# Distribution of immunity to pertussis in the population of England and Wales

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## SUMMARY

This paper presents three different methods of estimating the number and age distribution of individuals susceptible to pertussis in England and Wales. The first approach is an extrapolation from data in the prevaccine era, the second is based upon theoretical consideration of the transmission dynamics of pertussis, and the third is a detailed cohort analysis of available notification and vaccination data. Each of these analyses suggests that the total number of people susceptible to pertussis infection in England and Wales has remained at 3–4 million for the past 40 years, despite the increase and changes in numbers vaccinated. The effect of vaccination has been to reduce the incidence of infection and disease, but not to reduce the number of susceptibles. These findings, which are consistent with 'mass action theory', could be tested by an appropriately designed seroepidemiological survey.

## INTRODUCTION

Who in England and Wales are immune to pertussis, and how are they distributed in the community? Such questions are inevitably difficult when directed at an infection whose natural ecology has been disrupted by a vaccination campaign. They are especially complicated with reference to pertussis, as both the efficacy and the uptake of whooping-cough vaccines have varied considerably over the years, and there is a lack of serological survey data which might provide a reference for epidemiological studies. Such difficulties notwithstanding, the question of immunity to pertussis is particularly important today, given continued controversy over the efficacy of pertussis vaccines and their relationship to community patterns of disease.

Serological tests for pertussis antibodies have been studied for many years, ever since Bordet & Gengou (1906, 1907) first applied complement fixation in this context. Subsequent workers adapted direct agglutination (Miller *et al.* 1943; Kendrick *et al.* 1969), indirect haemagglutination (Macaulay, 1979) and indirect fluorescence (Bradstreet *et al.* 1972), complement fixation (Bradstreet *et al.* 1972; PHLS, 1970) and ELISA methods (Granstrom *et al.* 1982). Though some of these tests have proven useful as diagnostic procedures, it is unclear whether any of them is sensitive and specific as a measure of immunity to infection and there are very

few data pertaining to their application in populations. We have found no discussion in the literature of the effect of vaccination programmes upon population patterns of seropositivity as defined by any of these tests.

We present here three epidemiological approaches to the problem of defining population patterns of pertussis 'immunity': first by inferences from the pattern of pertussis in unvaccinated communities; second by theoretical considerations based on the dynamics of pertussis transmission; and lastly by analysis of routinely available statistics from England and Wales. These analyses highlight several important questions concerning the validity of available data and the immunological effects of current vaccines.

We must begin by defining what is meant by immunity in the context of this discussion. Many authors have commented upon the complexity of the immune response in pertussis, and how different responses may reflect protection against infection or against clinical disease (Pittman, 1979; Wardlaw & Parton, 1983). In addition there may be important quantitative variation in terms of protection against different levels of exposure or against different severities of disease. Population analyses such as those presented in this paper cannot hope to describe immunity in detailed categories. We thus define the term in an epidemiological sense, as follows: *immunity implies protection, under prevailing levels of exposure, against developing an infection which is itself transmissible.* In so far as an important goal of pertussis vaccination programmes is to reduce transmission in the community, this is one sort of immunity which a vaccine should produce. This is the 'immunity' whose distribution is investigated in this paper.

An additional introductory comment is in order concerning the predicted impact of a vaccination programme upon the number of susceptibles in a population. Though one might intuitively expect that the successful vaccination of children should reduce the number remaining susceptible in the population, there is a considerable body of theory which suggests that this is not necessarily so – that, on the contrary, moderate levels of vaccination should have very little impact upon the total susceptible population (Fine & Clarkson, 1982a; Anderson & May, 1983). According to this theory, recurrent epidemics of acute, contagious infections occur when the number of susceptibles increases above the critical 'epidemic threshold' for that infection and population. By this logic, the continued epidemics of whooping-cough in England and Wales imply that the numbers susceptible still fluctuate around this threshold, and that the reduced incidence of disease is attributable to the decreased rate of influx of susceptibles (because of vaccination of infants) but not to any decrease in their total number. Previous analyses have suggested that this theoretical prediction is valid for measles, at least under the conditions of 50 % vaccine uptake in England and Wales (Fine & Clarkson, 1982a). The present paper explores its validity with regard to pertussis.

## SOURCES OF DATA

Population statistics for England and Wales were drawn from age-specific tabulations published by the Registrar General (1940–73). Corrected population figures, allowing for immigration and emigration during the years 1974–9, were provided by the Office of Population Censuses and Surveys (OPCS). Age-specific pertussis notifications were taken from published tables in the Annual Reviews of

Notifications

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1969 | A | B | | C | | | | D | | | | E |
| 1968 | A/3 | B/2 | 0·17c | 0·17c | 0·16c | 0·163D | 0·162D | 0·075D | 0·075D | 0·025D | E/10 | E/10 |
| | 2A/3 | B/2 | 0·17c | 0·17c | 0·16c | 0·163D | 0·162D | 0·075D | 0·075D | 0·025D | E/10 | E/10 |
| 1967 | | | | | | | | | | | | |
| 1966 | | | | | | | | | | | | |

1966 cohort

Age: 0 1 2 3 4 5 6 7 8 9 10 11

Calendar year (vertical axis)

Vaccinations

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1969 | A | B | C | D | | E | | | | | F | |
| 1968 | A | B–A | 0·65D | 0·35D | 0·2E | 0·2E | 0·05E | 0·05E | F/17 | F/17 | F/17 | F/17 |
| | A | c–0·65D | 0·65D | 0·2E | 0·2E | 0·2E | 0·05E | F/17 | F/17 | F/17 | F/17 | F/17 |
| 1967 | | | | | | | | | | | | |
| 1966 | | | | | | | | | | | | |

