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# Controlled Field Trials of Paratyphoid B Vaccine and Evaluation of the Effectiveness of a Single Administration of Typhoid Vaccine *

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*In 1963 and 1964 field trials were organized in the USSR for the purpose of evaluating the effectiveness of paratyphoid B vaccine. An opportunity was thereby afforded to assess the effectiveness of a single administration of typhoid vaccine, used as the preparation administered to the paratyphoid control group of 89 046 persons. Similarly, the control group used for assessing the effectiveness of the typhoid vaccine was the group of 86 620 persons inoculated with the paratyphoid vaccine.*

*It was established that it is, in principle, possible to immunize people effectively against paratyphoid B by administering heat-killed paratyphoid B vaccine prepared from an aerated broth culture. It was found that the protective effect of the vaccine depends upon the size of the dose and the number of times it is administered. A protective effect was produced when a dose of $6 \times 10^8$ organisms was administered to persons from 7 to 16 years of age. Two inoculations of the paratyphoid B vaccine ensured protection over the 30 months that the observations lasted, whereas a single administration only conferred protection for up to one year.*

*It was also confirmed that it is possible to obtain a protective effect with a single administration of a heat-killed typhoid vaccine prepared from an aerated broth culture. A single administration of the typhoid vaccine had a less marked protective effect (index of effectiveness 58 %) than 2 administrations, a fall in the level of the protection conferred occurring during the year after immunization. The frequency and intensity of general and local reactions were identical for equal doses of typhoid and paratyphoid B vaccine.*

## INTRODUCTION

To solve the problem of immunizing man against paratyphoid, an appropriate ingredient used to be included in enterovaccines based on data obtained by determining agglutinin titres in the inoculated (Castellani, 1914; Kabeshima, 1914; Davison, 1918, etc.). This approach to determining the effectiveness of typhoid and paratyphoid vaccines has already been deservedly criticized in a paper by Benenson (1964).

Before controlled trials were carried out, the effectiveness of the paratyphoid ingredients was usually assessed on the basis of total typhoid and paratyphoid morbidity figures. Data showing the effectiveness against typhoid of monovalent typhoid vaccines and of the typhoid component of typhoid-paratyphoid vaccines were frequently mechanically extrapolated to evaluate the effectiveness of the paratyphoid components.

Analysing the present situation in regard to study of typhoid and paratyphoid vaccines, Cvjetanović & Uemura (1965) state that the results at present available from a small number of observations (most of them not controlled) are not such as to enable conclusions to be drawn from them regarding the possibility of effective immunization of man against paratyphoid B. The same authors, reviewing the results of controlled typhoid vaccine evaluation trials in Yugoslavia (Yugoslav Typhoid Commission, 1962, 1964) and the USSR (Hejfec, 1965), conclude that typhoid vaccines do not protect man against paratyphoid B. Similarly there is no convincing evidence in the literature to show that the paratyphoid element is effective and strictly controlled trials are therefore required to evaluate it, with concurrent laboratory investigations.

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The first controlled trial undertaken for the specific purpose of evaluating the protective capacity of the paratyphoid B component was arranged in 1962 in the USSR (Hejfec et al., 1966), when it was found that the paratyphoid B component ($1.2 \times 10^8$ organisms injected in heat-killed and alcohol-killed vaccines, or 0.05 mg of extracted antigen in 2 chemical vaccines) in a dose equal to one quarter of the dose of the typhoid component failed to protect man against paratyphoid B. The findings of the trial did not, however, rule out the theoretical possibility of effective immunization of man against paratyphoid B, since the absence of effect could be ascribed to the dosages used being too small. One of the purposes of the present work was to study the possibility of using a vaccine for prevention of paratyphoid B.

With regard to immunization against typhoid, earlier controlled field trials in the USSR (1958–61) had indicated that it was possible to obtain a protective effect in man by means of a single administration of a chemical sorbed vaccine (Hejfec, 1965). The same conclusion was reached by Cvjetanović & Uemura (1965) from an analysis of morbidity in groups given a single injection of acetone-dried and agar-grown heat-killed vaccines in a field trial in British Guiana (now Guyana) in 1961.

An interesting question to settle was whether, in a specially planned controlled field trial, the corpuscular broth-grown heat-killed vaccine that had proved the most effective of the typhoid vaccines tried out in the USSR when administered twice would have a protective effect if administered only once. The second object of the present work was therefore to determine the degree and duration of protective effect produced by a single administration of that preparation.

