at 2 months of age; however, immunization of neonates induced immunity to poliovirus at the earliest possible age.

The immunological response of neonates to live, oral polio vaccine depends mainly upon vaccine dosage, the titre of maternal antibody, and the type of milk feeding (1-10). Several investigators (1, 6, 8) have shown that the response to this vaccine is lower for neonates than older infants.

There is evidence that the incidence of poliomyelitis among infants below 1 year of age has risen gradually in recent years (11-16), and the protection of young infants against the disease has therefore become a necessity. Also, because competition from naturally occurring enteroviruses is rare among neonates, there might be advantages in administering oral polio vaccine to this age group. To probe the value of such a schedule, we investigated the immunological response of neonates to trivalent, live oral polio vaccine using a WHO protocol and report our findings here.

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⁵ TCID₅₀ signifies the quantity of virus that produces a cytopathic effect in 50% of vaccinees.

MATERIALS AND METHODS

Subjects

With the consent of their parents, over 400 healthy mature neonates were chosen from those born between November 1981 and April 1982 in selected hospitals in Xin-Xiang, Henan Province, in the Central-Southern Region of China. The neonates were assigned randomly to a test and a control group.

Administration of polio vaccine

Commercially available Sabin trivalent attenuated live polio vaccine was used.⁴ Its virus content per dose was 10⁶ TCID₅₀^b (type 1), 10⁵ TCID₅₀ (type 2), and 10^{5.5} TCID₅₀ (type 3).

Vaccine was administered using a dropper directly into the mouth by a specially assigned worker. For infants in the test group, the vaccine was administered at 3, 60, 90, and 120 days after birth, while those in the control group received vaccine at 60, 90, and 120 days after birth.

Collection of samples

Five blood samples were collected from each infant. The first sample was cord blood, while the remaining four were collected, respectively, on the

28th, 60th, 90th, and 140th days after birth. From each infant a total of 8 stool samples were collected on the 10th, 28th, 35th, 60th, 67th, 74th, 81st, and 90th days after birth. All the samples were taken by medical staff, and both the number of samples and the dates of collection were the same for test and control groups.

Laboratory procedures

All laboratory procedures were performed using methods recommended by WHO (17). In order to assure comparability of the results with those from other studies, criteria for a raised level of neutralizing antibodies were based on a fourfold or more increase in antibody titre and a half-life of 45 days for the decay of maternal antibody.

RESULTS

Altogether, 107 complete sets of blood samples and 108 stool samples were obtained for the test group, while for the control group 107 complete sets of blood samples and 109 of stool samples were collected. For a few infants, only seven stool samples were collected, but they were included in the series.

Clinical investigation

No serious adverse reactions were observed in any of the infants within 140 days of vaccination. Slight

diarrhoea occurred in a few, but cleared in 1–2 days without treatment.

Level of neutralizing antibodies in cord blood

The mean geometric titres of neutralizing antibody in cord blood are shown in Table 1. There was no significant difference between the titres of type 1 and 2 antibodies for the study and control groups, but the titres of type 3 were slightly higher in the test group. The lowest geometric mean titre in both the study and control groups was for type 1 antibody. Overall, 69.6% of the neonates had type 1 antibody titres less than 1:16.

Table 2 illustrates the decrease in the level of maternal antibodies to type 1, 2, and 3 poliovirus in control infants over the first 2 months of life. Both the number of infants with detectable antibodies and the geometric mean titres of the antibodies declined rapidly. The half-life of maternal antibody in the first month was 22.5 days and in the second month 26.5 days.

