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The Epidemiology of Diphtheria  
During the last forty years.

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THE  
EPIDEMIOLOGY OF DIPHTHERIA  
DURING THE LAST FORTY YEARS

by

W. T. RUSSELL.



LONDON  
HIS MAJESTY'S STATIONERY OFFICE

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## PREFACE

This report deals statistically with the incidence and mortality of diphtheria in Britain during the last forty years, and it includes a study of the results of the protective inoculation of children, with particular reference to experience in the United States and Canada, where inoculation has been extensively practised. The interests of the findings in relation to the campaign for the immunisation of children in Britain against diphtheria has been held to justify their publication at the present time.

In the first chapter of the monograph "Diphtheria" issued by the Council in 1923, the late Professor William Bulloch gave a masterly summary of the epidemiological history of the disease. So far as Europe is concerned, diphtheria first came into view as a serious epidemic disease in the Iberian Peninsula late in the 16th and early in the 17th century. Since then it has spread widely, although, in view of the difficulty of clinical and epidemiological differentiation of diphtheria from the anginal forms of scarlet fever in written descriptions, it is impossible to be certain of the biological nature of "throat" epidemics in the 18th century. A new epidemiological epoch opened in the third decennium of the 19th century when, thanks to the classical investigations of Bretonneau, clinical and epidemiological differentiations became clearer. About the middle of the 19th century a new pandemic period began; France was first involved and this country, in which scarlet fever had already attained a terrible importance, was included in the pandemic extension of diphtheria about 80 years ago. We have, then, a suggestion—it cannot be put higher—that our epidemiological invasion lines run from the south of Europe. The suggestion is worth bearing in mind now that North Africa has become a main theatre of war.

In the decennium 1861-70, 39,454 deaths in England and Wales were attributed to diphtheria and nearly 208,000 to scarlet fever, an epidemic disease which, in our generation has been but a minor cause of mortality. The history of diphtheria as a cause of mortality during the last 60 years is shown in the following table.

### *England and Wales*

<i>Period</i>	<i>Deaths at age</i> 0-15 years	<i>Population at age</i> 0-15 years
1881-1890 .. ..	41,269	9,820,413
1891-1900 .. ..	76,919	10,353,849
1901-1910 .. ..	58,756	10,781,340
1911-1920 .. ..	48,551	10,930,200
1921-1930 .. ..	30,916	10,015,322
1931-1938 .. ..	22,605	9,266,700

Although there is evidence of improvement, the progress is disappointing in view of the fact that, of the infectious diseases of childhood, diphtheria is the one of which exact biological knowledge is most complete and was earliest obtained. When the fathers of this generation of medical practitioners were young men, fifty years ago, laboratory research had already established the fundamental biological facts of the aetiology of diphtheria and a powerful method of treatment was available in diphtheria antitoxin, which has much reduced the fatality of the disease. Almost a generation ago, it became possible to measure precisely the liability of children to fall victims to diphtheria, and both laboratory and field experiments showed that artificial active immunisation much increased the resistance of persons exposed to the infection. Yet, in this country, diphtheria has continued to be a major cause of mortality. There is indeed reason to think that in certain sections of the population, the danger of infection has increased.

The researches of many workers have shown that, in the natural course of events, immunity or partial immunity is produced either by passing through a clinical attack of the disease or, more frequently, by a covert or sub-clinical, attack, due presumably to infection by micro-organisms too few in number or of too little infectivity and virulence to excite manifest or serious disease. Since diphtheria is commonly transmitted through the discharge of infective matter by coughing or spitting—or through the unhygienic use in common of spoons, pencils, etc.—it would be expected that, in over-crowded homes or schools, infection and resultant immunity would be earlier developed among the children of the less fortunate classes of society. That this was so, has been frequently demonstrated. Nevertheless, with the decline of the birth rate and an improved general standard of living the class differentiation has, as Mr. Russell shows, been much reduced, so that what may be called the natural resistance of certain sections of the community at school and later ages has weakened. There is also the possibility, mentioned in an earlier paragraph, that the epidemic strains may be reinforced by importation.

In some countries, notably the United States of America, the expediency of raising the general resistance of the child population to diphtheria, by widespread active immunisation, was realised years ago. These field experiments have been of a sufficient extent and duration to justify statistical appraisal, and the evidence here published amounts to proof that in those American and Canadian cities in which mass immunisation of children against diphtheria has been practised on a really large scale, thousands of lives have been saved which would have been sacrificed had not the procedure been adopted. In Britain, on the other hand, morbidity and mortality from diphtheria remain high. Prior to 1940, active immunisation of the child population was carried out only by a proportionately small number of local authorities. The practice was limited almost entirely to school children and to young children attending welfare centres. Since 1940, when the Government decided to issue an approved prophylactic free to all local authorities and urged the adoption of active immunisation as a public health measure, good progress has been made. By the end of 1942, 46·5 per cent. of the child population under 15 in England and Wales had been immunised, and in quite a number of areas almost the whole of the child population has been brought within the scheme. It cannot be stated with certainty that the world-wide adoption of mass immunisation, as in New York City and Toronto, would have had the same measure of success in all countries, for the history of epidemiology proves that factors not controllable by human intelligence may favourably, as in the case of scarlet fever, or unfavourably, as in the case of influenza, affect the progress of epidemic or pandemic diseases. None the less, the conclusions to be drawn from the whole body of evidence, to which this report makes a valuable addition, are impressively in favour of active immunisation against diphtheria as a life-saving measure which should be adopted in this country also on the widest possible scale.

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# THE EPIDEMIOLOGY OF DIPHTHERIA DURING THE LAST FORTY YEARS

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## INTRODUCTION

As a consequence of the decline in the birth rate, particularly during the last twenty years, the proportion of children and young adults in the population has decreased steadily. This steady decrease in the ratio will inevitably be accelerated owing to war conditions, such as the absence of men from their homes, and through crippling and fatal casualties. What the magnitude of this decrement will be in the immediate future it is impossible to prophesy, but there can be little question that national well-being will be adversely affected through any considerable decrease in the ratio of children and young adults to the total population. Accordingly, it is essential that all available safeguards be adopted to protect the health of the child population. In this respect, the attention at present being paid to the incidence of diphtheria is noteworthy. It is claimed that the disease can be largely prevented by artificial immunisation, and statistical experience, particularly of highly immunised populations in Canada and America, is quoted in affirmation. In the light of the results achieved in both these countries, the present rates of morbidity and mortality from diphtheria in Great Britain may be held to represent a needless and extravagant waste of child life.

In view of the great importance of diphtheria as a cause of morbidity and mortality, it is of practical interest to examine the epidemiology of the disease during the last forty years. Such was the purpose of the present investigation, in which the statistics of this country and of certain cities of Canada and of the United States have been analysed and compared, particularly in relation to the morbidity. The statistics of type infection—*milis*, *intermedius* and *gravis*—which were obtained from the Emergency Public Health Laboratory Service and its allied laboratories for the years 1940 and 1941, were examined, as were also the statistics relating to the number of children immunised in the County Boroughs during the same period.

## MORTALITY

Diphtheria is a frequent cause of death, especially in childhood, but its destruction of life is not to be measured solely by the number of deaths officially ascribed to it. Some of those who recover do so only at the price of a permanent weakening of vigour and efficiency, together with the likelihood of a relatively early death. This, of course, is similarly true of measles and whooping cough. According to the Annual Reports of the Registrar General for the years 1937 and 1938—the latest years for which the published Annual Reports were available—there were on the average 2,947 deaths annually from diphtheria in England and Wales, and, of these, 90 per cent. occurred amongst children under fifteen years of age. The significance of diphtheria as a cause of death in childhood can be illustrated more vividly if the chief causes of death in each of the age groups 1-5, 5-10 and 10-15 years are listed in numerical sequence. This arrangement has been made in Table I, in which the recorded number of

TABLE I

*Numerical sequence of diseases on the basis of average number of deaths during 1937 and 1938 in England and Wales*

<i>Age 1-5 years.</i>		<i>Age 5-10 years.</i>		<i>Age 10-15 years.</i>	
Pneumonia .. ..	2,822	Diphtheria .. ..	1,345	Violent Causes ..	547
Tuberculosis .. ..	1,030	Violent Causes .. ..	762	Tuberculosis .. ..	541
Diphtheria .. ..	985	Tuberculosis .. ..	471	Diphtheria .. ..	351
Violent Causes .. ..	961	Pneumonia .. ..	428	Heart Disease .. ..	345
Measles .. ..	823	Appendicitis .. ..	205	Pneumonia .. ..	211
Whooping Cough .. ..	668	Heart Disease .. ..	179	Appendicitis .. ..	186
Estimated population, 31st Dec., 1937 :—					
2,217,800		2,922,700		3,159,200	

deaths from each cause is the average based on the returns for 1937 and 1938. At the youngest age, diphtheria was third on the list, being exceeded by pneumonia and tuberculosis; at age 5-10 it occupied the first place, with 1,345 deaths, a total which is nearly twice that for violent causes and almost three times that for tuberculosis. Amongst the older children, of 10-15 years, it reverted to third place, but it still caused no fewer than 351 deaths, being exceeded by violence (547) and tuberculosis (541).

#### SECULAR TREND

The mortality as measured by the death rate among children under 15 years of age has declined greatly since 1901, but the decline has not been uniform. In 1901 and 1902 the death rates were 888 and 768 per million respectively, and in both 1937 and 1938 the rate was 310 per million. It is not easy to obtain a mathematical curve which will describe suitably the secular trend of the mortality from an infectious disease, such as diphtheria, which has an indistinct periodic character. It may be supposed that two factors are involved, (1) a secular trend of decrease, (2) a periodic or quasi-periodic rise and fall. Mathematically, this suggests that a suitable representation would be given by the product of two functions of the time, the former an exponential function in which the sign of the constant multiplying the highest power of  $t$  is negative, the latter a periodic function—in the easiest case, a simple exponential multiplied by a sine function. But in statistical practice, having regard to the comparatively short run of comparable data, an adequate determination of the constants would be impossible. It may be remarked that a simple exponential alone gives a fair graduation of the trend. The actual and calculated values obtained from the equation are shown in Table II and also in Fig. 1.

TABLE II

*Death rates per million from diphtheria amongst children at ages under 15 years in England and Wales*

<i>Period.</i>	<i>Actual.</i>	<i>Calculated.</i>	<i>Period.</i>	<i>Actual.</i>	<i>Calculated.</i>
1901 .. ..	888	618	1920 .. ..	510	391
1902 .. ..	768	603	1921 .. ..	430	381
1903 .. ..	592	589	1922 .. ..	372	373
1904 .. ..	564	575	1923 .. ..	249	364
1905 .. ..	532	561	1924 .. ..	230	355
1906 .. ..	587	548	1925 .. ..	259	347
1907 .. ..	541	535	1926 .. ..	281	338
1908 .. ..	521	522	1927 .. ..	256	330
1909 .. ..	484	510	1928 .. ..	303	322
1910 .. ..	384	498	1929 .. ..	328	315
1911 .. ..	433	486	1930 .. ..	340	307
1912 .. ..	376	474	1931 .. ..	258	300
1913 .. ..	392	463	1932 .. ..	228	293
1914 .. ..	510	452	1933 .. ..	261	286
1915 .. ..	510	441	1934 .. ..	402	279
1916 .. ..	468	431	1935 .. ..	351	273
1917 .. ..	393	420	1936 .. ..	318	266
1918 .. ..	430	410	1937 .. ..	310	260
1919 .. ..	447	400	1938 .. ..	310	253

It is first essential to ascertain the degree of success with which the curve describes the trend of the mortality. Without the knowledge derived from the best fitting curve, the best estimate that could be made of the size of the annual death rate would be the arithmetical mean of the series of annual rates, and the error involved would be proportional to the standard deviation. The curve which reduced this error to a minimal value would be most acceptable for



predictive purposes. The standard deviation ( $\sigma$ ) was originally 144, and the root mean square difference ( $S$ ) between the actual and predicted rates of mortality is 81; it will thus be seen that the error of precision in forecasting the mortality has been reduced by over 40 per cent.

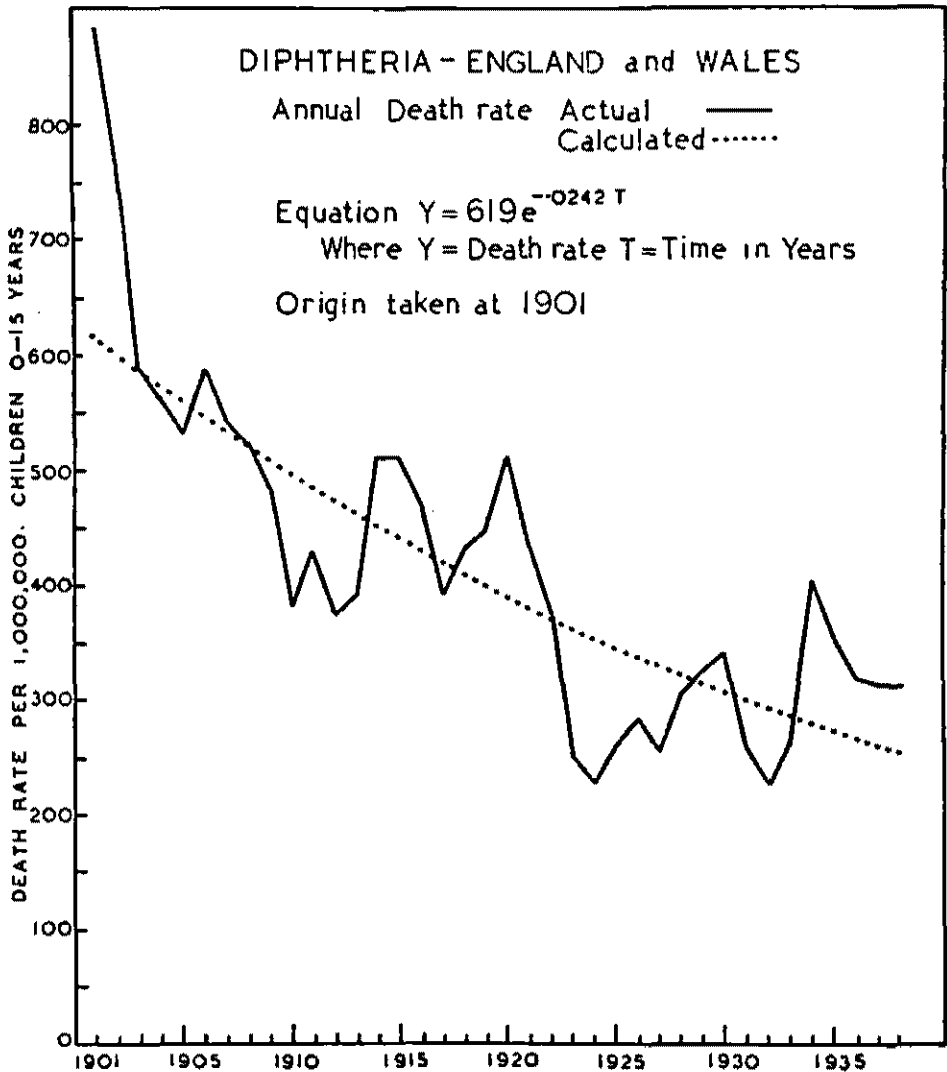


FIG. 1.

It is interesting to speculate on the factors which may have been responsible for the reduction in mortality. Amongst the many which may have operated are:—

- (1) change in the type of the disease,
- (2) greater recuperative powers of those attacked, as a result of living under improved social conditions during the last two decades,
- (3) increased hospitalisation at earlier stages of the disease,
- (4) changes in methods of treatment, included under which is the administration of progressively increased dosages of antitoxin.

For example, in 1916 the average dose of antitoxin given in the Infectious Diseases Hospitals of the Metropolitan Asylums Board in London was 16,607 units per patient; in 1925 this had increased to 26,335 units. The justification of this change of dosage was perhaps reflected in the case fatality, which in 1901-1910 was 12.2 per cent. but in the period 1925-9 had declined to 4.8 per cent.

The effects of isolation were studied by Elderton and Pearson (1915). Their data consisted of the annual number of diphtheria cases, the number of patients removed to hospital, and the number of deaths during a period of nine years, 1904–1912, for about eighty towns or districts with large populations. As a result of their investigation, they concluded that the extent to which isolation was practised had no appreciable influence on the prevalence of diphtheria or on the death rate, but that it was inversely related to the case fatality, the coefficient of correlation being of the order of  $-0.5$ . The negative correlation with case fatality is understandable, inasmuch as it implies that hospital treatment was an effective factor. On the other hand, the lack of association of the extent of isolation with prevalence is impossible to explain in the absence of knowledge of the epidemic constitution of the population at risk, and of the relative numbers of healthy carriers, latent or missed infections, immunes and susceptibles.