## THE VACCINES

To increase the inoculation dose, paratyphoid B vaccines were prepared containing $10^9$ organisms per ml (in place of the $2 \times 10^8$ organisms in the divalent vaccines). The preparation was issued in 1963 in liquid form and in 1964 in freeze-dried form. The vaccine was prepared from a culture of *Salmonella paratyphi* B (strain no. 42) grown on broth in reaction vessels under aeration. The suspension was inactivated by heating at 58°C for 1 hour and preserved with 0.5% phenol.

The typhoid vaccines (for immunizing the control group) were also prepared from an aerated broth culture of *Salmonella typhi* (Ty 2 strain), by inactivation at 56°C for 1 hour. These vaccines, also, contained $10^9$ organisms per ml. Like the paratyphoid B vaccine, the typhoid vaccine was issued in liquid form in 1963 and in freeze-dried form in 1964. The method of preparing all the vaccines was the same as that used for making heat-killed typhoid and typhoid-paratyphoid vaccines (Zamuhovskaja et al., 1965). In 1963 the paratyphoid B vaccine was named Ž-63 and the typhoid vaccine N-63, and in 1964 the paratyphoid B vaccine Ž-64 and the typhoid vaccine N-64.

The dose was 0.6 ml per injection, i.e., $6 \times 10^8$ organisms. The liquid vaccines (Ž-63 and N-63) were issued in 10-ml flasks and the freeze-dried vaccines (Ž-64 and N-64) in ampoules containing 5 ml (after dissolving). The solvent used in the ampoules was a 0.85% solution of sodium chloride.

## ORGANIZATION OF THE TRIALS

Observations were made upon sample groups of the population in 4 administrative areas in 1963, and in 9 in 1964. The groups consisted chiefly of schoolchildren. They were chosen on the basis of thorough analysis and forecasting of paratyphoid B and typhoid morbidity in the various areas, to ensure that the results were sufficiently reliable statistically. The method employed was the same as that used in organizing controlled field trials for evaluating enterovaccines, a description of which has already been published by one of the present writers (Hejfec & Hazanov, 1959; Hejfec, 1965).

In 1963 the Ž-63 paratyphoid B vaccine was administered in 2 injections, at an interval of 20–30 days, while the N-63 typhoid vaccine (for the control group) was given in a single injection. In 1964 both vaccines (Ž-64 and N-64) were administered in a single injection. The inoculation campaign was carried out by specially-trained inoculation teams (consisting of 1 doctor and 2 nurses) in April and the first half of May. In 1963, in the 4 administrative areas covered, a total of 40 051 persons were inoculated, 19 219 of them with the Ž-63 vaccine and 20 832 with the N-63 vaccine. In the 9 administrative areas covered by the 1964 campaign 135 615 persons were inoculated, 67 401 with the Ž-64 vaccine and 68 214 with the N-64 vaccine. As will be seen from the particulars concerning the groups of people inoculated (Tables 1 and 2), the trial group and the control group were sufficiently nearly equivalent.

TABLE 1

PARTICULARS OF THE GROUPS INOCULATED IN 1963 WITH LIQUID HEAT-KILLED PARATYPHOID B (Ž-63) AND TYPHOID (N-63) MONOVALENT VACCINES

| Particulars | | Number of persons inoculated with the preparations | |
|---|---|---|---|
| | | Ž-63 | N-63 |
| Administrative area | 1 | 7 958 | 8 729 |
| | 7 | 2 037 | 2 360 |
| | 8 | 893 | 1 048 |
| | 12 | 8 331 | 8 695 |
| Sex | Male | 9 770 | 10 830 |
| | Female | 9 449 | 10 002 |
| Age | 7 years | 3 096 | 3 427 |
| | 8 years | 4 477 | 4 797 |
| | 9 years | 953 | 1 078 |
| | 10 years | 462 | 563 |
| | 11 years | 377 | 464 |
| | 12 years | 435 | 472 |
| | 13 years | 356 | 392 |
| | 14 years | 266 | 315 |
| | 15 years | 196 | 266 |
| | 16 years and over | 8 601 | 9 058 |
| Water-supply conditions | Piped water in dwellings | 6 248 | 6 739 |
| | Street standpipe | 11 801 | 12 866 |
| | Well | 990 | 1 022 |
| | Open watercourse | 180 | 205 |
| Previous enteric infections (as reported verbally) | | 111 | 127 |
| Illness occurring during the observation period | Paratyphoid A | 5 | 4 |
| | Dysentery | 31 | 27 |
| | Hepatitis | 36 | 27 |
| | Pertussis | 4 | 8 |
| | Scarlet fever | 38 | 31 |
| | Measles | 71 | 68 |
| | Diphtheria | — | 1 |
| | Others | — | 4 |
| | Total | 185 | 170 |

