THE VALUE OF ACTIVE IMMUNIZATION TREATMENT AGAINST DIPHTHERIA

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(With 1 Diagram)

Although attempts to produce an active immunity against diphtheria were made as early as 1902, it is since the Schick test was described in 1913 that there has been available some clinically applicable measurement of individual immunity, naturally obtained or artificially produced; and it is probably true to say that large-scale active immunization has been practised in this country for only some 10 or 15 years.

Many workers have reported a high proportion of Schick-negative responses at different ages after various immunization courses; but observations on a wide scale of the rate of incidence of clinical diphtheria amongst those who have received immunization treatment must be of greater importance than this as a measure of assessing the value of artificial immunization against diphtheria. Underwood (1935 *a*, *b*) while reporting the incidence of diphtheria in his own Schick-negative population of 2761, collected the observations published prior to 1935.

In this paper we review the experiences in Bristol amongst children aged 0–15 years, making some comparative observations on the incidence of and mortality from clinical diphtheria in various groups of this child population over a period of 6 years, 1930–5 inclusive.

During the 6 years there were in the City 4860 notifications of diphtheria, 3924 of which related to the child population 0–15 years of age and were accepted as cases of clinical diphtheria. Of the total number, 4618 or 95 per cent were admitted to the Municipal Isolation Hospital, Ham Green. Table I gives the figures for each year.

Table I. *Notifications of diphtheria in Bristol*, 1930–5

Year	Total no. of notified cases	No. of notified cases admitted to Municipal Hospital	Percentage of notified cases admitted to Municipal Hospital	Cases accepted as of clinical diphtheria, aged 0–15 years
1930	1484	1395	94	1243
1931	828	786	95	683
1932	533	512	96	451
1933	639	637	99	538
1934	751	714	95	567
1935	625	574	92	442
Total	4860	4618	95	3924

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In Bristol, then, any personal factor in the diagnosis of clinical diphtheria is largely removed. For the clinical verification of the diagnosis in our cases we have been indebted to Dr B. A. I. Peters, and cases considered by him not to be of clinical diphtheria have been excluded. Four additional cases known to have received immunization treatment at the municipal clinics were treated at home for clinical diphtheria and are included in our survey.

Since October 1929, immunization treatment has been offered through the City Health services to children between the ages of 1 and 15 years. The prophylactics used have been Modified Toxoid and Formol Toxoid. From the commencement of the municipal immunization clinics the routine investigation concerning every notification of diphtheria has included inquiry as to any previous prophylactic treatment of the patient while the details of any such treatment and the patient's Schick response have been verified from the records of the health department.

Only those children who have undergone a course of three injections—the usually accepted course for the prophylactics used—will be considered to have had immunization treatment. They number 18,800, of whom 10,879 were proved to be Schick-negative reactors after the treatment. Concerning the other 7921 treated children the Schick condition remains unknown or was positive when last tested. In Table II we estimate the length of exposure to diphtheria of these groups from the time of their immunization to the end of 1935, assuming that the immunization treatment given was equally spread over each calendar year.

Table II. *Children, aged* 1–15 *years, who received immunization treatment* (*three injections*), 1930–5

Year	No. treated	Giving estimated no. of child-years-of-exposure to diphtheria during January 1930–December 1935*	No. proved Schick-negative after treatment	Giving estimated no. of child-years-of-exposure to diphtheria during January 1930–December 1935*
1930	7377	7377 × 5·5 = 40573·5	3597	3597 × 5·5 = 19783·5
1931	3486	3486 × 4·5 = 15687·0	1738	1738 × 4·5 = 7821·0
1932	1617	1617 × 3·5 = 5659·5	524	524 × 3·5 = 1834·0
1933	1796	1796 × 2·5 = 4490·0	842	842 × 2·5 = 2105·0
1934	1657	1657 × 1·5 = 2485·5	1486	1486 × 1·5 = 2229·0
1935	2867	2867 × ·5 = 1433·5	2692	2692 × ·5 = 1346·0
Total	18,800	70329·0	10,879	35118·5

* For the concept "child-years-of-exposure" as for other statistical suggestions we are indebted to Dr A. Bradford Hill.

One hundred and forty-six cases of clinical diphtheria have occurred amongst the 18,800 prophylactically treated children. Forty of these have been in children who were Schick-negative after the treatment, the other 106 cases being amongst the 7921 children who had received three injections of immunizing substance but whose Schick conditions after treatment were either positive or not ascertained. We give particulars of these cases in Table III.

