STATISTICAL STUDIES IN IMMUNITY. NATURAL IMMUNITY AND THE CAPACITY FOR ACQUIRING IMMUNITY IN THE ACUTE INFECTIOUS DISEASES.

BY

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The subject-matter of this paper is a study of the relationship which exists between the natural immunity enjoyed by an individual to any disease, and the capacity which he possesses of acquiring immunity if attacked. Most of the facts discussed are moderately well known. They are furnished by the statistics of the acute infectious diseases which have accumulated since the middle of last century. These statistics are in many respects very defective for the purpose required, but they refer to very considerable numbers of cases, and thus afford a basis for the estimation of different degrees of immunity with some accuracy. The most numerous collection of statistics relates to small-pox among the vaccinated and unvaccinated. These have been dealt with in an earlier paper[1], and the results alone will be referred to here. This group of statistics unfortunately practically exhausts the whole data concerning acquired immunity. The next statistics of importance are those referring to the different outbreaks of typhus, relapsing, and enteric fever, and of a few other less common diseases. Last must be placed those regarding the diseases which chiefly affect children. These for several reasons, however, afford less definite data.

The causation of an epidemic must depend on the capacity which an organism possesses for infecting, as much as on the susceptibility of the population attacked. The theory that an epidemic comes to an end because all the susceptible persons have been attacked has been rejected by most epidemiologists. The cause of the decline must rather be sought for in the loss of virulence of the organism or of its infecting power.

[1] *Biometrika*, Vol. IV.

The term "virulence of an organism," however, is one which is not clearly defined. It seems to be applied to the condition in which a considerable degree of infecting power is associated with a capacity for producing a severe type of disease. A marked capacity for producing a severe attack of a disease may, however, be associated with a very low degree of infectivity, while the presence of great power of infectivity in an organism does not imply that the type of disease produced will be necessarily severe. Examples of these conditions occur at once to the mind of all epidemiologists, *e.g.* the recent extensive mild epidemics of small-pox in America while in Britain and France the severity was very considerable.

The statistics which are available for the study of this point are not very numerous. Deaths have been accurately recorded for a large number of years, but compulsory notification of disease has been in force only for comparatively few, so that except in a few instances the fatality of any disease can only be ascertained for short periods. The yearly numbers of cases and deaths afford valuable information. They show the long waves of disease, and though the deaths may not be quite accurately assigned to the actual cases, yet, as the duration of infectious disease in fatal cases is as a rule short in comparison with the length of the year, no error of any moment is introduced. The comparison of the amount of any infectious disease and its fatality during the same series of years also yields some information; and lastly hospital statistics which exhibit the monthly numbers of cases, with the deaths which occur among these cases truly assigned to them, afford a means of tracing the severity of epidemics from start to finish. Unfortunately such are somewhat scanty. Most returns state such facts as the weekly number of cases and the weekly number of deaths, though the latter refer largely to different cases. The effect of this is to lessen the fatality during the rise of an epidemic and to exaggerate it during the decline. Even when, as is sometimes done with scarlet fever, the deaths of the week later are taken for comparison we get only a rough approximation to the truth.

The figures contained in the illustrative tables are taken chiefly from Dr Newsholme's work on "Epidemic Diphtheria" (with additions kindly supplied by himself), from the Report of the Medical Officer of the Local Government Board, 1899–1900 (pp. 268 *et seq.*), and from the Reports of the City of Glasgow Fever Hospitals 1865–1904. The Report of the Medical Officer of the Local Government Board referred to contains tables showing the number of cases notified and the number of deaths from scarlet fever, enteric fever, and diphtheria, in seventy-six English towns for the five years 1893–1897.

TABLE A.

Number of years in which diphtheria has been epidemic classified according to prevalence of the disease and the fatality.

(*a*) NORWAY, 1867–1891.

Fatality %	Case rates per 100,000: 0—100	100—200	200—300	300—400	400—500	500—600
13—18	4	2	—	—	—	—
18—21	3	—	—	—	—	—
21—24	1	3*[1]	—	4	—	1
24—27	1	1	1	2	2	—

r = +.57

(*b*) COPENHAGEN, 1855–1894.

Fatality %	Case rates per 100,000. 0—200	200—400	400—600	600—
10—12	—	5	—	6
12—14	2	1	2	1
14—16	1	3	1	2
16—20	—	4	1	1
20—	9	1	—	—

r = −.42

As the natural histories of infectious diseases present different characteristics it will be better in arranging the evidence to discuss each disease separately. With regard in the first place to diphtheria, it is to be noted that in the towns of England where the disease is least prevalent it is most fatal. This might well be a fictitious result, depending on the likelihood that where the disease is most common the serum treatment will be more efficaciously carried out, while mild cases will be more certainly recognised. A like relation, however, is observed to hold when the numbers of cases and deaths from diphtheria occurring in Copenhagen (Table A) for the series of years 1855–1894 are examined. On the other hand, the statistics of Norway and of Hamburg show the opposite tendency, the epidemic years being associated with a definitely higher case mortality. The factors of infectivity and virulence are thus capable of existing in very different degrees of association. I am not able to trace any individual outbreak of diphtheria from beginning to end and consequently cannot make any observations as to how the fatality varies as a single epidemic proceeds from start to finish.

[1] In explanation of table for instance the 3 marked by an asterisk indicates that in three years the amount of diphtheria was between 100 and 200 per 100,000 of population, and the fatality, *i.e.* the case mortality, between 21 and 24 %.

Table B.[1]

Table showing how the fatalities of certain diseases vary during the course of epidemics.

