THE MEASUREMENT OF THE DURATION OF INFECTION IN PARATYPHOID FEVER

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(With 1 Figure in the Text)

The duration of bacteriological infection as distinct from clinical illness has been recorded for a number of infectious diseases. Hartley & Martin (1919–20), Thomson, Mann & Marriner (1929) and Wright (1941) found in diphtheria that the proportion of cases continuing to harbour the bacillus fell exponentially with time. The logarithms of the population still positive, plotted against time, thus gave a straight line. The rate of recovery was not necessarily the same in all series, and Wright found a difference according to the type of the infecting strain.

Glass & Wright (1937) found for paratyphoid fever an initial lag, but thereafter, for many weeks, the population fell more rapidly. Holt, Vaughan & Wright (1942) and Kennedy & Payne (1950) reported similar findings for paratyphoid fever.

Recently Kwantes (1952) reported an outbreak of food poisoning caused by *Salmonella typhi-murium*, in which there was an exponential or logarithmic fall of the population remaining infected. The proportion of the remaining positives clearing themselves of infection was constant at 47% each week. Kwantes analysed also the figures of Mosher, Wheeler, Chant & Hardy (1941) relating to a similar experience with *Salm. typhi-murium*, and showed that a constant proportion (39 %) of the remaining positives cleared themselves of infection each week.

In an outbreak of food poisoning the clinical cases to be examined can be easily assembled, but the regular examination of faeces is much more difficult to arrange. The patients are treated at home, and Kwantes, for example, had to draw up his curve on the repeated examination of only two-thirds of his total cases. The remaining third had to be jettisoned because they refused to continue to provide the necessary specimens.

In paratyphoid fever it is difficult to assemble all the cases at once, and many are not diagnosed till the second and third weeks of illness or even later. A population assembled in this way is more difficult to analyse for clearance rates, and certain assumptions often made may not be justified.

The most satisfactory analyses dealing with clearance rates are probably those on diphtheria, as the disease is one which is promptly diagnosed and confirmed bacteriologically. The population to be studied is thus assembled at the beginning of the illness and kept under constant supervision in hospital, and specimens are easily collected for examination. In our opinion the slow assembling of the population on the one hand, and the jettisoning of patients from the population on the other hand, may lead to errors in the clearance rates. We have been unable to find in the literature one curve relating to enteric infection free from these errors which radically alter the shapes of the curves.

THE EFFECT OF ASSEMBLING THE POPULATION SLOWLY

Most authors, calculating the proportion of cases clearing themselves of infection each week, have based all their calculations throughout on the total number of cases identified. The clearance rate in any given week is defined as the number becoming negative in the week under consideration divided by the total cases. This method takes no account of the fact that many cases of paratyphoid fever are identified for the first time in the second and third week of illness or even later. Cases freeing themselves of infection in the first week of illness, however, can be found only from within the number already identified at this time, and the addition to the population of those identified at later stages must reduce the *proportion* becoming negative in the first week. This effect continues for as long as new cases are admitted to the population, and results in a greatly reduced rate of clearance in the early weeks. Expressed in another way, this method of analysis assumes that n cases, diagnosed in the xth week of illness, have been derived out of only n cases who fell ill. To introduce them into the calculations before the xth week is to assume that cases do not clear themselves of infection before the xth week, and the calculations proceed to show the assumption wrong. The procedure seems to us to be illogical. Tables and curves compiled in this way were published by Glass & Wright (1937), Kennedy & Payne (1950) and presumably also by Holt *et al.* (1942).

Alternatively, however, the clearance rate can be defined as the number becoming negative in a given week divided by the number known to be still positive at the beginning of the week. By this method the proportion becoming negative in the first week after onset of illness would be based only on those identified in the first week, and the smaller denominator produces a higher clearance rate than that found when the denominator is the total number of cases. Cases identified in the second, third and subsequent weeks would be brought into the calculations only from the week of illness when they were identified. By this method the clearance rates are higher for the early weeks when the population of identified cases is still growing.

