Bull. Org. mond. Santé } 1973, **48**, 756-757
Bull. Wld Hlth Org. }

Ineffectiveness of an oral killed typhoid vaccine in a field trial*

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Abstract

A field trial was carried out with a vaccine containing 300 × 10⁹ killed S. typhi *(strain Ty58) per tablet. A total of 12 564 children aged 1–15 years were given 3 tablets of the vaccine or a placebo at the rate of one tablet on each of 3 consecutive days. The results indicated that the vaccine, in its present form and at this dosage, gives no protection.*

The first controlled field trial with killed oral typhoid vaccine in a large child population was conducted by us in 1968–69 (Chuttani et al., 1971). The results of this trial were not very encouraging; the vaccine, administered in 3 doses of one tablet, each containing 100×10^9 killed *Salmonella typhi* bacteria, gave no significant protection against typhoid. However, a detailed examination of the data suggested that an increase in bacterial content might give fruitful results in view of the heavy quantum of infection in the endemic areas, which possibly required a higher dose of the vaccine to achieve the necessary immunizing effect in the gut. Hence the present trial was undertaken with another vaccine.

Materials and methods

The methods adopted for the present trial were similar to those followed in the first trial (Chuttani et al., 1971), and the population selected was from a similar area.

Area and sample population. As in the earlier trial, the area selected had no piped water supply and sanitation was poor. As the yearly incidence of typhoid in such areas is about 7 per thousand, a sample of 6 000 children in each of a vaccinated and a control group was considered sufficient to demonstrate a statistically significant difference between the 2 groups if the effectiveness of the vaccine was at least 50%. A total of 13 274 children in the 1–15-year age group were included in the trial.

Vaccine and dosage. Oral killed typhoid vaccine in the form of Typhoral [6] enteric-coated tablets was used in the trial. Each tablet contained 300×10^9 acetone-inactivated *S. typhi* (strain Ty58) organisms. A total of 3 tablets in doses of one tablet on each of 3 consecutive days was given to the vaccinated group. The control group received placebo tablets containing sugar.

Field trial. This second study was organized as a controlled field trial along the same lines as the first trial; it again included a population census and similar follow-up methods were used (Chuttani et al., 1971).

The following criteria were adopted for diagnosing typhoid fever:

(1) a blood culture positive for *S. typhi*;

(2) a stool culture positive for *S. typhi* in a clinically diagnosed case, with or without a positive blood culture.

The typhoid vaccine or placebo tablets were given to the participants according to whether the final digit in their serial number was odd or even. Children suffering from either diarrhoea or fever at the time of administration of vaccine were excluded from the list of participants, as were those who had already received TAB vaccine parenterally. Administration of vaccine was started on 23 February 1970 and completed on 30 April 1970. Follow-up surveillance ended in March 1971. No untoward reactions to the vaccine were observed.

* The trial was sponsored by the Indian Council of Medical Research with the financial assistance of Hoechst Pharmaceuticals (Behringwerke), Federal Republic of Germany.

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[6] Manufactured and supplied by Behringwerke, Marburg-Lahn, Federal Republic of Germany.

Table 1. Distribution of children according to the number of doses received in the control and vaccinated groups

No. of doses	Control group	Vaccinated group	Total
1	225	257	482
2	116	112	228
3	6 428	6 136	12 564
total	6 769	6 505	13 274

Results

Table 1 shows the distribution of children in the vaccinated and control groups according to the number of doses received. The age and sex distribution of the children in the 2 groups was similar.

All participating children who became sick were seen at a local medical clinic. A total of 564 patients with fever of 3 or more days' duration with or without any other signs of typhoid fever were investigated bacteriologically for typhoid. *S. typhi* were isolated from 101 patients. Of these, 83 were positive only in blood culture and 13 in both stool and blood cultures. In 5 cases stool cultures alone were positive for *S. typhi.*

During the period of surveillance, from February 1970 to March 1971, 49 cases of typhoid (7.6 per 1 000 participants) occurred in the control group, and 52 cases (8.5 per 1 000 participants in the vaccinated group (Table 2). The difference in incidence between the 2 groups was not significant. In order to assess if the vaccine gave any short-term immunity, the data were further analysed by intervals of 1 month and 3 months as well as by age-specific attack rate, but the difference in the number of typhoid cases in the 2 groups was not significant for any specific period or age.

Table 2. Incidence of typhoid among children in the control and vaccinated groups

Group	No. vaccinated	No. of cases [a]	Rate per 1 000
Control	6 428	49	7.6
Vaccinated	6 136	52	8.5

[a] Bacteriologically positive for *S. typhi* in blood culture, stool culture, or both.

Discussion

In our earlier trial, no significant difference was found in attack rate between the control and vaccinated groups. Nevertheless, the data suggested that the vaccine offered mild protection for a short period of time. Hence we undertook a second trial using a higher dose of vaccine in order to counteract the high infection rate in the areas where the trials were conducted.

The present trial with Typhoral tablets containing 300×10^9 killed *S. typhi* bacteria (strain Ty58) showed that the vaccine, even at the increased dosage, gave no protection against typhoid fever.

In its present form and at the dosage used, oral killed typhoid vaccine does not seem to be a good immunizing agent. Its failure may be caused by the poor antigenicity of strain Ty58, the small number of doses, or the inability of the tablets to dissolve rapidly and of the antigen to be absorbed. It may be that more doses and a larger quantity of more potent antigen are needed to induce immunity.

REFERENCE

Chuttani, C. S. et al. (1971) *Bull. Wld Hlth Org.*, **45**, 445-450