Enteric Fever—Glasgow, 1898-1899.

Months	Cases	Deaths		Fatality %	
June, July	68	17	11	25·0	
Aug., Sept.	233	44	41	18·8	
Oct., Nov.	338	56	60	16·5	$\chi^2 = 7.05$ $P = .22$
Dec., Jan.	145	29	25	20·0	
Feb., Mar.	115	15	20	13·1	
April, May	103	13	18	12·6	
	1012	174		17·4	

Enteric Fever—Glasgow, 1899-1900.

Months	Cases	Deaths		Fatality %	
June, July	98	17	20	17·4	
Aug., Sept.	275	42	56	15·3	
Oct., Nov.	206	40	42	19·4	$\chi^2 = 4.25$
Dec., Jan.	106	21	22	19·8	
Feb., Mar.	93	18	19	19·4	
April, May	49	11	10	22·5	
	827	169		20·4	

Scarlet Fever—Glasgow, 1886-1895.

Months	Cases	Deaths	Fatality %
Jan., Feb.	2,063	147	7·1
Mar., April	1,463	106	7·4
May, June	1,591	127	8·3
July, Aug.	2,079	149	7·2
Sept., Oct.	3,820	231	6·1[2]
Nov., Dec.	2,994	218	7·3

Measles—Glasgow, 1896-1899.

Period of Epidemics		Cases	Deaths	Fatality %	
Months before	5	43	3	7·0	5·8 (months 5–2 before)
	4	99	8	8·1	
	3	162	10	6·2	
	2	315	15	4·8	
	1	522	59	11·3	10·5 (month 1 before to month 2 after)
Centre of Epidemic		743	71	9·6	
Months after	1	625	63	10·1	
	2	478	57	11·9	
	3	338	23	6·8	6·6 (months 3–6 after)
	4	229	11	4·8	
	5	83	11	13·2	
	6	64	3	4·7	

[1] These tables have not been corrected for age differences. In the case of scarlet fever and small-pox in Glasgow the correction was found to be negligible.

[2] The same low fatality in September and October is seen also in the statistics of London, *vide* Reports by Sir Shirley Murphy.

Relapsing Fever—Glasgow, 1870-2.

Months	Cases	Deaths	Fatality %
June—Aug.	161	4	2·5
Sept.—Nov.	822	11	1·4
Dec.—Feb.	1,470	34	2·3
Mar.—May	739	16	2·3
June—Aug.	496	7	1·4
Sept.—Nov.	700	16	2·3
Dec.—Feb.	313	9	2·1

Small-pox—Gloucester, 1896.

Weeks ending	Vaccinated Cases	Vaccinated Deaths	Vaccinated Fatality %	Unvaccinated Cases	Unvaccinated Deaths	Unvaccinated Fatality %
Feb. 1—22	43	6	13·9 } 8·8	75	34	45·3
,, 29—21 Mar.	243	19	7·8 }	173	78	45·6
Mar. 28—18 Apr.	440	43	9·8	221	91	41·2
Apr. 25—16 May	240	24 }	8·1	117	49	42·0
May 25—13 Jan.	106	4 }		50	22 }	40·0
Jan. 20—11 July	32	1 }	8·0	11	2 }	
July 11—	5	2 }				

Small-pox—Glasgow, 1900–1901.

Periods	Vaccinated Cases	Vaccinated Deaths		Vaccinated Fatality %	
First outburst, Apr.—Aug. 1900	195	6	15	3·06	
Second ,, Jan. 1901	405	28	32	6·9	
Third ,, Feb. 20—28	133	7	10	5·2	$\chi^2 = 20.54$
,, ,, Mar. 1—31	394	37	31	9·3	
,, ,, Apr. 1—20	99	18	8	18·3	
	1226	96		7.85	

In enteric fever (Table B) a somewhat similar relationship between size of epidemic and severity of attack holds with regard to the large towns of England, and when the statistics of Glasgow for the last forty years are considered it is found that in general the years of epidemic have been the years of lowest case mortality or fatality. When, however, a like comparison is made between the prevalence of the disease and its fatality in London exactly the opposite relationship is observed. The experience of one town for a series of years is specially valuable as the personal equation of different observers is to some extent eliminated, a consideration which makes this divergence more interesting. The course of severity of single epidemics of enteric fever can be easily traced for Glasgow. When the cases occurring in the epidemics during a series of years are gathered together according to the corresponding dates it is found in the sum that the period of greatest prevalence is the period of lowest mortality. This is not necessarily the case in any individual epidemic. In the two tabulated a minimum mortality occurs during the maximum period of prevalence, but in the first of these, the beginning, and in the second, the end was the period during which the case mortality was highest.

The behaviour of scarlet fever exhibits some points of similarity with that of enteric fever. Here again the period of maximum prevalence in the autumn is associated with a lower case mortality than that in the rest of the year. There is, however, very little indication that in the epidemic periods it is more or less severe than in the inter-epidemic periods to any marked degree. For a series of years in any one place the data are hardly comparable, as the disease has shown such marked variations in fatality in recent years, but a comparison of the mortality in the towns of England 1892–97 indicates that the disease was slightly more severe in those towns in which it was most prevalent.

Regarding measles it is more difficult to obtain satisfactory information. If epidemics do not come at regular intervals then the age incidence of the cases varies so much from epidemic to epidemic that it is impossible to compare their crude death-rates, even if the number of cases were accurately known. The course of individual epidemics has seldom been traced, and the only figures which allow of tabulation are those of the Glasgow Fever Hospitals. A consideration of the figures in which five of the last severe epidemics of measles are gathered together indicates that the middle of the epidemic has been the time of greatest fatality.