Increase in level of neutralizing antibodies following immunization

Table 3 shows that 28 days after vaccination the level of type 1 antibody had increased in 41.1%, that of type 2 in 43%, and that of type 3 in 31.8% of infants in the study group. Furthermore, by 2 months after birth the level of type 1, 2, and 3 antibodies had increased in 46.7%, 60.7%, and 48.6% of infants, respectively. There was a large increase in the

Table 1. Distribution of neonates with antibody titres against type 1, 2, and 3 polioviruses in cord blood

Antibody titre (reciprocal)	No. of children					
	Test and control groups			Total		
	Type 1	Type 2	Type 3	Type 1	Type 2	Type 3
<4	23 ^a (27) ^b	8 (14)	11 (23)	50	22	34
4–16	56 (43)	23 (26)	31 (26)	99	49	57
23–64	21 (25)	30 (26)	44 (31)	46	56	75
90–256	4 (7)	32 (30)	15 (22)	11	62	37
360–512	3 (5)	14 (11)	6 (5)	8	25	11
Total	107 (107)	107 (99)	107 (107)	214	214	214
Geometric mean titre	7.0 (9.5)	43.9 (33.6)	22.9 (16.8)	9.1	37.2	19.7

^a Figures refer to test group.

^b Figures in parentheses refer to control group.

Table 2. Number of infants in the control group with passive polio type 1, 2, and 3 neutralizing antibodies at various times after birth

Antibody titre (reciprocal)	Type 1 ^a			Type 2 ^a			Type 3 ^a		
	Cord blood	28 days	2 months	Cord blood	28 days	2 months	Cord blood	28 days	2 months
< 4	27	38	57	14	24	36	23	30	43
4-16	43	46	31	26	35	27	26	38	43
23-64	25	14	12	26	21	29	31	27	9
90-256	7	7	7	30	21	12	22	8	8
360-512	5	2	0	11	6	3	5	4	4
Geometric mean titre	9.5	6.1	3.6	33.6	12.8	8.8	16.8	9.5	5.6

^a Data refer in each case to 107 infants.

Table 3. Characteristics of infants in the study with polio neutralizing antibodies after successive doses of live oral polio vaccine

Age of infants ^a	No. of infants with increased antibody level			Geometric mean titre (reciprocal)		
	Type 1	Type 2	Type 3	Type 1	Type 2	Type 3
28 days						
Test group	44 (41.1) ^b	46 (43.0)	34 (31.8)	20.3	86.6	28.8
Control group	8 (7.5)	6 (5.6)	8 (7.5)	6.1	12.8	9.5
2 months						
Test group	50 (46.7)	65 (60.7)	52 (48.6)	15.5	68.3	30.4
Control group	10 (9.3)	11 (10.3)	12 (11.2)	3.6	8.8	5.6
3 months						
Test group	93 (86.9)	102 (95.3)	104 (97.2)	106.2	349.8	232.5
Control group	77 (72.0)	88 (82.2)	97 (90.7)	29.7	181.8	132.8
140 days						
Test group	105 (98.1)	106 (99.1)	106 (99.1)	207.0	392.2	320.6
Control group	106 (99.1)	105 (98.1)	105 (98.1)	252.4	343.3	298.5

^a Data refer in each case to 107 infants in the test group (vaccine administered at the ages indicated in the text) and control group (unimmunized at 28 days, but immunized at 2 months, 3 months and 4 months), respectively.

^b Figures in parentheses are percentages.

proportion of infants producing an active immune response by 3 months of age, a month after the second dose of vaccine. The difference between the test and control groups at 28 days, 2 months, and 3 months of age was significant ($P < 0.01$) for all three antigenic types. At 140 days after birth, by which time the test group had received four doses and the control group three doses of vaccine, both groups exhibited approximately 100% seropositivity for all three serological types.

The geometric mean antibody titres were significantly different in the test and control groups until the 140th day (Table 3). Although for the test group the geometric mean titre of type 1 was lower at 28 days and 2 months of age, the geometric mean titres of all three antibody types increased to very high levels by 3 months of age.

