Simultaneous Immunization with B.C.G., Diphtheria-tetanus, and Oral Poliomyelitis Vaccines in Children Aged 13-14

N. S. GALBRAITH, G. CROSBY, JOAN M. BARNES, RAYNA FERNANDES

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Summary

The simultaneous administration of B.C.G. vaccine, diphtheria-tetanus toxoid aluminium hydroxide adsorbed vaccine, and oral poliovaccine was studied in 628 children aged 13-14 years between 1966 and 1969 in Newham, London. The efficacy of these vaccines was unaffected by administering them at the same time; routine simultaneous administration is considered justified when organizational difficulties prevent the attainment of high immunization rates with the vaccines given separately. No adverse reactions to B.C.G. or oral poliomyelitis vaccines took place, but 8% of children had moderately severe local reactions after diphtheria-tetanus aluminium hydroxide adsorbed vaccine, which were attributed to diphtheria toxoid.

Serological studies showed the need for immunization against diphtheria, tetanus, and poliomyelitis at 13-14 years of age. Because of the adverse reactions to diphtheria toxoid, however, simultaneous administration of tetanus toxoid aluminium hydroxide adsorbed, oral poliomyelitis, and B.C.G. vaccines only is recommended at present.

An "adult type" diphtheria-tetanus toxoid might overcome the problem of reactions, though in two to three years' time most children aged 13-14 years will have received diphtheria-tetanus-pertussis vaccine in infancy and reinforcement might then be accomplished by a small intradermal dose of the currently available fluid diphtheria-tetanus vaccine.

Continued serological studies of diphtheria and tetanus antitoxins and polio antibody are necessary to determine the future need for reinforcement of immunity; such studies should become an essential part of the surveillance of the community immunization programme.

Introduction

Routine B.C.G. vaccination of children in the United Kingdom is recommended at 10-13 years of age and poliomyelitis and tetanus reinforcing immunization on leaving school at 15-19 years of age (Central Health Services Council, 1968); diphtheria immunization may be necessary also on leaving school. In practice, most children are turberculin tested and if necessary given B.C.G. vaccine in school, but few receive diphtheria, tetanus, or poliomyelitis vaccines at this time because of organizational difficulties. One way of overcoming these difficulties is to administer the vaccines at the same time.

Borough of Newham, London E15 1HR

N. S. GALBRAITH, M.B., D.P.H., Medical Officer of Health
G. CROSBY, M.R.C.S., L.R.C.P. (Formerly Assistant Medical Officer, Newham)

Glaxo Laboratories Ltd., Greenford, Middlesex

JOAN M. BARNES, PH.D., Head of Biological Control Unit
RAYNA FERNANDES, M.SC., Virologist.

The purpose of this investigation was to measure the efficacy of B.C.G. vaccine, diphtheria-tetanus toxoid aluminium hydroxide adsorbed (P.T.A.H.), and live attenuated trivalent oral poliovaccine when given simultaneously to children aged 13-14 years. Rubella antibody titres were measured in sera remaining at the completion of the investigation.

Method

The investigation included two trials in children who attended four secondary schools in Newham, London. In the first trial, which took place between December 1966 and March 1967, B.C.G. and diphtheria-tetanus vaccines were studied; in the second, between December 1968 and March 1969, these two vaccines together with oral poliovaccine were studied.

THE CHILDREN

Children whose parents consented to their participation in the investigation were Heaf tested with tuberculin purified protein derivative (P.P.D.) at a concentration equivalent to 100,000 units of old tuberculin per ml, prepared at the Central Veterinary Laboratory, Weybridge; those who were Heaf negative or Heaf positive grade 1, were divided into three immunization groups by using random sampling numbers.

In trial 1 one group of children was given B.C.G. vaccine only (B.C.G. group), the second group was given B.C.G. and diphtheria-tetanus (P.T.A.H.) vaccines together (B.C.G./D.T. group), and the third group was given diphtheria-tetanus (P.T.A.H.) vaccine only (D.T. group). In trial 2 oral poliovaccine was given to children in the second and third groups (B.C.G./D.T./O.P.V. and D.T./O.P.V. groups).