As a last example, instances of small-pox may be cited. In the Gloucester epidemic in 1895 when the vaccinated and unvaccinated cases are grouped together the onset of the epidemic was apparently more severe than its decline, yet when the two are considered separately it is seen that throughout the fatality among the unvaccinated was approximately constant, while among the vaccinated there was no great variation. The explanation of the seeming initial severity is thus to be found in the fact that the unvaccinated were comparatively much more numerous in the earlier than in the latter ages of the epidemic. In Glasgow on the other hand, in 1900–1901, the epidemic became progressively more severe from the start to finish, and towards its close was nearly six times more fatal than at its commencement.

Another instance referring to relapsing fever is given in the table but does not call for any special comment. There is no indication, for instance, that during the epidemics of relapsing fever in Glasgow, 1870–72, any period of the epidemic was characterised by any special fatality. On the other hand, in the extensive outbreaks of typhus fever in Ireland, 1817–19, the year 1818, which represented the height of the epidemic, was marked by a lower fatality than that of the years immediately preceding and following. These instances show that in general there is no constant relationship between the infective power of an organism and its capacity for producing severe disease, and that in the same epidemics, at the same places, an organism may be most lethal during any period in the epidemic. In particular it is to be noted that during the latter periods of an epidemic when it might be surmised *à priori* that the severity would decrease the reverse is frequently found to be the case.

This leads to the consideration of the subject from the point of view of the attacked organism. Immunity is commonly considered as being of two kinds, natural and acquired. While this is quite true and while both of these forms of immunity have long been known to exist it would seem that the division should not be made between natural and acquired immunity, but between natural immunity and the capacity for acquiring immunity. These constitute two quite distinct properties, and are the properties in the invaded organism corresponding to those in the attacking organism just differentiated as infectivity and virulence. For the first is evidently the power which the invaded organism possesses of protecting itself against attack, while the latter is the power, if entry be established, of overcoming the virulence of the attacking organism and re-establishing health. Whether the acquired immunity which this implies is purely temporary or permanent is of no moment as regards the presence or absence of the capacity referred to.

These two properties, like infectivity and virulence, may exist in very varying degrees; natural immunity may be very high and the capacity for acquiring immunity very low, *e.g.*, glanders in man; or the reverse may be the case, the susceptibility being extreme, and yet the fatality almost non-existent, *e.g.*, relapsing fever or chicken-pox. Both may be present in a very slight degree (given the natural conditions of infection) as in plague, or cholera. The fourth possibility, high natural immunity combined with high capacity of acquiring immunity, is not so easily illustrated. Such diseases must necessarily be of rare occurrence and low mortality, and may consequently have largely escaped notice. Pfeiffer's glandular fever of children possibly approximates most nearly to this combination.

Before passing to the description of the manner in which these different properties vary as regards their presence or absence it is necessary to define the numbers on which the comparison is based. The ratio between the number of cases and the population may be considered as the measure of the prevalence of or susceptibility to any infectious disease; for purposes of convenience this number may be multiplied by some power of ten. The natural immunity obviously bears some inverse relationship to this number, while from the point of view of the attacking organism the infectivity has evidently some direct relationship.

The ratio between the number of deaths from any disease and the number of cases among which these deaths have occurred, may likewise be considered as the measure of the severity of the disease. This number bears a direct relationship to the virulence of the organism and an inverse relationship to the capacity for acquiring immunity. It is commonly known as the death-rate from the disease, or more correctly as the case mortality, but to avoid confusion it will be referred to under the term of the "fatality" throughout this paper.

A third ratio requires also to be noted. If the number of deaths be divided by the population we obtain a number which in this paper will be referred to as the "mortality" from the disease. This may also for purposes of convenience be multiplied by some power of ten. These ratios are not independent, and if any two be known the third can immediately be calculated. For the purposes required in this paper the first two are most important, but the third as throwing light on some of the problems will be frequently referred to.

In all that is said hereafter it must be clearly understood that averages alone are dealt with. There is no clinical observer of fevers with any experience but will be able to produce any number of examples of patients who differ to a very considerable extent in the relative and absolute quantities in which they possess the different properties of immunity here discussed from the average presented by all persons of the same age. But it must be remembered that this method of bringing individual exceptions of more or less diversity from the type is no argument against the type representing a fact, divergences on either side of the average being the rule in all biological measurements.

The statistics of the continued fevers, typhus, typhoid, and relapsing fever afford good examples of the relationship which exists between the three ratios just discussed, and in association with these miliary fever or sweating sickness may also be considered. The accompanying table (Table C) gives the series of figures which are obtained when the susceptibility, fatality, and mortality ratios are calculated for each age period for epidemics of these diseases. These figures with slight and unimportant differences hold true generally for all the epidemics examined.

Table C.

Table showing susceptibility, mortality, and fatality of typical epidemics of various diseases.

Typhus Fever—Glasgow, 1865–1872.

Age periods	Susceptibility	Mortality	Fatality %
0—1 1—5	422	32	7·6
5—10	1578	21	1·3
10—15	2440	44	1·8
15—20	2060	140	6·8
20—25	1330	143	10·8
25—30 30—35	1025	179	17·5
35—40 40—45	1167	319	28·2
45—50 50—55	804	343	41·1
55—60 60—65	466	248	53·2
65—70 70—75	120	154	80·0
75—80 80—	—	—	—

Relapsing Fever—Glasgow, 1870–72.

