CONTROL OF TYPHOID FEVER BY VACCINATION*

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For some years it has been generally accepted that the incorporation of paratyphoid A and B vaccines with the *S. typhi* vaccine serves no useful purpose in regions where paratyphoid fevers are rare and comparatively mild. On the contrary, it seems reasonable to suppose that, if the systemic and local reactions caused by the paratyphoid vaccines were removed, the dose of potent and effective *S. typhi* antigen could usefully be increased. The importance of larger dosages was made clear in the USSR controlled field trials (1959 - 1964) in which the effectiveness of small doses of different vaccines was compared with that of large doses.[1] The results were unequivocal and showed that 'inadequate protection may be conferred, irrespective of the method of production of the vaccine and the number of injections given, if the doses are not sufficiently large'.

It was decided therefore to try out a typhoid vaccine without including paratyphoid antigens. At the same time it was noted that, in the colossal field trials in the USSR, Poland, Yugoslavia and Guyana, the endotoxoid vaccines were found to be 'least immunogenic'[2] or (at the bottom of the list of 5 vaccines) to 'confer only a low degree of protection'.[3] Thus it was decided to use a whole-bacterium *S. typhi* vaccine without paratyphoid A and B for trial.

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A heat-killed phenol-preserved *S. typhi* vaccine with 1,000 M bacteria per 1 ml. was prepared for us by the Vaccine Institute of the SAIMR.

THE TRIALS

Preliminary Safety Trial

In March 1967, 74 schoolchildren volunteered for this test. Temperatures were recorded and axillary glands palpated, and their general condition was checked. They were then given varying doses of the vaccine subcutaneously. Reactions were checked the following day. All the children were afebrile, there was no adenitis, all had some tenderness at the site of injection and most arms had some degree of local heat and very slight swelling. Only 2 of the 74 children said that sleep had been disturbed. These reactions did not seem to vary according to dosage given.

Two weeks later the vaccinations were repeated in the same dosage, with similar but slighter reactions. These safety tests having proved satisfactory, a field trial was organized.

The Field Trial

On the basis that after typhoid vaccination there is little or no relationship between the results of serological

or animal potency tests and the actual protection afforded man, controlled field trials were undertaken from 1958 to 1962 in Guyana, Yugoslavia, Poland and the USSR. The purpose was simply to determine the comparative incidence of typhoid in different groups over a period of years. No quick evaluation of efficiency was possible, but by 1965 it was amply demonstrated that certain vaccines were definitely effective.

Encouraged by these results, a small field trial was undertaken in the Bushbuckridge area, starting in July 1967. It may be useful to recount briefly the method adopted and difficulties encountered in case a more ambitious test is contemplated at a later date.

Twenty-three schools were selected, with a total enrolment of about 7,500 pupils. Three copies of registers for each school were prepared with columns headed: serial number, name, sex, age, symbol of vaccine used, date of 1st inoculation, date of 2nd inoculation and remarks. One copy was intended for each of the 2 hospitals in the area, and in these the columns headed 'vaccine symbol' were left blank. The third copies were for the vaccinating teams.

Three vaccines were used, namely TAB endotoxoid, *S. typhi* whole bacilli, and tetanus toxoid (as a control). These were labelled O, S, and P respectively—the laboratory labels were replaced by labels with these symbols only.

Two teams were employed, each with 4 members, and each team went to a different school. Three of the members went to separate rooms and each was provided with a different vaccine. The fourth member sent the schoolchildren into the rooms in rotation and recorded O, S, or P against the child's name in the register.

Unfortunately, the second inoculation 2 weeks later was interfered with by an intervening outbreak of malaria in the area and a mass chemoprophylaxis campaign conducted by the malaria staff. One child died of pneumonia and the health staff were blamed by agitators, so that at some schools the children refused their second inoculations. However, 7,243 children were inoculated and, of these, 3,297 received a second inoculation, i.e. a total of 10,540 inoculations.

A check was made on the reactions to the different vaccines and 165 of the schoolchildren were examined on the day following vaccination. It is relevant to mention that the results had nothing to do with the ability of the operators, because these men took turns at giving the various vaccines, i.e. no one operator gave all the TAB or all the tetanus toxoid. The 165 scholars were examined at different schools and the results are shown in Table I.