IMMUNIZATION SCHEDULE

The immunizations and other procedures shown in Table I were carried out in school; children who were absent were visited at home and the appropriate procedures carried out there. At the end of the two trials the immunization of all the children against tuberculosis, diphtheria, tetanus, and poliomyelitis was completed.

The B.C.G. vaccination lesion was inspected at about six weeks after vaccination, and a Mantoux test, using P.P.D. 10 TU/0·1 ml and read at 72 hours, was carried out at about 12 weeks after vaccination. Sera were collected from a random sample of children (Table I); three sera in the first trial—that is, before immunization and at 6 and 12 weeks after immunization—and paired sera in the second trial—before and six weeks after immunization.

The sera were titrated for diphtheria antitoxin in guinea-pigs by a method based on that described by Römer and Sames (1909) and for tetanus antitoxin in mice by the method described by Glenny and Stevens (1938). The tests for neutralizing antibodies to the three types of poliovirus were carried out in primary monkey kidney cell tissue culture by

a method based on that described by the World Health Organization (1958).

VACCINES

The vaccines were taken from stock for distribution in the United Kingdom: (1) freeze dried B.C.G. vaccine, 0·1 ml by intradermal injection; (2) diphtheria-tetanus toxoid aluminium hydroxide adsorbed containing 25 Lf of diphtheria toxoid and 5 Lf of tetanus toxoid, 0·5 ml by intramuscular injection; (3) tetanus toxoid aluminium hydroxide adsorbed containing 10 Lf of toxoid, 0·5 ml by intramuscular injection; (4) live attenuated poliovaccine made from Sabin strains, type 1 $10^{6\cdot0}$ $TCID_{50}$, type 2 $10^{5\cdot0}$ $TCID_{50}$, and type 3 $10^{5\cdot5}$ $TCID_{50}$, orally on sugar.

Results

Altogther 628 children (314 boys and 314 girls) took part in the investigation (Table I).

B.C.G. VACCINATION

The B.C.G. vaccination lesion was inspected between 27 and 55 days (mean 43 days) after vaccination in 523 of the 525 children who were given B.C.G. vaccine. Vaccination was successful in all 523 children and there was no significant difference between the vaccine groups in each trial in the mean transverse diameter of the lesion, ulceration of the lesion, or purulent discharge. There were no adverse reactions to vaccination.

Mantoux tests were carried out between 76 and 89 days (mean 83 days) after B.C.G. vaccination in 489 children; the Mantoux reactions were similar in the children given B.C.G. vaccine alone to those in children given B.C.G. and diphtheria-tetanus (P.T.A.H.) vaccines or B.C.G. diphtheria-tetanus (P.T.A.H.), and oral poliomyelitis vaccines (Fig. 1). Three children were Mantoux negative but all of them had normal vaccination lesions. Mantoux tests carried out on 101 children in the immunization groups not given B.C.G. vaccine showed that 76 were Mantoux negative and in the remaining 25 the mean transverse diameter of induration was 7 mm, a finding that is consistent with the Heaf-negative and Heaf-positive grade 1 reactions of these children 12 weeks earlier at the start of the investigation.