Age periods	Susceptibility	Mortality	Fatality %
0—1 1—5	374	169	4·5
5—10	1066	38	·4
10—15	1495	21	·1
15—20	1601	62	·4
20—25	1153	79	·7
25—30 30—35	1916	207	2·3
35—40 40—45	1131	322	2·8
45—50 50—55	955	549	5·7
55—60 60—65	605	741	12·2
65—70 70—75	259	579	22·2
75—80 80—	—	—	—

ENTERIC FEVER—GLASGOW, 1895-1903.

Age periods	Susceptibility	Mortality	Fatality %
0—1, 1—5	309	22	7·1
5—10	1216	94	7·7
10—15	1321	139	10·6
15—20	991	182	18·4
20—25	1043	229	22·5
25—30, 30—35	830	221	26·6
35—40, 40—45	437	137	31·3
45—50, 50—55	148	41	27·8
55—60, 60—65	90	30	33·3
65—70, 70—75	13	13	100·0
75—80, 80—	—	—	—

MILIARY FEVER[1]—OISE, 1821.

0—1, 1—5, 5—10	113	88	7·8
10—15, 15—20	393	56	1·46
20—25, 25—30	1019	621	6·0
30—35, 35—40	1283	742	5·8
40—45, 45—50	1199	497	4·2
50—55, 55—60	989	566	5·7
60—65, 65—70	730	439	5·9
70—75, 75—80, 80—	242	180	6·7

[1] Rayer, *Suette Miliare en* 1821. Paris, 1822.

SMALL-POX UNVACCINATED[1]—SHEFFIELD, 1887–1888.

Age periods	Susceptibility		Mortality	Fatality %
0—1	54		27	50·5
1—5	332		117	33·6
5—10	577		122	21·2
10—15	682		133	19·6
15—20	626	626	173	28·6
20—25	271	333	109	39·5
25—30	73	177	24	33·3
30—35	90	94	38	42·4
35—40	59	50	26	43·5
40—45	24	27	9	37·5
45—50	26	14	15	57·1
50—55	7	7	3·5	50·1
55—60	4	4	—	—
60—65	6	2	4	66·6
65—70	—		—	—
70—75	—		—	—
75—80	—		—	—
80—	—		—	—

R = 3·534

For typhus and relapsing fever the relationship shown is almost identical. (See diagram 1 and table C.) The susceptibility is greatest at the same ages, namely, ten to twenty years, and from this period

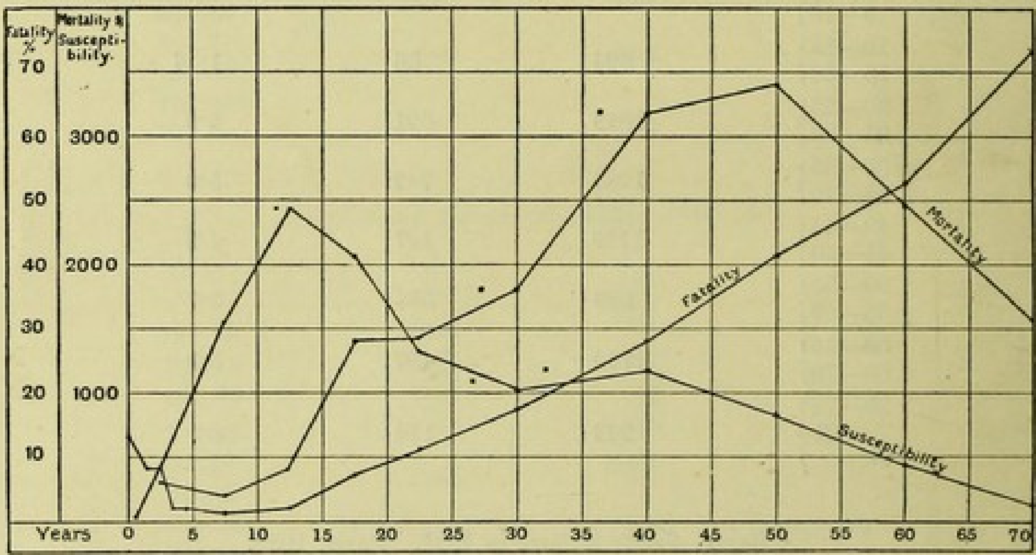

DIAGRAM I. Showing the course of the Susceptibility, Mortality, and Fatality Curves for Typhus Fever. (Glasgow, 1865–72.)

[1] These figures are based on the actual number of persons found to be unvaccinated when the census of the state of the population as regards vaccination was taken. (See Local Government Board Report by Dr Barry.)

towards youth and old age there is a gradual fall. The fatality bears an inverse relationship to this, being comparatively high among persons under five years, specially low during the period of maximum prevalence, and thence progressively increasing as the age becomes greater. The mortality in both shows a similar course, being high during the first five years, thence decreasing to a minimum about the period of greatest prevalence. It thereafter increases till it reaches a maximum during the ages of manhood or commencing old age and then declines. Enteric fever shows some differences from this. Its prevalence is much the same. The fatality, however, shows no special tendency to be high during the early years of life, and increases more or less steadily from youth to old age. The mortality curve of enteric fever has its maximum earliest of the continued fevers, this occurring between the ages of fifteen and twenty-five years. Miliary fever has its period of greatest prevalence somewhat later, namely, between thirty and forty years, and the mortality also reaches its maximum at this time. The fatality varies remarkably little, and, with the exception of the years five to twenty, showing a minimum almost discontinuous with the years before and after its constancy, is a most striking feature.