TABLE 2

PARTICULARS OF THE GROUPS OF SCHOOLCHILDREN INOCULATED IN 1964 WITH DRIED HEAT-KILLED PARATYPHOID B (Ž-64) AND TYPHOID (N-64) MONOVALENT VACCINES

| Particulars | | Number of persons inoculated with the preparations | |
|---|---|---|---|
| | | Ž-64 | N-64 |
| Administrative area | 1 | 5 069 | 5 112 |
| | 2 | 6 003 | 6 013 |
| | 3 | 4 119 | 4 068 |
| | 4 | 5 590 | 6 056 |
| | 5 | 8 102 | 8 193 |
| | 6 | 9 352 | 9 297 |
| | 9 | 8 200 | 8 150 |
| | 10 | 7 867 | 8 209 |
| | 11 | 13 099 | 13 116 |
| Sex | Male | 34 025 | 34 191 |
| | Female | 33 376 | 34 023 |
| Age | 7 years | 2 864 | 3 009 |
| | 8 years | 6 592 | 6 554 |
| | 9 years | 5 536 | 5 521 |
| | 10 years | 7 470 | 7 538 |
| | 11 years | 7 249 | 7 269 |
| | 12 years | 8 117 | 8 033 |
| | 13 years | 7 870 | 7 880 |
| | 14 years | 7 297 | 7 872 |
| | 15 years | 6 174 | 6 310 |
| | 16 years and over | 8 232 | 8 228 |
| Water-supply conditions | Piped water in dwellings | 8 160 | 7 126 |
| | Street standpipe | 28 240 | 29 727 |
| | Well | 670 | 684 |
| | Open watercourse | 7 038 | 7 291 |
| | Mixed | 23 293 | 23 386 |
| Previous enteric infections (as reported verbally) | | 270 | 284 |
| Illnesses occurring during the observation period | Paratyphoid A | 16 | 12 |
| | Dysentery | 62 | 61 |
| | Hepatitis | 63 | 60 |
| | Pertussis | 5 | 11 |
| | Scarlet fever | 33 | 40 |
| | Measles | 86 | 72 |
| | Others | 5 | 3 |
| | Total | 270 | 259 |

The frequency of illnesses (other than paratyphoid B and typhoid) detected during the observation period was identical in the groups compared.

### REACTIONS TO ADMINISTRATION OF THE VACCINES

Reactions to administration of the paratyphoid B vaccine were studied in 1963 before the epidemiological trials were carried out (Levina et al., 1965). They were of the same nature and frequency as the reactions to administration of typhoid vaccines. The general reaction began 5 or 6 hours after the injection, was most frequent and intense after 9 to 12 hours, and came to an end in the great majority of cases 24 to 48 hours after the injection. The general reaction was characterized by a rise in temperature, indisposition, and headache ; the local reaction took the form of moderate hyperaemia and oedema.

It was found, in a group of 2306 schoolchildren, to whom a paratyphoid vaccine (Ž-63) was administered twice at an interval of 20 to 30 days in a dose of 0.6 ml, that the frequency and intensity of temperature reactions to the second injection were less than in the case of the first (Table 3). Of the 120 children who showed a marked reaction to the first injection, only 6 had a reaction of the same intensity after the second ; in the remaining 114 the temperature reaction to the second injection consisted of a rise to not more than 37.5°C.

During the inoculation campaign the reaction was ascertained 18 to 22 hours after the injection, when the frequency of reactions was still fairly high. In the field trial the reactions to administration of the typhoid and the paratyphoid vaccines were read at the same time as one another. The numbers of persons examined were : 2830 inoculated with the Ž-63 vaccine and 3258 inoculated with the N-63 vaccine in 1963 ; and 2900 inoculated with the Ž-64 vaccine and 2518 inoculated with the N-64 vaccine in 1964. It was found that a temperature reaction occurred, in all the groups, in 25% to 30% of the persons inoculated, and that the temperature rose to above 37.5°C in 6% to 10%.