DIPHTHERIA IMMUNIZATION

Forty-nine (22%) of 219 children had preimmunization

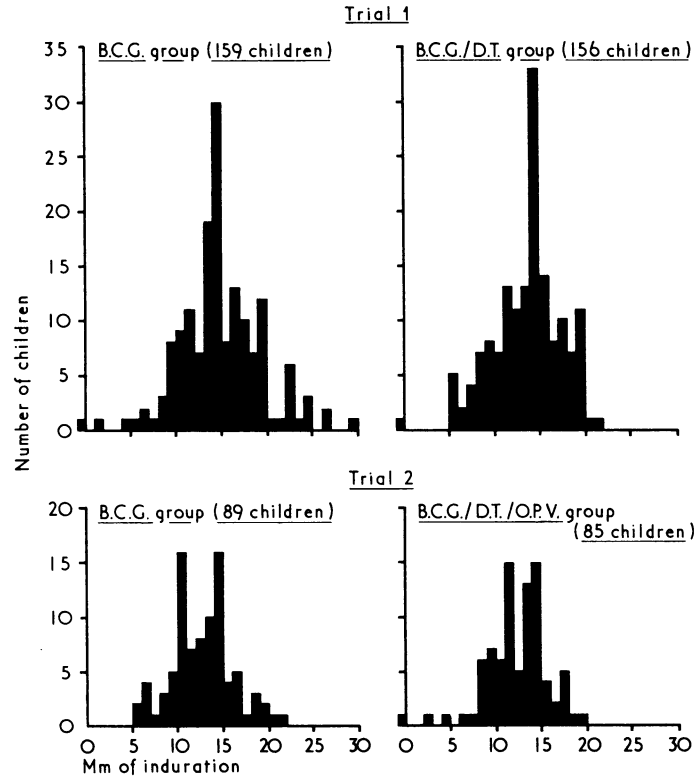

FIG. 1—Mantoux test 12 weeks after B.C.G. vaccination.

diphtheria antitoxin titres of less than 0·01 unit/ml (Table II). The proportion of children with this low titre was higher in those with no record of previous immunization (32%) than in those who had a record of three or more injections (18%). Though 170 (27%) of 628 children had no record, the parents of only 7 (1%) stated that their children had not been immunized. The antitoxin response to immunization in 189 children (Table III) suggests that about 3% had not been previously immunized—seven had antitoxin titres of less than 0·1 unit/ml six weeks after immunization and 6 (3%) of them had no record, the other child showed a delayed antitoxin response at 12 weeks of 0·5-1 unit/ml.

The antitoxin response after immunization was similar in all immunization groups (Table III, Fig. 2) and was unaffected by the simultaneous administration of tetanus toxoid and B.C.G. and oral poliomyelitis vaccines. Paired sera of 33 children given only B.C.G. vaccine showed no significant variation in diphtheria antitoxin titre during the trials.

Thirty (8%) of 363 children given diphtheria-tetanus (P.T.A.H.) vaccine experienced pain and swelling at the in-

TABLE I—*Schedule of Trials and Numbers of Participating Children*

Timing of Procedures	Immunization Groups. Vaccines Given, Procedures Carried Out, and Numbers of Children						Total Numbers of Children
	Trial 1 (400 children)			Trial 2 (228 children)			
	B.C.G.	B.C.G./D.T.	D.T.	B.C.G.	B.C.G./D.T./O.P.V.	D.T./O.P.V.	*All groups*—628
Day 0	B.C.G. vacc. 170 Serum 22	B.C.G. & diph-tet. vaccs. 169 Serum 55	Diph-tet. vacc. 61 Serum 61	B.C.G. vacc. 95 Serum 15	B.C.G., diph.-tet., & oral poliovaccs. 91 Serum 45	Diph.-tet. & oral polio-vaccs. 42 Serum 41	*Diph.-tet. vacc.*—363 Sera examined 189. Plus 33 given only B.C.G. vaccine
About 6 weeks	Inspect B.C.G. 168 Serum* 21	Inspect B.C.G. Tet. vacc. 169 Serum 52	Tet. vacc. 61 Serum 55	Inspect B.C.G. 95 Serum* 12	Inspect B.C.G. Tet. vacc. 91 Serum* 44	Tet. vacc. 42 Serum* 41	*Oral poliovaccine*—133 Sera examined 81, insufficient serum in 4. Plus 12 given only B.C.G.
About 12 weeks	Mantoux 159	Mantoux 156 Serum* 49	Mantoux 61 Serum* 55	Mantoux 89	Mantoux 85	Mantoux 40	*B.C.G. Vaccine*—525 Examined 6 weeks, 523 Mantoux 12 weeks, 489

* Serological studies were carried out only in the children from whom complete sets of serum specimens were obtained.