Woods (1928) analysed the data for London for the period 1923–6; the coefficients which she obtained were:—

Isolation rate and attack rate  $r = .147 \pm .127$

Isolation rate and death rate  $r = .371 \pm .112$

Isolation rate and case mortality  $r = .374 \pm .112$

from which she concluded—"as far as the analysis goes, and the method of correlation can show, there is no evidence pointing to the advantageous results of isolation of diphtheria in London." The positive coefficient between the isolation rate and the case mortality is certainly a surprising finding. It will be noted that she attached a proviso to her conclusions regarding the applicability of the correlation method to her London data, and she also stated that "owing to the large proportion of cases isolated in each of the boroughs and the consequent limitation of the possible range of variation of one factor, the meaning of the correlation is not always clear". But it may be argued that isolation *per se* is not the sole determinant of either morbidity or fatality. In addition to the epidemic constitution, the stage of the disease at which the patient is isolated is probably of great importance. Caiger (1924), in his comments on the statistics of infectious disease in Metropolitan Asylums Board Hospitals during 1923, stated:—

"Although the diphtheria mortality for the year 1923, as in two previous years, was brought down to under 7 per cent., this figure is higher than it should be. It could be materially reduced by the earlier administration of antitoxin. The very striking fact was reported by the medical superintendent of the Park Hospital (Dr. Woodfield) that of 150 deaths from diphtheria which occurred in that hospital during 1922, in 30 per cent., death occurred within 24 hours of admission, and in 42 per cent., within 48 hours. To anyone possessing the slightest knowledge of diphtheria, the inference to be drawn from these figures is obvious. The fatal effects which too often result from delay in the injection of antitoxin can only be regarded as an *opprobrium medicinae*. Sometimes, it is true, the patient is sent to the hospital too late for cure, owing to the ignorance of the parents and consequent delay in calling in a doctor, but more often, it must be confessed, owing to failure to recognise the nature of the disease, or to that fatal practice of waiting for the receipt of laboratory evidence."

Data such as those collected at the Park Hospital for the years 1897–1906, and recorded on p. 187 of the Annual Report of the Metropolitan Asylums Board for 1906, are instructive in illustrating the benefits derived from giving antitoxin in the initial stages of the disease. The case fatality is related to the day of disease on which antitoxin was given.

The results were as follows:—

<i>Antitoxin given on :</i>	<i>Cases</i>	<i>Case Fatality</i>
1st day of disease .. ..	225	0
2nd " " " .. ..	1,441	4.2
3rd " " " .. ..	1,600	11.1
4th " " " .. ..	1,276	17.3
5th day and upwards .. ..	1,645	18.7

There may be some error in the time recording, as it is difficult to obtain exact information as to the precise day on which the illness began. But the

intervals will, nevertheless, be correlated with progressive stages of the disease. The trend of the case fatality would seemingly indicate the paramount importance of giving antitoxin in the early stages of the illness. At two days, the fatality is 4·2 per cent. and at five + days it is 18·7 per cent. In fact, the curve suggests a "saturation point" at four days, after which the fatality remains constant and the progress of the disease is not influenced by the administration of antitoxin.

Statistics of this character have, however, been subjected to severe criticism. The critics have said that the comparison is fallacious, because patients admitted to hospital on the 4th, 5th or a later day form a select group, of necessarily severe cases: they were either missed initially or the parents delayed calling in a doctor until the patients became critically ill. Brownlee (1925), who was Superintendent of a large hospital for infectious disease in Glasgow, apparently did not share this opinion, because he quoted case fatality rates which showed a similar trend to those for London and wrote:—

"With treatment on the first day, a very low, or no mortality is found. Treatment on the second day is associated with a larger death rate, but when treatment is delayed till the fifth or sixth day, a maximum mortality has been attained. Here again, something like an absorption balance between the human organism and the toxin is found. The late use of anti-toxin cannot ensure recovery, though in the event of recovery it may markedly hasten convalescence."

It cannot be assumed with certainty that the cases of patients admitted to hospital on the 4th, 5th or later days will all be severe in character. They may be a "mixed bag". Patients with diphtheria are usually sent to hospital not because of the severity of the disease, but because diphtheria is suspected or a positive swab has been obtained. The point at issue can be satisfactorily determined only by ascertaining the proportion of cases in late admissions which are definitely mild and those which are definitely severe.

#### GEOGRAPHICAL DISTRIBUTION

To obtain some idea of the range of mortality from diphtheria in various boroughs, the death rate based on the average number of deaths between 1926 and 1936 amongst children aged 0-15 was calculated for each of the 83 county boroughs, and also for each of the London Metropolitan Boroughs. The frequency distribution of the mortality is given in Table III. In 13 county boroughs the death rate was less than 2 per 10,000, and in two it was as low

TABLE III

*Frequency distribution of the average annual death rates from diphtheria during the period 1926-36 amongst children aged 0-15 years*

Death Rates per 10,000.	England and Wales. County Boroughs.		London. Metropolitan Boroughs.	
	No.	Per cent.	No.	Per cent.
0-0 .. ..	2*	2·4	—	—
1-0 .. ..	11	13·3	—	—
2-0 .. ..	22	26·5	4	14·3
3-0 .. ..	19	22·9	15	53·6
4-0 .. ..	13	15·7	9	32·1
5-0 .. ..	8	9·6	—	—
6-0 .. ..	2	2·4	—	—
7-0 .. ..	3	3·6	—	—
8-0 .. ..	2†	2·4	—	—
9-0-10·0 .. ..	1‡	1·2	—	—
	83	100·0	28	100·0

\* = Oxford, Gloucester.

† = East Ham, Wakefield.

‡ = Merthyr Tydfil.

as 0.59 (Oxford) and 0.93 (Gloucester). At the other end of the scale, there were three county boroughs in which the rate exceeded 8 per 10,000, and in one—Merthyr Tydfil—it was as high as 9.3 per 10,000. The unweighted mean death rate for all boroughs was 3.7 per 10,000, and the average dispersion around the value was 1.8 per 10,000. The frequency distribution is slightly skew, but, on the basis of normality, one would expect the rates to range between the mean value and plus and minus twice the standard deviation, or between 0 and 7.3 per 10,000. According to this computation, East Ham with 8.2 per 10,000, Wakefield with 8.6 and Merthyr Tydfil with 9.3 have an excessively high mortality. The range of the mortality in London boroughs is much more restricted, as the death rates vary only from 2.0 to 5 per 10,000.

## AGE INCIDENCE

The age of the child plays an important part in determining the size of mortality. This fact is illustrated in Table IV, which shows the death rates at individual ages up to five years and in quinquennial age groups for older children at different periods of time—1906-10, 1916-20, 1926-30 and 1936-7. The curve of age mortality, as based on the experience during 1906-10 (which in shape is almost a replica of that at the other periods), is briefly this. The mortality is low, 30 per 100,000, amongst children under one year of age; it more than doubles itself at age 1-2 and then by steady gradations attains its maximum amongst children aged 3-4 years (in the other quinquennial periods the maximum is at age 4-5 years). Afterwards it declines, and it is lowest, 8 per 100,000, at age 10-15 years.

TABLE IV  
*Average death rate from diphtheria and croup per 100,000 in England and Wales*

Period.	Age.						
	0-	1-	2-	3-	4-	5-10	10-15
1906-10 .. ..	30	84	90	106	103	52	8
1916-20 .. ..	24	67	79	93	95	53	11
1926-30 .. ..	19	45	48	52	57	37	9
1936-37 .. ..	14	22	44	54	66	47	11

TABLE IVA  
*Death rates in subsequent periods expressed as a percentage of those during 1906-1910: England and Wales*

Period.	Age.						
	0-	1-	2-	3-	4-	5-10	10-15
1906-10 .. ..	100	100	100	100	100	100	100
1916-20 .. ..	80	90	88	88	92	102	138
1926-30 .. ..	63	54	53	49	55	71	113
1936-37 .. ..	47	26	49	51	64	90	138

To obtain an indication of the extent to which the mortality at ages has declined in recent years, the death rates in the subsequent periods were expressed as percentages of the values in 1906-10, and the results are stated in Table IVA. Under age 1 year, the death rate in 1936-7 was 47 per cent. of that which existed thirty years earlier, but the greatest reduction occurred amongst children aged 1-2 years, where the mortality has declined to 26 per cent. of the earlier rate. Between the ages of 2 and 5 years the decrease ranged

from 36 to 51 per cent. For the children in the age group 10 to 15, on the other hand, the rate increased by 38 per cent. It is noteworthy, however, that even amongst children aged 3-4 years and 4-5 years, respectively, there was a tendency for the rates (Table IV) to increase during 1936-7 as compared with 1926-30; at age 3-4 the comparable values were 52 and 54 per 100,000, and at age 4-5 the rates were 57 and 66.

Reverting to the large decrease in the mortality at age 1-2 years, it is tempting to speculate on the causes which produced this. In 1929 the writer was co-author of a paper based on the admissions of scarlet fever, diphtheria and enteric fever to the Eastern Fever Hospital of the London County Council during the period 1895-1914. From the analysis it was found that, of the three most frequent forms of diphtheria, (1) faucial, (2) rhinorrhoeal, (3) laryngeal and croup, the last named occurred mainly amongst children of pre-school age. Its incidence, when related to the total admissions at specific ages, was greatest at age 1-2 years. According to the Registrar General's data, it was the laryngeal and croupous form of the disease which contributed most heavily to the diphtheria mortality thirty years ago. In his Annual Report for the year 1911, he compiled a secondary classification of the causes of death from certain diseases, amongst which diphtheria was included. In Table B, page 571, of that report there were 692 deaths at all ages ascribed to laryngeal diphtheria, membranous croup, tracheotomy and diphtheritic croup, and, of this number, 150 occurred at age 1-2 years; whereas for all forms of diphtheritic paralysis the total deaths at all ages were 264, and of this number five occurred at age 1-2 years. There are no statistics to indicate the extent to which the laryngeal form of the disease has decreased, but there is some indirect evidence that it has declined because in Memorandum I issued by the Emergency Public Health Laboratory Service in January, 1942, it is stated that:—

"Infections with the *gravis* and *intermedius* types are more often characterized by pareses and cardiac weakness, and those with the *mitis* type by laryngeal complications."

Since the *mitis* type of the disease is associated nowadays with a low death rate, the inference would appear to be that the large reduction which has taken place in the mortality at age 1-2 years is attributable either to the lessened severity of the laryngeal form of diphtheria, or to its greater control by adequate and timely injections of antitoxin.

#### AGE SHIFT

The outstanding impression conveyed by the rates in Table IV is that the mortality has declined more rapidly for the pre-school than the school age. The result has been that the mortality statistics indicate a relative shift in age incidence, and the disease is now represented as concentrating on children of school age. This is clearly indicated in Table V, in which the death rates at ages 0-5 and 10-15 are expressed as percentages of that in age group 5-10.

TABLE V  
Death rates from diphtheria at ages 0-5 and 10-15 expressed as a percentage of the rate at age 5-10: England and Wales

Period.	Age Group.		
	0-5	5-10	10-15
1906-10 .. ..	163	100	15
1911-15 .. ..	134	100	20
1916-20 .. ..	133	100	21
1921-25 .. ..	137	100	22
1926-30 .. ..	120	100	24
1931-35 .. ..	95	100	24

During 1906-10 the pre-school mortality was 63 per cent. in excess, whereas during 1931-5 it was 5 per cent. in defect. The relative mortality in children aged 10-15 has risen gradually from 15 per cent. to 24 per cent. in the last quinquennium.

The mortality from the disease in the United States between 1920 and 1938 is given in Table VI, in which the rates per 100,000 are those recorded by Dublin and Spiegelman (1941). Their figures for the mortality amongst white children only will be discussed here, as a comparison of the statistics regarding white and coloured children must inevitably be influenced by ethnological and geographical factors. During the period 1920-4 the death rate from diphtheria amongst white children was 86·9 per 100,000 in the age group 1-5 years, 42·0 at ages 5-10 years, and 11·1 amongst children aged 10-15 years. The mortality at these periods of life decreased rapidly in the course of time, with the result that, during the period 1935-8, the death rate at pre-school age was 79 per cent. less than that which existed during 1920-4. The decrease was even greater amongst school children—86 per cent. in the age group 5-10 years and 88 per cent. amongst children aged 10-15 years.

TABLE VI

*The average annual death rates per 100,000 from diphtheria amongst white children at ages in the United States, and the death rates in subsequent periods expressed as a percentage of those in 1920-1924*

Period.	Age Period.					
	1-5		5-10		10-15	
	<i>Per cent.</i>		<i>Per cent.</i>		<i>Per cent.</i>	
1920-24 .. .. .	86·9	100	42·0	100	11·1	100
1925-29 .. .. .	49·5	57	22·0	52	5·0	45
1930-34 .. .. .	26·6	31	11·2	27	2·2	20
1935-38 .. .. .	18·6	21	5·9	14	1·3	12

TABLE VIA

*The death rates at ages 1-5 and 10-15 expressed as a percentage of those at age 5-10*

Period.	Age Period.		
	1-5	5-10	10-15
1920-24 .. .. .	207	100	26·4
1925-29 .. .. .	225	100	22·7
1930-34 .. .. .	238	100	19·6
1935-38 .. .. .	315	100	22·0

The size of the age-shift which has occurred is shown in Table VIA. It will be seen that the trend of the ratios in the United States is entirely different from that in this country, as in the former the ratio of the mortality in pre-school to that at immediate school age, 5-10 years, has increased. In 1920-4 the value for white children was 207, and in 1935-8 it was as high as 315. Thus the mortality at school age is declining more rapidly than that for the younger children. This result is interesting, because the health authorities concentrated at first on the immunisation of school children and it would seem that the greater reduction in the mortality at school age indicated the success which they achieved.

The phenomenon of age shift in mortality in England and Wales is also evident in Ireland and Scotland; it is characteristic of both town and country, and has been commented on by several investigators. Murphy (1907) reviewed

the trend of the mortality from the disease in London during the period 1859-1905. By a series of graphs, representing the deviations of the mortality at ages from the mean at all ages, he demonstrated that in the early epidemic years, 1859-65, the death rate at pre-school age was high in relation to that at ages 5-15; during the ensuing 20 years, when the prevalence declined, a reduction in the age mortality occurred, but chiefly amongst the younger children, and, when the disease reverted to epidemic proportions, as in 1891-5, the increased mortality "was most marked at ages 5-10 and 10-15". His conclusions were :—

"There has, therefore, been a change in age-incidence, which there is reason for thinking is rhythmical; but the whole story is not yet complete, for we need the periods 1906-10 and 1911-15, or indeed still later periods, to enable us to see whether the lines they will provide will resemble those of 1866-70 and 1871-5. Possibly, however, there will be less conspicuous curves in these years, owing to the greater aggregation of children in school, leading to increased incidence of mortality at school age."

Chalmers (1913) studied the age mortality in Scotland as a whole for triennial periods (1860-2 to 1909-11), the census years being intermediate, and was able to demonstrate the relative change which took place in the age incidence of the disease. He also examined notifications according to age for each year between 1903 and 1912 in Glasgow, and described his results in the following terms :—

"The changed age-incidence, which began here in the year 1906, is, I think, significant, because it has been maintained in each of the subsequent years, and raises questions which concern age immunity on the one hand, and the acquisition of a greater infecting power of the organism on the other. With the increasing prevalence there has been a relatively greater invasion of the age period.\*

The 'infectious diseases of childhood' is a convenient phrase whereby to express the increasing immunity to these diseases which individuals acquire on passing through childhood to maturity. Here, however, we have illustration of the spread of an epidemic associated with an alteration in the age-incidence of attack, and selecting not an earlier but a later age-period. It may be that a new page has been opened in the natural history of disease."

The most interesting and the most recent contribution to the subject was made by Picken (1937). From a very careful study, particularly of the morbidity and fatality in London, Manchester and Glasgow, he indicated that the shift was not one of morbidity, but rather of fatality and suggested as a possible explanation :—" . . . changes of strain of *Corynebacterium diphtheriae* ".

Although changes in the prevalence of types of infecting organism may have played a considerable part in the phenomenon, a factor of greater, and perhaps outstanding importance is the biological change which has resulted from the decline in the birth rate, to which must be added the improvement in social conditions. The view that the recent lowering of "family density" may be a significant factor in the shift in the age incidence of diphtheria was expressed by the author and his colleagues, Martin and Cheeseman, in 1939, the following considerations being advanced in its support.

During the last 30 to 40 years there has undoubtedly been a marked diminution in the average size of family in all classes in this country. First manifest in the higher social classes, it has now been experienced also in the lower social grades. In the small family of the higher social class there is no great chance of the pre-school children acquiring partial or complete immunity, since they are not much exposed to droplet infection. They live a rather sheltered existence and reach school as a "virgin" population susceptible to infection. The vital statistical experience of children living in residential districts is in complete accord with this picture. Their morbidity rates from infectious diseases at age 5-9 years are invariably higher than those of children of the same age in the lower social scale, whereas the opposite is true for the pre-school population. As the size of families in the lower social grades has become

\* Chalmers is here referring to the age period which covers school life.

smaller in course of time, and housing and environmental conditions have generally improved, it follows that the children born in such communities are probably approximating to those in the higher social classes as regards liability to infection, resistance and age of attack. Proportionately more of them will reach school age without a latent immunity and become infected in the "herd" environment of the school class-room.

