Public Health

VACCINATION AGAINST WHOOPING-COUGH
Efficacy versus Risks

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Summary Calculations based on the mortality of whooping-cough before 1957 predict accurately the subsequent decline and the present low mortality. Notifications of incidence, though variable and incomplete, follow the same pattern of steady decline in the United Kingdom and are unaffected either by small-scale vaccination beginning about 1948 or by nationwide vaccination beginning in 1957. When valid comparisons can be made, attack-rates may be lower and complications fewer in vaccinated children, but allowance has to be made for overcrowding and socio-economic differences which may be more important as determinants of attack-rates. No protection by vaccination is demonstrable in infants. Adverse reactions and neurotoxicity following vaccinations were studied in 160 cases. In 79, the relationship to pertussis vaccine was strong. In 14 of these cases, reaction was transient but characteristic of a syndrome of shock and cerebral disturbance, which, in the other 65 cases, was followed by convulsions, hyperkinesis, and severe mental defect. It seems likely that most adverse reactions are unreported and that many are overlooked. Precise information about the efficacy and safety of this vaccine is lacking, because existing provisions, national and international, for epidemiological surveillance and evaluation are inadequate. The claim by official bodies that the risks of whooping-cough exceed those of vaccination is questionable, at least in the U.K.

INTRODUCTION

IN circulars[1 2] about immunisation in childhood addressed to all physicians serving Health Authorities and Boards, the Chief Medical Officers for England and Wales and for Scotland expressed concern that, owing to recent controversy about pertussis vaccination, acceptance-rates may fall. On the basis of advice from the Joint Committee on Vaccination and Immunisation[3] and other experts, the Chief Medical Officers emphasise that pertussis vaccine should continue to be offered in a triple vaccine, with diphtheria and tetanus vaccines, during childhood. These recommendations are so strong as to leave no doubt that the writers and their advisers are certain of their grounds. So also, it seems, are the experts who advise the World Health Organisation[4] and the Government of the United States, which recommends even more intensive schedules, including booster doses of pertussis and other vaccines.[5]

It is nevertheless acknowledged by all these authorities that vaccination with *Bordetella pertussis* carries risks of adverse reactions, including, very rarely, an undefined encephalopathy. This risk is thought to be so slight and unpredictable as to be far less than the danger to life and health of whooping-cough.[3]

Most other experts[6–10] tend to support the official view that vaccination is "overwhelmingly beneficial", just as all Health Authorities and Boards seem to have accepted and implemented vaccination. There are, however, some exceptions, chiefly from those who have heeded reports about, or have themselves noted signs of, brain damage after pertussis vaccination.[11–18] No-one has offered exact figures for the incidence of brain damage. Notifications of adverse reactions to the Committee on Safety of Medicines or to manufacturers of the vaccine have not been disclosed officially. The records of some of the major local and health authorities in the U.K. and U.S.A. contain no entries indicative of brain damage. Publications and literature from manufacturers tend to discount reactions and do not mention the possiblity of death or permanent brain damage.[19 20]

In the face of all this, one must pause before contradicting accepted practices. Having paused, I am convinced that adverse reactions are more common and more serious than is generally recognised. Furthermore, examination of national data and a survey of the present position in Glasgow reinforces views already stated[21 22]—namely, that present schedules of vaccination with *B. pertussis* are ineffective and that epidemiological monitoring of efficacy and adverse reactions is incomplete. Additional findings to support these contentions are now presented.

METHODS

(1) National and local data about notifications and hospital admissions for whooping-cough and about vaccinations were obtained and analysed in the way already described.[22] Visits to homes, schools, and clinics were included in the survey.

(2) Information about children who had had adverse reactions after triple vaccine or pertussis vaccine was obtained and checked from various sources, including voluntary associations interested in handicapped children, hospital records, consultant pædiatricians, neurologists, general practitioners, and parents.