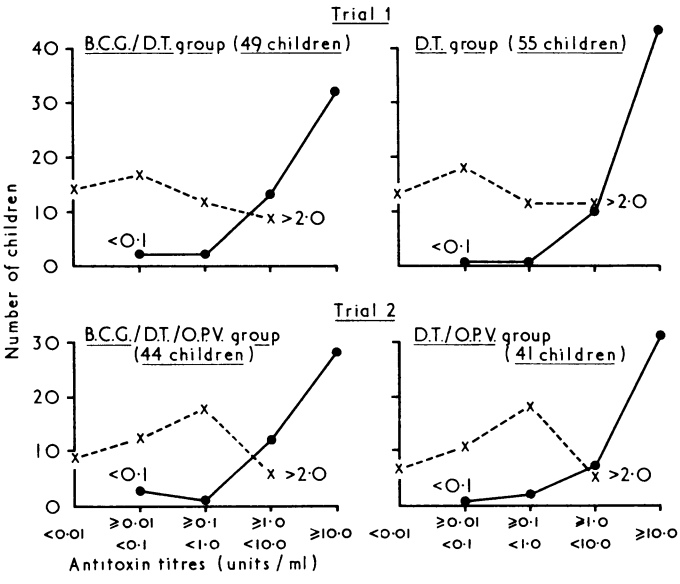

FIG. 2—Diphtheria antitoxin titres before and after immunization. X---X before immunization. ●——● after immunization (6 weeks).

jection site which caused their absence from school for a day or more. All of the children had been previously immunized against diphtheria and only three against tetanus.

TETANUS IMMUNIZATION

Seventy-seven (74%) of 104 children in trial 1 had tetanus antitoxin titres of less than 0·02 unit/ml before immunization and 54 (64%) of 85 in trial 2 (Table IV). There were no records of tetanus immunization, but parents of some children stated that their children had received "tetanus injections" in hospital, most parents thought their children in trial 2 had received tetanus immunization at 5 years of age when they were given "booster" diphtheria inoculation. The antitoxin response to immunization in 189 children (Table IV) suggests that about one-quarter in trial 1 and two-thirds in trial 2 had been previously immunized against tetanus—30 (28%) of 104 children in trial 1 had an antitoxin titre of 0·5 units/ml or more six weeks after immunization and 57 (67%) of 85 in trial 2.

The antitoxin response to immunization in each trial was similar in both immunization groups (Table IV, Fig. 3),

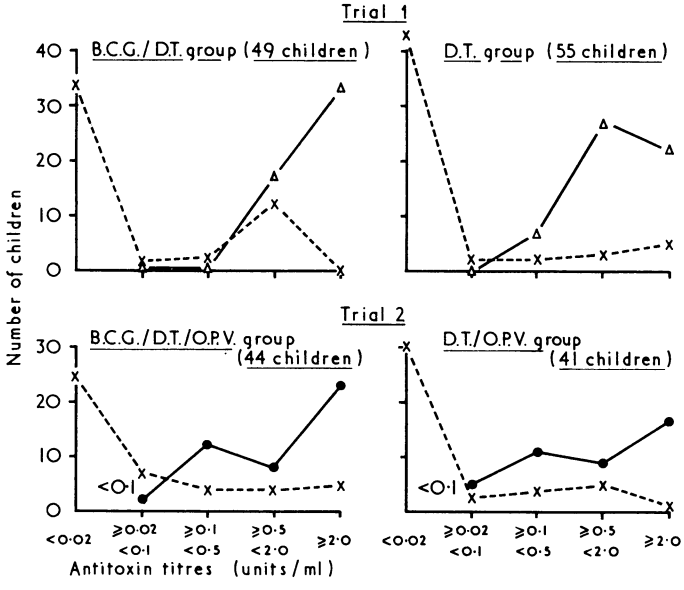

FIG. 3—Tetanus antitoxin titres before and after immunization. X---X before immunization. ●——● after immunization (6 weeks). ▷——△ 12 weeks after immunization and 6 weeks after second tetanus injection.

