A REPORT ON THE USE OF STOCK VACCINE IN INFECTION BY THE *BACILLUS TYPHOSUS*, WITH AN ANALYSIS OF TWO HUNDRED AND THIRTY CASES.

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METHODS ADOPTED IN THE INVESTIGATION.

The two hundred and thirty cases under consideration were in hospital during the winter 1914-1915. Half the cases were in my medical charge, the remainder being in the wards of Major Johnstone, Captain J. A. Torrens, Captain G. D. H. Wallace, and other medical officers. Careful notes were taken, and a summary of each case was made at its termination by the particular medical officer, and I am much indebted to them.

The notes of the cases were made on the same plan, which was carried out with various modifications by the other officers. At the end of the winter, with the cases fresh in mind, an analysis was made of my series. About 500 cases of the enteric group have now passed through my wards, and after this additional clinical experience an attempt has been made to judge the effects of vaccine, and to reconsider all the typhoid cases which have had this treatment.

To be certain of effects of the vaccine in any particular case is a difficult matter, as mere impressions in isolated cases often prove false. Vaccine given to a patient in the hope that it will do good is liable to get the credit of his excellent recovery, when there is no proof that he would not have done equally well without it. How, then, is one to judge of the effects? It is obvious that, even if a scientifically accurate method were available, carefully selected controls are necessary, and that impressions have to be checked by a comparison between the vaccinated cases and the unvaccinated controls, and that groups of the same kind of case should be compared with other control groups.

Altogether 176 cases have had vaccine treatment. The cases now considered number 230; half of these were on vaccine treatment, and the other 115 are the selected controls. To make a just comparison between the two sets of cases has been the object of this investigation. The analysis of the cases incidentally shows
what were the usual course and complications of the disease among
the soldiers in this hospital during the winter 1914-1915.

The Selection of the Cases.—In order that cases of typhoid fever
may be rightly compared they must conform to certain standards.
It was by a rigid conformity to these standards that the cases were
reduced in number to two hundred and thirty.

First, it must be certain that all the cases are true typhoid
fever, and not merely due to one or other of the three organisms of
the enteric group. For this reason neither the expression "typhoid
fever," nor "enteric fever" was used in the title of this paper, as
both these terms are often still applied clinically to any case of the
enteric group.

Paratyphoid fever is in the great majority of cases a much
milder disease than typhoid fever, the average prognosis being
better in every way, and the death-rate much lower. In the early
days of this hospital there had not been time or material to put
the laboratory into proper working order. Many cases, therefore,
were considered "typhoid fever" on clinical grounds, or after the
isolation from them of a Gram-negative motile bacillus which did
not ferment lactose. Several such cases were treated with vaccine,
and, making a good and rapid recovery, were considered at the
time good results for this treatment. Further investigation of the
organisms from some of these patients proved that the disease had
been paratyphoid fever and, as one came to recognize the usual
course of this disease, it was seen that these so-called good results
were fallacies (see Case 0).

It is with this memory of some of our earlier mistakes that
I place the bacteriological proof of the cases as the first essential.
The hospital has been most fortunate in having several bacteri-
ologists thoroughly acquainted with the bacilli of the enteric group.
It is especially due to the work of Captain J. L. Wood, R.A.M.C.,
and of Captain W. H. Tytler, C.A.M.C., that the cultures of the
organisms obtained from the cases are now in the laboratory, each
indexed with a full account of their reactions and the stringent
standards to which they had to conform before being finally named.
An analysis would have been useless without this sure foundation
of the accurate bacteriological diagnosis of the cases; 205 of the
230 cases had the Bacillus typhosus isolated from them. Of these,

1 Torrens and Whittington: "The Clinical Aspects of Paratyphoid Fever."
 Br i t. M ed. Journ., November 13, 1915, and J ournal o f the Royal Army Me di cal-
 Corps, October, 1915.
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177 were isolated from the blood-stream, 20 from the stools and 8 from the urine. In 43 of the fatal cases a post-mortem examination was made, and in 26 of the cases the *B. typhosus* was isolated from the gall-bladder and in 8 from the spleen. The remaining 25 cases, from which the organism was not isolated, were identified by the fact that their serum agglutinated the *B. typhosus* before vaccine was given, and as all were uninoculated this seems sufficient. All cases in which the laboratory evidence was incomplete or equivocal or suggested a double infection have been excluded. Cases sent in as "bacteriologically diagnosed enteric" or "typhoid" are not necessarily included, as often all that was meant was that one of the organisms of the enteric series had been isolated.

The state of inoculation complicates the question of typhoid fever among soldiers. One cannot properly compare the effect of vaccine in unprotected cases with that in cases which already have had some variable amount of protection given them by the use of the same vaccine. Also serious cases are comparatively rare among inoculated men, and thus only a few inoculated cases have been treated by vaccine at this hospital. For these reasons I have paid special attention to the uninoculated cases. Two hundred of the series are of this kind, 100 treated with vaccine and 100 unvaccinated controls. A few cases have been included in which the protective inoculation was given during the apparent onset of the disease (Case 164).