These figures have all been calculated on the actual populations living at each age at the nearest census, and are open to the objection that the lessened prevalence at higher ages not being calculated on the number of those who are actually susceptible becomes progressively more inaccurate from youth to old age, but the numbers of those who have passed through an attack of any of those diseases is always so small compared with the total population, even at high ages, that its effect may be neglected as producing a small absolute error in nowise affecting the general truth of the figures. With regard to relapsing fever the objection is of no moment, as the disease seems to confer practically no permanent immunity, so that a population fifteen years after one epidemic is practically virgin soil, while like remarks are also true with reference to miliary fever.

In the diseases of children there is some difficulty in obtaining accurate information regarding the period of maximum susceptibility. Two of them, measles and whooping-cough, are so common in early years and affect such a large percentage of the total children in the population, that by the time ten years of age is past there can be very few susceptible persons left. Thus, out of 1,245 consecutive cases of measles admitted to the hospital whose birth-place was ascertained, only 88 were above the age of ten years, and of these 88 only ten were born in Glasgow, the rest coming from country districts where measles is only present at intervals, so that the age of maximum susceptibility as shown in the statistics may probably differ largely from that which would be the case if the infection fell upon a population uniformly susceptible at all ages. The same remarks apply to whooping-cough and small-pox, and will be more fully illustrated with regard to the latter.

Scarlet fever and diphtheria, however, are so much less prevalent as to permit of the relationship of the constants being easily displayed with comparative accuracy. The average number of cases of scarlet fever in Glasgow is about 3,500 a year; of these only a tenth occur after the age of twenty years and an average of 6 % die, so that for the five yearly age period twenty to twenty-five years, there will only be living as an absolute maximum 15,000 persons who have passed through scarlet fever. This is calculated on the assumption that none have died up to this age of any other disease since their recovery from scarlet fever. Now as the population of Glasgow at this age period in 1901 was 83,319 it is evident that any error in the prevalence or mortality ratios will not exceed a fifth, nor unless the fact of having passed through scarlet fever either lengthens or diminishes subsequent chance of life will the error tend to vary much at higher ages from this amount. The census population thus affords a sufficiently accurate means of determining the prevalence and mortality ratios. The fatality ratio is quite independent of the population.

The accompanying table (Table D) gives these ratios for diphtheria and scarlet fever taken from the returns of Manchester. These are chosen as they are the only returns where the actually notified cases and the corresponding deaths are distributed in age periods. It is evident that a very marked difference from the relationships which have hitherto been observed exists here. The maximum period of susceptibility falls in youth and thereafter steadily declines, while a like relationship holds with regard to the mortality. In both these diseases the maximum of the latter occurs before the maximum of the former, thus showing a difference to what has been observed in the statistics of the continued fevers considered above. The fatality in both is specially high in infancy, and then steadily declines, and there is some indication that this reaches its minimum at the age of puberty, and that from thence to old age increases, though not to the same extent as that shown in the continued fevers. A like minimum is shown in the statistics of London and Glasgow. Children's infectious

TABLE D.

Table showing the Susceptibility, Mortality, and Fatality of Scarlet Fever and Diphtheria. Manchester, 1893—1903.

Scarlet Fever.				Diphtheria.			
Age Period	Suscepti-bility	Mortality	Fatality	Age Period	Suscepti-bility	Mortality	Fatality
0—1	205	45	21·5	0—1	89	62	71·2
1—2	671	114	17·1	1—2	271	160	58·4
2—3	1293	186	14·2	2—3	293	152	51·2
3—4	1708	195	11·6	3—4	392	161	40·9
4—5	1924	173	9·0	4—5	356	129	36·1
5—6	1971	93	4·7	5—6	325	100	33·2
6—7	1825	68	3·4	6—7	199	56	27·9
7—8	1675	53	3·1	7—8	187	44	24·6
8—9	1352	25	1·8	8—9	152	34	20·2
9—10	1172	21	1·8	9—10	124	14	11·6
10—15	682	11	1·6	10—15	74	5	7·2
15—20	214	6	2·7	15—20	46	2·1	4·4
20—25	93	3	2·3	20—25	37	1·1	2·8
25—35	44	1	2·3	25—35	29	2·5	4·4
35—45	15	·4	2·9	35—45	16	·6	3·7
45—55	7	·2	3·0	45—55	9	·4	4·8
55—65	3	—	—	55—65	5	—	—

diseases thus present points of very considerable difference to those observed in the diseases which chiefly affect adults[1].

The last disease of importance is small-pox. The facts with regard to this have been examined in a previous paper by myself published in *Biometrika* and need only be given here in *résumé*. Before the introduction of vaccination this was a disease of which the age prevalence and fatality did not differ greatly from those of measles at the present time. Youth seemed to be the period of much the greatest susceptibility, and the disease in any case was so infectious that when it broke out among a population from which it had been absent for a considerable time it attacked such a large proportion of the total persons not protected by previous attack as to render the detection of the period of greatest

[1] These remarks concerning the comparative immunity to scarlet fever possessed by persons over ten years of age apply generally to the manner in which that disease appears in the cities of this country, yet when an epidemic attacks a virgin community the period of high susceptibility does not cease till the age of twenty is reached. This is shown in the epidemic of scarlatina which broke out in the Faroe Islands in 1875, and it raises the question as to whether some degree of immunity may not be obtained by living in a centre where the infection is constantly present, even although an actual attack of the disease is not experienced; this however cannot be dealt with here.

susceptibility somewhat difficult. It had been calculated by Duvillard even at this time that during the years ten to fifteen there must be a slightly higher susceptibility, but the statistics of the recent epidemics, especially that of Sheffield in 1887, of which a census of the population was taken, show that this period is one which exhibits considerably greater susceptibility than Duvillard supposed. The prevalence, mortality, and fatality curves resemble those of relapsing fever and typhus, with the difference that both the susceptibility and the mortality are higher at early years. The chief interest of small-pox statistics, however, lies in their affording a certain amount of evidence on the subject of acquired immunity, which will be considered later.