TABLE I. RESULTS OF VACCINATION

Vaccine	No. of persons examined	Local tenderness		Glands +		Sleep disturbed	
		No.	%	No.	%	No.	%
TAB	49	40	80	12	24	14	30
S. typhi	53	43	81	7	13	8	15
Tetanus toxoid	63	8	13	2	3	2	3

Temperatures were taken, but unfortunately only 35 of these, taken by the medical officer, are reliable. Of the 35, two had temperatures of 99°F and one of these two had slightly enlarged and tender axillary glands. Three of the TAB children and one of the *S.-typhi* children had slight headaches.

It may be concluded that there were no untoward reactions and that both TAB and *S.-typhi* vaccines are safe.

The next part of the programme was to register any vaccinated children who contracted typhoid fever. The hospitals undertook to check in the registers supplied by us when a school-age typhoid case was admitted from any of the trial areas and to refer the serial number to this office. But with the best will in the world, the hospitals could not do this, because of the time required to go over hundreds of names in school registers looking for the name of a typhoid patient.

Then it became necessary to try to trace cases from positive laboratory reports, notifications, and special reports on cases treated with chloramphenicol. This is not satisfactory because the children are apt to use one name at school and give another one in hospital, and, also, the names are spelt differently by hospital staff, notifying officers and magistrates' clerks.

However, though some cases could have been missed, any incompleteness of records would apply equally to all the recipients of the different vaccines and the results may be accepted as comparable.

TABLE II. EFFICACY OF THE VACCINE

Vaccine	No. vaccinated	Cases notified†	Cases/1,000
S. typhi	2,683*	6	2·2
TAB	2,208	9	4·1
Tetanus toxoid	2,352	13	5·5

**S. typhi* figures high because children coming for the first time on the second tour were all given one dose of *S. typhi* only.
†Of the notified cases, 22 had positive blood cultures and the other 6 whose blood was not sent for culture had very high Widal titres.

The results for the first 12 months are given in Table II. The results did not justify extravagant claims of efficiency for the vaccine, but they did justify its use in an urgently needed antityphoid campaign.

THE CAMPAIGN

Typhoid fever is endemic in the eastern zone of the Northern Transvaal from Beit Bridge in the north to Komatipoort and Barberton in the south. Curiously enough, this is also the malaria endemic zone and is almost the same as the bilharzia endemic zone.

It is essentially agricultural, though there are some very important mines in the area. Effective immunization of the total population in scattered villages, hamlets and kraals—many in mountainous areas difficult to reach—would not be a practical undertaking and it would also be a waste of effort in view of the age distribution of the disease.

The vast majority of the cases occur in children of school-going age, i.e. from 4 to about 19 years, and it was decided to try to reduce the incidence significantly in this age-group in the expectation that this would eventually reduce the disease to controllable proportions.

A survey in the area showed there to be at least 250,000 children of school-going age. It was then clear that, for several reasons, coverage for this number by teams using needles and syringes would not be practicable. The use of a Ped-O-Jet was contemplated, and preliminary trials with conventional syringes were carried out using a 500 M bacilli dose subcutaneously and two different dosages, namely 250 M and 500 M, intradermally. Vaccines were provided by Dr P. A. Christensen of the Vaccine Institute of the SAIMR. A tuberculin syringe was used for the intradermal vaccine. The usual tests were carried out on 50 schoolchildren and the results were recorded 24 hours later.

With the intradermal vaccinations there was no local tenderness except for 3 cases who received the 500 M vaccine, and in them it was slight. Two others had temperatures of 99·4 and 99·5°F, but did not feel ill. There were no headaches or swollen glands, and all had slept well.

Children who were given 0·5 ml. of the 1,000 M vaccine subcutaneously all had marked local tenderness. When they were revisited 2 weeks later there were no residual traces and none had suffered any ill-effects.

A Ped-O-Jet was then brought into use.