The varying severity of the disease in individuals and the fact that some cases come under treatment late and others early in the course of their fever make comparisons difficult. In analysing the cases I have divided them into classes according to their apparent severity at the time of admission and into groups according to the prognosis. Similar classes and groups of cases can then be compared according as they have or have not been on vaccine treatment. It is well known that typhoid fever varies not only in its incidence but also in its severity according to the year and season of the year, the climate and locality, and the age and sex, and that the incidence of the complications is much affected by these factors. To judge the results of a method of treatment of any infectious disease, but especially of typhoid fever, the above conditions should be constant. The cases now considered occurred between November and May, the great majority occurring during the months of December to March inclusive. They came from the comparatively small area occupied at that time by the troops of the Expeditionary Force. Finally, the patients all being soldiers,
age and previous health were fairly constant. In this connexion it should be remembered that lack of care early in the disease increases the severity and mortality rate. To sum up, in judging the effect of vaccine in typhoid cases I have tried to be certain of the following essentials (without which results will be fallacious):

(1) Proof of infection by the B. typhosus in all the cases, including the controls.

(2) Accurate selection of these control cases, that is, (a) as far as possible the classes of cases and groups of cases compared are of the same degree of severity; (b) there is the same state (or lack) of inoculation in the cases compared; (c) all the cases occurred in the same season of the year and in the same climate and locality; (d) all were of the same sex and of about the same age and previous health; (e) other modes of treatment (nursing, etc.) were similar.

Clinical Grouping of the Cases.—The classes referred to, into which the 230 cases were divided, varied according to the apparent condition of the patient on admission or after observation for a day or two, each class of vaccinated cases having a control class of the same size. It should be noted that the final result of the case was not taken into account, but the state of the case before treatment was started. I will briefly explain the method of this classification. A flushed, drowsy patient, obviously ill, is said to be looking "toxic" (Cases 112, 162 and 8, etc.), and this expression is used by all the medical officers in describing their cases. For instance, a patient who has a typical typhoid aspect with a sallow, muddy complexion and malar flush, who is lying inert on his back, mentally fuddled or delirious, and looking obviously poisoned is described as "very toxic," whereas an alert, mentally clear man, merely looking slightly febrile, is described as "quite non-toxic." The severity of the case usually, but by no means always, varies directly with the degree of toxæmia thus evident. In judging the severity the following points were especially considered:

(a) The rate and type of the pulse.
(b) The amount of pulmonary involvement.
(c) The temperature.
(d) The amount of distension.
(e) The day of the disease.

The day of disease is counted from the day which appeared by the previous history to be the first day of illness. On these lines the two hundred and thirty cases were divided into:
Class 1.—Thirty-two cases, very severe and very toxic.
Class 2.—Eighty-six cases, severe and toxic.
Class 3.—Fifty-six cases of moderate severity.
Class 4.—Forty-four cases, moderately severe, but quite non-toxic.
Class 5.—Twelve cases, mild.

The Vaccine and Dosage.—The vaccine used (with four exceptions) was the stock Army vaccine made up for treatment purposes in the dilution of 250 millions to the cubic centimetre. The other four cases had a sensitized vaccine. The initial dose, the interval between the doses, and the rate of increase of the dose, were all the subject of careful trial, and in many of the earlier cases I had the benefit of the advice of Colonel Sir William Leishman. A small initial dose of 80 to 100 millions was tried in certain cases, but this did not seem sufficiently strong. There were some patients who had received their first inoculation during or immediately before the apparent onset of the disease (Case 164), and who were therefore considered to have had a big dose of vaccine (500 or 1,000 millions) early in their attack. Some of these patients did unusually well, and therefore a similar big initial dose was tried in other cases (Case 162). Also these and other cases seemed to support the view that the sooner the vaccine was given the better was its chance of doing good; but later there were some cases of this variety which did badly. At one time we had the impression that it was very important to get the vaccine in early; but perhaps this was due to the obvious fact that the sooner any case comes under ordinary treatment (bed, nursing, and dieting), the better chance has that patient of doing well. Eventually a first dose of 200 to 250 millions was given as a routine, and subsequent doses were usually injected at intervals of two to three days, rising by about 100 to 200 millions each time to 500 or 600 millions. The time of day for injection was varied in nearly all cases. I gave my patients their injections between 5 and 7.30 p.m., i.e., when the temperature was usually rising. The other medical officers gave the injections during the morning, when the temperature was down or falling. It was thought that, as there is frequently a decided difference in the temperature and state of the patient as observed in the morning and in the evening, the time of day might be important, but the result did not support this view. It seemed both impossible and unwise to keep to any strict rule, and the system of dosage varied much with the individual case. If there was much local reaction, or if there appeared to be a marked general reaction, there was no increase of dose, or the increase
was more gradual. Also if there was no local reaction, and apparently no general reaction, a bigger dose was often given the next day.