By either method the results can be presented in the form of a declining population beginning with 100 % in week 1. When the clearance rates are based only on those known to be positive at the week under consideration, the procedure is the same as that used for compiling a life table. We can find in the literature no analysis made in this way which seems to us to be the correct one.

THE EFFECT OF REJECTING CASES FROM THE POPULATION

Almost without exception tables and curves showing clearance rates for paratyphoid fever have been compiled from laboratory records, and an admission made that there was a selection of those cases for which laboratory records were satisfactorily complete (Glass & Wright, 1937; Gell & Knox, 1942; Holt *et al.* 1942; Kennedy & Payne, 1950). One of the reasons for rejecting cases from the population was that the laboratory records could not show them to have been followed until proved negative.

If the weekly clearance rates are based only on those known to be still positive

at the week under consideration, cases with incomplete records can be retained in the population for as long as they are known to be positive. If the weekly clearance rates, however, are based throughout on the total cases, those with incomplete records must be rejected because there is no way of dealing with them in the calculations. If the results are expressed in the form of a declining population showing the proportions (or percentages) remaining positive with the passage of time, the effect of overlooking those with incomplete records is to remove them from the numerator and denominator of the proportions. The rates of clearance are thus artificially increased. In several articles the numbers jettisoned for one reason or another amounted to one-third of the total cases.

SOUTH WALES OUTBREAK OF PARATYPHOID FEVER (*SALMONELLA PARATYPHI* B, VI-PHAGE TYPE I)

In a recent outbreak of paratyphoid fever in South Wales, the laboratory had records of patients from whom specimens of faeces were repeatedly examined until a series of negative results showed freedom from infection. The duration of infection was the interval elapsing between the onset of illness and the date of the first of the series of negative results. Logically, the duration of infection might have been measured from the date of infection had this been known with accuracy. In one group of cases (see group I below) the date of infection was known and the necessary adjustments can be made if desired. Some hospitals submitted specimens twice a week and others once a week, though occasionally two weeks passed between the examination of successive specimens. On the whole, however, specimens came regularly to the laboratory.

The last positive result before a series of negatives was recorded for all the cases, and the percentages remaining positive at successive weeks were calculated. When more than one week passed between the last positive and the first negative, a case was assumed negative in the weeks when no specimen was received. A duplicate analysis, however, was made assuming the patient to be still positive in any interval that may have elapsed between the last positive result and the first of a series of negatives.

In one group of cases (see group I below) specimens of faeces were regularly collected at weekly intervals. These patients were all infected on one day in a café of a small market town, and all but a few were treated at home as the hospitals were already full. This group of cases was analysed separately.

The laboratory had records of 267 cases of paratyphoid fever (Vi-phage Type I), the majority of which were infected by cream cakes. For the purposes of description, these were divided into two groups.

Group I consisted of seventy-two clinical cases and sixteen symptomless excreters, all of whom were infected on one day and from whom specimens were regularly collected at weekly intervals. In the first week of illness no case was diagnosed bacteriologically. The disease was mild and the true diagnosis was at first unsuspected. In the second week of illness only a few cases were confirmed bacteriologically, and arrangements were made for a bacteriological survey of all suspected cases to determine the extent of the outbreak. The specimens were

collected 23 days after the date of infection and 14–16 days after the onset of illness, as, in most cases, the incubation period was 7–10 days. The cases were thus confirmed bacteriologically at the beginning of the third week of illness. The reasons for separating this group of cases from the others were, first, that the population was assembled quickly, and secondly, specimens of faeces were collected regularly at weekly intervals after the diagnosis had been made. Sixteen symptomless excreters belonging to group I, and identified at the same time, were similarly followed, but a few more stubbornly refused to submit weekly specimens. As they were thus excluded from the population at the onset it was believed that there was no biased selection. Seven of the symptomless excreters were identified in the week corresponding to the third week of illness of the clinical cases, and the remaining nine in the following week.

In group II were 175 cases treated in hospital.

The main purpose of this article is to show great differences in the curves derived by different methods of calculation, many of which, formerly employed, appear to us to be wrong. From the data of group II, five curves can be drawn, but the curve derived from the data of group I is unique.