Table III. *Children who suffered from clinical diphtheria after receiving immunization treatment, their Schick responses, and the clinical nature of their illness*, 1930–5

Schick response after treatment									Interval between ultimate Schick test or completion of treatment, and attack of clinical diphtheria under
Positive			Negative			Not ascertained			
Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe	
.	.	.	.	.	.	.	3	.	7 days
.	.	.	.	.	.	.	.	1	14 days
.	.	.	.	.	.	.	1	.	21 days
.	.	.	.	.	.	.	2	.	28 days
.	.	.	.	1	.	1	3	2	2 months
.	.	1	.	.	1	1	2	4	3 months
								+1 death	
1	.	.	2	2	.	.	6	1	4 months
								+1 death	
.	1	.	.	.	.	1	2	1	5 months
.	.	1	.	1	.	1	1	1	6 months
2	3	1	.	6	.	2	2	.	9 months
.	.	.	1	2	1	1	1	.	1 year
1	2	.	3	4	1	.	2	.	1½ years
2	3	2	2	4	.	.	1	2	2 years
1	8	1	1	1	.	2	1	.	2½ years
3	1	3	.	.	1	1	1	1	3 years
4	2	.	2	.	1	1	2	.	4 years
1	.	1	.	1	1	1	.	.	5 years
.	.	.	.	.	.	1	.	.	6 years
15	20	10	11	22	6	13	30	13	
								+2 deaths	
Hospital cases 45 Deaths nil 1 additional case treated at home Total cases 46			Hospital cases 39 Deaths nil 1 additional case treated at home Total cases 40			Hospital cases 58, including 2 deaths 2 additional cases treated at home Total cases 60			

The Census population of Bristol in 1931 was 399,900, while the number of children under the age of 15 years as recorded by the Registrar-General in that year was 91,625, or 22·9 per cent of the total population. In Table IV it is assumed that this relation between the child and total populations remained throughout the period 1930–5, while by further assuming that immunization treatment took place at a constant rate throughout each year, the last column of this table has been calculated.

Table IV

Year	Estimated population of Bristol (Registrar-General)	Estimated population aged 0–15 years	No. of children 1–15 years old who received immunization treatment in the year	Estimated child-years-of-exposure to diphtheria of untreated children in each year
1930	391,445	89,641	7377	85,952
1931	399,900	91,625	3486	82,505
1932	403,900	92,493	1617	80,821
1933	410,870	94,089	1796	80,711
1934	410,500	94,004	1657	78,899
1935	413,100	94,600	2867	77,233
Estimated total child-years-of-exposure to diphtheria amongst untreated children				=486,121

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DISCUSSION

The incidence of diphtheria

There were 3924 cases of accepted diphtheria amongst children aged 0–15 years in Bristol during the 6 years under review (Table I). Of these cases 3778 occurred amongst untreated children, and 146 amongst children who had been submitted to immunization treatment, while 40 of those treated child victims were known further to have become Schick-negative.

Table V shows that the treated children escaped more lightly in every one of the 6 years under consideration.

Table V

Year	Estimated child-years-of-exposure to diphtheria of treated children*	Cases of diphtheria amongst treated children	Incidence of diphtheria per 1000 child-years-of-exposure; treated children	Estimated child-years-of-exposure to diphtheria of untreated children†	Cases of diphtheria amongst untreated children	Incidence of diphtheria per 1000 child-years-of-exposure; untreated children
1930	3,689	39	10·6	85,952	1204	14·0
1931	9,120	23	2·5	82,505	660	8·0
1932	11,672	15	1·3	80,821	436	5·4
1933	13,378	23	1·7	80,711	515	6·4
1934	15,104	30	1·9	78,899	537	6·8
1935	17,366	16	0·9	77,233	426	5·5

* The treated figure for 1930 equals half the immunized in that year; for 1931 half the immunized in that year plus all the immunized in the previous year, and so on.

† The untreated figure for 1930 equals the estimated child population minus half those immunized in that year; for 1931 the estimated child population minus half those immunized in that year and all those immunized in 1930 and so on.

Had the treated children suffered from diphtheria year by year at the same rate as the untreated children there would have been 472 cases amongst them in the 6 years. There were, however, only 146 such cases. This difference is statistically significant. Further, it must be conceded that amongst the untreated children there is included that number of them who already had had an attack of diphtheria, making the considered incidences of diphtheria amongst the untreated children lower than reality. For the subgroup of treated children who were also proved to have become Schick-negative the incidence of diphtheria is shown in Table VI.