As stated, it was decided to attempt the vaccination of all children of school-going age in the eastern zone; but before dealing with this it might be well to recapitulate the reasons for employing vaccination as the chief anti-typhoid measure and for using a particular dosage schedule and method:

1. Improvement in water supplies and sanitation is not an alternative to vaccination for typhoid control. The tendency unjustifiably to blame water supplies for typhoid outbreaks has been mentioned previously,[4] and in a specific investigation by Richardson *et al.*[5] it was concluded that the improvement of the water supply in a Western Transvaal Bantu area had had no effect on the prevalence of salmonella or shigella infections. The provision of an ample water supply is more important than purification of the water, because only with ample water will people use it for hand-washing and the like. It is at least possible that typhoid does not spread readily in communities with good sanitary facilities because such communities follow a way of life, including good personal hygiene, which is different from that of more primitive peoples.

2. It was decided to use intradermal rather than subcutaneous vaccination because it is quicker and causes much less local reaction. Five hundred people may be vaccinated without changing the 50-ml. container, whereas the container must be changed for every 100 subcutaneous vaccinations. Also, the subcutaneous nozzle must be pressed onto the skin and held firmly or it will slip and the jet will cut the skin, whereas the intradermal nozzle is placed lightly and quickly on the skin at an angle.

3. In spite of reports to the effect that one-fifth of a normal dose of vaccine given intradermally is just as efficient as a full dose given subcutaneously[6] it was decided to give a concentrated vaccine intradermally with a dose almost equal to that used for the subcutaneous method. The reasons for this are the advantage of large over small doses,[1] the safety and minimal side-effects of large doses given intradermally, and to compensate for the slight loss of vaccine which occurs with the Ped-O-Jet method.

4. Since the results of widely separated trials showed that in these areas one dose was equal to, or better than, 2 doses, one vaccination annually was adopted as a routine.[7] A controversy exists whether one dose is adequate in endemic areas only or also in non-endemic areas; the tendency is towards believing in its efficiency even in non-endemic areas. This controversy does not concern us since, as will be shown, our eastern zone is certainly an endemic one.

5. The single-dose regimen can be more efficiently carried out in schools where school-holidays, absenteeism and other *contretemps* interfere with double vaccination programmes. Annual revaccination is advised as a compromise between a 4½-month interval which was reported to have stopped one typhoid epidemic[7] and a 3-year interval programme which, though apparently effective with some vaccines, is unsatisfactory for the heat-inactivated vaccines which tend to lose their protective power after 12 months.

6. Finally, the importance of mass vaccination against typhoid is emphasized by an account of typhoid fever in Vietnam[8] which is reviewed in *Abstracts on Hygiene* of June 1968.[9] The reviewer states: 'Reference is made to the apparent immunity to typhoid of the American and Vietnam Special Forces members who had been actively protected with typhoid vaccine, compared with the locally recruited soldiers; an excellent example of the desirability of such protective procedures'.

Mass Vaccination

Mass vaccination is simple. The team comprises one vaccinator and a Bantu labourer. The equipment consists of a powerful truck (driven by the vaccinator) which is essential for driving along the almost impassable tracks in the hills, ordinary camping equipment, a small gas refrigerator for vaccines, a small pressure cooker used as an autoclave, and some cottonwool and commercial ether.

The Ped-O-Jet is easy to operate but tiring at first. A school of 500 children takes about half an hour to vaccinate, but much time is spent in travelling from school to school and in trying to find children of school-going age who do not attend school. These children are very independent, or undisciplined, and, if not watched carefully, simply vanish into the bush when a vaccinating team appears.

It is interesting to watch the children preparing for vaccination. The body contorts and twists into a semi-hysterical fear state and the face screws up into a mask of excruciating agony; but before these preparations are completed, the vaccination is finished. The child looks at the weal, realizes it is all over—no needle and no pain—and with relieved giggles or happy laughter dances away. It may be, therefore, that subsequent vaccination tours will be more popular.

Vaccination Tests

Results of the campaign will be assessed by the incidence of typhoid in the areas dealt with, but some indication was required as to whether the vaccine was actually being absorbed from the intradermal weal. From a welter

TABLE III. WIDAL RESULTS AFTER AND BEFORE INTRADERMAL VACCINATION

Days after vaccination	*Vaccine dose*	*Results*					
		Negative	*O+ve*	*H+ve*	*O+H+ve*	*Total*	*% negative*
15	500 M	4	2		6	12	33
21	400 M	2		6	1	9	22
Unvaccinated hospital cases		15		2	3	20	75
Unvaccinated schoolboys		15	1		1	17	88
Total		36	3	8	11	58	

of research literature on this matter it emerges that serological tests and animal potency tests do not correlate with a vaccine's protective efficiency for man. Since laboratory animals have not yet been infected with typhoid fever, challenge must be made with other bacteria, but results are not uniform, and sometimes they are contradictory. It was, however, established that the level of 'H' agglutinins in agglutination tests was the most reliable indicator of the effectiveness of typhoid vaccines.[3] 'O' antibodies gave variable results.