1966 cohort

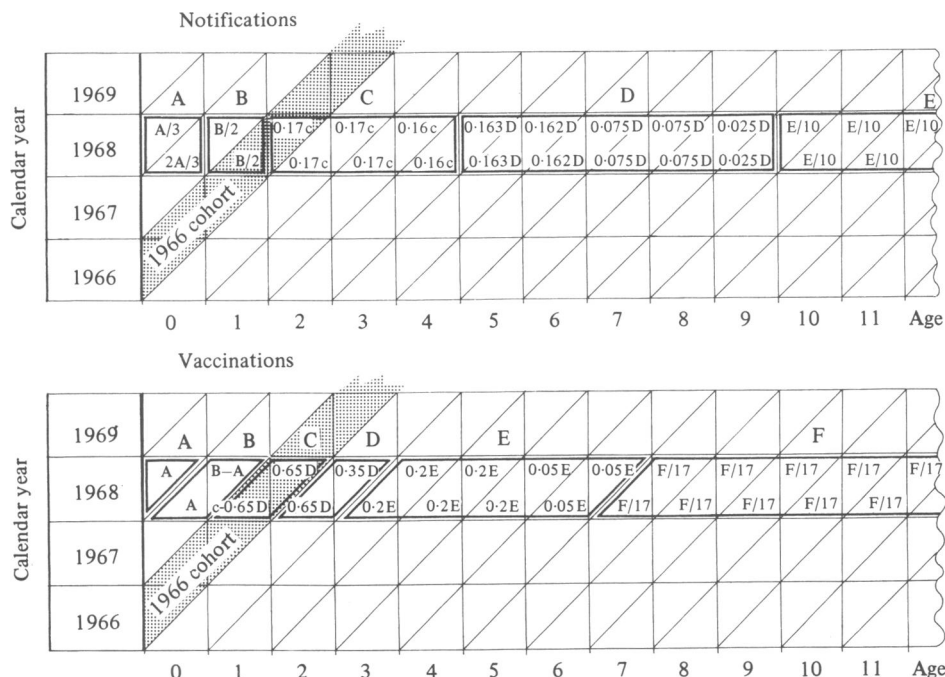Age: 0 1 2 3 4 5 6 7 8 9 10 11

Fig. 1. Lexis diagrams illustrating the structure of pertussis notifications and vaccination statistics, e.g. for the year 1968. Calendar year is on the vertical axis, and age is on the horizontal axis. Each cohort is represented by a diagonal bar, exemplified by the stippled bar for children born in 1966. Rectangles and parallelograms in dark outline represent the grouping of reported statistics: by year of age for notifications and by year of birth for vaccinations. These groups are labelled A, B, C, D,... within each diagram. The assumed distributions of notifications and vaccinations within these groups are given for the year 1968.

the Registrar General of England and Wales (Registrar General, 1940–1973) and Statistics of Infectious Diseases provided by the OPCS (Office of Population Censuses and Surveys, 1974–1980*a*). In order to obtain more detailed information on the age distribution of notified pertussis than is available in national statistics, actual notifications registers were consulted in six health districts. Estimated numbers of hospitalized pertussis cases were extracted from the Hospital In-Patient Enquiry (HIPE) (Office of Population Censuses and Surveys, 1957–1978*b*). Statistics on vaccinations were drawn from annual summaries submitted by the Area Health Authorities (AHAs) to the Department of Health and Social Security (DHSS). These statistics refer to completed courses (three injections) of vaccine containing pertussis antigen.

## METHODS OF ANALYSIS

Data were analysed in order to cumulate vaccination and disease notification experience within successive birth cohorts. The methods were similar to analyses carried out on measles data and described elsewhere (Fine & Clarkson, 1982*a*). The following discussion emphasizes features peculiar to pertussis.

The analyses are made complicated by the nature of the data available. Pertussis
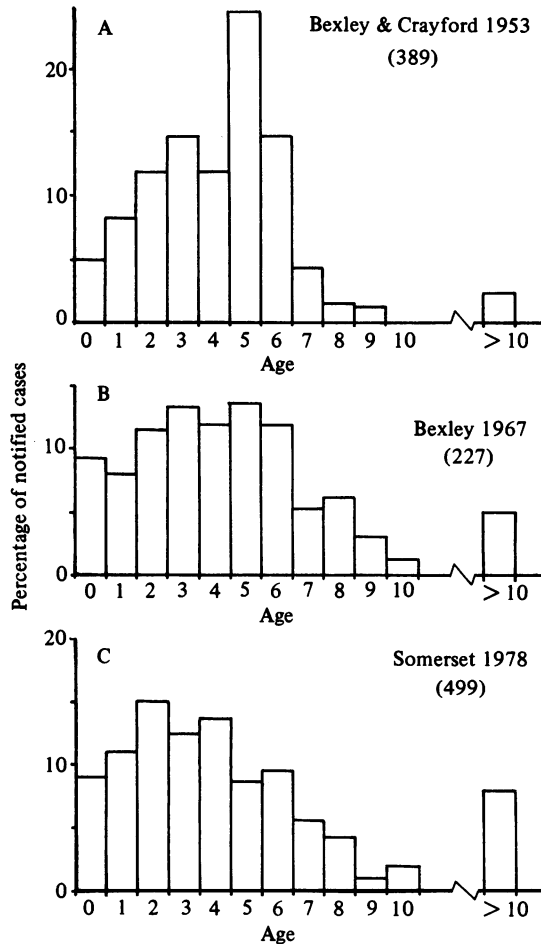
Fig. 2. Age distribution of actual pertussis notification slips as received in Bexley and Crayford District in 1953 (A), in Bexley in 1967 (B) and in Somerset in 1978 (C). The total number of notifications is given in parentheses. These distributions provide the basis for the allocations within age groups as illustrated in Fig. 1 A.