showing that primary immunization and reinforcement of immunity to tetanus was unaffected by simultaneous ad-

TABLE II—*Diphtheria Immunization History: Relation to Preimmunization Antitoxin Titres. (Last dose of diphtheria toxoid at least 5 years before collection of sera)*

Recorded Immunization History	All Children	Children Studied Serologically				
		Total	Preimmunization Titres (Units/ml)			
			< 0·01	⩾ 0·01 < 0·1	⩾ 0·1 < 1·0	⩾ 1·0
No record	170	53 (100)	17 (32)	15	16 (68)	5
1 and 2 injections	84	34 (100)	8 (24)	13	7 (76)	6
3 or more injections	374	132 (100)	24 (18)	41	48 (82)	19†
TOTAL	628	219* (100)	49 (22)	69	71 (78)	30

* In three additional children studied serologically there was insufficient serum for titration in the initial specimen.
† One child received a reinforcing dose 12 months before serum collection and 2 children 24 months before.
Percentages are given in parentheses.

TABLE III—*Diphtheria Antitoxin Titres before and after Immunization*

	Immunization Group	Serum Sample	Number of Children				
			Antitoxin Titre (Units/ml)				
			< 0·01	⩾ 0·01 < 0·1	⩾ 0·1 < 1·0	⩾ 1·0 < 10·0	⩾ 10·0
Trial 1	B.C.G./D.T. (49 children)	Preimm.	14	16	11	8	—
		Postimm. (6 weeks)	—	2	2	13	32
	D.T. (55 children)	Preimm.*	13	17	11	11	—
		Postimm. (6 weeks)	—	1	1	10	43
Trial 2	B.C.G./D.T./O.P.V. (44 children)	Preimm.	9	12	18	5	—
		Postimm. (6 weeks)	—	3	1	12	28
	D.T./O.P.V. (41 children)	Preimm.	7	11	18	5	—
		Postimm. (6 weeks)	—	1	2	7	31

* In three children there were insufficient sera for testing.
The preimmunization sera were titrated between 0·01 and 2 units, and the postimmunization sera between 0·1 and 20 units.

ministration of diphtheria toxoid and B.C.G. and oral poliomyelitis vaccines. Paired sera of 33 children given only B.C.G. vaccine showed no variation in tetanus antitoxin during the trials.

POLIOMYELITIS IMMUNIZATION

Oral poliovaccine was given in the second trial only, but 216 serum samples collected before immunization from children in both trials were tested for polioantibody; 29 (13%) had antibody titres of less than 1/8 to type 1 virus, 8 (4%) to type 2, and 10 (5%) to type 3. Most of the children had received inactivated (Salk) vaccine, the last dose having been given at least four years before the collection of the serum. In 93 children who had a record of four or more doses of poliovaccine, 7 (8%) had antibody titres of less than 1/8 to type 1 virus, all had antibody to type 2, and 1 (1%) had an antibody titre of less than 1/8 to type 3 virus.