The official statistics published in this country do not give material for testing this theory. Although the mortality data are available in much detail, the morbidity records of the disease are not given in age groups, even for the country as a whole, much less for the appropriate social grades; and this information is necessary for a complete examination of the problem. By the courtesy of the Medical Department of the London County Council, access was obtained to the weekly notification registers of infectious diseases covering the period 1901-34 inclusive. Particulars of age, sex, and of the borough in which the patient lived, were abstracted for each week, for specific groups of years—1901-5, 1909-13, 1919-23 and 1929-33. The social index for each London borough was next calculated, by a method which is akin to that of indirect standardisation. With the introduction of a genuinely occupational tabulation in the census of population of 1921, the late Dr. Stevenson grouped the nine hundred odd occupations in this country into five social classes, where I-V represented a well demarcated gradient in the social scale. We made a similar tabulation of the occupied males in London as a whole, and then measured each of the five London classes as a mean deviate on the normal scale. Those deviates were then applied to the corresponding occupational groups for each London borough, and the required index of its social status was thus obtained. An example will clarify the explanation:—

Social Class :	London		Battersea	
	Occupied Males.	Mean deviate on the normal scale.	Occupied Males.	(2) × (3)
	(1)	(2)	(3)	
I .. ..	42,116	2.2630	991	2,242.63
II .. ..	287,756	1.1591	10,636	12,328.19
III .. ..	581,538	0.1378	21,806	3,004.87
IV .. ..	231,179	-0.6543	8,731	-5,712.69
V .. ..	243,103	-1.4716	9,851	-14,496.73
			Totals 52,015	-2,633.74
			Index of social status for Battersea	
			$= \frac{-2,633.74}{52,015} = -0.0506$	

When the social index of each Metropolitan borough had been estimated, a frequency distribution of the results was made. Boroughs having indices

between + .2 and + .6	were put in Group I
0 and + .2	" " " " " II
- .2 and 0	" " " " " III
- .6 and - .2	" " " " " IV

The numerical sequence of the Groups represents a decreasing standard of environmental conditions, Group I being the best type of residential district. The boroughs listed in each group were:—

Group I	Group II	Group III	Group IV
Hampstead	City of London	Battersea	Bermondsey
Holborn	Camberwell	Deptford	Bethnal Green
Kensington	Chelsea	Greenwich	Finsbury
Lewisham	Fulham	Hammersmith	Poplar
Paddington	Hackney	Islington	Shoreditch
Stoke Newington	Lambeth	Stepney	Southwark
Wandsworth	St. Marylebone	Woolwich	
Westminster	St. Pancras		



In the present instance, the analysis was confined to Groups I and IV, because in this way a more distinctive demarcation between social grading was possible. In the discussion below, the expressions "highest" and "lowest" social groups refer to people living in Group I and Group IV districts, respectively. For each of these categories, the morbidity and mortality rates from diphtheria were calculated, and the latter are shown in Table VII.

TABLE VII

*Death rates from diphtheria per 10,000 of the population, and the ratio of the death rates at age 0-5 to those at age 5-15, in two groups of London Boroughs representing social class I and social class IV*

	1911-13.			1919-23.			1929-33.			1937-38.		
	Ages.		Ratio.	Ages.		Ratio.	Ages.		Ratio.	Ages.		Ratio.
	0-5	5-15		0-5	5-15		0-5	5-15		0-5	5-15	
Social Group I	5.51	2.61	2.11	11.09	4.98	2.23	5.23	2.42	2.16	3.63	1.75	2.05
Social Group IV	9.36	1.47	6.37	19.05	4.37	4.36	7.23	1.93	3.75	3.74	1.62	2.31

It was not possible to obtain the rates for the separate age groups 5-10 and 10-15, because the deaths for the individual boroughs are published only for the composite group 5-15 years. The results indicate the necessity of taking the type of district into consideration when discussing the significance of the age shift. In Group I, the ratio of the death rate at age 0-4 to that at age 5-14 has been constant over the whole period; it was 2.11 in 1911-3, 2.16 in 1929-33 and 2.05 during 1937-8. In Group IV, the trend is entirely different, as there has been a considerable decrease. The proportion in 1911-3 was 6.37, it dropped to 3.75 in 1929-33, and in the final period it was as low as 2.31. Thus the age shift in the diphtheria mortality from pre-school to school ages amongst the child population in London has been due largely to the influence of the trend of the death rates in the lowest social group.

It may be asked what are the factors which have produced this phenomenon? The hypothesis advanced here is that it is due to the changes which have taken place in "environmental conditions", using the term in a broad sense. There are no readily defined standards of "environmental conditions", but there are certain approximate indices which may be used to form an estimate of the goodness or badness of these conditions. They are:—

- A. The standardised death rate from all causes.
- B. The infant mortality.
- C. The percentage of the population living at a density of more than two in a room.

These measurements are, of course, highly interrelated. The values for A, B and C at two different periods, 1911-3 and 1930-2, were calculated, and the differences obtained for each index were accepted as indicative of environmental improvement or deterioration. There are no official statistics wherewith to measure the change which has occurred in the size of family within the social grades, but the difference between the legitimate birth rate in 1911-3 and 1930-2 is offered as a rough criterion.

The various results were:—

	<i>Difference between standardised death rates (all causes) 1911-3 and 1930-2.</i>	<i>Difference between infantile mortality 1911-3 and 1930-2.</i>	<i>Difference between overcrowding indices 1911-3 and 1930-2.</i>	<i>Difference between legitimate birth rates 1911-3 and 1930-2.</i>
Social Group I	-2.81 per 1,000	-30 per 1,000 births	-3.0	-63 per 1,000 married women.
Social Group IV	-6.21 per 1,000	-64 per 1,000 births	-4.8	-100 per 1,000 married women.

It will be seen that there was a greater alteration in the indices for social Group IV than in those in Group I. The standardised death rate for Group IV declined by 6·21 per 1,000, as compared with 2·81 for Group I, and the corresponding decreases in infant mortality were 64 and 30 per 1,000 births. The reduction in size of family, as represented by the decrease in the legitimate birth rate, was also greater in the lower social grade, being 100 per 1,000 married women in Group IV, as compared with 63 per 1,000 in Group I. This greater improvement in their "hygiene" life, and the greater reduction in their birth rate, are, it is maintained, the factors which are responsible for the larger age shift in the mortality amongst members of the lower than of the higher social class.

The children in the lower social grade now live a less congested existence than previously. One result of this would seem to be that fewer of them now acquire immunity to diphtheria, either by clinical or sub-clinical attack at pre-school age, and relatively more of them enter school life susceptible to the disease. This aspect will be discussed further in the section on morbidity (pp. 22-24).

#### SUMMARY

The outstanding features of the foregoing discussion of the mortality from diphtheria may be summarised as follows:—

- (1) There has been a decline of nearly 60 per cent. in the death rate from this disease in England and Wales during the past forty years. Although this is encouraging, it falls far short of what might be accomplished—in fact, it is unsatisfactory compared with what has been achieved elsewhere. In the United States, between 1920 and 1938, the mortality has been reduced by 80 per cent. amongst white children aged 1-15 years.
- (2) The mortality in England and Wales is declining relatively more quickly at pre-school than at school age. In an attempt to explain this phenomenon, the mortality in London was calculated for two distinct groupings of London boroughs, the one mainly residential, the other comprising chiefly the densely populated areas. It was found that in Group I, comprising the better districts, the death rate at age 0-5 as a percentage of that at age 5-15 was almost constant at 210 over a period of 30 years, whereas in the densely populated areas the index dropped from 637 during 1911-13 to 231 during 1937-8. This result is considered to be due to the fact that in overcrowded areas the families have become smaller and that, owing to improved housing and other environmental conditions, the children in the lowest social grade are not being subjected to the same intensity of exposure to infection in their pre-school life as hitherto. Such children are now living under conditions which are tending to approximate to those in residential districts. The result is that, in the lower social grades, relatively more children contract the disease and die from it during school life, than used to be the case.
- (3) In the United States, the mortality is declining more quickly at school than at pre-school age; and since the health authorities in that country concentrated initially on immunising the school population, it would seem that the greater reduction in the mortality of such children is an indication of the efficiency of active immunisation in controlling the mortality from diphtheria.

## MORBIDITY

Diphtheria, although it is to a large extent a preventable disease, still takes a heavy toll of life and health, particularly in children.

In 1941 no less than 51,104 cases were notified in England and Wales. This figure is subject, of course, to certain errors, the magnitude of which has not been determined. Amongst the sources of errors which occur and are never corrected in the national notification records are the following :—

- (1) Cases diagnosed clinically, and notified, which are not confirmed by bacteriological examination.
- (2) Cases of throat infection, impetigo, ear-discharge or infected wounds, from which the diphtheria organism is isolated but should be regarded as a saprophyte and not as a cause of the infection. Such cases may have been notified.
- (3) Sub-clinical or missed cases of diphtheria which are not notified. These may never be detected, but occasionally they become manifest by the appearance of diphtheritic paralysis following an infection which has been regarded only as a mild " sore throat ". Errors (1) and (2) tend to neutralise error (3) but to an unknown extent.

## SECULAR TREND

As judged solely by the annual number of notifications during the past 30 years, apart from epidemics in 1920 and 1930 when the notified cases were 69,407 and 73,728 respectively, there does not appear to have been any serious increase in incidence. The average annual number of cases in each of three decennial periods was :—

<i>Periods</i>	<i>Average number.</i>	<i>Coefficient of Variation.</i>
1911-20 .. ..	51,757	15
1921-30 .. ..	54,889	19
1931-40 .. ..	55,388	16

Between 1911 and 1930 the increase in the average yearly number of notifications was less than 4,000, and in 1931-40 as compared with 1921-30 the increment was less than 1,000. Furthermore, there were no violent fluctuations from the mean value within any of the three decennia, the relative variability, as represented by the coefficient of variation, being less than 20.

## CASE RATES

When the numbers of notified cases of infectious diseases are sent to the General Register Office, the ages of the patients are not stated; the Registrar-General is thus compelled to express the incidence in terms of the total population, and not in relation to the particular age groups which are at chief risk. These case rates for the whole country between 1911 and 1937 are recorded in Table VIII. The values indicate that there has been no serious increase in the notifications of diphtheria during the period under review. The case rates in the years 1914, 1915 and 1916 were 161, 152 and 150 per 100,000, and are almost identical with those at the end of the experience. As previously mentioned, the noteworthy features of the table are the apparent epidemics in 1920 and 1930. The interval of ten years between them might suggest a periodicity of such duration, but the data are too limited to test the permanence. The mortality statistics extend over a longer series of years, but they cannot safely be used for this purpose, because, in the early days of registration, the deaths from diphtheria and scarlet fever were often not sharply differentiated in their classification.

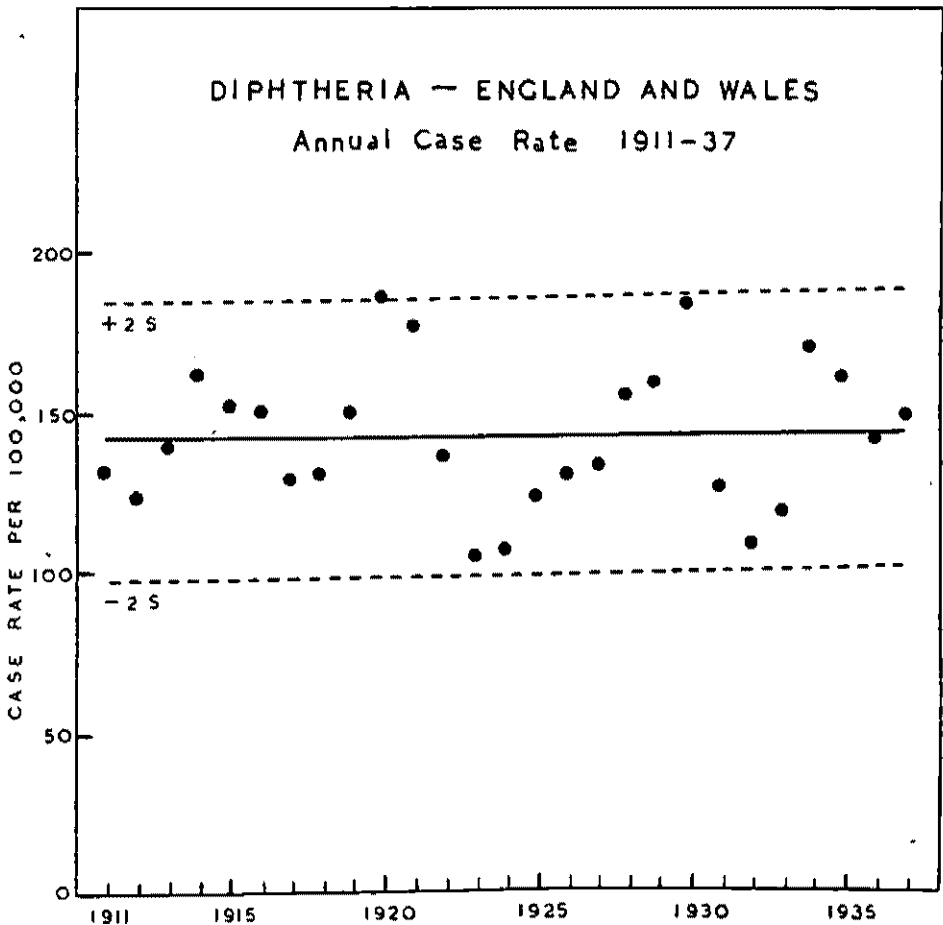
Although the trend of the case rates is in no distinct direction, a linear equation was employed for its description, and the equation was found to be  $y = 0.129x + 140.4$ . The observed rates, the best fitting straight line, and

TABLE VIII

*The annual case rates of diphtheria per 100,000 of the population in England and Wales, 1911-1937*

Year.			Case rates per 100,000.	Year.			Case rates per 100,000.
1911	..	..	132	1925	..	..	123
1912	..	..	124	1926	..	..	131
1913	..	..	139	1927	..	..	133
1914	..	..	161	1928	..	..	155
1915	..	..	152	1929	..	..	159
1916	..	..	150	1930	..	..	184
1917	..	..	128	1931	..	..	126
1918	..	..	131	1932	..	..	108
1919	..	..	150	1933	..	..	118
1920	..	..	186	1934	..	..	170
1921	..	..	176	1935	..	..	160
1922	..	..	137	1936	..	..	142
1923	..	..	105	1937	..	..	149
1924	..	..	107				

the zones demarcated by plus and minus twice the standard deviation around this best fitting line (s) are plotted in Fig. 2. When measured in terms of these limits, it will be seen that the prevalence in 1930 was not abnormal, whereas the epidemic in 1920 lay (just) outside the limits of chance. Expressed in terms of probability, an epidemic of the size of that in 1920 would occur by



chance once in twenty years. From this one might infer that the 1930 epidemic was of lesser importance than that in 1920, but the inference would be unjustified, because, in respect of the actual number of notified cases, the 1930 epidemic was slightly the larger. This exemplifies the false impression which may arise when the incidence of a childhood infection is measured in terms of the total population.

Diphtheria is mainly a disease of children, and probably 85 per cent. of the total cases occur under the age of 15 years. Accordingly, its incidence should be related to the number of children in the population. The size of this denominator has undergone appreciable changes during the last thirty years, as can be seen by comparing the percentage distribution of the population in age groups in 1901 and in 1931.

<i>Age groups.</i>	<i>1901. Per cent.</i>	<i>1931. Per cent.</i>
0-15 years .. ..	32	24
15-45 " .. ..	48	47
45 + " .. ..	20	29
	100	100

In 1901, children under age 15 formed nearly one third of the whole population; in 1931, their proportion had declined to less than one quarter. Hence, the position is that, although there are relatively fewer children in the population, the number of notified cases of diphtheria has increased, but not very greatly. This indicates that, unless the incidence throughout the country amongst adults has become greater, the case rates from diphtheria amongst children must have increased. It is not, of course, suggested that any such increment would necessarily indicate a real increase in diphtheria. More attention is now being paid to this disease than hitherto, and general practitioners, in the interests of safety, are probably notifying increasing numbers of doubtful cases and thus securing their isolation. These initially are entered, as previously stated, in the national records as notified cases of diphtheria, but no adjustment is subsequently made when a different diagnosis has been established in hospital—in the majority of cases, because either the Medical Officer of Health is not informed of the correction or he does not use the means provided to inform the Registrar-General of it.

#### GEOGRAPHICAL DISTRIBUTION

The statistics of the geographical distribution are given in Table IX. The incidence is based on the average of the annual case rates between 1921 and 1937 inclusive, in London, in each county borough having a population exceeding 150,000 in 1931, and in the residue of each region surrounding these towns. A direct comparison of areal rates must be treated with some reserve, because the magnitude of the case rates will depend, to some extent, on the standard of notification prevailing in the different regions. In a reference to this point, the Registrar-General stated in his Annual Report for 1937 :—

" Although the local differences in the standard of notification of diphtheria may affect comparison of local rates in a given year, this factor is not likely to affect comparison of the trend of prevalence or fatality in one town with the corresponding trend during the same period in another town. There are consistent differences apparent over periods of years, both as regards prevalence and fatality, between towns of similar size and situation such as Manchester and Liverpool, or Leeds and Sheffield."