notifications in England and Wales are reported in groups by year of age, whereas vaccinations are reported in different groupings and by year of birth of the vaccinees. The implications of such data are illustrated in Fig. 1, which shows the grouping of notification and vaccination statistics for the year 1968. These are 'Lexis' diagrams, with calendar year on the vertical axis, and age along the horizontal axis. The history of each birth cohort is represented as a diagonal on such a diagram, exemplified by the stippled bar for the 1966 cohort. Accumulation of vaccination and/or notified disease experience requires accumulation of the appropriate triangles or paralellograms along each cohort, stopping at a vertical line for estimates by a precise age, or at a horizontal line for estimates at the beginning of a calendar year.

Two additional complications should be mentioned. First, the age grouping of pertussis notification statistics changed in 1956, 1968 and 1969, and the grouping of vaccination statistics changed in 1961, 1965, 1969, 1970 and 1971. These
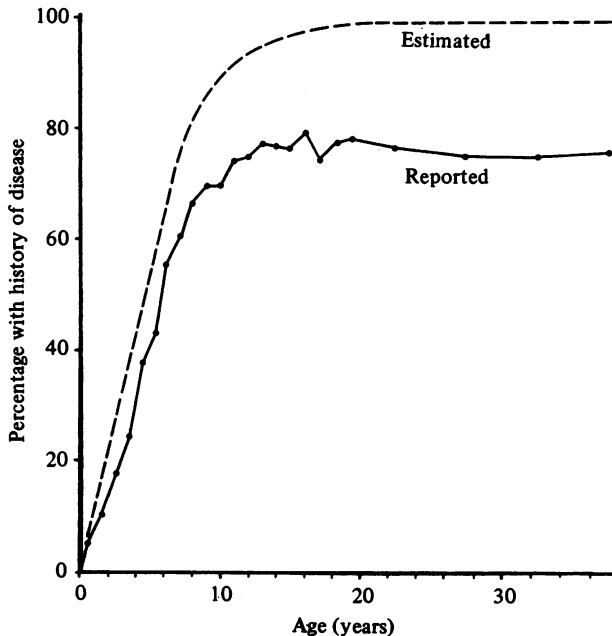
Fig. 3. Reported (——) and estimated (----) proportions with history of pertussis infection, by age, for several North American populations as reported by Collins in 1929. Reported data are a composite of surveys in school children in 15 localities in the U.S.A., in College students in 11 Universities in the U.S.A., in Hagerstown, Maryland, and in London, Canada. The estimated trend is based upon an assumption that the true proportion with history of pertussis infection was 100 % by age 15, and that 20 % of infections went unrecognized at all ages.

different breakdowns – variants on the 1968 pattern illustrated in Fig. 1 – had to be taken into consideration in the analyses. Secondly, notifications and vaccinations are not uniformly distributed within the broad age groups used in national statistics. This is most obvious with regard to notifications in the 5- to 9-year age group. We thus estimated allocation factors on the basis of actual notifications as observed at the District level, and illustrated for Bexley and Crayford in 1953 and 1967, and for Somerset in 1978, in Fig. 2. The allocation factors actually used for 1968 are given in Fig. 1.

A computer program was written in order to carry out the considerable arithmetic required to accumulate vaccination and notification data within cohorts. A listing of the program and details on age groupings and allocation factors are available from the authors on request.

## PERTUSSIS IN THE PRE-VACCINE ERA

Pertussis morbidity did not become nationally notifiable in England and Wales until 1940, and vaccination was first introduced in 1942 (Griffith, 1979). We are thus unable to use national statistics to investigate cohort patterns of morbidity in the pre-vaccination period.

Many early authors commented upon the ubiquity of whooping-cough. In a well-known review written in 1951, Gordon and Hood stated that 'probably 95 %

of persons have pertussis in classical or atypical form some time during life', and Morse (1968) claimed that 85 % of children had a history of pertussis by the age of 7 years. Stocks (1933) commented that data from four London areas where the disease was notifiable (Battersea, Greenwich, Holborn and Wandsworth) indicated that 'three-fifths of all children born in London have whooping cough at some time' and that a considerable proportion of infections were not manifest. Perhaps the most detailed early population studies of pertussis were those of Collins (1929) and Sydenstricker (1932), who found that the proportion of children reporting a history of pertussis rose to a plateau level of 75–80 % by age 12 in several populations in North America (Fig. 3.).