Table VI

Year	Estimated child-years-of-exposure to diphtheria of treated children who became Schick-negative*	Cases of diphtheria amongst these children	Incidence of diphtheria per 1000
1930	1799	6	3·3
1931	4466	9	2·0
1932	5597	4	0·7
1933	6280	5	0·8
1934	7444	10	1·3
1935	9533	6	0·6

* See note * to Table V.

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It is to be noted that as compared with the whole group of treated children this subgroup of Schick-negative children escaped more lightly in every year from diphtheria.

Had this subgroup suffered from diphtheria at the same rates as the untreated children there would have been 235 cases amongst them; had they suffered at the same rates as the treated group of children as a whole there would have been 71 cases amongst them. There were, however, only 40 such cases. These differences are statistically significant.

The incidence of diphtheria in these groups of children may also be compared by noting the incidence per 100 child-years-of-exposure to the disease.

The 3778 cases amongst untreated children occurred during the estimated 486,121 child-years-of-exposure (Table IV), an incidence of 0·777 per hundred child-years-of-exposure.

The 146 cases amongst the treated children occurred during the estimated 70,329 child-years-of-exposure (Table II), an incidence of 0·208 per hundred child-years-of-exposure.

In the latter group there were 40 cases amongst children known to have become Schick-negative after treatment during an estimated 35,119 child-years-of-exposure (Table II), an incidence of 0·114 per hundred child-years-of-exposure.

The incidence of clinical diphtheria, then, in the treated child population was only as 0·208 is to 0·777 compared with its incidence in untreated children; and further, in the treated children proved also to have become Schick-negative the incidence of diphtheria was only as 0·114 is to 0·208 compared with its incidence in all the treated children.

The mortality from diphtheria

Amongst untreated children there were 3778 cases of diphtheria with 131 deaths—a case mortality rate of 3·47 per cent. In the treated group there were 146 cases of diphtheria with 2 deaths—a case mortality rate of 1·37 per cent.

In the known Schick-negative group there were 40 cases of diphtheria with no deaths.

With regard to case mortality, then, it is demonstrated that there was a decrease in the fatality rate from 3·47 per cent in untreated children to 1·37 per cent in the treated children, and to nil in the Schick-negative group, a sequence which clearly suggests an increasing advantage to the treated children though we must admit that our figures are not extensive enough to establish a conclusion of statistical significance.

The clinical severity of the disease

In Table III the cases of diphtheria in the treated children are classified as mild, moderate, or severe. Our figures are insufficient for statistical deductions, but it is submitted that they may become of some value if considered in due course with the observations of other workers.

Certain recognized possible limitations of this investigation

(*a*) It is admitted that the notifications of diphtheria are those of the whole child population of the City while the children who received immunization treatment were in attendance at the Infant Welfare Clinics or the Public Elementary Schools, making some social class differences possible in the groups; but that the incidence of the infectious diseases is generally greater amongst the latter than amongst the children of the more well-to-do will surely be conceded, so that the possible bias is in favour of the untreated group.

(*b*) We do not refer to sex incidences in our study, but we do not believe this is a point of very great importance.

(*c*) It is admittedly important that immunization treatment was not given mainly at ages at which the risk of contracting diphtheria was relatively low.

The diagram on p. 394 shows:

(1) The average annual age distribution of the incidence of clinical diphtheria in the period 1930–5.

(2) The age distribution of those receiving immunization treatment in 1935, in no way recognized as an unusual year.

Diagram 1 demonstrates that the ages at which immunization treatment was generally given preceded the age groups in which the disease was most prevalent. This might have contributed to the advantage shown by those treated in the most recent years.

(*d*) In Table I it is recorded that the highest incidence of diphtheria was in 1930, at the beginning of immunization. Table VII shows that of the total estimated child-years-of-exposure to diphtheria amongst the treated children only 5·2 per cent belonged to that year, and that 24·7 per cent belonged to 1935 (when the incidence was relatively low), and that the percentage of the estimated child-years-of-exposure amongst the untreated children was relatively constant throughout the 6 years.