In view of this, some tests were made and the results are shown in Table III. These show that vaccination does significantly alter the sero-agglutination reaction, i.e. the vaccine is absorbed. The vaccinated cases were from the first batch vaccinated with the Ped-O-Jet and the raising of weals was not so uniform as when the operator was more experienced. Weals are now produced in 100% of vaccinations. Further tests will be made.

The unvaccinated hospital cases in the table included two with Widal titres diagnostic of typhoid fever, namely, O 1:400 and H 1:1,600. These two had been admitted to hospital with pyrexia of unknown origin and a sprained ankle, respectively. Among the vaccinated children were two with diagnostic Widal titres (O 1:400, H 1:50 and O 1:400, H 1:400). None of these 4 cases had symptoms of typhoid fever and they are merely mentioned as an indication of the endemicity of the disease.

DISCUSSION

Reasons have been put forward for advocating and inaugurating a programme of intradermal vaccination of children of school-going age. A point which seems to be confusing to some is that basal immunity, or artificially acquired immunity from vaccination, is not reflected in the results of sero-agglutination tests. Most chronic typhoid carriers are Widal negative except when in a febrile phase of their infection. In fact, it is considered that the ordinary Widal-negative person in an endemic area has some immunity to the disease and that this immunity is boosted by a single dose of vaccine. The vaccine does raise the H agglutinin titre, but though it may fall again this does not mean that the enhanced immunity has also fallen. Also it has been suggested that widespread vaccinating could produce a dangerous number of latent carriers. The fact is that the well-known provocative action of the vaccine should tend to uncover latent infections rather than the reverse. It is hoped that our campaign might have this useful action.

Sir Graham Wilson points out in *The Hazards of Immunization*[10] that this provocative action was used in the German army when reinoculation of typhoid contacts was advised in order to reveal the presence of latent infections. This article describes an attempt to translate into practice in a rural area of South Africa the well-substantiated findings of research and field trials elsewhere. The vaccine used is derived from the Ty-2 strains of *Salmonella typhi*, as were the vaccines used in the various field trials. The near uniformity of results from research trials held in such diverse climatic and social conditions as obtain in equatorial Guyana (lat. 5° North) and Poland (55° North) suggests that it would be a waste of time and money to try to duplicate these trials exactly in the Northern Transvaal (lat. 30° South).

SUMMARY

Owing to a high and increasing prevalence of typhoid fever in the north-eastern Transvaal of South Africa, it was decided to attempt control through the vaccination of children of school-going age.

Based on the results of the USSR, Yugoslavia, Poland and Guyana field trials, it was decided to use a whole bacterium vaccine of *S. typhi* instead of TAB endotoxoid type. The South African Institute for Medical Research prepared such a vaccine, and tests for safety and efficiency were carried out. The method of carrying out an annual programme of vaccination on a school-age population of about 250,000 was next considered. Vaccinating on this scale with needle and syringe teams was impracticable and the use of intradermal vaccination using the foot-operated jet was undertaken. Tests for the safety and efficiency of subcutaneous and intradermal methods were carried out and the intradermal method was found to be the more satisfactory. The campaign proceeds and results will be evaluated.

We should like to thank the South African Medical Research Institute Vaccine Laboratories, particularly Dr P. A. Christensen, for generous help in preparing and supplying the different types and strengths of vaccine used; Dr Alberts of the SAIMR Laboratory, Pietersburg, and Dr Robert of the Masana Hospital, Northern Transvaal, for advice and assistance; and the Bantu Education Department and Bantu school principals for their willing co-operation. We also wish to acknowledge the courage of the thousands of schoolchildren who are submitting to the assault of the latest and, to them, terrifying medical machine. We are indebted to the Secretary for Health for permission to publish this paper.

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