All of these early studies suggest that a very high proportion of children in large unvaccinated populations had been infected with *Bordetella pertussis* by age 10. There are several reasons to suppose that this proportion approached 100 % and that the shortfall in reported disease was due largely to atypical, asymptomatic or forgotten infections. First, recent authors have estimated that an appreciable proportion (e.g. 25 %) of infections are asymptomatic (Linneman, 1979), and *B. pertussis* has repeatedly been isolated from symptomless individuals (Broome, Fraser & English, 1979; Broome *et al.* 1981; Lambert, 1965; PHLS, 1969). Secondly, given the varied spectrum of clinical response to *B. pertussis* infection, it is reasonable to suppose that some attacks will not be recognized as whooping-cough. Thirdly, household secondary attack rate studies have shown that the risk of pertussis is very high – of the order of 90 % – in very young contacts with no history of disease or vaccination, but that this risk is small among adult contacts with no such history (Sydenstricker, 1932; Broome *et al.* 1981; PHLS, 1969). The most reasonable explanation for this observation would be that many of the adult contacts, though lacking in recognized history of disease, were not actually susceptible, and that most of them had in fact experienced a previous unrecognized infection. Fourthly, pertussis has traditionally been considered a childhood disease, rarely reported among adults. This in itself suggests that most persons were infected during childhood. The latter inference is important, as we may apply it to the current situation in England and Wales. Pertussis is still rarely recognized among adults. Though there have been a few reports of pertussis in adults in recent years (Williams, 1981), still more than 90 % of notifications refer to individuals under 10 years (Table 1). This implies that the proportion of adults immune – at least to recognizable pertussis – is still very high.

We may carry this analysis one step further. It is possible to use the age profile in Fig. 3 to estimate what the total numbers susceptible may have been during the pre-vaccine period. This requires two assumptions: first, that Collins's composite trend calculated from data on several North American communities was applicable to England and Wales; and secondly, that these figures reflect a 20 % deficit in reporting (i.e. that the true cumulative incidence rate of *B. pertussis* infection was virtually 100 % by age 15). The dotted line in Fig. 3 shows the estimated 'true' proportions with a history of pertussis infection at each age, on the latter assumption. If these percentages are applied to the England and Wales populations of the time we estimate that there were 3 050 000 persons in 1940, and 3 710 000 persons in 1950, who had never been infected with *B. pertussis*, and who should thus have been susceptible to infection.

## THEORETICAL APPROACH – PERTUSSIS DYNAMICS

Clinical pertussis is a manifestation of an acute, contagious airborne infection. One of its most striking properties, reported from several countries of Europe and North America, is a tendency to occur in cyclical epidemics at intervals of 3–4 years, as shown in Fig. 4 (Gordon & Hood, 1951; Anderson & May, 1982; Fine & Clarkson, 1982*b*). We have discussed the mechanism underlying this cyclical phenomenon in another publication (Fine & Clarkson, 1982*b*).

In the present context we would note that such cycles are a feature of contagious infections whose dynamics reflect an oscillating balance between numbers infected and numbers susceptible in the population. Periodic epidemics begin when the number of susceptibles rises above a certain threshold level. During an epidemic the incidence of infection comes to exceed the rate of influx of susceptibles, thus depleting their number below the critical threshold. This brings a fall in incidence, and ushers in an inter-epidemic period during which the incidence is less than the influx of susceptibles. The number of susceptibles then increases once again to the threshold number. In general, the accumulation of susceptibles is through births into the population, though it is possible that loss of immunity in older individuals could also contribute.

The magnitude of this epidemic threshold $(T_E)$ is important in the current discussion, as the number of susceptibles in the population should oscillate above and below this number. In principle it reflects the number susceptible in a situation where incidence would remain constant. In theory, the threshold should be approximately $N/R_0$, where $N$ is the total population and $R_0$ is the basic reproductive rate, or the average number of potential transmissions per case in the population (see Appendix). Dietz (1974) has provided a method of estimating $R_0$ as $(L/A+1)$, where $L$ is the average life-expectancy in the host population, and $A$ is the average age at infection, in an unvaccinated population. Using this approximation we can estimate the threshold number of susceptibles as $T_E = N/(L/A+1)$. Substituting rounded 1950 England and Wales figures for total population size $(45 \times 10^6)$, average life-expectancy (70 years) and average age of notified pertussis (5 years) into this equation gives us $T_E = 45 \times 10^6/(70/5+1) = 3 \times 10^6$. For further discussion on the theoretical basis of this argument, the reader is referred to the cited publications (Anderson & May, 1982; Dietz, 1974; Fine & Clarkson, 1982*b*). In the present context we wish only to point out that basic epidemic theory suggests that the total number of persons susceptible to pertussis infection in England and Wales has oscillated above and below a threshold of approximately $3 \times 10^6$.

## COHORT ANALYSIS OF ENGLAND AND WALES DATA

Fig. 4 presents crude numbers of notified pertussis cases, numbers of births and numbers of reported completed courses of pertussis vaccine, by year, since 1940. A dramatic fall in notified pertussis since the 1950s is clear. The sudden appearance of completed courses of vaccinations in the 1956 cohort is an artifact, as it is known that pertussis vaccination was carried out from 1942 (Griffith, 1979), though vaccination statistics were not officially collected until the onset of the national
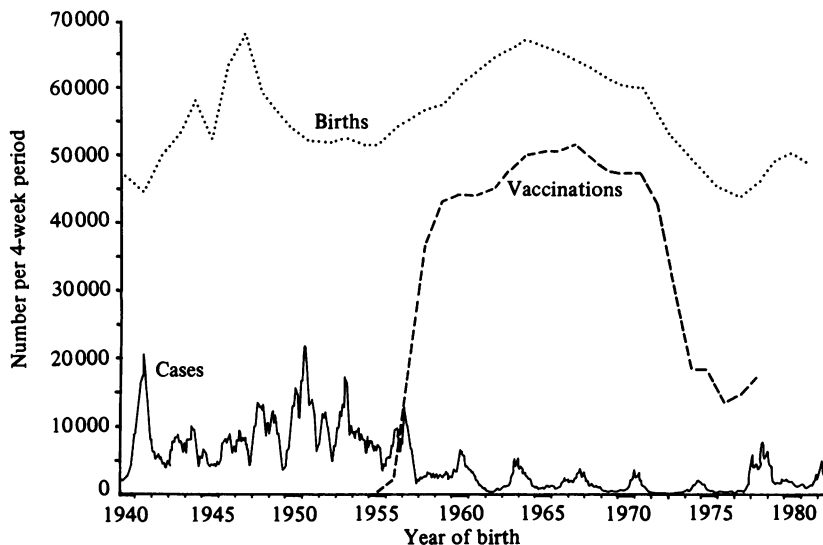
Fig. 4. Numbers of births, pertussis notifications and completed courses of pertussis vaccinations, by 4-week period, for England and Wales 1940–82. Average annual four-weekly estimates for births and vaccinations are calculated as annual totals/13.