### EFFECTIVENESS OF THE PARATYPHOID B VACCINE

Recording of cases of illness began one month after the inoculations were completed. In the areas where inoculated persons were kept under observation measures were taken to ensure extensive and early case-finding ; in particular, blood cultures were taken, not only on suspicion of typhoid or paratyphoid, but in any case of feverish illness lasting more than 3 days.

In the groups under observation a total of 59 cases of paratyphoid B confirmed by haemocultures were recorded, including 25 in the 30-month observation period among persons inoculated in 1963 (Table 4), and 34 in the 30-month period among those inoculated in 1964 (Table 5).

The data for the first 10 months of observation showed similar results for the 1963 and 1964 groups. These results can therefore be considered together (Table 6).

TABLE 3

FREQUENCY OF TEMPERATURE REACTIONS 24 HOURS AFTER THE FIRST AND THE SECOND INJECTIONS OF PARATYPHOID B VACCINE (Ž-63)

| | | Distribution of reactions after second injection | | | | | Total reactions after first injection | |
|---|---|---|---|---|---|---|---|---|
| | | Up to 37°C | 37.1°C-37.5°C | 37.6°C-38.0°C | 38.1°C-38.5°C | 38.6°C-39°C | No. | % |
| Distribution of reactions after first injection | Up to 37°C | 1 520 | 200 | 19 | 4 | 1 | 1 744 | 75.62 |
| | 37.1°C–37.5°C | 369 | 62 | 8 | 2 | 1 | 442 | 19.17 |
| | 37.6°C–38.0°C | 69 | 26 | 4 | 1 | | 100 | 4.34 |
| | 38.1°C–38.5°C | 9 | 5 | 1 | | | 15 | 0.65 |
| | 38.6°C and over | 4 | 1 | | | | 5 | 0.22 |
| Total reactions after second injection | No. | 1 971 | 294 | 32 | 7 | 7 | 2 306 | |
| | % | 85.47 | 12.75 | 1.39 | 0.30 | 0.09 | | |

TABLE 4

DISTRIBUTION OF CASES OF PARATYPHOID B IN THE TRIAL AND CONTROL GROUPS INOCULATED IN 1963

| Group | No. inoculated | No. of cases occurring: within 2-12 months | within 13-30 months | Total | Mean monthly incidence per 100 000 | Significance of difference according to $\chi^2$ test | Effectiveness % | 95% confidence interval |
|---|---|---|---|---|---|---|---|---|
| Trial | 19 219 | 1 | 4 | 5 | 0.87 | $P<0.05$ | 73 | 35-90 |
| Control | 20 832 | 8 | 12 | 20 | 3.20 | – | – | – |

TABLE 5

DISTRIBUTION OF CASES OF PARATYPHOID B IN THE TRIAL AND CONTROL GROUPS INOCULATED IN 1964

| Group | No. inoculated | No. of cases occurring: within 2-12 months | within 13-30 months | Mean monthly incidence during first period per 100 000 | Significane of difference according to $\chi^2$ test during first period | Effectiveness during first period % | 95% confidence interval |
|---|---|---|---|---|---|---|---|
| Trial | 67 401 | 3 | 9 | 0.45 | $P< 0.05$ | 75 | 19-94 |
| Control | 68 214 | 12 | 10 | 1.76 | – | – | – |

TABLE 6

EVALUATION OF THE EFFECTIVENESS OF PARATYPHOID B VACCINE DURING THE FIRST YEAR OF OBSERVATION FROM THE RESULTS OF TWO SETS OF OBSERVATIONS (1963 AND 1964)

| Group | No. of persons inoculated | No. of cases | No. of cases per 10 000 | Significance of difference according to $\chi^2$ test | Effectiveness % | 95% confidence interval |
|---|---|---|---|---|---|---|
| Trial | 86 620 | 4 | 0.46 | $P< 0.01$ | 79 | 47-93 |
| Control | 89 046 | 20 | 2.24 | – | – | – |

It may be concluded from the foregoing that it is possible to ensure satisfactory protection against paratyphoid B in man with 1 or 2 inoculations of paratyphoid vaccine administered in a sufficiently large dose ($6 \times 10^8$ organisms). It may also be considered established that two injections of the vaccine have a fairly long-lasting effect.