Table 4 shows the proportion of infants in each group with neutralizing antibody at various times after birth. Significantly higher proportions of

Table 4. Proportion of infants with polio neutralizing antibodies at various times after immunization

Time blood collected	Type 1 (%) ^a		Type 2 (%) ^a		Type 3 (%) ^a	
	Test group	Control group	Test group	Control group	Test group	Control group
Cord blood	78.5	73.8	92.5	86.9	89.7	78.5
28 days	87.9	64.5	99.1	77.6	85.1	72.0
2 months	76.6	46.7	96.3	66.4	77.6	59.8
3 months	98.1	86.0	100.0	96.3	98.1	97.2
140 days	99.1	100.0	100.0	98.1	100.0	99.1

^a Data refer in each case to 107 infants in the test and control groups, respectively.

infants in the test group had type 1, 2, and 3 antibodies at 28 days and 2 months of age. For both the test and control groups, the response was high to all three types of antibody. This finding differs from those reported in studies of monovalent poliomyelitis vaccine (2, 6), and may arise because of the lower interference between virus types in the trivalent polio vaccine.

Intestinal excretion of polioviruses

The excretion of poliovirus was measured each week after the administration of vaccine (Table 5). For the test group, 82.4% of neonates excreted at least one type of poliovirus for at least 1 week after the initial dose of vaccine. Subsequently, the proportion of infants who excreted poliovirus decreased progressively, but 12% were still excreting

Table 5. Number of infants excreting poliovirus in the test and control groups

Type of virus	Day when stool specimens were collected					
	10 ^a	28 + 35 ^b	60	67	74	81 + 90 ^b
<i>Test group</i>						
1	26	1	0	9	4	3
2	25	9	6	9	5	3
3	14	18	5	39	39	19
1+2	9	2	0	1	2	0
2+3	6	0	0	3	1	3
1+3	5	2	1	6	0	1
1+2+3	4	2	1	1	0	0
None	19	70	94	40	54	77
Total	107 (82.4) ^c	104 (32.7)	107 (12.2)	108 (63.0)	105 (48.8)	106 (27.4)
<i>Control group</i>						
1	3	0	0	6	4	7
2	3	1	0	11	12	6
3	0	2	2	31	71	47
1+2	0	0	0	6	1	2
2+3	0	0	2	14	6	7
1+3	0	0	0	11	3	4
1+2+3	0	0	0	24	3	0
None	103	106	104	6	7	34
Total	109 (5.5)	109 (2.8)	108 (3.7)	109 (94.5)	107 (93.5)	107 (68.2)

^a Stool specimens were collected on the 10th day after birth.

^b Stool specimens were collected on both days.

^c Figures in parentheses indicate the percentage virus excretion.

virus at 2 months of age. The intestinal tract of neonates is thus sensitive to live poliovirus vaccine and may maintain an infection over an extended period. Similar prolonged excretion also occurred after administration of the second dose of vaccine.

The proportion of infants in the control group who excreted virus one week after their first dose of vaccine at age 2 months was 94.5%. This is significantly higher than the test group, and excretion of virus was also more prolonged in the control group. All but one child in the test group excreted poliovirus at some stage during the first 4 months following immunization, but the type 1 neutralizing antibody titre in this child increased from 1:11 (cord blood) to 1:512 at 3 months of age, while the type 2 titre increased from 1:90 to 1:512. The type 3 antibody titre was not determined. The infant had therefore acquired immunity despite the absence of detectable virus in stools. Poliovirus was the only enterovirus detected in either group during the period of observation.

Polioviruses of types 1, 2, and 3 were excreted by 45-50% of infants in the test group after the initial dose of vaccine. There was no significant difference between the excretion of type 1 virus by the test and control groups after the initial dose, but for types 2

and 3 the proportion of infants who excreted virus was lower in the test group (type 2, $P=0.05$; type 3, $P=0.01$). There was no significant difference between the excretion levels of the two groups after the second dose of vaccine.

For 54 of the neonates the titre of virus excreted a week after the initial dose of vaccine was slightly lower than that of older infants, but the intestinal tract of the neonates was infected with poliovirus.

