COMBINED IMMUNIZATION AGAINST POLIOMYELITIS, DIPHTHERIA, WHOOPING COUGH, TETANUS AND SMALLPOX

P. A. D. WINTER, J. H. MASON, E. KUHR, A. W. SCHAAFSMA, and MARY ROBINSON, *Poliomyelitis Research Foundation and South African Institute for Medical Research, Johannesburg,* and L. R. SAAYMAN and R. G. SPENCE, *Boksburg Municipal Health Department*

Child immunization schedules in use at present entail numerous visits to the doctor or clinic. This is partly responsible for failure to achieve adequate immunization at an early age with the resultant unnecessarily high mortality and morbidity from childhood infections. From an administrative and psychological point of view the advantages of combining antigens in order to reduce the number of visits are obvious.

A combined vaccine containing inactivated poliovirus vaccine and 'triple vaccine' (diphtheria, whooping cough and tetanus antigens) has been in use for some years. At least 4 brands of commercial quadruple vaccines are available in the USA and Canada. It is regarded as a safe and effective approach to childhood immunization.[1-3] The combination of oral poliovirus vaccine (Sabin) with triple vaccine was first successfully used by Rethy.[4] Recently Spencer[5] showed that smallpox vaccination could safely be combined with triple vaccine.

With the object of reducing the number of visits to 3, we decided to carry out the immunization schedule summarized in Table I.

Unimmunized White infants and children attending a clinic of the Boksburg Municipal Health Department were selected for study with the consent of their parents. The minimum age was set at 3 months but older unimmunized infants and children were accepted. The object of the scheme was explained to the parents and they were asked to report all reactions and symptoms.

At monthly intervals, 7 or 8 antigens were administered on 3 occasions. The combined diphtheria, whooping cough

TABLE I. IMMUNIZATION SCHEDULE

Number of visits	*Interval*	*Minimum age of child*	*Antigens used*
First ..	—	3 months	Polio D.W.T. Vaccinia
Second ..	1 month	4 months	Polio D.W.T. (Vaccinia if necessary)
Third ..	1 month	5 months	Polio D.W.T. (Vaccinia if necessary)
Fourth .. (1st booster)	7 months	12 months	Polio D.W.T.
Fifth .. (2nd booster)	2 years	3 years	Diphtheria Tetanus Vaccinia
Sixth .. (pre-school)	2 years	5 years	Diphtheria Tetanus Vaccinia ? Polio

and tetanus prophylactic (D.W.T.) contained, per dose of 0·5 ml., 25 Lf of purified diphtheria toxoid, 6 Lf of purified tetanus toxoid, both absorbed on aluminium phosphate, and 10,000 million killed *Bordetella pertussis* organisms. The injection was given subcutaneously in the arm. Four drops of trivalent oral poliovirus vaccine, containing at least 300,000 T.C.I.D.$_{50}$ of each virus type, were mixed with half a teaspoonful of a raspberry-flavoured sucrose syrup and given to the children by mouth. Smallpox vaccine as supplied by the State Health Department was applied to the unused upper arm by the multiple pressure method. This was preferably done on the first visit, so as to allow for repeat vaccination in cases of failure to 'take'

When possible, blood specimens were obtained before immunization and the results of comparative pre- and post-vaccination responses will be reported at a later date. In all cases, blood was taken from the children 4 - 6 weeks after the last administration of the antigens. The following tests for neutralizing antibodies or antitoxins were carried out:

1. *Poliomyelitis.* A 1 : 5 dilution of serum was challenged with 100 T.C.I.D.$_{50}$ of each of the 3 types of poliovirus in tubes of monkey-kidney tissue culture.

2. *Diphtheria.* Guinea-pigs were tested intracutaneously, using a toxin capable of detecting 0·001 unit of antitoxin.

3. *Tetanus.* Mice were tested by the subcutaneous route using a toxin capable of detecting at least 0·01 unit of antitoxin.

4. *Smallpox.* The development of a pustule with later scar formation was taken to indicate adequate immunization.

5. *Whooping cough.* No attempt was made to test the response to *Bordetella pertussis* antigen.

At the Boksburg Municipal Clinics, 882 children completed the course of combined immunization without showing untoward reactions; with very few exceptions they attended for the full course and the parents expressed satisfaction with the scheme.

A local reaction, if present, usually took the form of a tender lump, the tenderness disappearing within 48 hours. When the vaccinia pustule developed, all traces of this tenderness had disappeared. Parents preferred to take care of the vaccinia reaction at an early age, as control of scratching of the vaccination site was then less difficult.

The assurance of protection at an early age and the fewer visits to the clinic were appreciated. From an administrative point of view the application of the scheme was not difficult and one of the most important aims of the undertaking, the encouragement of parents to bring their infants for immunization, was achieved.

Adequate amounts of serum for testing the antibody response were available from 22 children, and the results form the basis of this preliminary report.

RESULTS

With the exception of one child, who failed to develop antibody to poliovirus type 1, the sera of all 22 children contained antibodies, at the level tested, against all 3 types of poliovirus. Previous experience has shown positive correlation between this antibody level and immunity to poliomyelitis.

All the sera tested contained diphtheria antitoxin. The lowest titre compatible with protection against diphtheria is not known with certainty but is usually considered to be 0·04 unit/ml. of serum. The lowest titre, in 2 sera only, was 0·1 unit/ml.

The sera of the 21 children tested contained tetanus antitoxin. The response in 3 was not good (0·02 unit/ml.) but as 0·01 unit/ml. is considered to give protection, 0·02 unit/ml. may be considered adequate.