## EFFECTIVENESS OF A SINGLE ADMINISTRATION OF TYPHOID VACCINE

In the groups under observation a total of 120 typhoid cases were found, the diagnosis being confirmed with haemocultures. In addition, during the earlier field trials (No. 4 in 1961 and No. 5 in 1962) when the effectiveness of two administrations of vaccine was being evaluated, some of the persons in the group injected had been given only one injection, and among them 9 cases had been found. Thus the total number of cases available to the present writers for evaluating the effectiveness of a single injection was 129—39 of them in the trial group and 90 in the control group (Table 7).

The conclusion reached from the results obtained (Table 8) is that a single injection of heat-

TABLE 7

DISTRIBUTION OF TYPHOID CASES FOR EVALUATING THE EFFECTIVENESS OF A SINGLE ADMINISTRATION OF TYPHOID VACCINE

| Year observations began | Group | No. inoculated | No. of cases | | | Mean monthly incidence per 10 000 | | |
|---|---|---|---|---|---|---|---|---|
| | | | 2-12 months | 13-20 months | Total | 2-12 months | 13-30 months | Total |
| 1961 | Trial | 2 324 | 2 | 0 | 2 | 0.78 | 0 | 0.30 |
| | Control | 2 611 | 4 | 0 | 4 | 1.39 | 0 | 0.53 |
| 1962 | Trial | 2 575 | 0 | 0 | 0 | 0 | 0 | 0 |
| | Control | 2 194 | 3 | 0 | 3 | 1.24 | 0 | 0.47 |
| 1963 | Trial | 20 832 | 1 | 7 | 8 | 0.04 | 0.19 | 0.13 |
| | Control | 19 219 | 13 | 14 | 27 | 0.61 | 0.40 | 0.48 |
| 1964 | Trial | 68 214 | 9 | 20 | 29 | 0.12 | 0.16 | 0.15 |
| | Control | 67 401 | 23 | 33 | 56 | 0.31 | 0.27 | 0.29 |
| Total | Trial | 93 944 | 12 | 27 | 39 | 0.12 | 0.16 | 0.14 |
| | Control | 91 425 | 43 | 47 | 90 | 0.43 | 0.23 | 0.34 |

TABLE 8

EVALUATION OF THE EFFECTIVENESS OF A SINGLE ADMINISTRATION OF TYPHOID VACCINE DURING THE WHOLE OBSERVATION PERIOD

| Group | No. inoculated | No. of cases | Mean monthly incidence per 10 000 | Significance of difference according to $\chi^2$ test | Effectiveness | |
|---|---|---|---|---|---|---|
| | | | | | % | 95% confidence interval |
| Trial | 93 994 | 39 | 0.14 | $P<0.001$ | 58 | 42-70 |
| Control | 91 425 | 90 | 0.34 | | | |

TABLE 9

EVALUATION OF THE EFFECTIVENESS OF A SINGLE ADMINISTRATION OF TYPHOID VACCINE DURING THE FIRST AND SECOND OBSERVATION PERIODS

| Group | No. inoculated | First period (2-12 months) | | | | | Second period (13-30 months) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | No. of cases | Mean monthly incidence per 10 000 | Significance of difference according to $\chi^2$ test | Effectiveness | | No. of cases | Mean monthly incidence per 10 000 | Significance of difference according to $\chi^2$ test | Effectiveness | |
| | | | | | % | 95% confidence interval | | | | % | 95% confidence interval |
| Trial | 93 944 | 12 | 0.12 | $P<0.001$ | 74 | 52-85 | 27 | 0.16 | $P<0.05$ | 44 | 15-64 |
| Control | 91 425 | 43 | 0.43 | | | | 47 | 0.28 | | | |

killed broth-grown typhoid vaccine has a protective effect. Comparison of the figures obtained during the first observation period with those obtained during the second (Table 9) shows that the protective effect of a single injection of typhoid vaccine was fairly high (74%) during the first period (2–12 months), but considerably decreased (to 44%) during the second (13–30 months), the difference between the coefficients being statistically significant ($P < 0.05$).

Thus the protective effect of a single injection is less stable and one year after immunization the degree of protection given the inoculated persons substantially decreases.