According to the table, there would seem to be four centres in which the incidence is very high—London 254 per 100,000 with a dispersion ratio of 20 per cent., Kingston-upon-Hull 278, Liverpool 253 and Salford 241. At the other end of the scale are Bolton 53, Sunderland 88, Stoke 103 and Newcastle 105 per 100,000, but in each of these three towns there was considerable annual fluctuation during the 17 years, as the associated coefficient of variability in each

TABLE IX  
*Incidence of diphtheria in different parts of England and Wales*

	Average case rates between 1921 and 1937 per 100,000 of the population.	Coefficient of Variation.	Regression coefficient as a percentage of Mean Case Rate.
<i>England and Wales</i> .. ..	140	17.02	+0.67
<i>South East—</i>			
London A.C. .. ..	254	20.47	-2.81
Croydon .. ..	135	41.73	-2.71
Portsmouth .. ..	226	43.98	-6.07
Southampton .. ..	207	42.70	+2.53
West Ham .. ..	230	26.60	-0.93
Remainder .. ..	114	32.45	-2.75
<i>North, I—</i>			
Newcastle .. ..	105	56.09	+5.56
Sunderland .. ..	88	61.49	+9.26
Remainder .. ..	123	61.58	+8.95
<i>North, II—</i>			
Kingston-upon-Hull .. ..	278	38.58	+5.21
Remainder .. ..	80	33.00	+2.02
<i>North, III—</i>			
Bradford .. ..	156	52.26	+8.05
Leeds .. ..	164	61.88	+7.67
Sheffield .. ..	181	50.14	+7.03
Remainder .. ..	118	41.01	+7.42
<i>North, IV—</i>			
Birkenhead .. ..	176	65.28	+9.92
Bolton .. ..	53	51.90	+1.85
Liverpool .. ..	253	40.51	+6.17
Manchester .. ..	145	31.44	+4.30
Salford .. ..	241	36.51	+6.22
Remainder .. ..	112	31.81	+4.89
<i>Midlands, I—</i>			
Birmingham .. ..	186	23.88	-1.46
Bristol .. ..	207	39.51	-4.96
Coventry .. ..	122	55.84	+3.29
Stoke .. ..	103	28.00	+2.18
Remainder .. ..	107	22.36	+1.27
<i>Midlands, II—</i>			
Leicester .. ..	123	40.27	+1.40
Nottingham .. ..	148	66.55	-1.44
Remainder .. ..	97	82.71	-1.25
<i>East</i> .. ..	85	48.52	-3.39
<i>South West—</i>			
Plymouth .. ..	179	34.42	+3.51
Remainder .. ..	72	43.03	-0.84
<i>Wales, I—</i>			
Cardiff .. ..	192	39.53	+4.18
Swansea .. ..	206	23.66	+1.85
Remainder .. ..	160	19.69	+0.98
<i>Wales, II</i> .. ..	142	39.08	+4.16

instance exceeded 50. The very low incidence in Bolton as compared with that in Salford is rather surprising, since both boroughs are within the same division of the Northern Region. It would seem that the difference between them must be due to defective notification in the former, because the case fatality there is always the higher. It is improbable that this higher case fatality is due to the persistence of a virulent type of the organism in Bolton, because its continued presence over a period of 17 years would be unlikely to have passed unnoticed in the medical literature.

As regards the trend of the case rates in the different areas, it would appear that in South Eastern England the annual incidence has declined, as the regression coefficient is negative in five out of the six boroughs included in this area. In the North of England and in Wales, on the other hand, the incidence has increased—particularly in Birkenhead and Sunderland, where the average annual increment in the case rates was 9.92 and 9.26 per cent., respectively.

#### ENVIRONMENT AND AGE OF ATTACK

The environmental conditions at home and in school are likely to play a big part in determining the age at which children either contract a disease or develop an active immunity, of greater or lesser degree, against it. Attendance at school involves the close association of large numbers of children, and this facilitates the spread of infection. But this spread of infection presupposes a non-immune population, and the existence of such a population depends, in respect of its freedom from exposure to the causal organism, upon the domestic environment of the child during its pre-school life.

Accordingly, it seemed of interest to study the incidence of the disease in two different types of environment, as represented by the two groups of London boroughs, I and IV, the constitution of which has been described on p. 15. The case rates per 1,000 in the two social groups at ages 0-5, 5-10 and 10-15 years, for four quinquennial periods 1901-5, 1909-13, 1919-23, 1929-33 and for the year 1938, are shown in Table X. At the pre-school age, the case rate is always higher in social group IV than in group I, the excess during the period under review ranging from 31 to 85 per cent. In fact, the highest incidence at any age in this social category occurs amongst children aged 0-5 years. On the other hand, in residential districts, which are represented by Group I, the incidence is highest amongst children between the ages of 5 and 10 years. During 1901-5 their case rate was slightly higher than that for children of similar age in Group IV, and in the period 1909-13 it was much greater, the respective values being 6.50 and 4.24 per 1,000. There was a reversal in 1919-23, as the rate in the lower social group was the larger, the comparable

TABLE X

*Average annual case rates per 1,000 from diphtheria amongst children in two groups of London Boroughs*

	1901-5.	1909-13.	1919-23.	1929-33.	1938.
<i>Age 0-5 years—</i>					
Group I .. ..	5.34 100	4.58 100	7.98 100	7.94 100	7.62 100
Group IV .. ..	7.88 148	5.99 131	13.78 172	14.72 185	12.88 169
<i>Age 5-10 years—</i>					
Group I .. ..	6.12 100	6.50 100	11.12 100	10.09 100	8.91 100
Group IV .. ..	5.92 97	4.24 65	12.38 111	12.97 129	12.52 141
<i>Age 10-15 years—</i>					
Group I .. ..	2.22 100	2.50 100	4.89 100	3.42 100	2.72 100
Group IV .. ..	2.29 103	1.59 64	5.67 116	4.64 136	4.20 154

values being 12·38 and 11·12 per 1,000. In the subsequent periods the incidence in Group IV was progressively greater than in Group I. The excess, which was 11 per cent. in 1919-23 and 29 per cent. in 1929-33, reached 41 per cent. in 1938. In the years 1920 and 1930 the disease was very prevalent in London, and it may be that during epidemics children living in the overcrowded boroughs experience higher attack rates than do children living in residential areas. But this is not an adequate explanation of the statistical record in 1938, because the case rate amongst children aged 5-10 in Group IV was 41 per cent. greater than that in Group I, yet the disease was not abnormally prevalent that year. The only adequate hypothesis would seem to be that, as a consequence of the biological and sociological changes which have operated more fully amongst the lower than amongst the higher social classes, relatively more of the children in Group IV now have a lessened chance of acquiring immunity in their pre-school life.

## SURVIVORSHIP

The influence of environment on the incidence of diphtheria can be demonstrated in another—and probably more appealing—fashion by the answer to the question:—If 10,000 children are born and live in two distinct health environments, how many of each group will contract diphtheria before reaching certain specific ages? Using the notification rate (imperfect though it is) at an individual age as a measure of the probability that a child of that precise age will contract diphtheria before it attains its next birthday, it is possible, by the ordinary life table methods, to deduce the number of those who will and will not be attacked. The appropriate calculations were made from the data for Group I and Group IV of the London boroughs, and the results for the period 1909-13 and 1929-33 were:—

Age.	1909-13				1929-33			
	Groups.							
	I		IV		I		IV	
0	A	B	A	B	A	B	A	B
5	10,000	227	10,000	299	10,000	396	10,000	712
10	9,773	312	9,701	203	9,604	482	9,288	596
15	9,461	119	9,498	74	9,122	158	8,692	200
	9,342		9,424		8,964		8,492	

*A* represents number "Not attacked."  
*B* represents number "Attacked."

It will be seen that during 1909-13 there were more survivors at age 5 in Group I than in Group IV, the numbers being 9,773 and 9,701, respectively. During school life, the former were the more heavily attacked, with the result that out of 10,000 births in Group I, 658 would be subsequently notified as cases of diphtheria before they attained the age of 15 years, as compared with 576 in Group IV. According to the experience in 1929-33 (in which the number of survivors in either group would be necessarily reduced as a result of the epidemic in 1930), the position would be reversed during school life, there being more notifications in Group IV than in Group I. In other words, in the earlier period, 1909-13, Group I would contain a relatively greater number of susceptible children at school age than Group IV, because in the latter, as a consequence of the large size of family, etc., the child population would have a better opportunity of acquiring previous immunity by sub-clinical attack. The



figures in both time periods illustrate clearly the age differentiation in attack. In Group I the modal age in both periods is located in the age group 5-10 years, when 312 and 482 notifications would be expected to occur, whereas in Group IV the main concentration would be in pre-school life.

Bearing directly on this question of environment and the incidence of the disease is the history of "evacuated" and "native" children in reception areas during the present war. When evacuation was contemplated, there was much concern as to the epidemiological consequences of mixing town and country children in the reception areas. The experience resembled, to a certain degree, the classic work by Topley and Greenwood on experimental epidemiology with mice, but it differed inasmuch as these investigators did not introduce infective migrants to a herd of non-immunes, as was likely to have happened when town children were brought to the country and mixed with the local population. The consequences which ensued from this intermingling of town and country children were indicated by Stocks (1941) in his illuminating study of the statistics. His conclusion was that "the influx of children drawn from these towns to the reception areas, with consequent increase in their population at ages under 15 by about 30 per cent., was followed by an immediate rise of diphtheria incidence amounting to 60 or 70 per cent. as measured by notifications, but the rate in the whole population of children in these areas declined again within six months to its original level."

#### AGE INCIDENCE

Although we have no national statistics on the age incidence of infectious disease, it is possible to get local information. Many Medical Officers of Health, particularly those in the large county boroughs, publish in their annual reports the ages in notified cases occurring within their areas. Figures for 1936-7 in respect of London and Manchester, and for 1940 in Halifax (Nova Scotia), are given in Table XI. In the two English cities, the largest number of diphtheria notifications is at the age group 5-10 years, which in London contains 40.0 per cent. of the total cases and in Manchester 44.0 per cent. The distributions in the two towns are dissimilar, because, when the appropriate test was made, the value of  $P$  was less than .0000001 which means that not once in a million trials would the observed differences between the two distributions have arisen by chance. The percentage of cases at pre-school age differs considerably in the two cities. In Manchester, the proportion was only 21.8 per cent. of the total, and this is not a unique experience in that city, referable only to the period 1936-7; it was also characteristic of the years 1934 and 1935. It might be thought that the difference at this age period between London and Manchester was ascribable to differences in the age constitution of the respective populations, but this is not so. According to the census of 1931, the number of children in the age group 0-5 years in London was 6.76 per cent. of the total

TABLE XI

*Age incidence of cases of diphtheria in certain cities*

			<i>London</i> (1936-1937).	<i>Manchester</i> (1936-1937).	<i>Halifax</i> (Nova Scotia) 1940.
0	..	..	32.2	21.8	13.9
5	..	..	40.0	44.0	19.6
10	..	..	12.1	20.0	13.1
15	..	..	9.0	10.2	31.1
25	..	..	5.8	3.3	17.5
45+	..	..	0.9	0.7	4.8
			100.0 (14,840)*	100.0 (2,599)	100.0 (588)

\* Total number of cases.

population, whereas in Manchester the proportion was 7.52 per cent. On the basis of the age distribution of the population, other factors being equal, one would expect a relatively higher incidence amongst pre-school children in Manchester than in London. It may well be that in London there is a greater readiness to consult the family doctor and that, as a result, fewer cases are missed.

The figures for Halifax (Nova Scotia) are quoted as illustrative of an abnormal age incidence. In that city an epidemic of the *gravis* type started in September, 1940, and unlike the case of other Canadian cities, little artificial immunisation had been done prior to the outbreak.

An account of the epidemic was given by Morton (1941), who was appointed Health Commissioner in October, 1940. There were 588 civil cases and 203 in the Forces. The age distribution of the former, which is recorded above, is entirely different from that for the English cities, as 53.4 per cent. of the cases occurred amongst adults aged 15 years and upwards. This age differentiation was stressed by Morton as follows:—

"How then can we explain such a high number in the older population? I grant that the population of the city in the age-group has increased by reason of the influx from the country areas due to war conditions, but in turn to some extent our male population has decreased slightly owing to men being in the Forces. These facts alone possibly do not prove that diphtheria morbidity is changing, but are definite indications which must be further studied. In comparing the incidence rate in this epidemic with the incidence rate with other centres, and with the rate over the past few years here in Halifax, one finds a definite trend towards the higher age-group.

Schick tests also, in my opinion, bear out to some extent this fact. Diphtheria susceptibility measured by the Schick test was found in adult groups in different sections of both Halifax and the province to run as high as 80 per cent. Schick-test-positive, or in other words there was little difference between the susceptibility rate amongst children and adults."

#### INCIDENCE AMONGST ADULTS

So far nothing has been said about the incidence of diphtheria amongst adults, but the recent history of the disease in that section of the population has attracted some attention. It has been noted by some observers that there is a tendency for the case rate of adults to increase. In the epidemic in Halifax (Nova Scotia) the greater proportion of cases occurred after age 15 years, and Wright (1941) found in Liverpool that the case rate in the age period 15 + in 1940 was statistically greater than that in 1937, the Difference/S.E. being 5.6.

Several investigators have estimated the immunity indices of different samples of the population. For the present purpose, two examples will be cited—(1) Wilson and his colleagues (1942) Schick-tested 4,901 boys and girls in residential and non-residential schools in Oxfordshire, Buckinghamshire, Berkshire and Wiltshire during the period November 1939 to November 1941; (2) during 1932–3 children in L.C.C. residential and approved schools, children's homes and in the training ship "Exmouth" were Schick-tested.

The results in both experiments for some of the age groups common to the two series of data were:—

(1)			(2)		
Age	Number	Percentage Negative	Age	Number	Percentage Negative
1 and 2 years ..	21	0	2-3 years ..	275	27.7
3-4 .. ..	28	7.1	3-4 .. ..	451	39.5
5-6 .. ..	159	14.5	5-6 .. ..	421	54.2
10-11 .. ..	456	15.8	10-11 ..	677	75.7
15+ .. ..	486	51.6	15+ .. ..	324	73.8

The percentages of Schick negatives in (1) and (2) differ very considerably, the proportions in (2) being much the greater. At age 5-6 in (1) the incidence is 14.5 per cent., whereas in (2) it is 54.2 per cent. At age 15 +, the respective values are 51.6 per cent. and 73.8 per cent., and the former value is really too

large because the authors wrote: "At age 14 years and later the rates (the percentage positive) showed a rapid fall, but undue importance should not be attached to these figures, since they were heavily weighted by the inclusion of a training colony in which a considerable proportion of the boys have been previously immunised and in which diphtheria had been occurring during recent months."

It would be true to assert that in the general adult population in large towns the percentage who are Schick negative is very high, probably as high as 70 per cent. Yet instances are cited in which about 60 per cent. of certain social groups of adults, particularly medical students and laboratory workers, when tested, gave a positive reaction. The explanation offered for their susceptibility is that they had not previously been freely exposed to infection. In view of this possibility, it was of interest to compare the morbidity experience of adults in the two contrasted social groups (I and IV) in London. The case rates in each, per 100,000 of the population, are given according to age in Table XII, for the periods 1909-13, 1919-23 and 1929-33. It will be seen that in the first period the rates were higher in Group I than in Group IV; at age 15-25 the comparable values are 74 and 55 per 100,000. In the next age period they are 42 and 26, respectively. In 1919-23, the rates, when compared with those in the previous quinquennium, are very much larger, due mainly to the 1920 epidemic, and, with the exception of age 15 to 25, the incidence was slightly greater in Group I. During 1929-33, at each age period the notification rates in Group IV exceed those in Group I. According to existing theories, the incidence amongst adults in Group I should always be higher than in Group IV, because the adults in the former group are presumed to have been less exposed to risk and therefore not to have developed immunity through sub-clinical infection. The case rates during the period 1909-13 justify this assumption. It may be asked, then, what factors were responsible for the transition, first noticeable at age 15-25 during the period 1919-23? The view here advanced is that it is a further manifestation of the biological consequences which have resulted from the decline in the birth rate and the improvement in social conditions. The people in social Group IV who were aged 15-25 during the period 1919-23 were born at a time when the birth rate was beginning to decline fairly rapidly. The results of this would be that each child came into contact with fewer children than would have been the case if it had been born earlier; it thus passed through childhood with a reduced chance of acquiring immunity and reached adult life with a fair degree of susceptibility. The older people (25+) in the same social group, having been born earlier and also being members of larger families, lived under environmental conditions in which they were most likely to obtain immunity in childhood, either by clinical or sub-clinical attack. This is the explanation offered here as to why the greater case rate in Group IV than in Group I during 1919-23 was at first localised in the age group 15-25, and why it did not affect the older people. By 1929-33, a sufficient period had elapsed for the higher ages to be involved, and here, for the first time, we find that the proportion of susceptible adults at each age is greater in overcrowded boroughs than in residential districts.

TABLE XII

*Average annual notification rate of diphtheria per 100,000 of the population, amongst adult persons in two groups (I) and (IV) of London Boroughs*

Age Group.	Periods.					
	1909-1913.		1919-1923.		1929-1933.	
	(I)	(IV)	(I)	(IV)	(I)	(IV)
15-25 years .. ..	74	55	161	162	107	127
25-35 years .. ..	42	26	74	72	51	69
35+ years .. ..	11	5	21	18	13	18

## IMMUNISATION

Bacteriologists recognise three ways in which individual immunity to diphtheria may be secured. The immunity may be :

(1) natural or inborn, (2) acquired by clinical or sub-clinical attack or by exposure to repeated small doses of diphtheria organisms which, however, do not give rise to any manifest infection, (3) artificially produced by the injection of immunising agents.

Whilst it is impossible to differentiate the respective quotas contributed by (1) and (2) to the "protected" populations, their joint contribution can be ascertained by Schick testing the child population.

In this connexion, a sample inquiry made in Baltimore, and described by Frost (1941), is of interest. During the course of three years, 1922-25, 9,000 children, constituting, it is claimed, a fair sample of the population residing in six wards of the city, were Schick tested. It was found that 68 per cent. of the children were Schick negative (*i.e.*, immune) by age 15, and, as far as could be ascertained by careful inquiry, only 12 per cent. had a history of having suffered from clinical diphtheria. Frost points out that only 21.5 per cent. were Schick negative on reaching the age of 5 years. This indicates that the children had been immunised at an average rate of 4.3 per cent. per annum in the first 5 years of life ; at a rate of 6.1 per cent. per annum between 5 and 10 years, and at a rate of 3.2 per cent. per annum between 10 and 15 years. He contrasts these rates with the official morbidity rate for clinical diphtheria between 1920-3. His tabulated results were :—

Age groups.	Mean annual rates per 10,000		
	Immunisations as indicated by Schick tests. (a)	Clinical diphtheria. (b)	Ratio a : b
Under 5 years .. .. .	430	96	4.5 : 1
5 to 10 years .. .. .	610	86	7.1 : 1
10 to 15 years .. .. .	320	21	15.2 : 1
0 to 15 years. . . . .	453	69	6.6 : 1

In Column 4, in which the mean annual immunisation rate as indicated by Schick tests is expressed as a ratio of the clinical diphtheria case rate, it will be seen that there is a progressive increase in the size of this ratio : under age 5 the value was 4.5 to 1, and at age 10-15 it reached 15.2 to 1. From this trend, Frost concluded that, "with increasing age, children suffering infection with the diphtheria bacillus are progressively likely to develop immunity rather than the disease".