To be certain that a general reaction to the vaccine has occurred at any particular time in the course of a case is most difficult. All the medical officers here, after observing a large number of cases, eventually came to the conclusion that the temperature chart was a fallacious guide to the effect of any particular dose. In this matter I am unable to follow those who have described cases of typhoid fever in which rises and falls in the temperature were stated with assurance to have been due to the vaccine. Many of the control cases would have been considered good results for vaccine had they received it (Case 23).

THE RESULTS.

(1) The Whole Series of 230 Cases (115 Vaccinated, 115 Selected Controls).

The total mortality in the 230 cases was 52 (22.6 per cent), this being made up by 29 deaths in the vaccinated cases (25 per cent) and 23 deaths in the unvaccinated (20 per cent).

The average length of the primary period of pyrexia (neglecting fatal cases) was 27.5 days. The average date on which the temperature settled was the twenty-ninth day in the vaccinated cases and the twenty-sixth day in the controls.

The total number of cases having a relapse was 22 (9.5 per cent), and of these 12 occurred among the vaccinated and 10 among the unvaccinated. In this investigation a relapse was taken to mean a rise of temperature lasting several days, during which there was some recurrence of the previous typhoid symptoms and signs. Rises of temperature due only to a complication or sequel are not included. The total number of patients with complications or sequel of some kind or another was 111, and of these 58 were among those who had vaccine and 53 among the unvaccinated. The more important of these complications were distributed as follows:

<table>
<thead>
<tr>
<th>In the total 230 cases</th>
<th>In the vaccinated</th>
<th>In the controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per cent</td>
<td>Per cent</td>
<td>Per cent</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>30 cases (13.0)</td>
<td>17 cases (14.7)</td>
</tr>
<tr>
<td>Perforation</td>
<td>7 &quot; (3.0)</td>
<td>5 &quot; (4.3)</td>
</tr>
<tr>
<td>Thrombosis and phlebitis</td>
<td>7 &quot; (3.0)</td>
<td>4 &quot; (3.4)</td>
</tr>
<tr>
<td>Severe post-typhoid debility, or prolonged convalescence</td>
<td>33 &quot; (14.0)</td>
<td>19 &quot; (15.7)</td>
</tr>
</tbody>
</table>
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"Hæmorrhage" does not include the fairly numerous cases in which only streaks of blood or minute quantities were present in the stools: Hæmorrhage from the bowel was the cause of death or the deciding factor in six of the fatal vaccinated cases and in five of the controls. It was noted that in some of the cases the hæmorrhage started just after a dose of vaccine or recurred after a dose (see Cases 162 and 164). Such cases may have been coincidences, like many other things, good and bad, which occur during vaccine treatment. There is, however, the possibility that after a dose a greater inflammatory reaction may occur in the ulcerated Peyer's patches, and the increase in the local blood-pressure then occurring at these spots may be the decisive cause of the bleeding.

Pulmonary involvement and meteorrhagism are not in the above list, as, except in the mildest cases; there is always more or less chest trouble and more or less abdominal distension, and it has seemed difficult to say at what stage conditions so frequently present become complications, and are no longer to be considered part of the usual course of the disease. It seems certain, however, that vaccine has no power to prevent or to produce them, or to diminish them when present except in so far as it may affect the general health of the patient. The presence or absence of these conditions was always carefully noted in attempting to judge the effect of vaccine, and the vaccine rarely seemed to have any good effect in cases with much bronchitis or broncho-pneumonia.

[Note.—It must be remembered that (a) this high death-rate is the rate for a particular series of cases only; (b) that 200 of the cases were uninoculated, and that they occurred during the winter months, and many of them under adverse conditions unavoidable at that time (slow evacuation to fever hospital, etc.) ; and (c) that 177 of them had the B. typhosus isolated from the blood-stream, and were therefore very definitely infected.]

The present death-rate at this hospital of the true typhoid cases is 12·3 per cent, being made up of a rate of 16·5 per cent in the uninoculated, and 8·1 per cent in the inoculated (November, 1915).

(2) In the 200 Uninoculated Cases (100 on Vaccine and 100 Controls).

<table>
<thead>
<tr>
<th>In the 200 cases</th>
<th>In the vaccine series</th>
<th>In the controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>47</td>
<td>25 per cent</td>
</tr>
<tr>
<td>Average length of pyrexia in days</td>
<td>27·5 days</td>
<td>29·4 days</td>
</tr>
<tr>
<td>Number of cases with relapses</td>
<td>19</td>
<td>10 per cent</td>
</tr>
<tr>
<td>Number of cases with complications or sequelae</td>
<td>101</td>
<td>51 &quot;</td>
</tr>
</tbody>
</table>
These results require a close analysis to show how the various types of case were affected. The classes will now be dealt with separately. (For summary see table.)

Class 1.—Very severe and toxic, 28 cases (14 with vaccine and 14 without).