It would be unwise to conclude that any of the curves, even that derived from group I, is true in an *absolute* sense, as modern treatment with chloramphenicol may produce more rapid clearing from infection, especially in the early stages. The *differences* between the many curves derived from the data of group II, however, are true.

RESULTS

Group I

The decline in the number remaining positive, of the 72 clinical cases of group I, is shown in Table 1 and recorded graphically in Fig. 1 (curve 1), where the logarithms of the population are plotted against time. As these cases were identified at the beginning of their third week of illness, the proportions remaining positive were calculated on the third week population of 72. If the 72 cases are shown as positive as from week 1 the curve is quite flat for two weeks. This is represented in the figure by a dotted line as an extension backwards of curve 1. This shows that the effect of assembling the total population at week 1, irrespective of the stage of illness when the diagnosis is made, is to flatten the curve at its beginning.

Nevertheless, the figure shows, even for the 72 cases assembled at week 3, a slight lag before the rate of clearance increases at the fifth week. Thereafter the population falls more or less logarithmically until the carriers reveal themselves. There is a very sharp turn in the curve at the eleventh week. As specimens from the cases came regularly at weekly intervals the analysis was unique. The duplicate analysis was unnecessary.

Although only 16 symptomless excreters were regularly examined it appeared that they cleared themselves of infection rather more quickly than those who were ill. Of the 7 identified in the third week of the outbreak, 1 was never again found positive. The remaining 6 along with 9 identified for the first time in the fourth

week gave a fourth week population of 15. The numbers remaining positive declined thus (beginning with the fourth week population of 15): 15, 11, 7, 5, 3, 1 and 0.

Table 1. *Group I. Numbers and proportions remaining infected at successive weeks (72 cases)*

	Clinical cases	
Week	No.	%
3	72	100
4	67	93
5	59	82
6	46	64
7	28	39
8	22	31
9	14	19
10	10	14
11	8	11
12	8	11
13	8	11
14	7	10
15	7	10
16	7	10
17	7	10
18	7	10
19	6	8

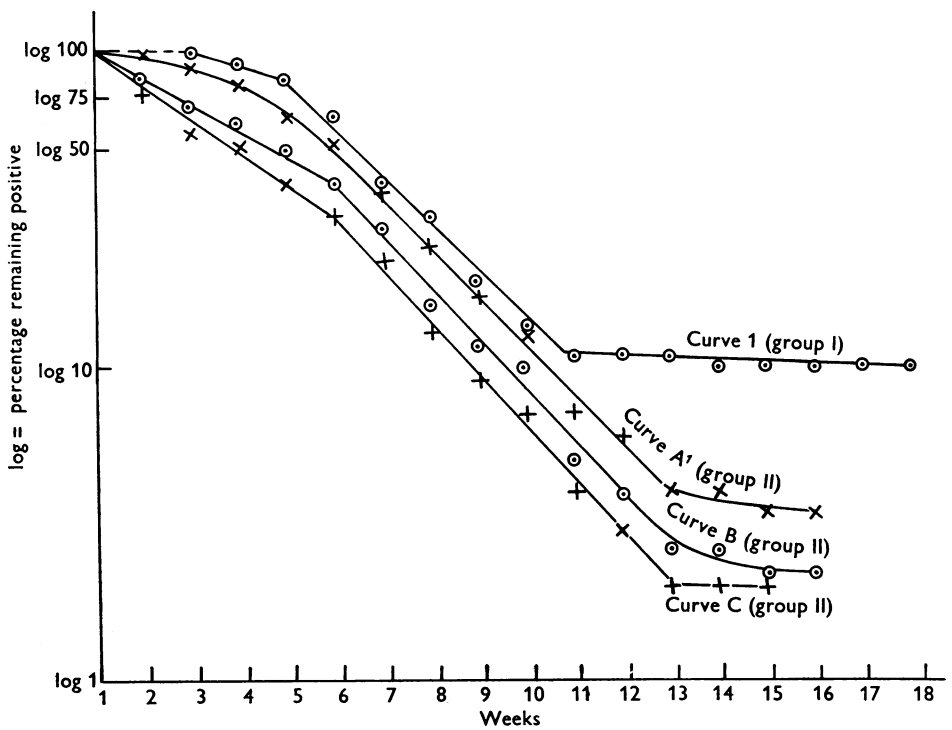

Fig. 1. Curve 1 begins at 100 % opposite week 3.