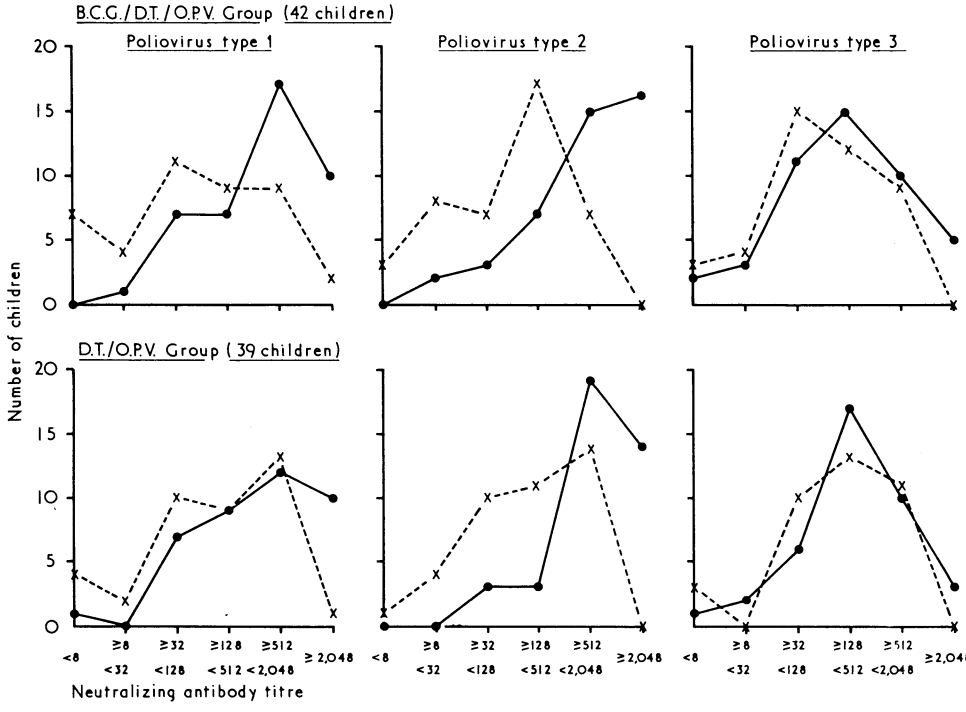

FIG. 4—Polioantibody titres before and after immunization.
X---X before immunization.
●——● after immunization (6 weeks).

TABLE IV—*Tetanus Antitoxin Titres before and after Immunization*

	Immunization Group	Serum sample	Number of Children: Antitoxin Titre (Units/ml) < 0·02	⩾ 0·02 < 0·1	⩾ 0·1 < 0·5	⩾ 0·5 < 2·0	⩾ 2·0
Trial 1	B.C.G./D.T. (49 children)	Preimm.	34	1	2	12	0
		Postimm. (6 weeks)	—	32	0	1	16
		Postimm. (12 weeks) 6 weeks after 2nd tet. inj.	—	0	0	16	33
	D.T. (55 children)	Preimm.	43	2	2	3	5
		Postimm. (6 weeks)	—	40	2	1	12
		Postimm. (12 weeks) 6 weeks after 2nd tet. inj.	—	0	6	27	22
Trial 2	B.C.G./D.T./O.P.V. (44 children)	Preimm.	24	7	4	4	5
		Postimm. (6 weeks)	—	1	12	8	23
	D.T./O.P.V. (41 children)	Preimm.	30	2	3	5	1
		Postimm. (6 weeks)	—	4	11	9	17

Preimmunization sera were titrated between 0·02 and 5 units and the postimmunization sera between 0·1 and 5 units.

TABLE V—*Polioantibody Titres before and after Immunization*

Immunization Group	Type of Poliovirus	Serum Sample	Number of Children: Antibody Titre Reciprocal of Highest Dilution of Neutralization < 8	⩾ 8 < 32	⩾ 32 < 128	⩾ 128 < 512	⩾ 512 < 2,048	⩾ 2,048
B.C.G./D.T./O.P.V. (42 children)	1	Preimm.	7	4	11	9	9	2
		Postimm.	0	1	7	7	17	10
	2	Preimm.	3	8	7	17	7	0
		Postimm.	0	2	3	7	14	16
	3	Preimm.	3	4	15	12	8	0
		Postimm.	1	3	10	15	9	4
D.T./O.P.V. (39 children)	1	Preimm.	4	2	10	9	13	1
		Postimm.	1	0	7	9	12	10
	2	Preimm.	1	3	10	11	14	0
		Postimm.	0	0	3	3	19	14
	3	Preimm.	5	0	11	14	11	0
		Postimm.	1	2	6	17	10	3

Paired sera from 81 children in trial 2 were tested for antibody to the three types of virus; in a further four children there was insufficient serum for testing (Table I). The response to vaccination was similar in both immunization groups (Table V, Fig. 4). Many of the children had high initial antibody titres and it is not surprising, therefore, that not all of them increased after vaccination; most of the children had postvaccination antibody titres of 1/128 or more to all three types of virus. Two children had antibody titres of less than 1/8 to type 3 virus after vaccination—one had no record of past poliomyelitis immunization and the other had received three doses of oral poliovaccine six years previously. One child who had never been immunized had no antibody to type 1 virus after vaccination.