(a) Among the vaccinated cases there were nine deaths (64.2 per cent) and five recoveries. Of the fatal cases, five died of toxæmia and cardiac failure, with basal congestion and broncho-pneumonia in varying degrees, seven, three, eleven, five, and seven days after admission respectively. These cases in this order had two, one, two, three, and two injections of vaccine, and I doubt if it had any influence on them at all. Of the other four fatal cases one got steadily worse and died of perforation eleven days after admission, and vaccine possibly did harm in this case. Perforation occurred the day after the second dose. Another case became steadily worse, having two severe hæmorrhages after the injection, and died thirteen days after admission; and here also vaccine possibly did harm, as the case was admitted early in its course and the bleeding occurred on the tenth and eleventh days (see Case 162).

Another case died of hæmorrhage thirty-six hours after admission, having arrived in a collapsed condition as a result of severe bleeding during the journey. A small dose of vaccine (100 millions) was given after he had revived, and the hæmorrhage recurred. I do not think vaccine did him harm, as no form of treatment could have saved him. In the remaining fatal case the temperature came down steadily after four doses of vaccine, but at the same time the pulse-rate and the delirium were bad, the patient was in a very asthenic condition, and he died fifteen days after admission of a rapidly spreading pneumonia.

Of the five survivors, in one vaccine certainly appeared to do good. Details of this case are given and it is one of those in which the temperature is no guide to the effect of vaccine (Case 112). In another the patient did not look as if he were going to pull through during his second week, but he began to get better after the third dose, and finally reached a normal temperature on the twenty-fourth day, which was rather soon considering the severity of the case, and I think vaccine may have benefited him. The other three cases all ran a severe and long course and all got rather worse after the first two or three doses of vaccine, and except for the fact that they did survive there is no reason to suppose that vaccine had a good effect, and one had a very tedious convalescence. Notes of these cases are given with a similar control case (Cases
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111 and 8). The average length of the primary fever in the five surviving cases was thirty-one days.

(b) Among the unvaccinated cases there were ten deaths (71.4 per cent) and four recoveries. Of the fatal cases six died of toxæmia and cardiac failure with broncho-pneumonia: eight, six, two, six, sixteen and thirteen days after admission, living on the average three days longer than the five similar vaccine cases. The four other deaths were due respectively to (a) hæmorrhage, (β) acute glomerular nephritis, (γ) acute gangrenous decubitus and septæmia coming on twenty-one days after admission and lastly (δ) toxæmia associated with facial erysipelas. The four surviving unvaccinated cases were all critically ill during their course. Two in the end did very well and had an uninterrupted convalescence, and notes of one of these (Case 8) are given with a similar case on vaccine treatment (Case 111). The average length of the primary fever in these four surviving cases was thirty-six days. The effect of vaccine in this class may be summed up thus: In one case it certainly appeared to do good and it may have done good in another. In one case it did not have a fair chance. In one case it appeared to do harm and it possibly did harm in two others. In four it certainly did no good, and in the remaining five it cannot justly be said to have had an effect one way or the other. I do not think that a conclusion for or against should be drawn from a comparison of the mortality-rates as the total number of cases was small and in two of the non-vaccinated cases the cause of death was most unusual.

CHARTS.

[Note.—All cases are uninoculated patients unless otherwise stated. The average pulse and respiration rates for the day are noted. The figures against the arrows denote the amount of vaccine given in millions of bacilli.]


Summary.—A very toxic severe case soon after admission (Class 1). Noticeable for quick improvement in mental symptoms and cardiac weakness. Apparently a good result for vaccine. Note
entire absence of pulmonary involvement. Blood culture showed *B. typhosus*.


**Summary.**—A typical very severe toxic case (Class I). Vaccine possibly did harm, as patient got steadily more toxic, pulmonary involvement became worse, and he had two severe haemorrhages in association with the injections.

**Case 111 (Chart 3).**—On admission, seventh day: Pinched and
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flushed and looks ill, drowsy, and cannot remember. Pulse regular, but soft and dicrotic. Tongue has dry, brown fur. Abdomen full and moves badly. Slight bronchitis. Blood culture showed *B. typhosus*. Thirteenth day: Toxic and drowsy, tongue still dry, pulse poor, more distended. Twenty-third day: Very drowsy, poor pulse, cardiac weakness the chief danger, more bronchitis. Twenty-ninth day: Poor pulse, slight but steady general improvement. Slow convalescence owing to dilated heart with rapid pulse.

Summary.—Typical severe toxic and prolonged case. Class 1. Did not look like pulling through at one time. Vaccine not thought to have had any definite effect. Note rise in temperature and pulse-rate after second dose. Compare with Case 8.

Stools frequent and undigested. Pulse is steady and of better volume. Thirty-third day: No distension. Pulse fair. Does not look toxic. Slow, steady improvement from now onwards.

**Summary.**—Very severe, toxic and prolonged case, (Class 1), which has done very well in the end without vaccine. Compare with Case 111.

**Case 0 (Chart “A”).**—On admission, eighth day: Looks ill and seems slightly delirious. Pulse of low tension but not dicrotic. Abdomen distended and slightly tender. Little or no bronchitis. Spleen felt, and large crop of large spots. Sent into hospital with culture from the blood stated to be *B. typhosus*. Tenth day: Delirious. Dry, brown, toxic tongue. Twelfth day: Improving. Not delirious. Fourteenth day: Markedly improved all round. Abdomen flaccid.