Group II

The 175 cases in this group were not all diagnosed at the same stage of their illness. Some were notified and admitted to hospital before specimens were sent to the laboratory, but as often as not a diagnostic laboratory report preceded the notification. The earlier of these possible events was accepted as the criterion that the case should be admitted into the population and the numbers identified at successive weeks of illness were 67, 73, 18, 8, 0, 5, 1 and 3.

When it was assumed that a patient was negative immediately after the last recorded positive result the numbers removed from the population at successive weeks after onset of illness were 10, 28, 10, 23, 19, 23, 25, 10, 5, 10, 3, 3, 0, 1 and 0, leaving 5 at week 16. When the patients were assumed to be positive up to the week preceding the first of a series of negative results the numbers removed at successive weeks were 3, 13, 20, 30, 20, 25, 22, 13, 7, 10, 2, 3, 0, 1 and 0, leaving 6 at week 16.

In the first analysis, the percentages freeing themselves of infection at successive weeks were calculated throughout on a constant population of 175, thus following the usual practice. The results, presented in the form of a declining population, are shown in Table 2, columns A and A^1, which differ according to the assumption as

Table 2. *Group II. Percentages of original population remaining infected at successive weeks calculated in four different ways*

Week	Method A	Method A^1	Method B	Method B^1
1	100	100	100	100
2	94	98	85	96
3	78	91	67	86
4	73	79	61	74
5	59	62	49	57
6	49	51	39	46
7	35	37	28	32
8	21	24	16	21
9	15	17	12	14
10	13	13	10	11
11	7	7	5	6
12	5	6	4	5
13	3·5	4	2·6	3·5
14	3·5	4	2·6	3·5
15	2·8	3·5	2·2	3
16	2·8	3·5	2·2	3

to when the patients became negative. There was a comparatively slow initial rate of clearance which would have been greater if groups I and II had been merged, thus adding a constant total of 72 to the populations at each of weeks 1, 2 and 3. The data of column A^1 are represented graphically in the figure (curve A^1). These two curves, in spite of modern treatment with chloramphenicol, agree well with curves formerly published.

For the second method, to compile the table showing the percentages of cases remaining positive at successive weeks, the cases were admitted to the population

at different weeks of illness. Of the 67 cases diagnosed in the first week, 10 (15 %) were never again found positive; of 130 still positive in the second week of illness, i.e. 73 new cases and 57 remaining positive out of the 67 diagnosed in their first week of illness, 28 (22 %) were never again found positive. The percentages clearing themselves of infection in the early weeks, therefore, may have been quite appreciable. Accordingly, the percentages clearing themselves each week were calculated only on the population identified and known to be still infected, and from these was assembled a table showing the percentages remaining positive at successive weeks. The results are shown in Table 2, columns B and B^1 which, as before, differ according to the assumption as to the time the patients became negative when there was an interval between the last positive result and the first of a series of negatives. The data of column B are represented graphically in the figure (curve B).

Table 3. *Population remaining infected at successive weeks after onset of illness*

Week	No. positive	No. becoming negative	Clearance rate %	Percentage remaining positive
1	67	10	15	100
2	130	28	22	85
3	120	10	8	67
4	118	23	19	61
5	95	19	20	49
6	81	23	28	39
7	59	25	42	28
8	37	10	27	16
9	27	5	19	12
10	22	10	45	10
11	12	3	25	5
12	9	3	33	4
13	6	0	0	2·6
14	6	1	17	2·6
15	5	0	0	2·2
16	5	2	40	2·2

The patients were assumed negative in any interval elapsing between the last recorded positive and the first of a series of negatives.

The four methods of analysis give very different results, method A^1 showing the greatest initial lag and method B the least. If the cases of groups I and II had been merged, the lag found by method A^1 would have been even greater.

Table 3 was compiled to show more clearly how the percentages in column II B were obtained.