programme in 1957. The extent of vaccination prior to this date has been a controversial subject, as some critics of vaccine efficacy have suggested that little vaccination was carried out before 1957, and thus that the fall in notifications during the 1950s represented a natural secular trend, and was not due to vaccine (Bassili & Stewart, 1976). An accumulation of *recorded* notification and vaccination experience is presented in Fig. 5 for each cohort born since 1940. We see that approximately 15 % of children born before 1957 were notified as having had pertussis before their 10th birthday. On the other hand, approximately 80 % of children born between 1957 and 1972 were recorded as experiencing either notified disease or a complete course of pertussis vaccine. This percentage then falls precipitously for cohorts born after 1972, a consequence of the fall in vaccine uptake associated with public fears over safety of pertussis vaccines.

   To what extent do these data reflect this distribution of immunity in these cohorts? We must admit several major problems in the available data: incomplete notifications of disease, absent statistics on vaccination, and uncertain vaccine efficacy. Let us try to assess the extent of each of these sources of error.

   For an initial estimate of notification efficiency (i.e. *cases* notified divided by total *infections*) we may examine the cohorts born before 1950, when there was relatively little vaccine use. Despite the evidence cited above that a very high proportion of individuals born in that period experienced infection at an early age we see that less than 20 % were actually notified as pertussis cases by age 20 (except for the 1946 cohort, in which the percentage reached 21 %). This suggests that less than 25 % of actual infections were notified during that period. The extent to which this notification rate may have changed over time is difficult to assess. However, we note from Table 1 that the number of hospitalized pertussis cases represented a steadily increasing proportion of all notified cases during the years 1957 through
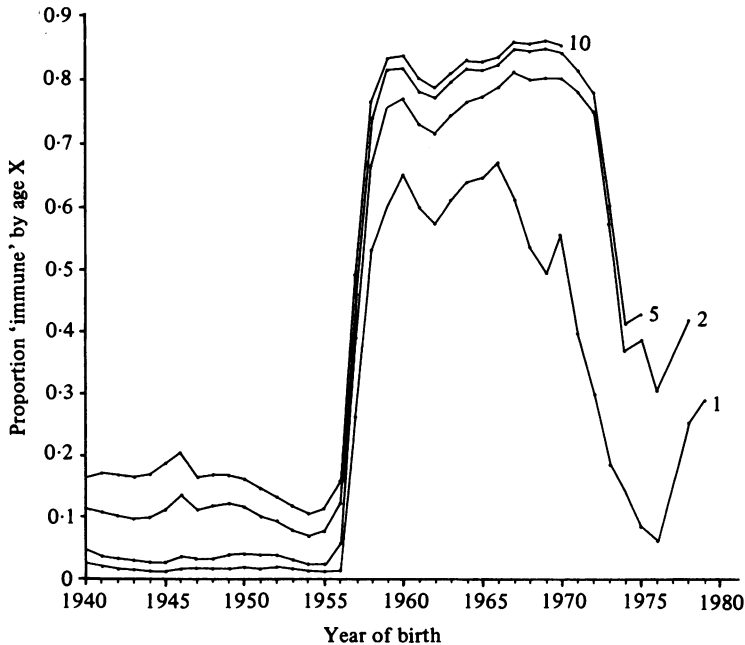
Fig. 5. Cumulated proportions with history of either vaccination or notified pertussis, by age 1, 2, 5 and 10, for annual birth cohorts 1940–80 in England and Wales. This assumes 100 % vaccine efficacy (i.e. that no child was both fully vaccinated and also notified as a pertussis case).

1976. It is unlikely that this was due to increased severity of pertussis during this period, given the widespread use of effective antibiotic therapy. It is also unlikely that this was due to changing criteria for hospitalization; as this would not explain the sudden reversal in the HIPE/notifications ratio after 1976. A more reasonable interpretation of this trend is that the proportion of notified cases among actual infections fell progressively during the 1957–76 period (Clarkson & Fine, 1984). If we were to assume that the proportion hospitalized among all infections actually remained constant, this would indicate that the notification efficiency fell from approximately 25 % in the early 1940s to only 5·5 % in 1976. The trend in the HIPE/notifications ratio then reversed, indicating an improvement in notification efficiency, probably as a consequence of increased publicity concerning pertussis.

We know that pertussis vaccines were used on an increasing scale in England and Wales from 1942 until the official national programme began in 1957 (Griffith, 1979). It is probable that the apparent fall in history of disease reported in children born 1949–55 (see Fig. 5) reflects increased vaccine usage and an associated fall in disease incidence in these cohorts. As a rough estimate of actual vaccine coverage in these early years, we might assume that vaccination began in 1942 and that the numbers vaccinated increased in a constant linear fashion until the first recorded figure of 470290 completed courses in 1958.