**Summary.**—A severe typical toxic case. “Considered a good result for vaccine treatment, which markedly affected for the better both temperature and general condition” (quoted from notes made at time of patient’s discharge from hospital). The culture obtained from the blood was subsequently further examined and gave quite definitely all the cultural reactions of the *B. paratyphosus A*, and also fulfilled the agglutination and absorption tests. It is rather a characteristic of paratyphoid cases to take a sudden turn for the better a few days after admission. The supposed “good result,” therefore, was a fallacy.

**Class 2.**—Severe and toxic, 74 cases (37 treated with vaccine and 37 without).

(a) Among the vaccinated cases there were thirteen deaths (thirty-five per cent) and twenty-four recoveries. In six of the fatal cases one is not justified in saying that vaccine affected the result. The causes of death in these six cases were as follows:
Toxæmia and broncho-pneumonia in three cases; cellulitis and terminal septicæmia in one case; intestinal obstruction by adhesions resulting from a shut-off and healed perforation in one case; and lastly, toxæmia with, in addition, ulceration of the vocal cords and epiglottis, in one case. In two of the fatal cases vaccine certainly appeared to have a bad effect. In one of these (Case 159) the patient became worse in every way after four injections and died on the seventeenth day after admission. In the other fatal case vaccine was given on the thirtieth day to see if it would stimulate the patient to finish off a long course, and this single dose was followed by fatal haemorrhages (Case 164).

In the five remaining fatal cases there is a strong suspicion that the vaccine was harmful. In one the vaccine was given a good chance as he had seven injections, but he slowly and steadily became worse, and perforation finally occurred twenty-two days after admission. The second, who had five injections, died of toxæmia and pulmonary congestion fourteen days after admission. The third died in three days of haemorrhage commencing thirty-six hours after an injection of 250 millions. In the fourth case death occurred from toxæmia and broncho-pneumonia, but he had some haemorrhage following on two doses of vaccine. The fifth of these cases died also of toxæmia and lung involvement, but he had become more delirious and altogether worse after two injections.

Of the twenty-four recoveries, two certainly appeared to have been benefited by the vaccine, that is to say, not only did they do well and quickly, but much more so than might have been expected, considering their severe condition on admission (Case 117). Another case appeared to have done unusually well, but had a severe relapse, and therefore cannot be considered a good result for vaccine. In one case vaccine was only given in a relapse, and as this was quite short it may have done good in this way. In four other cases it may possibly have been beneficial, as they all did fairly well and made a good convalescence. Eight of the cases ran a severe and rather long course, but this was no more than might have been expected, and one cannot say that vaccine affected them one way or the other (Case 114 and Case 177). In one case the vaccine was stopped after two injections, as the patient was doing badly owing to severe involvement of the lungs. In six of the cases vaccine appeared to do harm, as although it was thoroughly tried, all these cases had long courses (two of over eighty days) which were associated with great weakness, wasting, and other complications. The average day of the disease
on which the temperature first settled was the thirty-sixth, whereas in the controls it was the twenty-seventh day.

(b) In the non-vaccinated cases there were ten deaths (twenty-seven per cent) and twenty-seven recoveries. Six of the fatal cases died of toxæmia and broncho-pneumonia, with a course similar to that of the vaccinated cases of this type. One of the six had a severe and one a slight hæmorrhage.

Two cases died of perforation. In one of these the perforation did not occur till about the seventh week of the disease, and the other one had a hæmorrhage preceding the perforation. One case which had suppurating parotitis died of a confluent broncho-pneumonia. The remaining fatal case had thrombosis of the left femoral and the external iliac vein, and finally died as the result of pulmonary infarct and pleurisy.

Of the twenty-seven recoveries, ten ran the usual course of such cases, nearly all of these making a good convalescence. Two cases did remarkably well considering their apparent severity on admission. Details of these cases are given, as, had they been given vaccine they would have appeared good results for this treatment (Cases 32 and 23). Two cases ran a course worse than the average, one being very prolonged and complicated by hæmorrhage, parotitis and pyelitis, and the other was prolonged for six weeks but without complications. Of the remainder, six patients did rather better than usual and had no complications or sequelæ, whereas eight others did rather worse than usual and all had one or more complications.

Summary of this Class.—I wish to draw particular attention to this class of a test of vaccine, because, whereas in Class 1 the prognosis is bad, and in Classes 3, 4, and 5 fair to very good, it is in Class 2 that the prognosis is doubtful. It was hoped that in this class vaccine treatment might be found to turn the balance. It will be seen from the above analysis that this is not so. The mortality-rate is not lowered, neither is the incidence of relapses or complications lessened by this stock vaccine. Also, the average cases which did well with vaccine ran a course very much the same as the average case which did well without it, and the cases which did exceptionally well in either group are balanced by such cases in the other. Finally, the average length of the primary period of pyrexia in the vaccine-treated was longer by nine days than that of these cases which had received no vaccine.