Other analyses

The two results (B and B^1) shown in Table 2 do not exhaust the possible analyses of the data of group II by the life-table method. Some cases were accepted into the population when admitted to hospital and before specimens of faeces were sent to the laboratory. There was thus a selection of those cases which yielded positive cultures after admission to hospital. The procedure is open to the

same kind of criticism as that which applies to the calculation of clearance rates on a constant population throughout, because it overlooks the possible existence of cases admitted to hospital *correctly diagnosed* and from whom no positive result was obtained as they cleared themselves of infection before the specimens were sent. Laboratory records alone cannot identify these cases. Our laboratory records, however, showed nine positive Widal reports relating to individuals from whom no positive culture was obtained. It appeared that only a few cases were missing from the population upon which the calculations were based.

Admission to population on clinical diagnosis only

Clinical diagnosis could not be accepted as the sole criterion that a case should be admitted to the population. During an outbreak many sick people with fever are investigated as suspected cases, and laboratory reports play an important part in deciding the diagnosis. If cases were brought into the population on clinical evidence only, many *wrongly diagnosed* would appear as genuine cases which had cleared themselves of infection very quickly.

Admission to population on bacteriological diagnosis only

On the other hand, it might appear logical to admit cases to the population only when the faeces have been shown positive. Had this been done, the numbers admitted at successive weeks would have been 39, 80, 21, 15, 9, 5, 1, 3, 0 and 1. An analysis corresponding to column B of Table 2 (proceeding by the life-table method and assuming a patient negative in any interval between the last positive result and the first of a series of negatives) would then give the following as the percentages remaining positive at successive weeks: 100, 74, 55, 50, 39, 31, 22, 13, 9, 7, 4, 3, 2, 2 and 2. This series shows a very rapid decline and no initial lag (curve C of the figure). The method which accepts the examination of faeces as the criterion that a case can be brought into the population would appear to be the logical one, as those which cleared themselves of infection in the first week, for example, were derived only from the thirty-nine whose faeces had been shown positive in the first week. This method would have been the method of choice had it not been known that many cases, unchallengeably diagnosed on clinical and serological grounds, were admitted to hospital in the first week of illness but specimens of faeces were not submitted until later. In only nine of these cases did it appear from our records that *Salm. paratyphi* B was never isolated from the faeces. In this method of analysis it would be necessary to admit a case to the population when the first specimen of faeces was submitted, whether the result was positive or negative, provided a positive result was recorded at some stage. The literature on paratyphoid fever records that a negative result is not infrequently found in the early weeks. In our experience only once in the 175 cases of group II did a negative result precede a positive.

Effect of chloramphenicol

No compensation could be made for the effect of chloramphenicol on these curves, and even the unique curve derived from the data of group I might have been influenced by its use. It is possible, however, that this curve was only

slightly influenced by drugs, as the population, for the purposes of our analyses, was assembled at the third week after onset of illness, by which time the patients had recovered from their mild illness. Even then, however, there was a lag before the numbers remaining positive declined logarithmically. The lag might have been reduced by chloramphenicol treatment, but could not have been increased or produced by it.

It would not be justifiable to make too strict a comparison between the curves presented here and those published before chloramphenicol was used. Curves A and A^1, which were derived by the methods formerly used, agree well with the curves formerly published. Curves B and B^1, however, derived by different and more logical methods of calculation, are very different from A and A^1.

SUMMARY AND CONCLUSIONS

Cases of paratyphoid fever are often not diagnosed until the second, third or subsequent weeks of illness. When calculating clearance rates of a series of cases the calculations must be based only on the numbers known to be positive at the week under consideration. If based throughout on the total number of cases the rates of clearance in the early weeks are greatly reduced.

Cases for which laboratory records are incomplete must not be entirely rejected when calculating clearance rates but must be retained in the population for as long as they were known to be positive.

Analyses designed to show the duration of infection in paratyphoid fever can only be made with accuracy under the most favourable conditions.

A large number of cases of paratyphoid fever were repeatedly examined bacteriologically to establish the duration of the infection as distinct from the clinical illness. After an initial lag the proportion of cases remaining infected fell logarithmically until the carriers revealed themselves.

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