With regard to artificial immunisation, it is a simple task to ascertain the number receiving the immunising agents, but the health authorities do not claim complete protection for the entire inoculated population—probably a 90 per cent. success. In this connexion, it may be of interest to recapitulate opinions expressed by some previous investigators. Forbes (1927), in reference to the Schick test and to toxin-antitoxin immunisation, maintained that there was very little doubt that their systematic adoption would result in a great yearly saving of child life. Woods (1928) thought that some reservation should be attached to this statement, because she wrote :—

"The statistical evidence in support of this statement is perhaps ambiguous. To give one instance, the New York experience does not give any support to the contention that immunisation has had any effect upon either the death rate or case rate, if one fits a straight line to the trend of mortality previous to 1918 and extrapolates for the years of treatment. The mortality falls very near the extended trend line."

When Woods made her test, however, relatively little immunisation had been done, and hence the data were insufficient to provide a final answer. This she fully recognised, because she wrote :—

“ It is not intended here to dispute the efficacy of these prophylactic measures, only to suggest that some caution is necessary in accepting statements for which the statistical evidence at present is inadequate.”

She used a linear equation for the prediction and, according to the circumstances existing at the time, it was as justifiable to adopt this curve as any other. But when it is employed to forecast a “ long term policy ” it is theoretically unsound, because the extrapolate from a straight line will ultimately be a case rate of zero. In practice, this is never likely to occur, because bacteriologists have never promised complete protection to an immunised population, and hence there will always be a number of cases of diphtheria.

## NEW YORK

### Mortality

The experience in New York City has received very wide attention, and has been offered as a complete confirmation of the efficacy of preventive inoculation against diphtheria. It will not be amiss to discuss here the statistical picture of the disease in that city, and also in the City of Toronto. Starting with New York, the death rate under age 10 years is shown in Fig. 3, in which are also indicated the time periods when the various progressive health measures were adopted. (The diagram is, in the main, a reproduction of one which has previously appeared in the Statistical Bulletin of the Metropolitan Insurance Company of New York, but it now includes the most recent information available.)

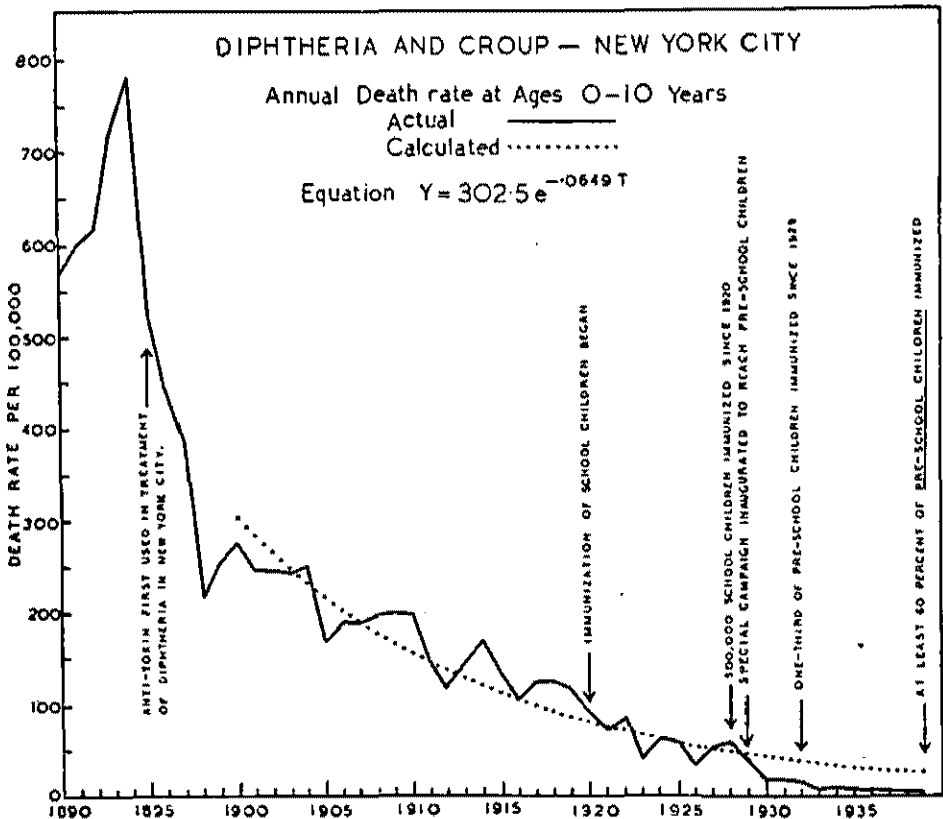


FIG 3.

Before the introduction of antitoxin for the treatment of diphtheria, the mortality from this disease amongst children aged 0-10 years in New York City was very high. In 1894 the rate was 785 per 100,000; it was less than 300 in 1900, and in 1920 it fell below 100. In that year the active immunisation of school children began, and it is claimed that, by 1928, 500,000 had been immunised. This number, although seemingly large, represents less than 50 per cent. of the school child population. The authorities next concentrated their attention on the pre-school children, and in 1940 it was estimated that no less than 60 per cent. of them were "protected". By this time, it will be noted that the disease had been virtually eliminated as a cause of death, the mortality being 1.1 per 100,000—a striking contrast to the rate fifty years earlier.

Judging from the trend of the annual death rates, it would appear that the curve which would most accurately describe their course is asymptotic in character. Hence, in any attempt to appraise by means of this curve the value of active immunisation as a factor in the reduction of mortality, the actual death rates in the post-immunisation period must be compared with the extrapolatory values deduced from a curve of this type. Accordingly, the death rates at age 0-10 years between 1900 and 1928 were fitted to an exponential curve, and the subsequent mortality was predicted. In this connexion, it is essential to measure the exactitude with which the curve described the trend of the mortality between 1900 and 1928, the pre-immunisation period, because the ensuing argument depends on the closeness of the theoretical curve to the actual experience. The standard deviation of the annual rates of mortality between 1900 and 1928 was 69.4; the root mean square error obtained by using the exponential curve was 13.4, which means that the dispersion was reduced by nearly 80 per cent. From this fact, one can reasonably conclude that the curve gives an adequate representation of the trend of the mortality between 1900 and 1928. It cannot be denied that the mortality at age 0-10 was declining steadily (attributable presumably, in part, to antitoxin treatment) before active immunisation was started, but it is equally true, as will be seen from the extrapolated values, that the subsequent decrease was greater than could have been anticipated. The values for the years 1931, 1935 and 1940 were:—

			<i>Actual death rates per 100,000.</i>	<i>Calculated or expected death rates.</i>
1931	..	..	15.2	40.4
1935	..	..	4.9	31.2
1940	..	..	0.8	24.0

The results suggest that active immunisation played an important part in the reduction of the mortality from diphtheria, because (1) the differences between the actual and predicted rates are obviously significant, and (2) this divergence becomes more accentuated with time, as would be expected when progressively increasing numbers of the population were being "protected" annually.

Many papers in American scientific journals have been devoted to this problem of determining the extent to which immunisation has affected the morbidity and mortality. The consensus of opinion is that nothing completely satisfactory was accomplished until a definite proportion of the pre-school children was inoculated. Godfrey, Director of the State Department of Health, New York State, was of the opinion that the attainment of a high degree of herd immunity among children 5-9 and 10-14, as secured by the injection of three doses of toxin-antitoxin in 50 per cent. or more of the numbers of these groups, produced no definite effect on diphtheria incidence in the community, but that when the immunisation of 30 per cent. or more of the children

under 5 years was superimposed, there was an immediate decline in the current prevalence of the disease. Lee (1931) stated that—

"In the very large American cities up to 1929 there was no reduction of diphtheria mortality such that it could be attributed to the results of diphtheria immunization. In spite of the large numbers immunized by Park and his associates in New York City, the rates in that city showed no significant depression."

Lee stressed the importance of protecting the pre-school child and quoted the experience in Philadelphia to support his view. In that city, it was estimated that 40 per cent. of children under 5, 80–85 per cent. of those between 5 and 9 years, and 60–65 per cent. of those between 10 and 14 years had been immunised, with the result that the mortality rates for 1930 "are below the expected rates for 1930 at distances far beyond the range of pure chance and therefore attributable in large degree to diphtheria immunisation."

The primary importance of concentrating on the pre-school child is obvious when one studies the age distribution of the diphtheria deaths in the large American cities. In fact, it seems rather surprising that the health authorities in America should ever have hoped seriously to reduce the existing diphtheria mortality without first immunising the pre-school children. Lee quotes the statistics of the percentage distribution of the deaths according to age from diphtheria in large American cities between 1916 and 1930, when approximately 119,000 children died from the disease. His values, in contrast with those for the county boroughs of England and Wales for the same period, and in Toronto during 1925–30, are:—

	0-5	5-15	0-15	All ages.
U.S.A. . . . .	69.5	27.0	96.5	100
County Boroughs, England and Wales	51.8	44.2	96.0	100
Toronto . . . . .	43.9	50.9	94.8	100

These data have one common feature, inasmuch as over 90 per cent. of the total deaths from diphtheria occurred amongst children under the age of 15, but, within the component age groups, there exists a wide differentiation. In American cities, 70 per cent. of the total deaths occur at age 0–5, whereas in England and Wales the proportion is only slightly greater than a half—51.8 per cent.—and in Toronto it is less than a half—43.9 per cent. This divergence between the age distribution of the deaths in Britain and America does not accrue from a corresponding difference in age distribution of the respective populations. The percentages of the total population at ages 0–5 and 5–15, according to the 1930 census, were:—

	0-5	5-15	All ages.
U.S.A. Cities . . . . .	9.6	17.6	100
County Boroughs, England and Wales . . . . .	8.9	19.1	100

It will be seen that the disparity is slight at pre-school age. It is thus apparent that the total death rate from diphtheria in American cities is determined largely by the contribution made by the children aged 0–5 years. Hence, to effect a reduction in total incidence, it must be necessary to control the prevalence at the pre-school age. In New York City, it will be remembered, it was claimed that in 1940, 60 per cent. of children under age 5 were immunised. It would seem that the fruition of this policy is revealed by the comparison between the expected and actual rates of mortality in that year.

Expected death rate = 24.0 per 100,000

Actual death rate = 0.8 per 100,000

#### NEW YORK AND TORONTO

##### *Morbidity*

A sound criticism can be raised against using mortality figures to justify the efficacy of active immunisation against diphtheria, because mortality can be, and has been, reduced by the administration of antitoxin in the treatment of the disease. Hence, active immunisation is not the sole determinant in the

control of the death rate. For this reason, a discussion referable to the morbidity, rather than to the mortality, is basically the more valid. We have previously seen that a simple exponential curve graduated the trend of mortality with a high degree of accuracy. The case rates, however, oscillate more than the death rates, and, for that reason, it was thought that a different type of curve might be required to describe the trend of the morbidity. Various tests of other methods were made, but it was finally decided to use the exponential type in which the index, at first, contained a single power of  $T$ , the time, and, later, higher powers of  $T$ . The resultant equations were:—

*New York, 1900-1928.*

(A) .. ..  $Y = 459e^{-.03983T}$   
 (B) .. ..  $Y = 415e^{-.01732T} - .000798T^2$   
 (C) .. ..  $Y = 378e^{-.02686T} - .0048214T^2 + .000096T^3$

*Toronto, 1900-1931.*

(A) .. ..  $Y = 491e^{-.03932T}$   
 (B) .. ..  $Y = 478e^{-.03353T} - .000193T^2$   
 (C) .. ..  $Y = 522e^{-.072304T} + .003092T^2 - .000073T^3$

When the root mean square difference between the actual and expected case rates for the years 1900 to 1928 was obtained, it was found that there was practically no advantage to be gained by using the curves of the higher orders for prediction, in preference to the simple exponential; the values of the root mean square difference were:—

				<i>New York</i>	<i>Toronto</i>
A	..	..	..	46	86
B	:	..	..	41	86
C	..	..	..	40	85

Equation A described the trend of the morbidity between 1900 and 1928 in New York, and between 1900 and 1931 in Toronto, with a satisfactory degree of accuracy, particularly as regards New York. In that city the original variability of the annual case rates as measured by the standard deviation was 96; by the use of the equation, this variation has been reduced by 52 per cent. In Toronto the corresponding reduction was somewhat less—33 per cent. Accordingly, equation A was used to forecast the morbidity in both cities in the post-immunisation period.

The rates at different periods of time (Figs. 4 and 5) were as follows:—

	Year.	<i>New York</i>		<i>Toronto</i>	
		<i>Case rates per 100,000.</i> <i>Actual.</i>	<i>Calculated.</i>	<i>Case rates per 100,000.</i> <i>Actual.</i>	<i>Calculated.</i>
Pre-immunisation	1915	279	253	161	272
	1916	241	243	271	261
	1917	220	234	305	252
Moderate immunisation	1920	250	207	440	224
	1921	263	199	347	215
	1922	179	192	209	207
	1928	160	151	101	163
Intensive immunisation	1926	116	163	197	176
	1927	204	157	215	170
	1928	160	151	101	163
	1930	54	139	164	151
	1931	56	134	85	145
	1932	50	129	27	140
	1938	9	101	4	110
	1939	7	97	1	106
	1940	5	94	0	102



## EPIDEMIOLOGY OF DIPHTHERIA

The difference between the actual and expected rates in the post-immunisation period, chiefly since 1928 in New York and since 1931 in Toronto, is so large that, having regard to the size of the populations on which the rates are based, there is little doubt that it is significant. Furthermore, the difference increases with time, and this is what one would expect to occur. The critics may retort that this correlation with time is not necessarily conclusive evidence that the

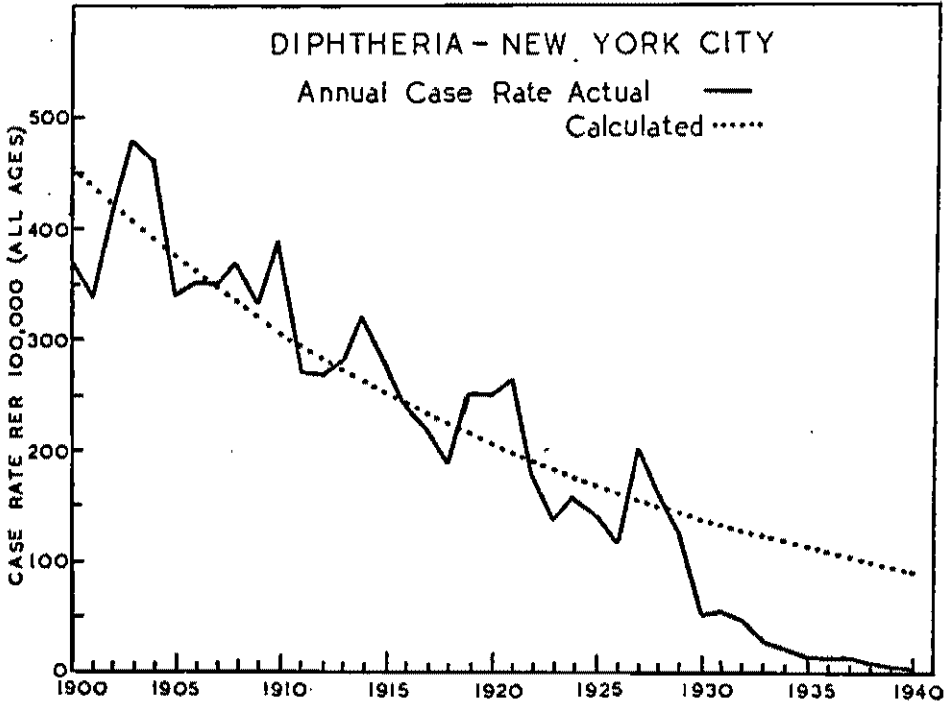


FIG. 4.