Case 159 (Chart 5).—On admission, tenth day: Looks toxic but quite sensible. Pulse soft and dicrotic. 'Abdomen slightly distended
and generally tender. Bronchitis both bases. Blood culture gave
*B. typhosus*. Thirteenth day: Delirious. Bases congested and
broncho-pneumonia of influenzal type. Fifteenth day: Rigor
followed vaccine. General condition is not so good, he is more
delirious and abdomen is more distended. Twentieth day: Vaccine
given at 7 p.m. last night. At 3 a.m. this morning much worse,
temperature rose to 105°F. and pulse to 150. Is now very toxic,
with widely dilated pupils. Patient continued very toxic, and finally
died of exhaustion.

Summary.—A severe case (Class 2) which got decidedly more
toxic while on vaccine. Vaccine certainly appeared to do harm, as
patient was worse after each individual dose.

Case 117 (Chart 6).—On admission, tenth day: Looks rather
toxic, but mental condition is clear. Pulse is soft but not dicrotic.
Abdomen distended and slightly tender. Heart sounds good. Much
big tube bronchitis. Thirteenth day: Toxic and delirious and trying
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to get out of bed. Blood culture gave B. typhosus. Fifteenth day: Decidedly better. Tongue moistening. Profuse crop of spots all over body. Continued to make rapid progress.

Summary.—A rather severe and decidedly toxic case (Class 2) which has done remarkably well and rapidly and is apparently a good result for vaccine, but the absence of severe pulmonary involvement and the comparatively slow pulse throughout suggested a fairly good prognosis.


Summary.—A typical severe case (Class 2), marked by myocardial weakness. Final result good. There does not appear to be much evidence, however, that vaccine did any good. Case was prolonged and temperature was irregular independently of the vaccine. An example of several similar cases.

Case 32 (Chart 8).—On admission, seventh day: Toxic, flushed, incoherent, and later had muttering delirium. Regular, good pulse, not dicrotic. Tongue is dry with brown fur. Abdomen full. Respirations rapid, but no moist sounds in chest. Blood culture not done. Widal reaction, negative. Eighth day: Restless, delirious and noisy. Flushed and toxic. Tenth day: Remarkable change.
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No delirium. Does not look toxic and is at his ease. Widal reaction positive to B. typhosus. Patient went straight ahead to make an uninterrupted recovery.

Summary.—Appeared a typical severe and very toxic case (Class 2). Made a remarkably good and rapid recovery. If vaccine had been given would undoubtedly have been thought a good result for this treatment, and the case therefore should be compared with Case 117.

Case 177 (Chart 9).—On admission, fourteenth day: Flushed, toxic and delirious, picking at bed-clothes and very talkative. Pulse is full and bounding, but dicrotic. Tongue, dry brown fur. Abdomen distended. Coarse bronchitis. Blood culture negative. Agglutination positive to B. typhosus. Eighteenth day: Flushed. Still a little delirious. Temperature fell, but general condition was not altered. Twenty-fourth day: Quieter the last few days and is now definitely improving. Thirtieth day: Slow improvement. Mental condition poor and he is frequently incontinent. Vaccine seems to have no effect. Despite big dose there is no local or
general reaction. Thirty-second day: Slow general improvement from now onwards, but mental condition did not recover for another ten days.

Summary.—A severe toxic case (Class 2), with mental weakness. Pyrexia prolonged to end of fifth week. Ultimate result good. Had seven injections of vaccine, which certainly did not shorten case, and it is doubtful whether vaccine had effect. Case is shown as an example of many similar cases which eventually did well but in which vaccine appeared to have no definite effect.

Case 23 (Chart 10).—On admission, eighteenth day: Flushed; looks toxic; laboured breathing. Pulse of big volume but soft. Abdomen not at all distended. No moist sounds, although slightly cyanosed and breathing deeply. Twenty-first day: Much better all round and has lost his toxic look. Went ahead rapidly after this. Blood culture before admission reported as B. typhosus. Blood culture was negative here, but agglutination reactions strong with B. typhosus.

![Chart 10](http://militaryhealth.bmj.com/)

Summary.—Typical toxic and apparently severe case (Class 2) on admission, which rapidly improved in an unexpected manner without vaccine and made a rapid convalescence. Case is shown as an example of several which, if they had received vaccine, would have been thought good results.

Case 124 (Chart 11).—On admission, eleventh day: Sallow, with slight malar flush. Lethargic, but clear mentally when roused. Regular good volume soft dicrotic pulse. Normal abdomen and no moist sounds in chest. Blood culture negative. Stool of thirteenth day contained B. typhosus.

Summary.—A case which looked moderately severe (Class 4), but with an excellent prognosis. Improved very rapidly, but had a
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relapse. Case is shown as one of the few in which each individual dose of vaccine appeared to have a marked effect both on temperature and general condition.