Now we come to the question of vaccine efficacy, and how this may affect the estimates of age-specific immunity levels illustrated in Fig. 5. There is an implicit assumption in this figure that all vaccinations were recorded, and that all were
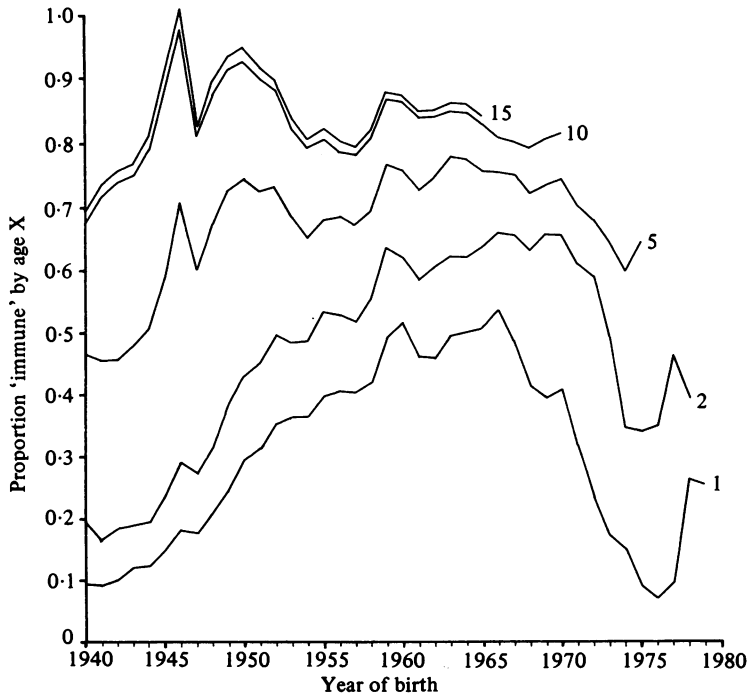
Fig. 6. 'Corrected' estimate of proportions 'immune' to pertussis by age 1, 2, 5, 10 and 15, for annual birth cohorts 1940–80 in England and Wales. This assumes (a) a linear increase in vaccination between 1942 and the first recorded levels in 1958 (see Table 1); (b) 75 % vaccine efficacy; and (c) 25 % efficiency of morbidity notification prior to 1957, a linear fall in notification efficiency to 5·5 % in 1976 and 10 % efficiency thereafter.

effective in immunising their hosts. This is certainly not true. It is unlikely that all completed courses of vaccination are recorded, and no attempt is made to record incomplete courses (less than three doses of vaccine). More importantly, it is recognized that pertussis vaccine does not always immunize and that pertussis is not uncommonly reported in individuals who received a complete course of vaccine (PHLS, 1982; Miller & Fletcher, 1976). Furthermore there is evidence that the efficacy of pertussis vaccines has varied over the period since their introduction. Early trials of pertussis vaccines suggested a reasonably high efficacy against clinical disease for vaccines used in the late 1950s. But a study carried out by the Public Health Laboratory Service (1969) reported that the efficacy had fallen to approximately 20 % by 1967, perhaps owing to shifts in the prevailing serotypes of *B. pertussis*. Through pertussis trends during the 1960s provide little evidence of so drastic a fall in vaccine efficacy (see Fig. 4), this report led to a reformulation of pertussis vaccines in England and Wales. More recent estimates of vaccine efficacy have provided estimates varying from 49 % to 95 %, and a recent survey by the Public Health Laboratory Service (1982) found an overall efficacy of 80 % in the general population though only 50 % among household contacts of cases. Selection of a best estimate value from so many conflicting results is perilous. In addition it should be noted that all these estimates of vaccine efficacy

Table 1. *Statistics on pertussis notifications, vaccinations, hospitalizations and deaths, for England and Wales, 1940–1981*