Of 12 children given only B.C.G. vaccine in the trial and from whom paired sera were obtained, two showed a fourfold rise in antibody to type 1 virus, two to type 2, and two to type 3. These children were close associates of the vaccinated children. There were no cases of neurological illness associated with vaccination either in the vaccinated children or their school contacts.

RUBELLA ANTIBODY

Sera from 120 children (62 boys and 58 girls) in the first trial were tested for rubella antibody by the haemagglutinin-inhibition (H.A.I.) test by the method described by Stewart *et al.* (1967). One hundred (83%) of the 120 children had an H.A.I. antibody titre of 8 units or more; 50 (86%) girls and 50 (81%) boys.

Discussion

The results recorded here show that the simultaneous administration of B.C.G., diphtheria-tetanus (P.T.A.H.), and oral poliomyelitis vaccines in children aged 13-14 years produces satisfactory responses to all these vaccines and does not affect their efficacy.

The proportion of children (22%) with preimmunization diphtheria antitoxin titres of less than 0·01 unit/ml is similar to our finding in 1963-4 in children aged 10-12 years (Galbraith *et al.*, 1966) and again indicates the need for reinforcement of immunity. Diphtheria toxoid should be offered as soon as practicable to all children at about 13 years of age who have not been immunized since the age of 5 years.

Eight per cent. of children had moderately severe local reactions to diphtheria-tetanus (P.T.A.H) vaccine, which we consider makes it unacceptable for routine use in 13-year-old children. An "adult type" diphtheria-tetanus toxoid containing a low dose of diphtheria toxoid, and perhaps without adjuvant, might overcome the problem for this age group. Within two to three years most 13-year-old children in the United Kingdom will have been immunized against both diphtheria and tetanus in infancy and reinforcement may then be possible with a small dose of fluid diphtheria-tetanus toxoid given by intramuscular or intradermal injection (Galbraith *et al.*, 1966).

This study confirms the need for tetanus immunization in teenage children. The high proportion of children in trial 2 with low preimmunization antitoxin titres who responded rapidly to immunization at six weeks (Table IV) suggests that many of them had received inadequate primary immunization, probably a single injection of diphtheria-tetanus toxoid at the age of 5 years.

The polioantibody titres before immunization were similar to those previously reported (Galbraith and Fernandes, 1969). Because 8% of children with a record of four or more doses of poliovaccine had antibody titres of less than 1/8 to type 1 virus, we suggest that the recommended reinforcing dose before leaving school should be given to all children irrespective of their previous immunization history.

We recommend, therefore, that all children at about the age of 13 years should be given tetanus toxoid aluminium hydroxide adsorbed vaccine and oral poliovaccine at the same time as B.C.G. vaccination in schools in areas where organizational difficulties otherwise prevent a high immunization rate at this age. Our experience indicates that such a combined immunization session in secondary schools would increase the acceptance rate for tetanus and poliomyelitis immunization in teenage children in the Borough of Newham from less than 5% to over 80%. We think that the advantages of this considerable increase in immunization rate outweigh the disadvantage of the theoretical possibility that simultaneous administration of these vaccines may result in live-vaccine-induced disease, a possibility which did not occur after the introduction of simultaneous administration of diphtheria-tetanus-pertussis and oral poliomyelitis vaccines in infancy.

We have previously directed attention to the need for continued serological studies of polioantibody in children (Galbraith and Fernandes, 1969), and this investigation shows that similar studies of diphtheria and tetanus antitoxins should become an essential part of the surveillance of community immunization programmes. Only by such studies can the future need for reinforcing doses of these vaccines be determined.

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