This completes the tables showing the statistical facts relating to natural immunity, and the capacity for acquiring immunity. So far the diseases belong to two groups, the one including those diseases which chiefly affect adults, and the other those which chiefly affect children. In all the former there is a general agreement. The susceptibility increases from birth up till ten to fifteen years, and thereafter diminishes, while the fatality shows an exactly opposite course. The latter is high in the early years of childhood, decreases till the age period ten to fifteen, and thereafter increases steadily towards age. With enteric fever there is an absence of this special fatality in youth, but with this exception the general course is the same. It would seem as if there was an inverse relationship between the natural immunity and the capacity for acquiring immunity. As the natural immunity increases with age the possession of high capacity for acquiring immunity becomes less necessary. It is to be noted that in the only disease in this group in which the fatality remains practically constant, namely, miliary fever, there is by no means the same increase of natural immunity towards old age, so that protection here also is given with a like economy. That the high death-rate is not due merely to the aging of the tissues, nor to the fact that the respiratory system becomes more liable to break down as age advances, is shown from the instance of miliary fever. Measles, however, affords a better example. Age alone apart from acquired immunity does not bring any special increase of natural immunity, and yet the fatality of measles at high ages remains very low. Out of 12,000 cases of measles treated in the City of Glasgow Fever Hospital, Belvidere, 1885–1902, 71 were over the age of thirty, and of these three died, though the general mortality of all ages was 9 %. These 71 were almost without exception persons born in the country who had not passed through measles in early youth.

This inverse relationship between natural immunity and the capacity for acquiring immunity, so distinctly shown in the diseases which chiefly affect adults, is not nearly so marked a characteristic of the diseases which affect children. As already stated measles and whooping-cough do not lend themselves to this statistical study, so that the figures concerning scarlet fever and diphtheria must be taken to illustrate this type. The facts have been already stated. There is one point of similarity with the continued fevers. In both scarlet fever and diphtheria at ages over fifteen years the inverse relationship under discussion obtains. The natural immunity in both diseases increases from this period, and the fatality also increases, though the increase is very small in proportion to that observed in the continued fevers. It is also much more definite in scarlet fever than in diphtheria. The differences, however, predominate. The maximum susceptibility to scarlet fever is between the years of four and five, while the maximum mortality is between the years of three and four. It is, however, to be noted that from 0–5 years, during which the susceptibility steadily increases, the fatality as steadily declines, and so far the inverse relationship is observed to exist. From the age of five years, however, both fatality and susceptibility diminish together, and it is not until the age of fifteen is reached that they again hold an opposite course. The case of diphtheria presents no essential difference to this. There is thus no absolutely constant relationship between the degrees in which natural immunity and the capacity for acquiring immunity may be present, but they are generally found present in inverse amounts during the different periods of life at which diseases may be acquired. The chief exception to this occurs in the disease of childhood between the age of five and fifteen years. The measure of this inverse relationship is not absolute for disease in general, but requires to be investigated specially for each disease in particular.

Further, some diseases not definitely proved parasitic, such as cancer, display a somewhat similar condition of affairs. It is well known clinically that when this disease developes in a person under thirty years of age it advances with startling rapidity, the organism apparently being unable to bring into play any forces in the least adequate to combat the illness, while if the disease develope later at those periods of life when apparently the susceptibility is greatest a long and, it would seem occasionally, a successful fight may be maintained against the growth of the tumour. Somewhat similar remarks might be made regarding diabetes, but to survey this field would demand the description of much detail on which evidence can be displayed only with doubt and difficulty.

As a general rule it would seem that the two qualities discussed are rarely present at their maximum at the same ages. Nature is a well-known economist. No more material is used for any definite purpose than is required for its adequate fulfilment, and as life in bulk may be readily protected if either natural immunity or the capacity for acquiring immunity is present in a high degree the means are sufficient to the end.

Several explanations may be proposed to explain this association of high natural immunity with low capacity for acquiring immunity in certain instances suggested by cases of the specific fevers. One is that in age the tissues are less resistant to disease, but this has already been rejected for these diseases, and the examples of cancer and diabetes just cited fall in the same way. A second is that a specially virulent bacillus must be present to ensure the infection of a person of high natural immunity. To this the course of the mortality curve offers the best answer (see diagram I), although as has been shown the infectivity and virulence of an organism are not necessarily associated. Were a bacillus of any definite virulence required to produce a severe attack, then the mortality curve would more or less take the form of a straight line, unless some particular age or ages were more exposed to the risk of infection than others, and of this there is no satisfactory evidence in the continued fevers. In the accompanying table (Table E) the mortalities for several zymotic diseases are tabulated as given by the Registrar-General for the decade 1881–91. It is seen that very large variation is exhibited, especially in these diseases which attack children. Though the variation is not so marked with enteric fever and typhus fever as with scarlet fever and diphtheria it is still considerable. The variation, however, of the mortality in the former diseases given by the statistics of fever hospitals where the diagnosis is verified is much more considerable and leads to the conclusion that many deaths occurring in youth are wrongly ascribed to these diseases. When reference is made further back to the decade 1871–81 the age distribution of deaths given by the Registrar-General is totally different for both these fevers from that just cited. There the mortality among children is yet more considerable, and the comparison makes belief in the official figures almost impossible. The variation, considerable in the statistics of the Registrar-General, is thus yet more considerable where opportunity for checking the diagnosis is available, and is too large to admit of the

TABLE E.