| Year | Total OPCS notifications | OPCS notifications aged > 10 years (% of total) | Total vaccinations recorded | Estimated vaccinations not recorded | HIPE estimated hospitalized cases (as proportion of total OPCS notifications) | Deaths attributed to pertussis |
|---|---|---|---|---|---|---|
| 1940 | 53607 | n.a. | — | — | — | 678 |
| 1 | 173330 | n.a. | — | — | — | 2383 |
| 2 | 66016 | n.a. | — | 27670 | — | 799 |
| 3 | 96136 | n.a. | — | 55330 | — | 1114 |
| 4 | 94044 | n.a. | — | 83000 | — | 1054 |
| 1945 | 62691 | 2522 (4·0) | — | 110660 | — | 689 |
| 6 | 92936 | 3080 (3·3) | — | 138330 | — | 808 |
| 7 | 92682 | 3153 (3·4) | — | 165990 | — | 905 |
| 8 | 146410 | 4574 (3·1) | — | 193650 | — | 748 |
| 9 | 102816 | 3466 (3·4) | — | 221320 | — | 527 |
| 1950 | 157781 | 4095 (2·6) | — | 248980 | — | 394 |
| 1 | 169441 | 5191 (3·1) | — | 296650 | — | 453 |
| 2 | 114869 | 3073 (2·7) | — | 304310 | — | 181 |
| 3 | 157842 | 4425 (2·8) | — | 331970 | — | 243 |
| 4 | 105912 | 3656 (3·5) | — | 359640 | — | 139 |
| 1955 | 79133 | 2716 (3·4) | — | 387300 | — | 87 |
| 6 | 92410 | 3416 (3·7) | — | 414970 | — | 92 |
| 7 | 85018 | 4563 (5·4) | — | 442630 | 6000 (0·071) | 87 |
| 8 | 33404 | 1638 (4·9) | 470290 | — | 2230 (0·066) | 27 |
| 9 | 33253 | 1757 (5·3) | 527945 | — | 2630 (0·079) | 25 |
| 1960 | 58030 | 3907 (6·7) | 626401 | — | 4940 (0·085) | 37 |
| 1 | 24470 | 2044 (8·4) | 690070 | — | 2420 (0·099) | 27 |
| 2 | 8348 | 563 (6·7) | 578474 | — | 890 (0·106) | 24 |
| 3 | 34737 | 2370 (6·8) | 619201 | — | 4110 (0·118) | 36 |
| 4 | 31596 | 2334 (7·4) | 679382 | — | 4330 (0·137) | 44 |
| 1965 | 12945 | 769 (5·9) | 697653 | — | 1660 (0·128) | 21 |
| 6 | 19417 | 980 (5·0) | 693805 | — | 3020 (0·156) | 23 |
| 7 | 33533 | 1961 (5·8) | 711254 | — | 3970 (0·118) | 27 |
| 8 | 17369 | 1035 (6·0) | 629183 | — | 2610 (0·150) | 15 |
| 9 | 4995 | 327 (6·5) | 457407 | — | 880 (0·176) | 6 |
| 1970 | 16596 | 879 (5·3) | 620534 | — | 2580 (0·155) | 15 |
| 1 | 16846 | 1261 (7·5) | 642533 | — | 3020 (0·179) | 26 |
| 2 | 2069 | 127 (6·1) | 643495 | — | 520 (0·251) | 2 |
| 3 | 2441 | 147 (6·0) | 588516 | — | 600 (0·246) | 2 |
| 4 | 16230 | 1272 (7·8) | 441491 | — | 3410 (0·210) | 13 |
| 1975 | 8913 | 721 (8·1) | 256252 | — | 2430 (0·273) | 12 |
| 6 | 3907 | 269 (6·9) | 245240 | — | 900 (0·230) | 3 |
| 7 | 17475 | 1191 (6·8) | 199624 | — | 2050 (0·117) | 7 |
| 8 | 65942 | 4705 (7·1) | 206966 | — | 5570 (0·084) | 12 |
| 9 | 30808 | 1778 (5·8) | 248518 | — | n.a. | 7 |
| 1980 | 21131 | 1135 (5·4) | 283466 | — | n.a. | 6 |
| 1 | 19395 | 954 (4·9) | n.a. | — | n.a. | n.a. |

n.a. = not available.

Table 2. *Estimates of total numbers of people still susceptible to* Bordetella pertussis *infection below* 5, 10 *and* 20 *years of age in England and Wales in* 1981

(The centre line (marked with an *) represents the 'best estimate' as illustrated in Figs 6 and 7. The other lines represent the effect of changing assumed notification efficiency and vaccine efficacy.)

| Assumptions | | | Estimated total number susceptible (millions) | | |
|---|---|---|---|---|---|
| | Notification efficiency | | | | |
| Vaccine efficacy | 1957–76 | 1977– | Below 5 years | Below 10 years | Below 20 years |
| 0·65 | 20 → 4 % | 8 % | 1·57 | 2·49 | 3·83 |
| 0·65 | 25 → 5 % | 10 % | 1·69 | 2·86 | 4·84 |
| 0·65 | 30 → 6 % | 12 % | 1·76 | 3·06 | 5·21 |
| 0·75 | 20 → 4 % | 8 % | 1·49 | 2·20 | 2·90 |
| * 0·75 | 25 → 5 % | 10 % | 1·61 | 2·58 | 3·91 |
| 0·75 | 30 → 6 % | 12 % | 1·68 | 2·78 | 4·28 |
| 0·85 | 20 → 4 % | 8 % | 1·42 | 1·92 | 2·07 |
| 0·85 | 25 → 5 % | 10 % | 1·53 | 2·29 | 2·98 |
| 0·85 | 30 → 6 % | 12 % | 1·61 | 2·49 | 3·35 |

refer to protection against clinical disease, whereas we are trying in this context to assess protection against infection. Despite all these difficulties, we may not be too far wrong in assuming that the average protective efficacy of pertussis vaccines against transmissible *B. pertussis* infection has been in the order of 75 %.

Fig. 6 presents a revised version of Fig. 5, an attempt to portray a best estimate of the age-specific prevalence rates of pertussis immunity for cohorts born since 1940. In this diagram we have assumed that vaccinations increased from 0 in 1941 to recorded levels in 1958 (Table 1), and that 75 % of these vaccinations were effective in immunizing the recipient. We also assume that 25 % of infections were notified in the years 1940–57, that this proportion fell linearly to 5·5 % by 1976, and that 10 % of infections have been notified in subsequent years.

Fig. 7 presents these data in an alternative fashion, to show the estimated numbers of people susceptible to pertussis in England and Wales, under these 'revised' assumptions. This suggests that the total number of susceptibles under age 20 has remained relatively constant for the past 20 years, at approximately 4 million. A slight oscillation is seen, with peak numbers of susceptibles coinciding with the initiation of the periodic epidemic (compare with Fig. 4). Table 2 shows the effect of varying the vaccine efficacy and notification efficiency assumptions upon the estimate of numbers susceptible in 1981.