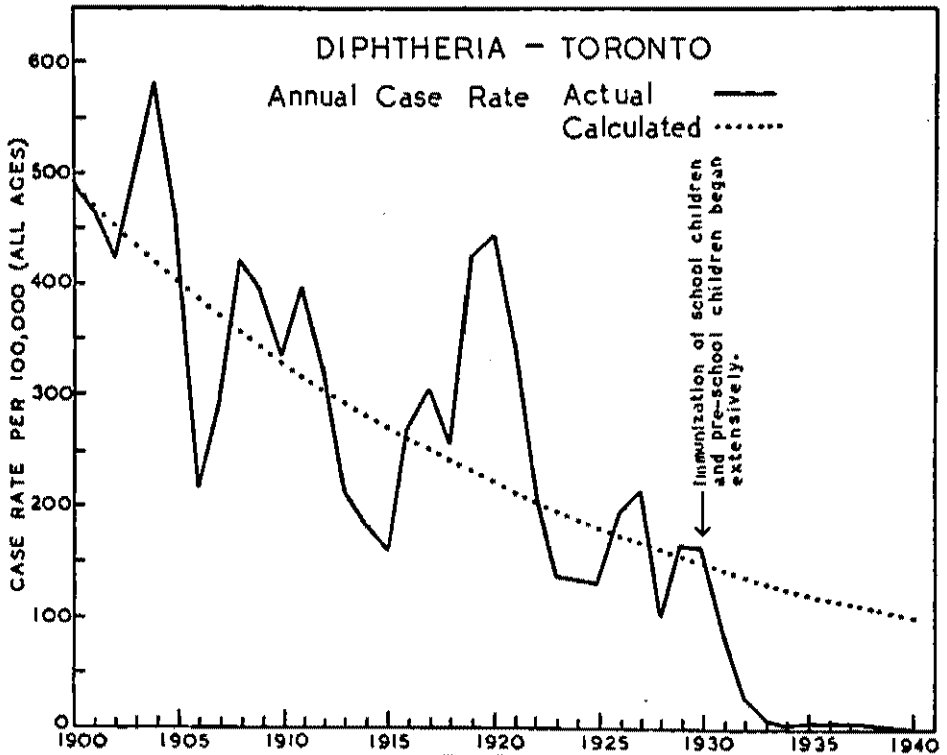


FIG. 5.

lowered incidence after 1931 was attributable to immunisation. They can truly say that the decline started long before artificial immunisation was introduced, and that it may probably have been due, in the first instance, to improved environmental and social conditions which reduced the chances of the children being infected. If further hygienic improvements were made about 1931, they might then declare that the lowered incidence of morbidity would accrue as a direct consequence. But it would seem a rather remarkable coincidence that such hygienic improvements should occur simultaneously in two cities as far apart as New York and Toronto. Furthermore, it has been previously indicated that in Halifax (Nova Scotia), where little immunisation had been done prior to 1941, there was a severe epidemic of the *gravis* type of diphtheria in September, 1940. The more likely explanation of the decline in incidence in New York and Toronto is that it is due to the policy of immunising the pre-school children and the school children in both cities.

PERIODICITY

The results of the American experience have been accepted with reserve by some observers and criticised by others. It has been stated that, since the disease has a long periodic swing, and as artificial immunisation was started during a periodic peak, the subsequent low incidence is attributable to the mass immunisation which arose as a result of the epidemic. This line of argument is particularly characteristic of German writers, and Friedberger (1931) has pointed out that in Germany no success on the scale claimed in America was obtained as a result of the immunisation policy. The immediate answer to such criticism is that prior to the introduction of artificial immunisation there had been epidemics of diphtheria in both New York and Toronto, but on no occasion did the inter-epidemic incidence fall to as low a level as that which has occurred since 1930, nor had the curve of incidence ever continued for as long a period as 10 years without an epidemic rise.

The discussion does, however, involve the question: what is the periodicity of the disease in New York and Toronto? Before the presence or absence of a periodic peak can be determined, it is first necessary to eliminate the secular trend of the morbidity. Accordingly, exponential curves were fitted to the statistics for New York and Toronto, and the differences between the observed and calculated case rates were next obtained. The periodicity indicated by these residual values was then determined. The figures were written out in rows of 3, 4, 5, etc., up to 8 years, and summed. By a Fourier Analysis the proportional amplitude of each period was evaluated, the equation being

$$y = a_0 + a_1 \sin x + b_1 \cos x$$

and the proportional amplitude

$$= \sqrt{\frac{a_1^2 + b_1^2}{a_0}} \times 100$$

Admittedly, the data are rather scanty for testing the periodicity, and the amplitudes must necessarily have an appreciable chance error. Nevertheless, they will serve as rough pointers. The size of the proportional amplitude for each period was:—

Period in years.				New York.	Toronto.	
3	..	..	..	155	..	106
4	..	..	..	88	..	399
5	..	..	..	152	..	150
6	..	..	..	368	..	216
7	..	..	..	44	..	156
8	..	..	..	179	..	208

For the New York data, the available evidence suggests the existence of a six years cycle, the proportional amplitude being the greatest with this period. The last epidemic in New York occurred in 1927, when the case rate was 204 per 100,000. The immunisation of school children began, as we know, in 1920, but it would seem that sufficient children had not been protected to prevent the 1927 epidemic. Between that year and 1940 there should, according to past experience of a six years cycle, have been two epidemics ; but none has occurred. Their absence is a further strong indication of the value of the intensive immunisation policy carried out since 1930, especially amongst children of pre-school age.

In Toronto, the analysis suggests that the cycle has been one of four years (proportional amplitude 399). It is certainly true that between 1893 and 1920 this cycle was much more persistent than any other. In the peak year, 1920, the case rate was as high as 440 per 100,000 of the population at all ages. According to prediction, there should have been an epidemic in 1928, but it appeared a year earlier, the incidence in 1927 being 215 per 100,000, as compared with 101 in 1928. Since 1927 there has been no epidemic, although three epidemics with a four years cycle should have occurred between 1928 and 1940. In two of those expected crest years, namely 1936 and 1940, the case rates were actually 7 and 0 per 100,000. In the light of this experience, it may be claimed with very substantial evidence that by artificially immunising the child population, the Public Health Authorities in Toronto have practically eliminated diphtheria from their city.

#### CARRIERS

The role of the carrier in the spread of diphtheria infection is a problem of primary importance. The endemicity of the disease is possibly due to this cause : it is certainly true that the persistence of infection within a particular community may be caused by the presence of one or more chronic carriers. There is no accurate record of the number of such persons in the general population, but it has been estimated that from 2 to 5 per cent. of school children in London are carriers of virulent diphtheria organisms, and in barracks the incidence may be as high as 15 per cent. Some authorities have suggested that the carrier rate will be substantially increased through the inoculation of increasing numbers of the child population, and that, in consequence, the non-protected Schick positives will be exposed to greater risk of contracting the disease.

It is not possible to explain why a person, healthy in all other respects, should be a carrier, or why some clinical cases of diphtheria are probably never completely cured of the carrier state. Some interesting work bearing on this problem has, however, been done, in discovering the rate at which the population of carriers (from clinical cases) decreases during convalescence. Hartley and Martin (1919-20) carried out an investigation on 457 adults with faucial diphtheria. They found that there was a logarithmic relationship between the number of patients who still carried the organism and the days after onset of the disease. The equation connecting the two variables was :—

$$\log y = 2.6002 - 0.0218x$$

in which the coefficient of  $x$  (0.0218) " means that approximately 5 per cent. of those remaining each day become free from the bacilli within 24 hours ".

An investigation on similar lines, but on a much larger scale, was made by Thomson, Mann and Marriner (1928-29). The scheme of their inquiry was that " all cases of diphtheria were cultured on admission (three negative cultures on successive days being required before the patient was considered a negative case) and were cultured once during the second week, and once in the third week. After that, cultures were taken twice weekly, patients being required to

be negative for a period of three weeks before discharge. Cases in which the bacilli were found after the twelfth week from the commencement of the illness were classed as carriers". The data obtained by these authors were published in the M.A.B. Annual Report. So as to make a more effective comparison with the results obtained by Hartley and Martin, the statistics of Thomson, Mann and Marriner are now presented in a different form, but the revised presentation does not invalidate the conclusion previously reached by these authors. Their data relating to the period from August 1st, 1924, to December, 1928, cover 3,208 cases, of which 242 or 7.5 per cent. persisted as carriers. Excluding the carriers, there were 1,726 cases "classified as positive in throat only" and 1,240 positive in nose or nose and throat. The distribution of these cases in age groups, and the percentage of this population carrying in successive weeks of convalescence up to the 12th week, are recorded in Table XIII. It will be seen that there was a distinct difference between the proportions of patients who at specified periods still carried the organism in the nose or nose and throat, as compared with the throat cases only. Amongst the latter, only 20.6 per cent. of the original clinical cases were still infectious at the 5th week, as compared with 48.3 per cent. for the former. In other words, when the throat only is involved, the rate of elimination is quicker and age is a factor of little consequence. On the other hand, there is some evidence that in the nose or nose and throat group there is a correlation with age, as the younger children react more slowly. For example, within or about the sixth week of convalescence approximately 39 per cent. of the children under age 10 years are still infected, whereas for those aged 15+ years the proportion is 19.8 per cent.

On the whole, it would seem from the trend of the figures in the table that the numbers who are still "casualties" at successive weeks decline in geometric progression, as was found by Hartley and Martin (1920) in their study. The curve when expressed in the exponential form is—

$$N_2 = N_1 e^{-K(t_2 - t_1)}$$

where  $N_1$  and  $N_2$  represent the numbers still carrying at times  $t_1$  and  $t_2$ , and where  $K$  represents the rate of recovery in the interval  $t_2 - t_1$ . The distributions within each age group were fitted to this type of curve, and the calculated values of  $K$  were:—

Age Group.	Nose, Nose and Throat.		Throat only.	
	$K$ .	Percentage recovering daily.	$K$ .	Percentage recovering daily.
0-5 .. ..	-.01973	4.45	-.03106	6.90
5-10 .. ..	-.02176	4.89	-.02975	6.62
10-15 .. ..	-.02271	5.10	-.02914	6.49
15+ .. ..	-.02526	5.65	-.03269	7.25
All ages .. ..	-.02103	4.73	-.03162	7.02

It will be seen that the values of the constant are smaller when the nose or nose and throat are involved than when the throat only is infected. Translating the values of  $K$  for each age group into terms of the percentage of patients who became free from the bacilli within twenty-four hours, it was found that when the bacillus was localised in the throat, on the average, 7.02 per cent. of the patients carrying the organism ceased to do so on the following day; in the data of Hartley and Martin the average for faucial diphtheria was 5 per cent. The age of the patient does not tend to accelerate the rate of recovery. Amongst children aged 0-5 years, the percentage daily recovery is 6.90; it is less than this value for children aged 5-15, and only slightly greater for adults. On the other hand, when the infection is more widespread—as when both the nose and throat are involved—the proportion of daily recoveries is somewhat smaller (on the average 4.73 per cent.), but there is some evidence of a slight

TABLE XIII  
*Percentage of clinical cases carrying the bacillus during weeks of convalescence*

<i>Week of Convalescence.</i>	<i>Nose or Nose and Throat.</i>					<i>Throat.</i>				
	<i>Age Groups.</i>					<i>Age Groups.</i>				
	<i>0-5</i>	<i>5-10</i>	<i>10-15</i>	<i>15+</i>	<i>All Ages.</i>	<i>0-5</i>	<i>5-10</i>	<i>10-15</i>	<i>15+</i>	<i>All Ages.</i>
0 .. ..	100 (428)	100 (522)	100 (169)	100 (121)	100 (1240)	100 (471)	100 (684)	100 (313)	100 (258)	100 (1726)
2 .. ..	81.1	75.9	72.2	63.6	76.0	51.4	48.5	52.4	49.2	50.1
3 .. ..	67.5	64.2	59.8	47.9	63.1	38.2	36.0	32.3	32.2	35.3
4 .. ..	52.6	50.6	39.6	35.5	48.3	22.7	21.6	18.5	16.7	20.6
5 .. ..	39.5	38.3	28.4	19.8	35.6	12.5	14.3	11.2	10.1	12.6
6 .. ..	28.7	25.7	21.3	9.9	24.6	6.6	9.6	6.4	5.8	7.6
7 .. ..	19.6	18.6	11.2	6.6	16.8	4.2	6.7	3.8	3.1	5.0
8 .. ..	15.2	13.2	8.9	5.8	12.6	2.3	3.5	2.2	1.2	2.6
9 .. ..	9.6	9.4	7.1	2.5	8.5	1.3	2.0	1.3	1.2	1.6
10 .. ..	5.8	5.0	3.6	2.5	4.8	—	1.0	1.0	0.8	0.7
11 .. ..	3.0	1.9	1.8	1.7	2.3	—	0.4	1.0	0.4	0.4

(From data collected by Thomson, Mann and Marriner, and published in Annual Report of the Metropolitan Asylums Board, 1928-29).

correlation with age. For the youngest children the rate is 4.45 per cent. ; there is a progressive increase in its size, and at ages 15 years and upwards the percentage of daily recoveries is 5.65.

IMMUNISATION IN COUNTY BOROUGHES OF ENGLAND

In view of the amount of immunisation done in New York City and Toronto—in the latter city nearly all school children and approximately 65 per cent. of pre-school children are protected—it is cogent to inquire into the position regarding diphtheria immunisation in the larger towns in this country. It is true to say that, with a few exceptions, little immunisation was done here prior to 1940. In that and the subsequent year, the Chief Medical Officer of the Ministry of Health persistently stressed the necessity for protecting children against the disease, and, by his encouragement, local authorities were stirred to action in publicising the advantages of immunisation. The result has been satisfactory, in that, apart from those immunised privately by family physicians, 2,300,000 children under the age of 15 years had been immunised at clinics and welfare centres up to December 1941, but much still remains to be accomplished.\*

By the courtesy of the Chief Medical Officer, I was given access to the returns for the County boroughs for the two years 1940 and 1941. Dr. P. Stocks, of the General Register Office, kindly supplied particulars which enabled the population of children aged 0-15 years at the beginning of 1940 to be approximately estimated for each county borough. From this information the immunisation rate per 1,000 of the child population in each town was calculated, and the frequency distribution of these values is given in Table XIV. It should be

TABLE XIV

*Frequency distribution of the number of children immunised per 1,000 of the population aged 0-15 during the two years 1940 and 1941 in County Boroughs of England*

<i>Rate per 1,000.</i>	<i>Frequency.</i>	
0	2	Hastings and Kingston-upon-Hull.
50	8	
100	16	
150	23	
200	10	
250	4	
300	6	
350	5	
400	—	
450	4	Exeter, Nottingham, Oxford, Middlesbrough.
500-550	1	Lincoln.
Total	79	

remembered that these figures represent the minimum for each town, because they do not include children immunised by the family physician during the period under consideration. The average rate of immunisation was 205 per 1,000, although the rate in some boroughs was exceptionally low. In Hastings and Kingston-upon-Hull the rate was less than 50 per 1,000, and included in the 50-100 group is Liverpool, with an index of 57. At the other end of the scale, the position was more satisfactory ; in Exeter, Nottingham, Oxford and Middlesbrough at least 450 out of every 1,000 of the children were immunised, and in Lincoln the ratio exceeded 500 per 1,000.

\* Figures obtained since this Report was written show that the proportion immunised up to the end of 1942 was 46.5 per cent. (see Preface p. 4).

If immunisation will prevent or appreciably reduce the incidence of diphtheria, it is of primary importance that it should be carried out in towns or districts which contribute a large quota to the total morbidity and mortality. Until this is done, there can be little substance in the claim that a fairly high proportion of the children at risk have been inoculated. It is not of much avail to immunise practically all the children in rural and small urban districts and leave relatively untouched the children in the large towns, who are subject to much greater intensity and duration of exposure. In this respect, it is of interest to study the statistical experience in county boroughs which had a population of 150,000 or more persons. The salient facts are given in Table XV. So as to avoid chance fluctuations, and thereby to obtain a reliable picture of morbidity, the case rate was based on the average of the annual rates between 1921 and 1937, and the death rate on the data for the years 1926-36, both variables being set in apposition to the immunisation indices for 1940-1. The statistics in two cities stand out conspicuously. Liverpool and Kingston-upon-Hull experienced the highest morbidity and mortality, yet the immunisation rate in these boroughs during the period 1940-1941 was almost negligible, in the one 57 and in the other 47 per 1,000.

TABLE XV

*Immunisation, morbidity and mortality in towns with a population exceeding 150,000 at the 1931 census*

	<i>Immunisation rate per 1,000 of population 0-15 during 1940 and 1941.</i>	<i>Average of the Annual Case rates between 1921-37 per 100,000 of population. All Ages.</i>	<i>Average Annual Death rate, 1926-36 per 100,000 of population. 0-15 Years.</i>
London A.C. .. .. .	149	254	37.1
Croydon .. .. .	240	135	32.7
Portsmouth .. .. .	177	226	44.5
Southampton .. .. .	75	207	37.2
West Ham .. .. .	79	230	36.9
Newcastle .. .. .	306	105	19.7
Sunderland .. .. .	108	88	22.2
Kingston-upon-Hull .. .. .	47	278	72.7
Bradford .. .. .	392	156	46.5
Leeds .. .. .	164	164	51.9
Sheffield .. .. .	108	181	28.3
Birkenhead .. .. .	164	176	33.3
Bolton .. .. .	346	53	17.9
Liverpool .. .. .	57	253	60.5
Manchester .. .. .	191	145	41.9
Salford .. .. .	164	241	45.5
Birmingham .. .. .	189	186	26.5
Bristol .. .. .	137	207	29.5
Coventry .. .. .	108	122	45.7
Stoke .. .. .	163	103	14.6
Leicester .. .. .	162	123	24.1
Nottingham .. .. .	466	148	44.6
Plymouth .. .. .	255	179	49.5

The general picture can be more succinctly presented by a correlation coefficient. It was found that when morbidity (1) and mortality (2) were each correlated with immunisation (3) the coefficients were:—

$$r_{13} = -.495 \pm .182$$

$$r_{23} = -.199 \pm .205$$

In both instances, as one would expect, the sign is negative, meaning that in those towns in which the incidence either of morbidity or mortality has been and still is high, a relatively small amount of inoculation has been carried out. This is truer for morbidity than for mortality, because the correlation with mortality is small and insignificant, whereas that for morbidity is fairly large and statistically significant.

### TYPES OF DISEASE

As is now well known, there are three types of diphtheria bacilli, *mitis*, *intermedius* and *gravis*, which were first distinguished by McLeod and his colleagues, Anderson, Happold and Thomson, at Leeds in 1931. It is generally said that *gravis* and *intermedius* types are found in the severe forms of the disease and are associated with a high case fatality, whereas infections caused by the *mitis* type are usually much milder.