## DISCUSSION

### *Paratyphoid vaccine*

The results of the controlled field trial to evaluate the effectiveness of immunization against paratyphoid B which was carried out earlier using divalent vaccines (Hejfec et al., 1966) indicated that the paratyphoid component was ineffective. The possible reasons for the negative result were either that it was impossible to protect man against paratyphoid B by artificial immunization, or that the preparations used were in some way defective. In the light of the relationship found between the protective effect and the dose in the case of typhoid vaccines, the hypothesis was advanced that the unfavourable results might be due to the dose of the paratyphoid B component in the divalent vaccines not being large enough (one quarter as large as the typhoid component).

Accordingly, to determine whether it was possible to immunize man effectively against paratyphoid B, preparations with a considerably higher content of the paratyphoid component were employed. The dose per injection was increased fivefold (from $1.2 \times 10^8$ to $6 \times 10^8$ million organisms).

The results obtained show that it is possible to protect man against paratyphoid B. Admittedly, a protective effect can be claimed with full confidence only for the type of preparation tested—a vaccine prepared from an aerated broth culture, inactivated by heating and preserved with phenol, and used in the liquid or freeze-dried state. This does not, of course, mean that effective immunization against paratyphoid B cannot be provided by employing other types of vaccine, but that question will probably require special study.

The degree of protective effect of heat-killed paratyphoid B vaccine is quantitatively comparable with that of heat-killed typhoid vaccine. As had been found earlier for typhoid vaccine, a relationship was also found for paratyphoid vaccine between the protective effect and the size of the immunizing dose: the duration of the protective effect depended on the number of injections given. Two injections of a heat-killed broth-grown paratyphoid B vaccine administered at an interval of 20–30 days in a dose of $6 \times 10^8$ organisms per injection afforded effective protection against paratyphoid B for about 3 years. A single injection of the preparation conferred protection for a shorter period, 1 year or less.

The data obtained provide a basis for the effective use of immunization against paratyphoid B as part of a set of measures for prevention of the disease where this is called for by the epidemiological situation. In addition, they open up fresh prospects of developing combined typhoid-paratyphoid vaccines—preparations containing an equal number of typhoid and paratyphoid organisms. However, it appears that such combined preparations can be used for immunizing adults only, since there is a danger that more children will show reactions when a greater total antigenic load, due to the paratyphoid component, is administered. Such being the case, and in view of the fact that very frequently immunization against both typhoid and paratyphoid B is not indicated, it would be best to use, where appropriate, a monovalent paratyphoid vaccine for administration to children.

### *Typhoid vaccines*

From the data obtained in these specially planned controlled field trials it may be concluded that a single injection of heat-killed broth-grown typhoid vaccine has a very marked protective effect.

These data differ substantially from those obtained when the protective effect of 2 injections of the same preparation was evaluated in the earlier field trials.

The protective effect of a single injection is less stable, however, and 1 year after immunization the degree of protection afforded the inoculated person substantially decreases.

Two injections of the heat-killed broth-grown vaccine had a very great protective effect (index of effectiveness 83.4%, with a 95% confidence inter-

val of 76.5 %–88.9 %), which did not decrease for over 3 years (Hejfec et al., 1966). The 2 injections had a stable protective effect during each of the 2 observation periods (index of effectiveness 83.2% and 83.9% respectively). In this lies the undoubted advantage of 2 injections of the preparation over a single injection. However, the possibility of securing a smaller but yet quite marked effect (at any rate for 1 year) after a single injection of heat-killed broth-grown vaccine is of great practical importance in cases in which it is not possible to inoculate a group twice, or where some of the persons inoculated have 1 injection only.

Comparison of the data obtained with data on the effectiveness of a single injection of a chemical typhoid vaccine published earlier (Hejfec, 1965) shows that the protective effect of a single injection of the heat-killed broth-grown vaccine is at least as great as that of the chemical vaccine. Two injections of the chemical vaccine did not produce a greater effect than a single injection, whereas the difference in the case of the heat-killed vaccine is clearly shown by the results described above. Consequently, when the effects of 2 administrations of the 2 preparations were compared (Hejfec et al., 1966), the heat-killed vaccine was found to be considerably more effective.

Thus data have now been obtained showing that it is possible to produce a protective effect with a single administration of 4 types of vaccine: chemical vaccine, heat-killed broth-grown vaccine, and vaccines K and L (acetone-dried and heat-killed agar-grown vaccines). The establishment of post-vaccinal immunity against typhoid after a single administration of vaccine is accordingly a property common to a number of different types of typhoid vaccine.