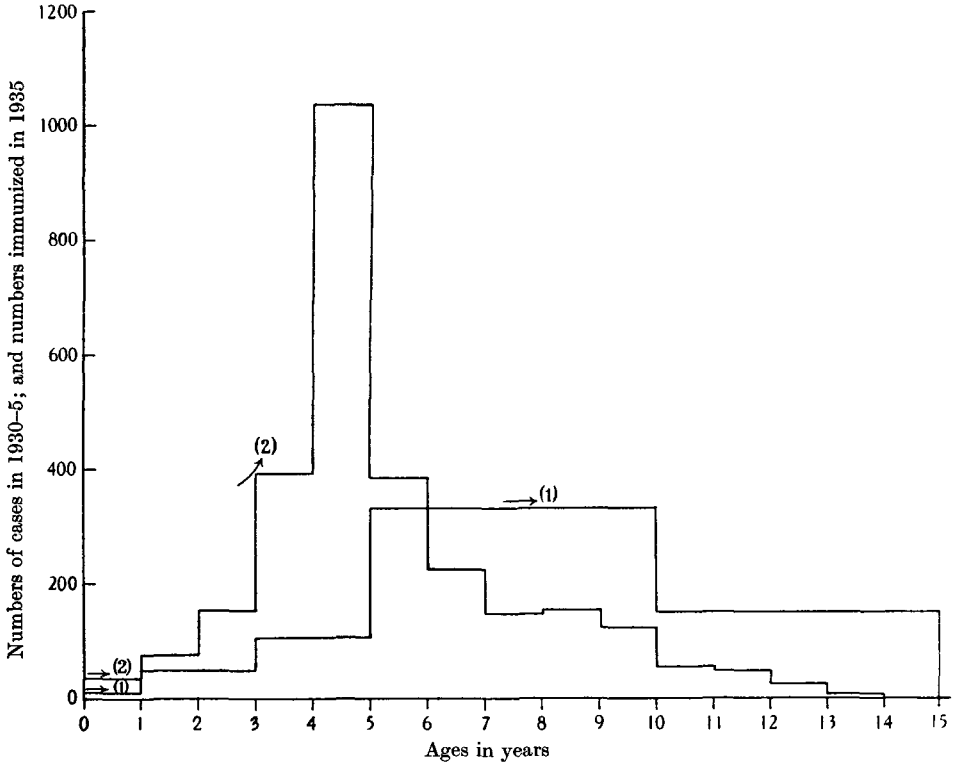
Table VII

Year	Estimated child-years-of-exposure; treated	Percentage	Estimated child-years-of-exposure; untreated	Percentage
1930	3,689	5·2	85,952	17·7
1931	9,120	13·0	82,505	17·0
1932	11,672	16·6	80,821	16·6
1933	13,378	19·0	80,711	16·6
1934	15,104	21·5	78,899	16·2
1935	17,366	24·7	77,233	15·9
Total	70,329	100·0	486,121	100·0

In view of such a varied percentage distribution of the treated population throughout the period under review, it might have been that any difference in the incidence of diphtheria amongst the treated and untreated children was due to these changing proportions at risk, associated with a changing incidence

of the disease. Table V, however, shows that in every year the treated children were at an advantage.

Diphtheria is a disease of the respiratory tract and, as pointed out by others, such diseases are generally little influenced by any reasonable and practicable improvements in individual or community hygiene. Our results, however, confirm the observations already reported that prophylactic treatment against diphtheria of appreciable value is available for those who care to have it.



(1) Age distribution of incidence of diphtheria—1930–5.
(2) Ages at which children were immunized—1935.

Diagram 1

At the same time, it must be admitted that the method of providing this by three injections of an immunizing agent, together with Schick testing, is cumbersome, comparing very unfavourably for example with the method of protection available against smallpox. The period of time required to produce an immunity after the injection treatment must also be recognized. We believe that such drawbacks are largely responsible for the defaulting which has been encountered at all the various stages of the process.

Conclusions

A study of the incidence of diphtheria during a period of 6 years in a large city of child population of over 90,000, of whom 18,800 received immunization

treatment, proves statistically the value of this treatment while still greater benefits won by those who are definitely known to have become Schick-negative are proved after considering 10,879 such treated and ascertained Schick-negative children. For treated children the risk of contracting clinical diphtheria was less than one third that of the untreated children. For treated children who were also proved to have become Schick-negative after treatment the risk was still further lowered, so that as compared with untreated children their incidence rate of clinical diphtheria was less than one sixth.

There was a decrease in the case mortality rates of the disease in the treated classes which is suggestive, but our observations are too few to give conclusive results.

Greater advance in the field would come with the production of a substance capable in a single dose of providing a rapid and satisfactory immunity, in the same way as vaccination provides a rapid protection against smallpox (recent reports may indicate that such a substance is now almost here). It is likely that, as with vaccination against smallpox, the protection will require periodic enhancement, for the work of others shows that natural protection is obtained and sustained in this way. But until immunization against diphtheria can be more rapidly and less cumbersomely obtained it seems unlikely that the public will avail itself of prophylaxis against one of the serious diseases of childhood to the extent that the value of this measure appears to warrant.

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