### LEEDS

Since the identification of the three types was made at Leeds, it is of interest to study the statistical history of the disease in that city before and after 1931, to see if there is any evidence which would suggest the occurrence of the various types of infection. The annual case rate and fatality rates between 1921 and 1937 are given in Table XVI. Apart from 1921, when the

TABLE XVI

*Notified cases of diphtheria per 100,000 of population, and deaths per 1,000 notified cases, during the period 1921-37 in Leeds*

	Case Rate per 100,000 population.	Case Fatality per 1,000 Notified Cases.		Case Rate per 100,000 population.	Case Fatality per 1,000 Notified Cases.
1921 .. ..	143	57	1930 .. ..	207	54
1922 .. ..	100	62	1931 .. ..	203	88
1923 .. ..	78	87	1932 .. ..	183	54
1924 .. ..	61	92	1933 .. ..	216	83
1925 .. ..	89	93	1934 .. ..	455	70
1926 .. ..	79	69	1935 .. ..	278	44
1927 .. ..	91	64	1936 .. ..	166	43
1928 .. ..	133	33	1937 .. ..	191	47
1929 .. ..	110	47			

notification rate was 143 per 100,000, the incidence of diphtheria up to 1927 was of a fairly low order—about 80 per 100,000—but in two of the intervening years—1924 and 1925, the fatality rates—9·2 and 9·3 per cent., respectively—were the highest ever experienced in Leeds during the seventeen years under examination. There was a minor epidemic in 1928—a case rate of 133 per 100,000—but the outbreak was of a mild character, as the associated case fatality was only 3·3 per cent. The first definite epidemic occurred in 1930—1,014 cases—representing a case rate of 207 per 100,000, but the severity of attack, although greater than in the immediately preceding years, was no sharper than in 1921. The high prevalence persisted in 1931 when, for the first time, it was associated with heavy fatality, the rate being 8·8 per cent. In the next year the fatality declined relatively more than the morbidity: both subsequently increased, and in 1934 the city had its largest epidemic—2,212 cases with 155 deaths. Since then the morbidity has fallen, but never below the endemic level of 1921-30, whereas the fatality has declined



relatively much more, the average rate being of the order of 4·6 per cent. According to the latest available information, kindly supplied by the Medical Officer of Health, the case fatality in 1940 was 3·7 per cent. It would thus seem that the morbidity and mortality in Leeds prior to 1931 afford little or no clue to the existence of those factors which are responsible for the presence of either the *intermedius* or *gravis* type. All that can be said is that between 1921 and 1930 the case rate was of a fairly low order and was attended by a fairly high fatality. The history of the disease subsequent to 1931—particularly the large decline in fatality—would seemingly indicate that the type has changed again and that *mitis* has replaced *gravis*.

#### OTHER CITIES

It was impracticable to obtain type data for several geographical areas of the country until the Emergency Public Health Laboratory Service came into existence. The laboratories of this Service began typing in 1940, but it was not until 1941 that the machinery was fully in motion. Prior to this, however, and, apart from the investigations made in Leeds, some very interesting work had been published on the records in a few cities—particularly by the late H. D. Wright (1941) for Liverpool and by H. A. Wright (1940) for Edinburgh. The Liverpool data were the more extensive, and they were analysed in greater detail than was possible with the Edinburgh statistics. They include all cases sent to the hospitals for infectious disease in Liverpool during the four years 1937–40 (Professor H. D. Wright sent me his records for 1941 and these have now been added to his table). For Edinburgh, the statistics refer to the period 1932–9, but it is only since 1936 that they relate to complete years; Dr. H. A. Wright differentiated six types of diphtheria bacilli in that city, but for present comparative purposes her figures for types III and IV have been added together. At Southampton, Dr. Williams, M.O.H., typed the bacilli from all diphtheria cases admitted to the Isolation Hospital at Millbrook in each year from 1935 to 1940, and he has very kindly supplied all the particulars, including the age incidence—as has also Dr. W. Gunn, Medical Superintendent of the North Western Fever Hospital of the London County Council for the diphtheria patients admitted and discharged from his hospital in 1941. It is the practice in the latter hospital to type all cases on admission. The results for these four cities are given in Table XVII, and they present a very interesting picture. In this and in subsequent tables, type I represents *mitis*, type II *intermedius*, type III *gravis*. It has been justifiably said that the type incidence changes from place to place, and even from time to time within a specific locality. The present distribution is in accord with this viewpoint. In Southampton the *mitis* type has been predominant. During the six years, its proportion of the total incidence has ranged from 61 to 70 per cent. The *intermedius* type fluctuated between 17 and 26 per cent., and the *gravis* from 10 to 18 per cent. Of the 192 typed cases in the North Western Fever Hospital, London, no less than 51 per cent. had the *gravis* strain, the proportions with *mitis* and *intermedius* strains being 22 per cent. and 27 per cent. respectively. As a routine practice at this hospital only *mitis* cases are subjected to virulence test, all *gravis* and *intermedius* being regarded as virulent. Included amongst the 43 cases with the *mitis* strain were 4 which were not virulent on the intra-cutaneous test in the guinea pig. Of these 4 cases, 3 had clinical diphtheria, one being tonsillar, one nasal, one tonsillar and laryngeal; the remaining patient showed no evidence of diphtheria.

In the northern cities the prevailing type is *gravis*, but it has not always been so. In Edinburgh, from 1932 until the beginning of 1936, the *intermedius* strain occurred the most frequently, with an incidence of approximately 70 per cent.; *mitis* was next, with about 20 per cent., but both were rapidly replaced by *gravis*, which, in 1939, constituted 83 per cent. of all typed cases. The alteration which has occurred in the proportional distribution of the types in

TABLE XVII

Percentage incidence of infection with the different types of diphtheria bacillus in four county boroughs

	Edinburgh.				Southampton.				Liverpool.				London (North Western Fever Hospital).			
	Type.			Total cases.	Type.			Total cases.	Type.			Total cases.	Type.			Total cases.
	I.	II.	III.		I.	II.	III.		I.	II.	III.		I.	II.	III.	
	Percentage.				Percentage.				Percentage.				Percentage.			
Oct. 1932-Dec. 1933 ..	24.5	70.9	4.6	151	—	—	—	—	—	—	—	—	—	—	—	—
March 1934-May 1934 ..	21.0	74.0	5.0	60	—	—	—	—	—	—	—	—	—	—	—	—
Oct. 1934-April 1935 ..	22.6	71.1	6.3	159	—	—	—	—	—	—	—	—	—	—	—	—
1935 .. .. .	—	—	—	—	61.4	25.9	12.7	717	—	—	—	—	—	—	—	—
1936 .. .. .	17.4	54.4	28.1	419*	62.3	19.2	18.4	385	—	—	—	—	—	—	—	—
1937 .. .. .	11.7	31.4	56.9	538	64.1	25.9	10.0	309	41.1	24.7	34.2	2,179	—	—	—	—
1938 .. .. .	7.2	22.3	70.5	471	70.6	17.5	11.9	143	33.4	22.1	44.5	2,207	—	—	—	—
1939 .. .. .	5.9	10.8	83.3	102	67.8	17.4	14.9	121	25.7	13.7	60.6	1,593	—	—	—	—
1940 .. .. .	—	—	—	—	65.6	21.9	12.5	64	17.1	13.3	69.6	2,061	—	—	—	—
1941 .. .. .	—	—	—	—	—	—	—	—	11.1	17.9	71.1	2,805	22.4	27.1	50.5	192

I = mitis,

II = intermedius,

III = gravis.

\* September 1935 to December 1936, inclusive.

TYPES OF DISEASE

TABLE XVIII

Quarterly incidence of infection with the different types of diphtheria bacillus in Edinburgh, Liverpool and London

Year.	Quarter.	Edinburgh.				Liverpool.				London (North Western Fever Hospital).					
		I.	II.	III.	Total cases.	I.	II.	III.	Total cases.	I.	II.	III.	Total cases.		
		Percentage.					Percentage.					Percentage.			
1936 .. .. .	2 } 3 } 4 }	26.2	58.9	15.0	107	—	—	—	—	—	—	—	—		
		11.0	60.8	28.2	209	—	—	—	—	—	—	—	—		
1937 .. .. .	1	17.6	36.3	46.1	102	40.6	25.0	34.4	613	—	—	—	—		
	2	10.1	37.2	52.7	129	44.2	18.4	37.4	489	—	—	—	—		
	3	9.0	31.0	60.0	100	39.7	27.5	32.8	408	—	—	—	—		
	4	11.1	25.6	63.3	207	40.2	27.4	32.4	669	—	—	—	—		
1938 .. .. .	1	5.5	18.1	76.4	127	41.6	22.1	36.3	746	—	—	—	—		
	2	5.3	30.1	64.7	133	29.6	25.5	44.9	436	—	—	—	—		
	3	7.5	9.0	83.6	67	29.7	21.6	48.7	468	—	—	—	—		
	4	10.4	25.0	64.6	144	28.5	19.9	51.6	557	—	—	—	—		
1939 .. .. .	1	2.4	17.1	80.5	41	24.6	14.4	61.0	529	—	—	—	—		
	2	8.2	6.6	85.2	61	28.3	14.0	57.7	357	—	—	—	—		
	3	—	—	—	—	24.4	16.2	59.4	291	—	—	—	—		
	4	—	—	—	—	26.0	10.8	63.2	416	—	—	—	—		
1940 .. .. .	1	—	—	—	—	15.4	13.3	71.3	293	—	—	—	—		
	2	—	—	—	—	20.2	13.0	66.8	386	—	—	—	—		
	3	—	—	—	—	19.5	12.0	68.5	435	—	—	—	—		
	4	—	—	—	—	15.3	14.1	70.6	945	—	—	—	—		
1941 .. .. .	1	—	—	—	—	12.0	16.2	71.8	755	21.1	23.9	54.9	71		
	2	—	—	—	—	10.9	13.3	75.8	562	23.4	37.5	39.1	64		
	3	—	—	—	—	8.7	17.9	73.4	624	28.6	16.7	54.8	42		
	4	—	—	—	—	12.2	22.5	65.3	857	6.7	26.7	66.7	15		

I = mitis.      II = intermedius.      III = gravis.

Edinburgh is so great that no statistical test is necessary to measure its significance. In Liverpool, the transference has been mainly from *mitis* to *gravis*. In 1937 *mitis* formed 41·1 per cent. of the total incidence, as compared with 24·7 per cent. for *intermedius* and 34·2 per cent. for *gravis*, but in 1941 the proportions were 11·1 per cent. *mitis*, 17·9 per cent. *intermedius* and 71·1 per cent. *gravis*. The magnitude of the change in Liverpool, although not numerically as great as in Edinburgh, was nevertheless significant, because when the appropriate test was made it was found that

$$\begin{aligned} \chi^2 &= 1099\cdot3 \\ n' &= 9 \\ P &= < \cdot0000001 \end{aligned}$$

A value of *P* of the size indicated means that the alterations which have been observed in the incidence of the types would not arise once in a million times by pure chance.

QUARTERLY INCIDENCE OF TYPES

*Edinburgh and Liverpool*

To ascertain the extent to which the change was related to the season of the year, the investigators at these centres tabulated the proportional incidence of each type within each quarter of the year. The results from 1936 onwards are given in Table XVIII, in which the incidence in London is also included. The figures now given for Edinburgh differ slightly from those originally published by H. A. Wright, because the data for her type VI, also for atypical organisms and for cases due to two or more types, have been excluded.

It will be seen that the transition occurred earlier in Edinburgh than in Liverpool. In Edinburgh in the last quarter of 1936 the proportion of *gravis* was 28·2 per cent. of the total infections in that period, but in the first quarter of 1937 it was 46·1 per cent. and, at the end of that year, it reached 63·3 per cent. In 1938—apart from the high incidence of 83·6 per cent. in the third quarter, which is, however, based on a relatively small number of cases—the experience was more stabilised; nevertheless, there was an appreciable rise in the first quarter of 1939, as compared with the last quarter of 1938. In Liverpool the change did not start until 1938, and it was progressive in each quarter of that year. In the first quarter the incidence of *gravis* was 36·3 per cent., and it increased to 51·6 per cent. in the last quarter. Although the proportion in subsequent quarters was higher, the variation within any year was not as great as in 1938.

The relative importance of seasonal and secular change in the type of the disease can be satisfactorily resolved by the analysis of variance. Since the Liverpool data are the more numerous, the test was applied to the incidence of *gravis* infection in that city, with the following result:—

Source of Variation	Sums of Squares.	Degrees of Freedom.	Mean Variance.
Between years .. .. .	247531·8	4	61883·
Within a year .. .. .	166700·0	15	11113·
	414231·8	19	
	Z = 0·8586	5 per cent. = 0·56	

As this value of *Z* is greater than the 5 per cent. level, one may conclude that the result is nearly significant.

Between quarters .. .. .	68890·6	3	22963·533
Within quarters .. .. .	345341·2	16	21583·825

In this instance the value of  $Z$  is 0.0310 and, as the 5 per cent. level is 0.59, the result is of no statistical importance. Hence one can conclude that the secular trend is more important than the seasonal.

Although the quarterly incidence of the types in London fluctuates appreciably, it must be remembered that the proportional values are based on rather small numbers of cases—the total in one quarter being only 15. With the exception of the statistically higher incidence of *intermedius* in the second quarter than in the third, the deviations lie within the limits of chance variation.

## AGE INCIDENCE OF TYPES

*Liverpool and Southampton*

Although we possess fairly accurate knowledge of the age incidence of diphtheria—obtained largely from the notifications and admissions to fever hospitals in our large cities—until Wright reported his Liverpool experience we had very few data wherewith to measure the correlation between age and type of the disease. So as to give increased reliability to the age incidence as indicated by Wright, his data for 1937 and 1938—when, on the average, *mitis* infection was the most frequent—have been combined into one series; likewise those for 1939 and 1940, when *gravis* infection was the most prevalent. These combinations will make it possible immediately to trace the effect, if any, which the change of type produced on the age distribution of the cases. The percentage distribution of the cases according to age is given in Table XIX, in which are also included the results for Southampton (where no change in type has occurred) for the two triennial periods 1935–7 and 1938–40, and those for London (North Western Fever Hospital) for 1941.

TABLE XIX

*Percentage distribution of each type of infection according to age*

	Age Groups.				
	0-5	5-	10-	15+	All Ages.
<i>Mitis.</i>					
<i>Southampton</i> —					
1935-7 .. ..	24	31	16	29	100 (878)
1938-40 .. ..	28	26	16	30	100 (225)
<i>Liverpool</i> —					
1937-8 .. ..	32	45	14	9	100 (1610)
1939-40 .. ..	35	37	15	14	100 (754)
<i>London*</i> —					
1941 .. .. .	23	28	12	38	100 (43)
<i>Intermedius.</i>					
<i>Southampton</i> —					
1935-7 .. ..	20	43	17	21	100 (340)
1938-40 .. ..	12	40	10	38	100 (60)
<i>Liverpool</i> —					
1935-8 .. ..	26	46	19	9	100 (1014)
1939-40 .. ..	28	41	18	13	100 (487)
<i>London</i> —					
1941 .. .. .	31	31	4	35	100 (52)
<i>Gravis.</i>					
<i>Southampton</i> —					
1935-7 .. ..	28	47	16	9	100 (193)
1938-40 .. ..	5	63	9	23	100 (43)
<i>Liverpool</i> —					
1935-8 .. ..	26	47	16	11	100 (1705)
1939-40 .. ..	30	40	16	14	100 (2377)
<i>London</i> —					
1941 .. .. .	27	26	17	27	100 (97)

\* North Western Fever Hospital.

It will be seen that, with the exception of the values at ages 0-5 and 15 + years for the period 1938-40 in Southampton, the highest incidence in that city and in Liverpool for each of the three types occurred in the age group 5-10, where the proportion of *gravis* cases was higher than the corresponding rates for either *mitis* or *intermedius*. In Southampton, the index was 47 per cent. in 1935-7 and 63 per cent. in 1938-40; in Liverpool, it was 47 per cent. in 1937-8 and 40 per cent. in 1939-40. In London, on the other hand, the maximum incidence for *mitis* (38 per cent.) and for *intermedius* (35 per cent.) was in the age group 15 +. The high incidence of these two types at this age is also observable in Southampton. The values in both cities are higher than those amongst pre-school children and far exceed the recorded percentage amongst adults in Liverpool.

*Changes in Age Incidence*

It was next of interest to discover whether any alteration in the age incidence accompanied the change of type of the disease in Liverpool, and if any movement was observable in Southampton, where the type was static. Accordingly, for both towns the age distribution of each type in the earlier time period was compared with that in the later, and the observed changes tested for significance.

	Liverpool.			Southampton.		
	$\chi^2$	n'	P	$\chi^2$	n'	P
Gravis .. .. .	20.82	4	.0001	16.80	4	.0002
Intermedius .. .	6.40	4	.0970	9.87	4	.0200
Mitis .. .. .	19.45	4	.0002	2.86	4	.4164

From the value of *P* for *gravis*, we infer that the age incidence of this type in Liverpool has changed significantly between the two periods—in fact, the alteration which has occurred would arise by chance only about once in ten thousand times. There has been little change in the age incidence of *intermedius* (at least, it is not a statistical one except at age 15+) and, although the amount of *mitis* has decreased considerably, the age constitution of the cases has altered significantly. There is now a tendency for both *mitis* and *gravis* in Liverpool to concentrate relatively more on pre-school children and adults. The increases in the respective proportions of the total cases of these two types which have occurred at these ages are statistically significant, and they counterbalance the statistical decrease which has occurred amongst children of immediate school age.

In Southampton the age distribution of *mitis* during 1938-40 has not differed from that in 1935-37. There has been a major change both for *intermedius* and *gravis*, the most noticeable feature being the large increase in the percentage incidence of each type amongst adults.