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## RÉSUMÉ

Plusieurs essais contrôlés ont été organisés en URSS en 1963 et 1964 en vue, d'une part, d'évaluer le pouvoir protecteur d'un vaccin antiparatyphoïdique B et, d'autre part, de fixer la valeur et la durée de la protection conférée après administration d'une dose unique d'un vaccin antityphoïdique reconnu précédemment comme le plus efficace après injection de deux doses.

Les vaccins antiparatyphoïdiques, préparés à partir d'une culture de *Salmonella paratyphi* B (souche 42), ont été inactivés par la chaleur et le phénol. Les vaccins antityphoïdiques ont été obtenus à partir d'une culture de *S. typhi* (souche Ty 2). Toutes ces préparations contenaient $10^9$ organismes par millilitre et ont été utilisées sous forme liquide en 1963 et sous forme lyophilisée en 1964. La dose administrée a été dans chaque cas de 0,6 ml par injection, soit $6 \times 10^8$ organismes.

Les essais ont porté sur divers groupes de population, principalement des écoliers, choisis dans 4 districts en 1963 et dans 9 districts en 1964. En 1963, 40 051 personnes au total ont été vaccinées: 19 219 par le vaccin antiparatyphoïdique B liquide (2 injections à intervalle de 20-30 jours) et 20 832 par le vaccin antityphoïdique liquide (injection unique). En 1964, 135 615 personnes ont été immunisées (injection unique): 67 401 au moyen de vaccin antiparatyphoïdique B lyophilisé et 68 214 au moyen de vaccin antityphoïdique lyophilisé. Deux groupes de personnes ont été mis sous surveillance durant ces deux années: 86 620 vaccinés à l'aide du vaccin antiparatyphoïdique B ont servi de groupe témoin pour vérifier l'efficacité d'une injection unique de vaccin antityphoïdique, et 89 406 personnes ayant reçu ce dernier vaccin ont permis de contrôler la valeur de la protection conférée par le vaccin antiparatyphoïdique B.

Les essais ont montré qu'il est possible en principe d'obtenir une protection satisfaisante contre la fièvre paratyphoïde B par l'administration de 1 ou 2 injections de vaccin tué par la chaleur à doses suffisantes ($6 \times 10^8$ organismes). On a mis en évidence une relation entre l'effet protecteur, la dose et le nombre d'injections. L'administration de 2 doses de vaccin a permis d'obtenir une immunisation efficace pendant les 30 mois de la période d'observation; en cas d'injection d'une seule dose, la durée de la protection n'a pas dépassé un an.

Quant à l'immunisation contre la fièvre typhoïde, elle peut être obtenue par une injection unique de vaccin tué par la chaleur. La protection ainsi conférée a été de l'ordre de 74% pendant la première année, mais son taux n'atteignait plus que 44% du 13e au 30e mois. L'effet immunisant d'une seule dose de vaccin est donc moins durable que celui obtenu par l'injection de deux doses.

Les réactions générales et locales, étudiées en 1963, ont été de même nature et de même fréquence après la vaccination antityphoïdique et la vaccination antiparatyphoïdique.

## REFERENCES


Benenson, A. S. (1964) *Bull. Wld Hlth Org.*, **30**, 653

Castellani, A. (1914) *Zbl. Bakt. I. Abt. Orig.*, **72**, 536

Cvjetanović, B. & Uemura, K. (1965) *Bull. Wld Hlth Org.*, **32**, 29

Davison, W. (1918) *Arch. int. Med.*, **21**, 437

Hejfec, L. B. (1965) *Bull. Wld Hlth Org.*, **32**, 1

Hejfec, L. B. & Hazanov, M. I. (1959) [*Methods and organization of field trials for studying the effectiveness of enteric vaccines*], Moscow, Scientific Information Bureau

Hejfec, L. B. et al. (1966) *Bull. Wld Hlth Org.*, **34**, 321

Kabeshima, T. (1914) *Zbl. Bakt. I. Abt. Orig.*, **74**, 294

Levina, L. A. et al. (1965) [*Typhoid vaccines*], Moscow, Medicina, p. 195

Yugoslav Typhoid Commission (1962) *Bull. Wld Hlth Org.*, **26**, 357

Yugoslav Typhoid Commission (1964) *Bull. Wld Hlth Org.*, **30**, 623

Zamuhovskaja, A. N. et al. (1965) [*Typhoid vaccines*], Moscow, Medicina, p. 33