RESULTS

National Data

Since notifications are at best incomplete indicators of prevalence and are in no way indicators of severity, the epidemiological trend of whooping-cough was plotted from the figures for mortality in Scotland held by the Registrar General. There was a continuous decline, equal in each sex, from 1937 onward (fig. 1). Vaccination, beginning on a small scale in some places around 1948 and on a national scale in 1957, did not affect the rate of decline if it be assumed that one attack usually confers immunity, as in most major communicable diseases of childhood. The logarithmic regression line (B) between 1943 and 1957 predicts very accurately the subsequent slope of the actual curve to the low level reached in 1963. If the exponent is corrected (line A) to include the recurrence in 1967, it predicts exactly 2·0 deaths (1·7 per million children below 15 years) in 1974 when there were, in fact, 2 deaths. The decay-rate in incidence and mortality in Glasgow during epidemic years is continuous from 1900 until 1957, when large-scale vaccination began. There were no deaths in 485 notified cases out of about 900 estimated cases in the 1974–75 epidemic. In England and Wales there was a sharp rise in

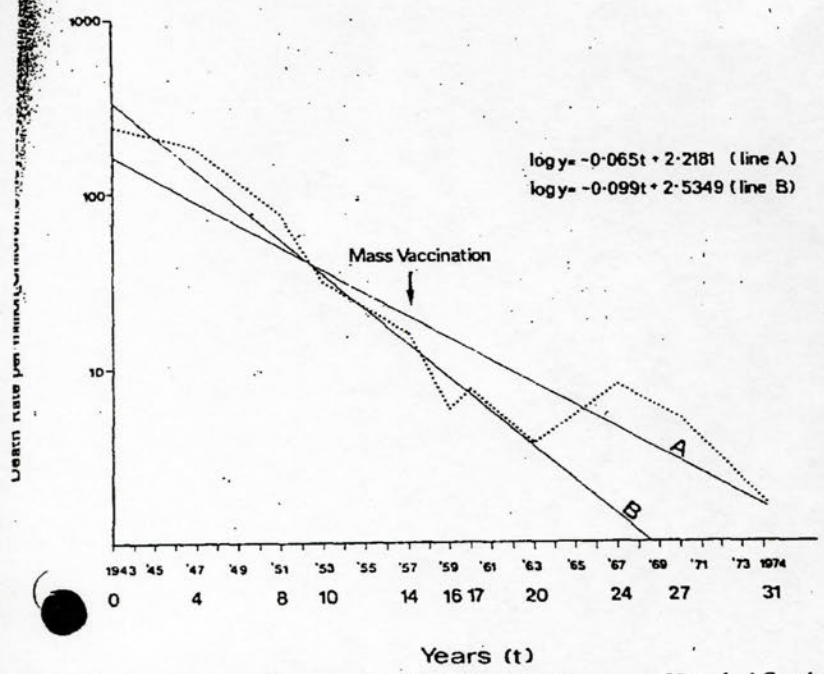

Fig. 1—Death-rates from whooping-cough in epidemic years in Scotland, 1943–74 (0–15 years of age).

1940, but not subsequently until 1965. Including the wartime peak in 1941, the rate of exponential decay in England and Wales is also linear from 1929 until 1957, predicting a death-rate in 1974 of 1·1 as against the actual rate of 1·06 per million children at risk (fig. 2).

Family Study

Incidence (93%) and severity among family contacts were greatest in infants. Among 69 older cases, 47 (68%) had been fully vaccinated. Of the unvaccinated, a significantly higher proportion of children and cases came from overcrowded homes in social classes IV and V. Apart from an excess of unvaccinated female children, there were no other significant differences between the vaccinated and unvaccinated groups (table I). The overall secondary attack-rate was 67%, with no significant difference between "introducers" (mean age 5·9±2·1 years) and "contact" cases (3·8±2·8 years). None of these cases was admitted to hospital.

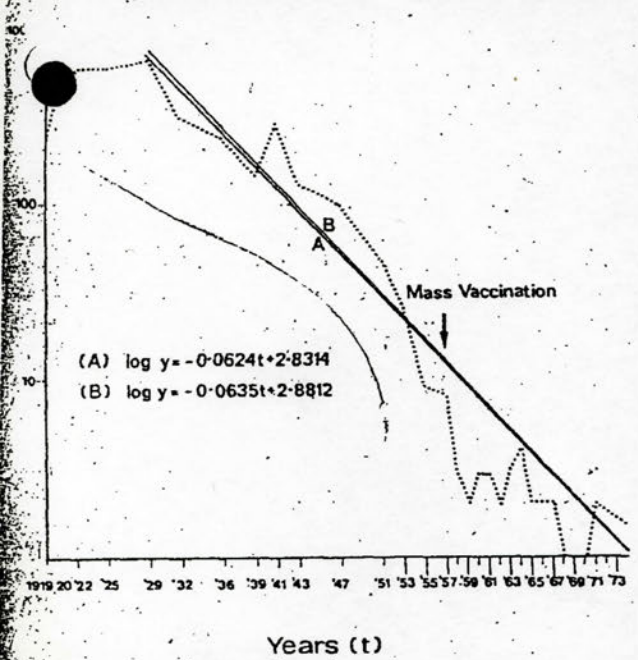

Fig. 2—Death-rates from whooping-cough in epidemic years in England and Wales, 1919–73 (0–15 years of age). Line A excludes and line B includes the 1941 peak.