Table showing Death-rates (mortality) per 100,000 *for certain fevers. England,* 1881—1891.

Age period	Scarlet Fever	Diphtheria	[1]Enteric Fever	[1]Typhus Fever
0—1	672	282	49	1
1—2	1885	686	108	2
2—3	2115	773	141	3
3—4	2042	896	170	5
4—5	1708	849	187	8
5—10	762	424	180	7
10—15	153	100	208	9
15—20	41	36	289	16
20—25	26	20	282	15
25—35	22	17	232	18
35—45	12	16	182	26
45—55	4	14	155	21
55—65	2	17	142	17
65—75	3	17	113	12
75—	1	12	62	6

explanation holding true. There is besides no disease in which the mortality is constant at all ages.

Exactly the same remarks apply to infection by a large dose of the poison and by the same reasoning it will be seen that persons more or less immune to a poison who become infected are not, taken all over, those who receive a larger dose than the average.

Explanations associated with method of infection do not seem much more satisfactory. If it could be proved that enteric fever in young adults was more commonly acquired by eating shell-fish, for instance, a cause which is said to produce mild attacks, then a certain amount of explanation would be afforded, but such outbreaks seem more commonly to affect adults. With regard to the children's diseases this explanation also fails. Here it might be assumed that the mortality was higher at early ages because children are brought into specially close contact with one another in schools, but the maximum mortality occurs in none of these diseases during school ages, and the variation in the amount of the mortality at different ages is so large as to make such an explanation impossible.

The question of acquired immunity remains to be considered. The only statistics which are at all suitable for the investigation of this are those relating to small-pox and vaccination. Small-pox is a disease

[1] In both of these diseases the Registrar-General's returns give a number of deaths at early ages in considerable excess of what is found in hospital statistics.

which displays some peculiarities; there is the stage of initial fever, associated with very severe constitutional symptoms, which occurs prior to the appearance of the eruption, and which suddenly abates as the rash becomes visible. The secondary fever differs absolutely in its character from the primary. It begins generally when the eruption reaches the stage of vesiculation, increases as the rash developes, and subsides as it dries up. It is this second stage which vaccination clinically resembles and against which the latter affords the greatest protection. In cases of small-pox modified by vaccination it is no uncommon thing to find a primary fever of great severity associated with an almost complete absence of eruptive elements, showing that the toxines produced in the two stages of the disease are in some way considerably different. Being thus a complex disease the statistics of the type of small-pox which follows vaccination allow the decline of acquired immunity to be measured at two levels, (1) strength of protection against attack, and (2) strength of protection against death. It is found that the duration of the protection against attack is very much less than that against death.

The course of both is exhibited in the accompanying diagram as determined from the statistics of the great epidemic of small-pox at Sheffield in the year 1887–88. These figures are calculated from the numbers at each separate age period of the vaccinated and the unvaccinated. On account of the alteration which age produces as regards natural immunity and fatality quite apart from the presence or absence of vaccination it is easily seen that a comparison can only be valid if made in this way. The diagram shows that against attack the protection remains fairly complete until the age of fifteen years, thence it declines rapidly until it is practically absent at the age of thirty, though it never absolutely disappears.

With regard, however, to the protection against death, that is to say, against that stage of the fever to which vaccination clinically corresponds, the decline, though marked from fifteen to thirty years, falls but little after this date and always remains considerable. This latter fact is of specially great importance as indicating that immunity which is acquired and not natural is not only never lost, but though the absolute protection may diminish with old age, yet a great relative protection remains in spite of this.

If the relative natural immunity at different ages among the unvaccinated be measured it is found to vary in the manner shown in diagram II, which, taking the susceptibility of small-pox under one year of age as the standard for comparison, shows in another form what has already been stated when the prevalence of the disease among the unvaccinated was mentioned earlier in this paper. It is seen from this that the natural immunity is least between the ages of 10 and 15 years. Between the ages of fifteen to twenty years, it is again approximately equal to that during the first year of life and thereafter steadily increases.

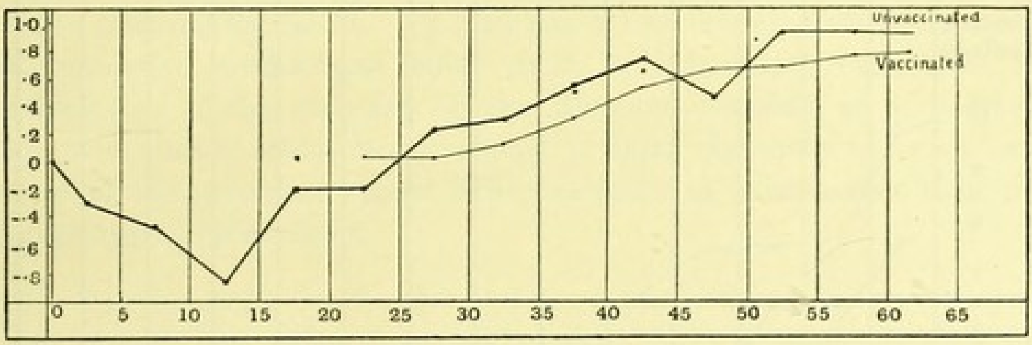

Diagram II. Curves indicating the growth of natural immunities among vaccinated and unvaccinated for the Sheffield Epidemic of Small-pox, 1887–8. The increase of susceptibility is to be noted among the latter up to the age period 10—15 years, and the gradual growth of immunity from that date onwards. Taking the age period 15—20 years as a standard for the vaccinated the growth of natural immunity thence onwards is shown. Remembering that the latter curve starts from a level of acquired immunity still considerable, it is curious to note how similarly natural immunity increases in the vaccinated and unvaccinated alike.