## DISCUSSION

Three epidemiological approaches have been explored in an effort to estimate the level and distribution of immunity to pertussis in England and Wales. Despite their very different strategies, and the different data upon which they are based, their results bear an intriguing similarity. Each suggests that the total number of susceptibles has hovered in the range 3–4 million for the past several decades.
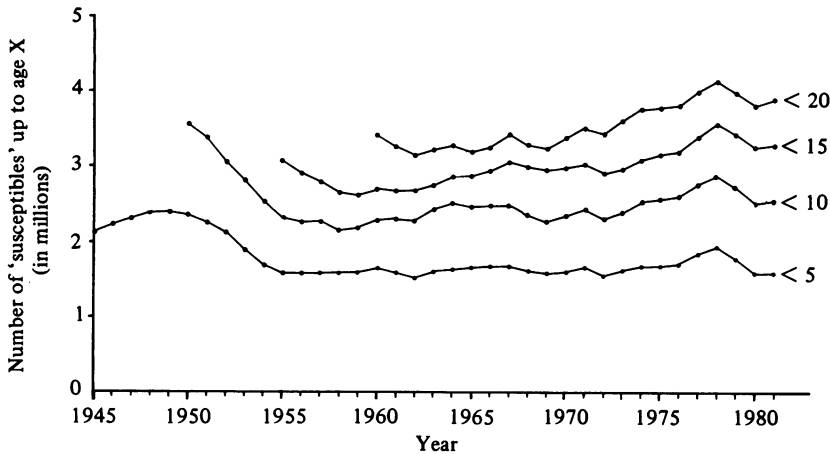
Fig. 7. Estimated numbers of people susceptible to pertussis, below ages 5, 10, 15 and 20, by year since 1945. These estimates are derived from the proportions illustrated in Fig. 6 and age-specific population numbers for England and Wales.

The literature on pertussis in the pre-vaccine era suggests that almost all children had experienced the infection by age 12. Application of detailed age trends, based on North American data, to the England and Wales population provides estimates of 3 and 3·7 million susceptibles for 1940 and 1950 respectively. The precise appropriateness of these age trends for England and Wales may be questioned, but we believe that they are not likely to be far wrong.

The simple epidemic theory approach produced a similar estimate for the threshold number of susceptibles in England and Wales: approximately $3 \times 10^6$. We should note that the theory underlying this calculation is based upon an assumption of a homogenous and random-mixing population. This is surely a suspect description of reality. On the other hand, the extent to which this assumption may be misleading in this context is unclear; and we may at least note that the theory is satisfactory in so far as it explains the continued periodic epidemics (Fig. 4) and it provides an estimate of numbers susceptible which is broadly consistent with other data (Fig. 7).

Our third approach, based upon Lexis analysis, may appear the more credible in that it is based upon recorded figures. On the other hand, there are major problems with the validity of these data, and we have been forced to make bold assumptions concerning unrecorded vaccinations (a linear increase from 0 in 1941 to the first recorded figure of 470 290 completed courses in 1958), notification efficiency (25 % before 1958 falling to 5·5 % in 1976 and 10 % thereafter) and vaccine efficacy (75 %). We provide evidence in support of each of these assumptions, and they predict patterns of immunity distribution (Figs 6 and 7) which appear broadly reasonable, at least in the context of our alternative approaches to the same problem. The robustness of the approach is illustrated in Table 2, which shows that an estimate of between 3 and 5 million susceptibles arises except under rather extreme sets of assumptions.

All of these results are consistent with the theoretical prediction that pertussis behaves according to a mass-action process (Fine & Clarkson, 1982b), with rises and falls of incidence being determined chiefly by rises and falls of numbers

susceptible around a threshold value estimated at approximately 3·5 million people in England and Wales. Theory also predicts that the total number of susceptibles should not be affected by a vaccination programme, unless the vaccination levels are high enough to eradicate the infection from the general population. The data and analyses presented here agree with this prediction. In this sense they agree with similar findings – that vaccination has not reduced the overall numbers susceptible in the population – relating to measles in England and Wales (Fine & Clarkson, 1982*a*). This parallel bears emphasis, lest anyone interpret these findings as a criticism of pertussis vaccine *per se*. The prediction of little change in overall numbers susceptible holds even when a high-quality vaccine is distributed in amounts insufficient to approach eradication of the infection. It is a reflexion of the population dynamics of infections and not of vaccine quality.

Despite the theoretical arguments supporting them, these results should not be accepted uncritically. The data appear to suggest that larger numbers of cases should occur among older people (e.g. above 10 years) than are in fact reported (Table 1). We may thus ask whether these occur as asymptomatic infections, or as unrecognized or unreported disease, or whether the current immunity levels among adults are in fact higher than these analyses suggest. It is hoped that the development and application of sensitive and specific tests for pertussis immunity may resolve this question. In particular it would be of interest to assess the prevalence rate of serological immunity in appropriate samples of 5-, 10- and 20-year-olds in order to monitor trends in the distribution of immunity in the population and to test the predictions made in this paper. Such studies could provide a crucial link between theory and observation which is necessary to resolve continuing arguments over the impact of pertussis vaccines.

## APPENDIX

This $R_0$, or basic reproductive rate, is also defined as the average expected number of secondary cases of infection which would occur after introduction of a single infected case into a fully susceptible population. Thus in a situation where each case contacts 10 persons ($= R_0$), but only 10 % (i.e. $1/R_0$) of these contacts are susceptible, each case would lead on average to only a single secondary case. As this is by definition the circumstance when the population contains precisely the threshold number of susceptibles, we have $1/R_0 = T_E/N$, and thus $T_E = N/R_0$.

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