Table 6 shows the relationship between the level of maternal antibodies to type 1, 2, and 3 poliovirus (as determined in cord blood) and the number of infants with increased antibodies after immunization with polio vaccine. Maternal antibody titres of 1:360 to 1:512 suppressed the antibody response completely for the first 2 months after birth, but had little or no effect thereafter. Up to this age there is an inverse relationship between antibody titres in cord blood and the response to type 1, 2, and 3 polioviruses, although the suppression is less marked for type 2, and titres below 1:90 did not prevent the progressive development of antibody during the 2 months after administration of the initial dose of vaccine.

The effect of maternal antibodies on the response to the dose of vaccine given at 2 months to the control group is also shown in Table 6. There was mild

Table 6. Influence of maternal antibody level on production of polioviruses in the test and control groups at various times after birth

Antibody titre (reciprocal)	No. of children	No. of infants with increased antibody levels					
		Cord blood	28 days	2 months	3 months	140 days	
<i>Type 1</i>							
≤16	79, 70 ^a	42 (53.2), ^b 10 (14.3) ^b	39 (49.4), 8 (11.4)	73 (92.4), 56 (80.0)	79 (100), 70 (100)		
23-64	21, 25	1 (4.8), 1 (4.0)	7 (33.3), 3 (12.0)	17 (80.9), 13 (52.0)	21 (100), 25 (100)		
90-256	4, 7	1 (25.0), 0	1 (25.0), 1 (14.3)	1 (25.0), 4 (57.1)	4 (100), 6 (85.7)		
360-512	3, 5	0, 0	0, 0	2 (66.7), 3 (60.0)	3 (100), 4 (80.0)		
Total	107, 107	44 (41.1), 11 (10.3)	47 (43.9), 12 (11.2)	93 (86.9), 76 (71.0)	107 (100), 105 (98.1)		
<i>Type 2</i>							
≤16	31, 40	24 (77.4), 5 (12.5)	29 (93.5), 6 (15.0)	31 (100), 37 (92.5)	31 (100), 39 (97.5)		
23-64	30, 26	12 (40.0), 1 (3.8)	24 (80.0), 2 (7.7)	30 (100), 26 (100)	30 (100), 26 (100)		
90-256	32, 30	9 (28.1), 0	12 (37.5), 1 (3.3)	30 (93.8), 21 (70.0)	31 (96.9), 28 (93.3)		
360-512	14, 11	0, 0	0, 0	9 (64.3), 4 (36.4)	13 (92.9), 11 (100)		
Total	107, 107	45 (42.1), 6 (5.6)	65 (60.7), 9 (8.4)	100 (93.5), 88 (82.2)	105 (98.1), 104 (97.2)		
<i>Type 3</i>							
≤16	42, 49	20 (47.6), 8 (16.3)	22 (52.4), 11 (22.4)	41 (97.6), 45 (98.1)	42 (100), 48 (98.0)		
23-64	44, 31	15 (34.1), 1 (3.2)	23 (52.3), 0	43 (97.7), 30 (96.8)	44 (100), 31 (100)		
90-256	15, 22	0, 1 (4.5)	6 (40.0), 1 (4.5)	14 (93.3), 20 (90.9)	15 (100), 22 (100)		
360-512	6, 5	0, 0	0, 0	5 (83.3), 2 (40.0)	6 (100), 5 (100)		
Total	107, 107	35 (32.7), 10 (9.3)	51 (47.7), 12 (11.2)	103 (96.3), 97 (90.7)	107 (100), 106 (99.1)		

^a Figures in italics refer to the control group.

^b Figures in parentheses are percentages.

suppression of response to the initial dose among infants whose maternal antibody titre in cord blood had been 1:360 or more, but this was not observed with subsequent doses.