If for the vaccinated the curve representing the combination of natural and acquired immunity is drawn it is seen that the protection against attack is at a minimum between the ages of fifteen and twenty years, and thereafter gradually increases. The minimum between fifteen and twenty years does not represent a period at which the acquired immunity is absent, but taking it as a standard and representing the susceptibility at the succeeding ages in the same way as has been done for the unvaccinated, it will be noted that the increase of natural immunity due to age among the vaccinated as indicated in the diagram, follows very closely that shown by the like curve referring to the unvaccinated, in other words, the development of natural immunity due to age is quite independent of the presence or absence of acquired immunity. Lastly, in this connection it is to be noted that the fatality of the disease increasing with age among persons who have been vaccinated does not indicate a corresponding loss of the protection produced by acquired immunity, because it increases *pari passu* with that among the unvaccinated. This is shown by diagram III, where it is seen that after thirty years of age there is no further relative loss in the protection against death displayed by the vaccinated as against the unvaccinated, the increase in fatality is due to the lessened capacity for acquiring immunity, which is a feature shown by the human system in regard to small-pox as well as some other diseases, though as before remarked not a necessary consequence of age itself.

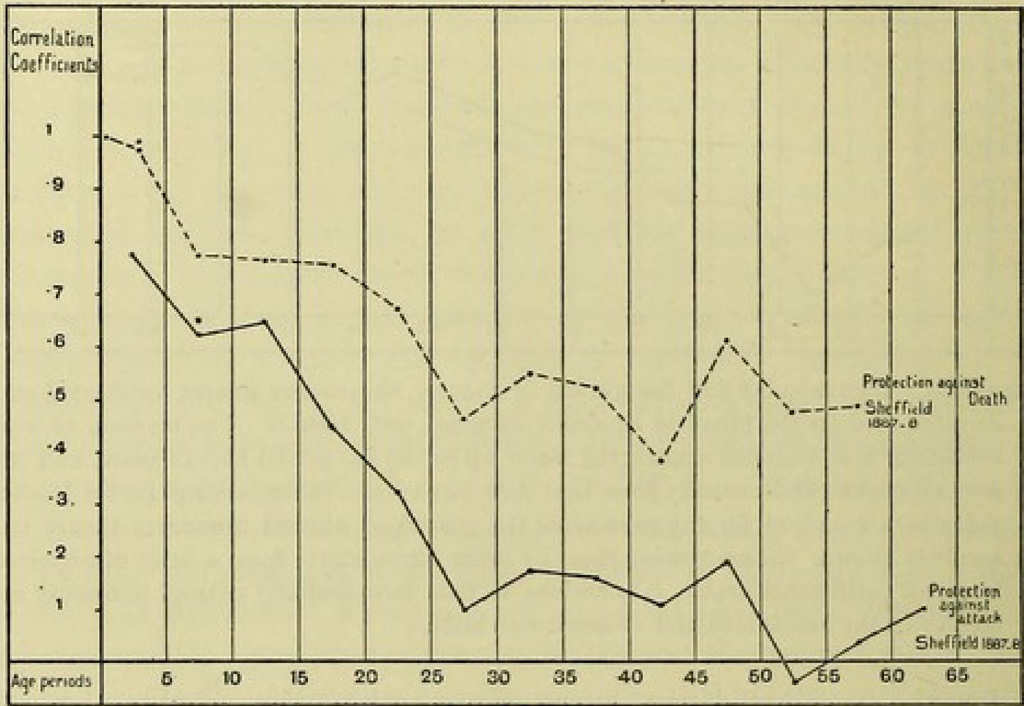

DIAGRAM III. Diagram showing the manner in which the protection afforded by vaccination decreases. The lowest line refers to the protection against attack which it is seen nearly vanishes between the ages of 25 and 30. The upper represents the loss of protection against death. It is to be noted that while this tends to fall rapidly up to the age period 25—30 years, thereafter there is no further loss, so that some permanent change is made in the tissues by vaccination. The statistics for other towns show essentially the same phenomena.

In conclusion, to bring the argument in the preceding pages into line with the experimental theory of immunity the following points may be noted. There are at present two different means known by which an organism is protected against infective agents, one independent of the character of the body fluids, and the other dependent on the actual presence or rapid production of certain protective agents in these fluids. The former is seen, for example, in the immunity possessed by fowls to the toxin of tetanus which is not the result of any known chemical reaction of the tissues or fluids of the body. Of the second the immunity of the horse towards diphtheria is an example; for though it may be said that the horse is an animal naturally immune to this disease, it would appear that it is rather an animal which possesses a remarkably small amount of natural immunity in the sense in which this is exhibited by the fowl against the poison of tetanus, but on the other hand possesses a capacity for acquiring immunity of such amount as to render its defence against the disease practically absolute. It would probably be better to restrict the term natural immunity to the former of these and to use some other term to describe the latter. To correlate these two properties with the two protective mechanisms which must be inferred to exist from a consideration of the statistics of the infectious diseases, is, of course, conjectural, but it seems more rational to infer that they are manifestations of the processes known experimentally to exist rather than to suggest other explanations.