The vaccinia inoculation failed to 'take' in only one child, who was vaccinated once at the third visit.

The results are given in Table II and are summarized in Table III. In Table IV, the results obtained with the sera of 3 unimmunized chiludren are recorded.

TABLE II. TESTS ON SERA TAKEN 4–6 WEEKS AFTER 3 COMBINED IMMUNIZATIONS

Child	*Sex*	*Age at bleeding, in months*	*Poliomyelitis antibodies types 1, 2, 3*	*Vaccinia 'take'*	*Antitoxin units per ml. of serum*	
					Diphtheria	*Tetanus*
1. J.O'D	M	17	+++	+	3·0	0·5
2. L.H.	F	8	+++	+	1·0	0·2
3. K.L.	M	12	+++	+	0·75	1·0
4. S.A.	F	7	+++	+	0·75	1·0
5. O'D.K.	F	5	+++	+	0·50	2·0
6. G.R.J.	M	7	+++	+	0·75	1·5
7. S.R.	M	8	+++	+	0·75	2·0
8. D.B.	M	12	+++	+	0·75	1·5
9. P.W.	M	8	+++	+	0·75	1·0
10. F.H.	M	7	+++	+	0·75	1·5
11. vZ.N.	F	12	+++	+	0·75	0·75
12. C.S.	F	9	+++	+	0·50	0·02
13. S.A.	F	11	+++	+	0·1	0·1
14. S.M.	M	9	—++	+	1·0	NS*
15. N.C.	F	8	+++	+	2·0	2·0
16. K.S.	F	13	+++	+	0·5	0·02
17. C.M-A.	F	6	+++	+	0·75	2·0
18. C.Z-A.	F	12	+++	+	0·20	0·5
19. M.H-M.	M	10	+++	+	0·5	0·02
20. N.A.	M	13	+++	+	0·5	1·5
21. du P.G.	M	19	+++	—	0·1	0·5
22. V.A.	F	7	+++	+	1·5	2·0

* NS=No serum available.

DISCUSSION

The results of this trial show that most children may be immunized satisfactorily against diphtheria, tetanus, poliomyelitis (types 1, 2 and 3) and smallpox if the

TABLE III. SUMMARY OF RESULTS

Antigen	*Number of sera tested*	*Adequate immunity acquired*	*Percentage immune*
Poliovirus type 1 ..	22	21	95·5%
Poliovirus type 2 ..	22	22	100%
Poliovirus type 3 ..	22	22	100%
Diphtheria toxoid ..	22	22	100%
Tetanus toxoid	21	21*	100%*

* See text.

TABLE IV. PRE-IMMUNIZATION SERA

Name	*Sex*	*Age in months*	*Polio 1 2 3*	*Diphtheria at units/ml.*	*Tetanus at units/ml.*
C.L. ..	F	3	+—+	<0·002	<0·04
M.M. ..	F	6	———	<0·001	<0·1
P.N. ..	F	17	++—	<0·002	<0·04

immunization scheme summarized in Table I is followed. It confirms previous work which showed that the spacing of the poliomyelitis vaccine administrations was satisfactory.

The spacing of the injections for the production of immunity to diphtheria and tetanus was not optimal. An interval of 6 - 8 weeks between the first and second injections of D.W.T. and of 3 - 6 months between the second and third injections would undoubtedly have produced higher titres. But we feel it is better to produce a good, if not the best obtainable, immunity in the very young child, particularly if the parents can be persuaded of the necessity of a booster dose later on, rather than confuse the parents with attendances at odd times.

It is probably advisable, in the absence of serological tests, to give the poliomyelitis vaccine again when the child is 1 year old so as to stimulate the production of antibodies in those children who did not produce them after their basic immunization. It is doubtful if it is necessary to repeat this procedure at the time of the first diphtheria-tetanus booster dose or when the pre-school booster dose of diphtheria, tetanus and smallpox antigens is given, but as poliomyelitis vaccine is harmless and easy to give, another dose at one or both of the later boosting periods could only have a beneficial effect.

Until a simple, uncontroversial method of assaying the immunity of man to whooping cough is developed, it will be difficult if not impossible to find out how much immunity is produced by a vaccine. However, as field trials have shown that its injection does reduce the incidence of the disease, it is a wise precaution to include it in any immunization programme embracing children younger than 3 years of age.

The application of the immunization scheme has shown such encouraging results that it is being continued on a routine basis. Over 1,500 children have now been immunized with no untoward reaction. Tests on a much larger number of sera have been carried out and will be reported at a later date. In general the results for the White children are similar to those reported here; the non-Whites show a slightly less complete response to the poliovirus vaccine. This is being investigated.

SUMMARY

1. The immunization of 882 infants against poliomyelitis, vaccinia, diphtheria, whooping cough and tetanus was carried out at the Boksburg Municipal Health Clinics and was well tolerated by the recipients. Parents were in favour of the method and supported it enthusiastically.

2. The results of testing 22 sera taken 1 month after the course of immunization were satisfactory. One serum contained no antibody to poliovirus type 1. All contained diphtheria antitoxin, the lowest titre, in 2 sera, being 0·1 unit per ml. All of 21 sera contained tetanus antitoxin, 3 in rather low concentration. The vaccinia inoculation failed to 'take' in 1 of 22 children.

3. The spacing of the immunization is discussed. An increase of the intervals between doses is considered in the light of the early achievement of protection. An early booster dose is recommended.

4. An immunization scheme up to pre-school age is outlined.

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