Table 7 shows the relationship between levels of maternal antibody and poliovirus excretion after the first dose of vaccine in 179 infants in both groups. Excretion of types 1 and 3 virus was greatly influenced by the level of maternal antibodies, and an inverse relationship exists between the levels of antibody in cord blood and the duration of excretion of these two types of virus. In contrast, there was no correlation between the level of maternal antibody and excretion of poliovirus type 2 by the infants.

Excretion of poliovirus and production of antibody

No virus was isolated from the stools of 12 of the 108 infants in the test group during the 2 months after the initial dose of vaccine. Ten of these infants had levels of maternal antibody to types 1 and 2 virus of 1:64 or less, which suggests that the absence of virus excretion was not due to suppression by maternal antibody. Although poliovirus was not isolated from any of these 12 infants, increased levels of neutralizing antibodies against types 1 and 3 poliovirus were found in three of them aged 2 months, suggesting that there had been some replication of the virus in the intestine. After the second dose of vaccine there was a brisk immune response and polioviruses were isolated from the stools of all 12 infants: type 3 in six infants, both type 1 and 3 viruses in three infants, and both

type 2 and 3 viruses in the remaining three. Further increments of antibody levels to very high geometric mean titres occurred after the fourth dose of vaccine. This corroborates the results of previous studies that oral polio vaccine does not induce immunological tolerance in neonates (5, 7).

DISCUSSION

Because of the apparent increase in incidence of poliomyelitis in infants below 1 year of age (11-16) there is interest in improving the effectiveness of oral polio vaccine by either increasing the number of doses or administering the vaccine to younger infants. In the present study, we used Sabin trivalent live oral polio vaccine, which is currently employed in the great majority of countries, in a schedule of four doses starting on the third day of life. The results indicate that such a scheme is effective in inducing early and prolonged immunity. For example, the proportion of infants who actively produced antibodies against type 1, 2 and 3 polioviruses in the 2 months following the initial dose of vaccine was 46.7%, 60.7%, and 48.6%, respectively. These levels are markedly higher than those reported by Krugman et al. (2) and Sabin et al. (6), which were determined 3 months after vaccination with large doses ($10^{6.7}$ - $10^{7.7}$ TCID₅₀) of type 1 and trivalent live oral polio vaccine, respectively, within 3 days of birth.

After the second dose of vaccine, 86.9%, 95.3%, and 97.2% of infants aged 3 months in the test group had developed antibodies against poliovirus type 1, 2,

Table 7. Relationship between level of maternal antibody and excretion of virus by infants in the test and control groups after initial dose of vaccine

Antibody titre (reciprocal)	Type 1		Type 2		Type 3	
	No. of infants investigated	No. excreting virus	No. of infants investigated	No. excreting virus	No. of infants investigated	No. excreting virus
<i>Test group</i>						
≤ 16	68	43 (63.2)*	24	18 (75.0)	35	31 (88.6)
23-64	17	10 (58.8)	29	17 (58.6)	38	32 (84.2)
90-256	2	1 (50.0)	26	14 (53.8)	13	6 (46.2)
360-512	3	1 (33.3)	11	8 (72.7)	4	1 (25.0)
Total	90	55 (61.1)	90	57 (63.3)	90	70 (77.8)
<i>Control group</i>						
≤ 16	57	34 (59.6)	31	21 (67.7)	40	33 (82.5)
23-64	24	11 (45.8)	24	18 (75.0)	26	25 (96.2)
90-256	5	2 (40.0)	23	13 (56.5)	20	14 (70.0)
350-512	3	0	11	8 (72.7)	3	1 (33.3)
Total	89	47 (52.8)	89	60 (67.4)	89	73 (82.0)

* Figures in parentheses are percentages.

and 3, respectively; the geometric mean of titres to these antibodies were, respectively, 1:106.2, 1:349.8, and 1:232.5. The proportion of infants developing antibodies is much higher than that previously reported (2, 6). After four doses of vaccine, almost 100% of infants in the present study exhibited antibodies to poliovirus, with geometric mean titres ranging from 1:207 to 1:392.2.