Case 140 (Chart 12).—On admission, seventh day: Pale and looks ill. Lethargic, but quite clear when roused. Big volume, but very soft and dicrotic pulse. Abdomen is not distended. No moist sounds heard in chest. Blood culture, *B. typhosus* found. Fourteenth day: For the first few days was bright in the mornings and could read the paper. Is now getting a little more toxic. Wanders at night. Abdomen now tumid. Pulse good and rarely above 100. Eighteenth day: Continuous as above. Sleeping draught required at night. Tongue now quite dry and typical. Pulse soft and dicrotic. Is now rather a severe case. Twentieth day: Very restless. Is distended and has diarrhea. Heart is getting dilated. Twenty-third day: Heart shows cantering rhythm. Tubular breathing left lower lobe, but rapid respiration mostly toxic. Seems to be going downhill with cardiac weakness asso-
associated with a steadily increasing and now severe toxæmia. Vaccine quite useless (? has increased toxæmia).

Summary.—A typical slightly toxic and moderately severe case (Class 3)—vide pulse-rate, respiration-rate, absence of distension, etc., on admission. Patient had the appearance of one likely to do well, and vaccine therefore undoubtedly appeared to do harm.

Classes 3 and 4.—Moderately severe and slightly toxic or not toxic; 88 cases (44 treated with vaccine and 44 without).

These two classes of case are considered together as they form degrees of the same kind of case in which the prognosis varies from "good" to "very good." It is especially in this class of case that a good effect of vaccine is difficult to judge, as all are likely to do well, and vaccine is therefore liable to get undeserved credit unless the unvaccinated controls are considered. The statistics of the control cases must be carefully examined (see table below), and it will then be seen that the effect of vaccine in so far as it has a good influence is practically negligible.

(a) In five of the vaccinated cases there did certainly appear to be an effect on the case as a whole, and in one each injection seemed to have a marked effect (Case 124). But cases of a similar nature may occur without vaccine treatment. In ten other cases vaccine may have shortened the fever and therefore may have done good in these. In one fatal case it certainly appeared to do harm, as this patient was neither very severe nor toxic, and yet he got progressively worse while on vaccine, and died of toxæmia and cardiac failure (Case 140). In the other fatal case who had vaccine death was due to sudden haemorrhage on the seventeenth day of disease following on a dose of vaccine. There was, however, just such a case of fatal haemorrhage occurring on the eighteenth day of disease in one of the controls. Vaccine may have been the decisive factor, but the haemorrhage may thus have been a coincidence. In five other cases the course was long or otherwise worse than the average, and vaccine may possibly have done harm to these. In the remaining twenty-two cases the patients did well, but just as might have been expected, and I do not think vaccine affected them either way.

(b) In the forty-four unvaccinated cases there were also two deaths. One already referred to died of haemorrhage, and the other also had haemorrhage, but died with increasing severity and toxæmia. The great majority of the cases ran the course that was expected. The average length of fever in the vaccinated and unvaccinated cases of these classes was about the same, and is shown, together
## Two Hundred Uninoculated Cases

Statistics of the Five Classes with and without Vaccine, and of the Total 200.

<table>
<thead>
<tr>
<th>Class</th>
<th>Class 1</th>
<th>Class 2</th>
<th>Class 3</th>
<th>Class 4</th>
<th>Class 5</th>
<th>Class 6</th>
<th>Total 200</th>
<th>100 on vaccine</th>
<th>100 no vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>With (+) or without (0) vaccine...</td>
<td>+14 +10 +24 +20 +21 +5</td>
<td>+15 +10 +24 +20 +21 +5</td>
<td>+14 +10 +24 +20 +21 +5</td>
<td>+15 +10 +24 +20 +21 +5</td>
<td>+14 +10 +24 +20 +21 +5</td>
<td>+15 +10 +24 +20 +21 +5</td>
<td>+15 +10 +24 +20 +21 +5</td>
<td>+15 +10 +24 +20 +21 +5</td>
<td>+15 +10 +24 +20 +21 +5</td>
</tr>
<tr>
<td>Total number in class...</td>
<td>200</td>
<td>100</td>
<td>50</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>200</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Mortality...</td>
<td>5</td>
<td>10</td>
<td>15</td>
<td>20</td>
<td>25</td>
<td>30</td>
<td>5</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Length (days) of primary fever...</td>
<td>31</td>
<td>36</td>
<td>36</td>
<td>37</td>
<td>37</td>
<td>37</td>
<td>31</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Total number of cases having one or more complications of any kind, viz., or sequelae...</td>
<td>6</td>
<td>6</td>
<td>21</td>
<td>23</td>
<td>14</td>
<td>14</td>
<td>6</td>
<td>6</td>
<td>21</td>
</tr>
<tr>
<td>Relapses...</td>
<td>-</td>
<td>-</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Haemorrhage...</td>
<td>2</td>
<td>1</td>
<td>9</td>
<td>6</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Perforation...</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Thrombosis...</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Phlebitis...</td>
<td>-</td>
<td>-</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Slight rises in temperature in convalescence...</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Tachycardia in convalescence...</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Pleurisy...</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Otorrhoea...</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Marked wasting with bed-sores...</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Parotitis...</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Laryngitis...</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Other complications or sequelae...</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Prolonged convalescence from severe debility and other causes not mentioned...</td>
<td>1</td>
<td>2</td>
<td>12</td>
<td>11</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

1. Was the cause of, or was associated with, death in six vaccinated cases and five unvaccinated.
2. By this is meant evanescent rises of temperature which are not relapses and which are not associated with a complication or sequelae.
3. Only cases in which there were destructive changes in the larynx are included (sore throat, &c., not necessarily included).