It has previously been shown that in Liverpool there is a relatively high morbidity and mortality from diphtheria, and that a relatively insignificant proportion of the children have been artificially immunised. The undesirability of this position can be demonstrated more clearly in a comparison with the incidence of the disease in Toronto over a similar period of years.

If Liverpool children under age 15 years experienced the same average annual rate of morbidity as did children of the same age in the Canadian city during the decennium 1931-40, the expected number of notified cases of diphtheria would be approximately 1,242. The actual number of notified cases of diphtheria in Liverpool in this period was 22,080, which is eighteen times in excess of expectation. Some of the difference between the morbidity rates in the two cities is possibly due to difference between their respective environmental conditions. In Liverpool, there may, and probably does, exist a greater concatenation of adverse factors which facilitate the spread of

infection. But, even when allowance is made for these, the Liverpool experience still remains extremely unsatisfactory, and, particularly so, since in that city there is a preponderance of the most serious type of the infection.

### EMERGENCY PUBLIC HEALTH LABORATORIES

#### *Type Incidence*

In view of the contrast afforded by Southampton, on the one hand, where no change of type was observed during the period 1935-40, and by the Northern cities of Liverpool and Edinburgh on the other, where there has been a transference to *gravis*, it was very important to find out the prevailing type of the disease in the country generally.

At the beginning of the war the Emergency Public Health Service set up constituent laboratories in different regional areas and typing was begun in 1940, but it was not until 1941 that typing was universally carried out. Subsequently, some existing laboratories were associated with the Service. The cases which are typed at these laboratories are chiefly from the local population of the district in which the laboratory is located, but in some instances the laboratory acts for parts of the county, the whole county and even for contiguous counties. It must be made clear, also, that in some instances—for example, in Exeter and Winchester—although the Emergency Public Health Laboratory is located in the city, it does not carry out the bacteriological work for that city. Hence the information about the type incidence experienced by these laboratories is derived not from the city but from districts outside the city and often at some considerable distance from it.

At the Associated Laboratories, at Leeds and Liverpool, the typed statistics comprise practically all cases of diphtheria occurring in each city. By the courtesy of Professor G. S. Wilson, Scientific Director of the Service, I was given access to the data accumulated at twenty laboratory centres. The number of cases of each type of infection, and the proportion of the total incidence that each type represented during 1941 in the specific area, are given in Table XX, from which doubtful, untyped cases and carriers have been excluded. The total number of typed cases was 8,457, of which 1,838 or 21·7 per cent. were *mitis*, 2,739 or 32·4 per cent. *intermedius* and 3,880 or 45·9 per cent. *gravis* infections. Apart from Cardiff, Bristol, Winchester and Carmarthen, in which *intermedius* was the most prevalent—the proportions being 51·8 per cent., 77·1 per cent., 45·6 per cent. and 82·0 per cent., respectively—it would seem that *gravis* infection is the most frequent type found in this country. It represented 40 per cent. and upwards of the cases examined by 14 of the 20 laboratory centres; while, in the Wakefield area, although the number of cases examined was small, the proportion of *gravis* was as high as 84·2 per cent. No clear picture can be made of any peculiar or characteristic distribution of any one of the types of diphtheria in the different regions of the country as a whole. There is, however, a suggestion that the proportion of *gravis* infections is higher in the North than elsewhere.

#### *Fatality*

It is generally recognised that the fatality accompanying each of the three types of diphtheria is different. The rate for *mitis* is the lowest, but there is some interchangeability in the sequence of the other two. In Liverpool, H. D. Wright found that the fatality for *intermedius* was higher than that for *gravis*, the rate for each during the period 1937-40 being 10·67 and 6·30 per cent., respectively. In Edinburgh, according to figures given by H. A. Wright, *gravis* was the more serious infection, the fatality rates being 5·2 per cent. for *gravis* and 3·4 per cent. for *intermedius*. In London, the case fatality from *gravis* in 1941 was 8·2 per cent., as compared with 5·8 per cent. from *intermedius*.

TABLE XX  
Type incidence during 1941 at Emergency Public Health Laboratory Centres

Location of Laboratory Centre.	Mitis.		Intermedius.		Gravis.		Total.		Deaths per 100 notifications in 1941.
	Cases.	Percentage of Total.	Cases.	Percentage of Total.	Cases.	Percentage of Total.	Cases.		
Aberystwyth .. .. .	11	14.9	19	25.7	44	59.5	74	100.0	—
Bristol* .. .. .	50	14.7	262	77.1	28	8.2	340	100.0	2.6
Cambridge .. .. .	41	23.0	53	29.8	84	47.2	178	100.0	5.6
Cardiff .. .. .	706	41.4	882	51.8	116	6.8	1,704	100.0	2.6
Carmarthen .. .. .	15	3.6	346	82.0	61	14.5	422	100.0	—
Conway .. .. .	196	22.5	235	26.9	442	50.6	873	100.0	—
Dorchester* .. .. .	5	62.5	—	—	3	37.5	8	100.0	—
Epsom .. .. .	1	11.1	1	11.1	7	77.8	9	100.0	—
Exeter .. .. .	83	27.6	94	31.2	124	41.2	301	100.0	—
Horsham .. .. .	7	18.4	9	23.7	22	57.9	38	100.0	—
Ipswich .. .. .	4	11.1	7	19.4	25	69.4	36	100.0	4.0
Leeds* .. .. .	246	33.4	113	15.3	378	51.3	737	100.0	3.8
Leicester .. .. .	39	7.8	104	20.7	359	71.5	502	100.0	4.1
Liverpool* .. .. .	310	11.1	502	17.9	1,993	71.1	2,805	100.0	7.1
Oxford .. .. .	64	31.2	36	17.6	105	51.2	205	100.0	7.7
Pocklington, E.R. .. .. .	19	26.8	23	32.4	29	40.8	71	100.0	—
Reading* .. .. .	8	100.0	—	—	—	—	8	100.0	4.9
Stafford* .. .. .	11	18.6	19	32.2	29	49.2	59	100.0	—
Wakefield*, W.R. .. .. .	—	—	3	15.8	16	84.2	19	100.0	5.2
Winchester .. .. .	22	32.4	31	45.6	15	22.1	68	100.0	—
<b>Total .. .. .</b>	<b>1,838</b>	<b>21.7</b>	<b>2,739</b>	<b>32.4</b>	<b>3,880</b>	<b>45.9</b>	<b>8,457</b>	<b>100.0</b>	

\* Associated Laboratories.



TABLE XXI

*Type incidence during 1940 and 1941 in certain Emergency Public Health Laboratory Centres*

<i>Location of Laboratory Centre.</i>	<i>Year.</i>	<i>Mitis.</i>		<i>Intermedius.</i>		<i>Gravis.</i>		<i>Total.</i>	
Bristol* .. .. .	1940	112	14·9	625	83·3	13	1·7	750	100·0
	1941	50	14·7	262	77·1	28	8·2	340	100·0
Cambridge .. .. .	1940	20	11·6	47	27·3	105	61·0	172	100·0
	1941	41	23·0	53	29·8	84	47·2	178	100·0
Carmarthen .. .. .	1940	3	3·1	71	74·0	22	22·9	96	100·0
	1941	15	3·6	346	82·0	61	14·5	422	100·0
Conway .. .. .	1940	167	28·4	68	11·5	354	60·1	589	100·0
	1941	196	22·5	235	26·9	442	50·6	873	100·0
Leeds* .. .. .	1940	274	52·1	46	8·8	206	39·2	526	100·0
	1941	246	33·4	113	15·3	378	51·3	737	100·0
Liverpool* .. .. .	1940	352	17·1	274	13·3	1,434	69·6	2,061	100·0
	1941	310	11·1	502	17·9	1,993	71·1	2,805	100·0
Oxford .. .. .	1940	14	17·7	22	27·8	43	54·4	79	100·0
	1941	64	31·2	36	17·6	105	51·2	205	100·0

\* Associated Laboratories.

In the hope of throwing further light on the relationship between fatality and type incidence, the deaths from diphtheria as given in the Reports of the Registrar-General for 1941 were related to the number of notified cases during the same period. The calculated fatality rates are stated in the last column of Table XX. This method of assessing the fatality can be only an approximation, because all the deaths did not necessarily occur amongst these particular notifications. Furthermore, regional imperfection in the standard of notification will obviously affect the size of the contrasted rates of fatality. In Liverpool, where 71·1 per cent. of the total infections were of the *gravis* type, the fatality was 7·1 per cent. In Oxford and in Leeds, where the proportions of *gravis* infections were almost identical (51 per cent.), the fatality differed widely, being 7·7 per cent. in the former and 3·8 per cent. in the latter.

In Bristol and Cardiff, the *intermedius* type was dominant, but in the latter town there was also a high incidence of *mitis* infections. It might therefore be expected that the fatality rate in Cardiff would be lower than that in Bristol, but the rates in both towns were identical—2·6 per cent. From the foregoing experience—admittedly a somewhat imperfect criterion—it cannot readily be stated that the prevalence of a particular type of diphtheria is reflected in the size of the current rate of fatality from the disease. The coefficient of correlation between the proportion of *gravis* infections and the fatality rate in nine laboratory centres was + 0·542, but when Fisher's test was applied, it was found that the coefficient should be 0·666 to satisfy the 0·05 level of significance.

*Comparison between Types in 1940 and in 1941*

A comparison of the type incidence found during 1940 and 1941 in seven of the largest laboratories in which typing was done in both years is shown in Table XXI. The statistics substantiate the claim that the type of the disease may change from place to place, and from time to time within a specific district. In 1940, *mitis* infection was dominant in Leeds, the proportion being 52·1 per cent. of the total incidence for that year; but in 1941 the concentration was on *gravis* infection, which increased from 39·2 per cent. to 51·3 per cent. In Bristol, where *intermedius* is the principal type, there was slightly more of it in 1940 than in 1941—83·3 per cent. as against 77·1 per cent. Although the proportion of *gravis* cases is small, there was a notable increment in 1941, the ratio, which was 1·7 per cent. in 1940, increasing to 8·2 per cent. in 1941. The statistics for Liverpool indicate clearly that *gravis* has become the chief type in that city; in 1940 it constituted 69·6 per cent. of the total incidence, and in 1941 the proportion increased to 71·1 per cent. In Cambridge, the swing has been from *gravis* to *mitis*; and, in Oxford, chiefly from *intermedius* to *mitis*. In Conway there has been a substantial decrease in the proportional incidence of *mitis* and *gravis*, and a large increase in that for *intermedius*.

Are these observed changes mere random fluctuations or do they lie outside the limits usually assigned to chance? In tests for significance the following values were found:—

	$\chi^2$	$n'$	P
Bristol ..	26·55	3	0·000001
Cambridge ..	9·77	3	0·007752
Carmarthen ..	4·14	3	0·127880
Conway ..	50·82	3	0·000000
Leeds ..	45·71	3	0·000000
Liverpool ..	48·39	3	0·000000
Oxford ..	7·29	3	0·026740

For Leeds, Bristol, Liverpool and Conway, the changes which have occurred in the relative incidence of the types during 1941 as compared with 1940 would hardly occur by chance once in a million times. In Cambridge and Oxford,

particularly in the latter, the alterations are less dramatic, but they fulfil the criterion of significance; Carmarthen is the only town in which no significant change has taken place. Hence we can safely conclude that the changes demonstrated in Table XXI represent something fundamental in the aetiology of the disease, so far as six of these seven towns are concerned.

What is the particular causal factor? It seems possible that the type change is in some way related to, or dependent on, the existing number of susceptible children in the population. In Liverpool and in Leeds, the proportions of the children under the age of 15 who were artificially immunised during 1940 and 1941 were relatively small in comparison with that in Oxford: the figures were 5·7 per cent. in Liverpool, 16·4 per cent. in Leeds, and 48·1 per cent. in Oxford. In the two northern towns the directional change of type was from *mitis* to *gravis*, whereas in Oxford the swing was from *gravis* and *intermedius* to *mitis*. It may then be true that when the proportion of protected children is low, the *gravis* type prevails, and that, when it is high, *mitis* is the dominant strain. The history of diphtheria in New York lends some support to this view. In that city, as is well known, a very high proportion of the child population has been artificially immunised and the incidence of *gravis* infection is apparently low. Seligmann (1941) wrote:—

“It is noteworthy to record that British investigators have emphasised the preponderance of so-called *mitis* strains among those collected from areas of the United States during a period of steady decrease in morbidity.”

and he found from his own investigation that

“among 191 strains of diphtheria bacilli isolated from cases and carriers during 1940, five were found which fermented starch and glycogen and resembled the *gravis* type. The remaining 175 strains failed to ferment these polysaccharides. Of these 176 strains, 96 possessed the characteristics of the *mitis* type, while 80 differed in some respect or another from either group. The latter were therefore designated as ‘indeterminate’ strains.”

## CONCLUSIONS

From this study of the epidemiology of diphtheria during the last forty years, the following points emerge:—

1. The notification rate, based on the population at all ages, increased slightly in England and Wales as a whole between 1921 and 1934, but the increase varied appreciably in the main geographical regions. The increase was greatest in the north of England, where the coefficient of regression, when expressed as a percentage of the mean case rate, is about 6 per cent. (Table II). If the notifications could be related to the part of the population in which the vast majority of the cases occur, namely the child population aged 0–15 years, the secular incidence would probably show a very much larger increase, because the proportion of children in the total population has steadily declined. There are, however, no national statistics of the ages of notified cases. Part of the observed increment, in some areas, at least, is undoubtedly due to more accurate notification. On the other hand, an important part of the increase in the notification rate is also due to the inclusion of cases which the medical practitioner notified because he suspected that they might be diphtheria, but which on further observation and investigation in the isolation hospital, were found to have a different diagnosis. This practice does not imply any lack of skill on the part of the clinician, but is evidence rather of a better understanding of the disease, since it is wiser to treat a case which may be diphtheria as serious, than to wait for the possible development of unmistakable grave symptoms. In London, for the two years 1901–2, the diagnostic error was 15 per cent.; in 1928–9 it amounted to 23 per cent.; and at the North Western Fever Hospital in 1941, to nearly 50 per cent. In Liverpool, Wright found in a series of 570 cases that the error was 33 per cent.

2. The incidence of the morbidity, like that of the mortality, amongst

children of pre-school age living in densely populated boroughs in London is always higher than amongst children of the same age in residential areas. But the case rates amongst school children and adults, which previously were the higher in social group I, are now lower in that group than in social group IV (Table X). The reason offered for this alteration is the same as that advanced to explain the age shift in the mortality—namely, that, as a consequence of the decline in the birth rate, and of improved hygienic conditions involving less overcrowding, there is now less chance of children in the lowest social grade acquiring immunity in their pre-school life, so that a higher proportion of them now enter school or adult life still susceptible to the disease.

3. A comparison (Table XIII) between two series of clinical cases, (1) in which the bacilli were localised in the throat only and (2) in which the infection involved the nose or nose and throat, reveals that the average daily rate of recovery, *i.e.*, the percentage of patients who were carriers on one day and not on the following day, was in (1) 7·02 per cent. and the age of the patient was of no importance. In (2), the proportion was 4·73 per cent. and it was correlated with age; for children in the age group 0–5 years the rate was 4·45 per cent., but for subjects aged 15 + it was 5·65 per cent.

4. There is very strong evidence that immunisation, particularly since the inclusion of the pre-school children, has reduced the morbidity and the mortality from diphtheria in New York City and in Toronto. The statistical experience of diphtheria in these cities in the post-immunisation period is significantly better than might have been expected from the trend of either the morbidity or mortality in the pre-immunisation period. According to past experience, the disease had a periodicity of six years in New York and of four years in Toronto. On this basis, there should have been epidemics in both cities between 1930 and 1940, but none has occurred; the best explanation of this absence is that the Health Authorities in both cities, by artificially immunising the school and pre-school children, have prevented the occurrence of the epidemics.

The number of children immunised in Britain before 1940 was very small, but since then fairly satisfactory progress has been made. There are, however, some county boroughs in which less than 6 per cent. of the children were immunised during the two years 1940–41 (Table XIV), and in which the numbers previously immunised were negligible. In some of these boroughs, the morbidity and mortality from diphtheria are amongst the highest in the country.

5. The prevailing type of the infection in England and Wales during 1941 was mainly *gravis* (Table XX); in 14 out of 20 Emergency Public Health Laboratories and Associated Laboratories, it was found to range from 40·8 per cent. to 84·2 per cent. of the total infections. There is some evidence that the incidence of this type of infection is higher in the northern towns than elsewhere in Britain.

6. Of the total infections at all ages, the highest proportion for each type was in the age group 5–10 years in Liverpool and in Southampton, but in London (the North Western Fever Hospital, L.C.C.) the percentage was greatest amongst subjects aged 15 years and upwards (Table XIX). There is evidence that in Liverpool during the period 1939–40, as against 1937–8, the incidence amongst pre-school children and adults was forming a greater proportion of the total incidence for each type. In Southampton there was a significant increase in the proportional incidence of *intermedius* and *gravis* infections amongst adults.

7. There is evidence that the type of diphtheria infection may change from year to year within a district (Table XXI). In six out of seven of the laboratories from which statistics are available for both years 1940 and 1941, the distribution of type incidence in 1941 was significantly different from that in 1940. It is

suggested that this change in type incidence may be related to, or dependent on, the proportion of children who are protected against the disease.

8. There is no definite statistical evidence that the *gravis* type of infection is always accompanied by a high mortality. The coefficient of correlation between the proportion of *gravis* infections and the fatality rate in nine Emergency Public Health Laboratory Service centres was + 0.542, but this value is not sufficiently large to satisfy the 0.05 level of significance.

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