Poliovirus was excreted by 82.4% of the neonates after the first dose of vaccine, indicating that the virus had replicated successfully in their intestines. After the second dose, 99% of the infants excreted virus persistently, a higher proportion than that reported by other workers.

Although serious intertype interference was prevented in this study by the differential titres for

the three types of virus in the polio vaccine, the immunological response to type 1 virus was lower than that to types 2 and 3, possibly indicating some degree of inhibition associated with the type 2 virus. The results also show that both antibody response and virus excretion are influenced by the level of maternal antibodies, which is consistent with the results of previous studies (2, 3, 5-8). Our findings indicate that this is not a barrier to effective and early immunization.

If a schedule of four doses of Sabin trivalent live polio vaccine is started in the first week of life, a statistically significant proportion of infants will acquire humoral and local intestinal immunity very early in life, and may thus be effectively protected from infection with virulent polioviruses.

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RÉSUMÉ

VACCINATION DES NOUVEAU-NÉS PAR LE VACCIN ANTIPOLIOMYÉLITIQUE BUCCAL TRIVALENT (SABIN)

Étant donné l'augmentation apparente, dans de nombreux pays, de l'incidence de la poliomyélite chez les nourrissons de moins d'un an, il serait intéressant d'améliorer l'efficacité du vaccin antipoliomyélitique buccal soit en augmentant le nombre de doses, soit en vaccinant les enfants plus jeunes. Dans le présent travail, nous avons étudié l'effet sérologique, chez le nouveau-né, du vaccin antipoliomyélitique buccal vivant trivalent souche Sabin, actuellement employé dans la grande majorité des pays, que nous avons administré en quatre doses, la première à l'âge de trois jours.

Les résultats montrent que ce schéma est capable d'induire rapidement une immunité durable. Par exemple, la proportion de nourrissons chez lesquels on a observé une production notable d'anticorps dirigés contre les poliovirus des types 1, 2 et 3 dans les deux mois suivant l'administration de la première dose de vaccin était respectivement de 46,7%, 60,7% et 48,6%. Ces pourcentages sont nettement supérieurs à ceux que l'on connaissait déjà.

Après l'administration de la deuxième dose de vaccin, 86,9%, 95,3% et 97,2% des nourrissons de trois mois appartenant au groupe expérimental présentaient des anticorps contre les poliovirus des types 1, 2 et 3; les titres moyens géométriques de ces anticorps étaient respectivement de 1:106,2, 1:349,8 et 1:232,5. La proportion de nourrissons porteurs d'anticorps est très supérieure à celle

relevée lors d'études antérieures. Après quatre doses de vaccin, près de 100% des nourrissons possédaient des anticorps anti-poliovirus, avec un titre moyen géométrique compris entre 1:207 et 1:392,2.

Après la première dose de vaccin, 82,4% des nouveau-nés excrétaient le poliovirus, ce qui indique que le virus se réplique efficacement dans l'intestin. Après la deuxième dose, 99% des nourrissons continuaient à excréter le virus, ce qui est très supérieur aux chiffres relevés par d'autres auteurs. La réponse immunitaire vis-à-vis du virus de type 1 était plus faible que vis-à-vis des types 2 et 3, bien que, dans cette étude, on ait évité la présence d'interférences intertypes trop marquées en utilisant des titres différents pour les trois types de virus contenus dans le vaccin. De plus, la réponse en anticorps et l'excrétion du virus sont influencées par le taux maternel d'anticorps anti-poliovirus, mais cela ne constitue pas un obstacle à l'efficacité d'une vaccination précoce.

L'administration du vaccin antipoliomyélitique vivant trivalent souche Sabin selon un calendrier en quatre doses, la première étant administrée au cours de la première semaine de la vie, est donc capable d'induire une immunité humorale ainsi qu'une immunité locale (intestinale) chez les nourrissons dans les toutes premières semaines de la vie, les protégeant ainsi efficacement contre une infection par des poliovirus virulents.

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