- a. One death in a case admitted in a dying condition.
- b. The supposed cause of a pulmonary infarct (fatal).
- c. With abscess formation.
- d. Two with abscess and two without.
- e. Ulceration followed by cicatrization requiring tracheotomy.
- f. Temporary insanity.
- g. Tonsillitis.
- h. Includes one case of biliary colic and jaundice.
- i. Includes one case of septicemia and endocarditis (fatal), and one case of glomerular nephritis (fatal).
with the incidence of complications and sequelae, in the subjoined table.

**Class 5.**—Very mild, 10 cases (5 treated with and 5 without vaccine).

One death occurred in this class in a man who had a severe relapse (?) and prolonged fever, after what appeared to be a very mild preliminary attack. It was only when in this acute stage that he had vaccine, and the death is therefore in brackets in the comparative tables. Two vaccinated cases ran an unusually long course, and it should be noted that the average length of fever in the vaccine-treated cases was much longer than in those which did not receive it. As the numbers are small one can only say that in this class the vaccine did not appear to have any good effect.

**The Inoculated Cases.**—There are thirty of these, half being treated with vaccine. They had all been inoculated once or twice during the nine months preceding their illness. The B. typhosus was isolated from each. As the number in each series is small, I do not think that much can be deduced from the statistics. The more important facts are set out in the following table:

<table>
<thead>
<tr>
<th>With (+) or without (0) vaccine</th>
<th>Class 1</th>
<th>Class 2</th>
<th>Class 3</th>
<th>Class 4</th>
<th>Class 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases in class</td>
<td>2+2</td>
<td>6+2</td>
<td>4+2</td>
<td>2+2</td>
<td>1+2</td>
</tr>
<tr>
<td>Mortality</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Average length of fever in days</td>
<td>255</td>
<td>35</td>
<td>27</td>
<td>27</td>
<td>21</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Perforation</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Relapse</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Prolonged convalescence</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

It will be seen that in the above fifteen cases vaccine had no good effect on the mortality or on the incidence of complications, I do not think that one can say that it definitely had a bad effect on the cases, as a whole, as the numbers are small. One outstanding fact, however, is that the average length of fever amongst the vaccinated cases of Class 2 (the largest class) was much longer than that of those in this class which had no vaccine.

One of the cases of Class 1 which died was admitted in a critical condition with a subnormal temperature. He had one injection, after which the temperature steadily rose, and he died thirty-six hours afterwards. In the other fatal case of this Class the temperature took six weeks to reach normal; the patient then had a relapse, during which he died from perforation of an old
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ulcer. Of the two fatal vaccinated cases of Class 2 one died of perforation after three injections, and the other died of a confluent broncho-pneumonia, being then in a very asthenic state with a subnormal temperature. There was no case among the series receiving vaccine which did markedly better than any of the control cases.

In none of the four cases which were given the serum-treated vaccine is there any reason to suppose that the course was definitely affected. One of the cases died of toxæmia. It was a severe, prolonged case, and the serum-treated vaccine was given late in the disease to see if it could stimulate the patient to further efforts, but without effect.

SUMMARY AND CONCLUSIONS.

In the total vaccinated cases there were twenty-nine in which it appeared that vaccine had a definite good influence. Of these, twenty belonged to Classes 3 and 4, i.e., to those classes in which the prognosis is good. In other words, "good results" are more often obtained where good results can be expected by ordinary methods of treatment alone. On the other hand, the mortality rate and the average length of fever in these classes was slightly worse among the cases who had vaccine.

Among the cases belonging to Classes 1 and 2, in which the vaccine appeared to do good, none had severe lung involvement. Those cases which had much bronchitis or broncho-pneumonia (the average severe case) ran the severe course which is usual, and vaccine appeared to be of no avail. To say that, if the average severity of the cases treated had been less, the vaccine would have had better results, is merely to say, I think, that the cases would then have done better anyhow. From all this it would appear: (a) That it is in just those cases in which the physician so much requires help that vaccine is so disappointing; (b) that vaccine neither shortens the fever nor reduces the number of complications in even that class of case which is likely to do well; (c) that there is a decided suspicion that vaccine increases the incidence of hæmorrhage.

The conclusion, therefore, is that the use of a stock vaccine in typhoid fever cannot be recommended as a routine treatment. I should add that these conclusions are largely contrary to the impressions which I received during the treatment of the earlier cases. I had not then seen a sufficient number of similar cases which did well without vaccine, and being rather biased in its favour, I gave undeserved credit to this treatment.