School Study

59 cases were identified from absence records in ten primary schools. All were either siblings or in the same class as other cases. The majority (61%) of these cases were in children who had received three injections of D.P.T. Notifications in this group by general practitioners to the Health Department were significantly fewer than notifications of whooping-cough in children who were unvaccinated or incompletely vaccinated.

Hospital Study

Between 1935 and 1953, fewer than half the children admitted to hospital in Glasgow because of whooping-cough were infants below one year, whereas in 1970–71 and 1974–75 infants formed 82% and 81% respectively of admissions. The case-fatality rate in 1935 was 37%, diminishing through the '60s (0·8–1·5%) to zero in 1974–75. Average duration of stay in hospital fell from 74 days in 1935 to 39–40 days in 1960–75. Over 30% of cases had severe complications in 1935–41, compared with 9% in 1974–75.

TABLE I—WHOOPING-COUGH IN GLASGOW 1974-75: COMPARISON OF VARIABLES IN VACCINATED AND UNVACCINATED CHILDREN

Variable	Observed/expected
Family contacts (n=112)	
Incidence	No difference
Primary and secondary cases	No difference
Duration of illness	No difference
Severity of illness	No difference
Mean age (excluding 13 infants)	No difference
Females	Higher in unvaccinated ($P<0.05$)
Overcrowding in home	Higher in unvaccinated ($P<0.05$)
Social classes IV–V	Higher in unvaccinated ($P<0.01$)
Incidence of other infectious diseases	No difference
Low birth weight	No difference
School children (n=59)	
Incidence	No difference
Notifications by G.P.	Higher in unvaccinated ($P<0.05$)

Of 203 infants admitted in 1971 and 1974–75, only 5 had received three doses of pertussis vaccine, compared with 178 who had not begun or completed their full course of three injections. Among 49 older children, 9 had received three doses of vaccine, compared with 30 who had received none. The majority (93%) of children admitted were from social classes III, IV, and V, among whom vaccination-rates were appreciably lower than among classes I and II. There was no significant difference between vaccinated and other cases in the presence or absence of *B. pertussis* or in the predominant serotype 1, 3; nor between vaccinated and other children in complications either for the series as a whole or for the smaller group of 141 bacteriologically proven cases.

TABLE II—NEUROTOXICITY OF PERTUSSIS VACCINE

Cases reviewed	160	
Adverse reaction attributed to vaccine*	41	with ensuing mental defect
Adverse reaction* attributed to vaccine on more than one occasion	24	with ensuing mental defect
Transient neurological deficit with partial or complete recovery	14	
Reaction not attributed to vaccine	21	
Further information awaited	60	

* Short time interval; no previous history of same signs; milestones normal; opinion of hospital consultant; no alternative explanation.

Severe complications, such as convulsions, pneumonia, and atelectasis, were more common in infants and younger children who were incompletely vaccinated, more or less in proportion to the higher number of admissions in this category. The incidence of complications in fully vaccinated children was too small for statistical comparison.

ADVERSE REACTIONS AND NEUROTOXICITY

Severe reactions, as estimated from official reports, are extremely rare. 5 infants were admitted to hospitals in Scotland in 1968–72 with encephalopathies soon after injections of D.P.T. If it be assumed that about 270 000 children received about 840 000 injections of D.P.T. during this period, the incidence of encephalopathy is 1 per 54 000 children or 1 per 168 000 injections. All 5 cases were in males. 3 recovered more or less completely, but 2 became mentally retarded.

Such reactions anywhere in the U.K. are supposed to be reported to the Committee on Safety of Medicines, but many are not. It seems that some deaths, and many non-fatal reactions, after injections of D.P.T. were reported to the committee between 1964 and 1975, but no information was available about the exact number and the circumstances of these deaths. More than any other vaccine in common use, pertussis vaccine is known pharmacologically to provoke increased sensitivity to histamine, a decreased response to adrenaline (epinephrine), hypoglycæmia due to increased production of insulin, and alterations in heart-rate, among other effects.[23–27] The vaccine also has powerful adjuvant effects on certain other antigens and allergens. It is known to produce, in some recipients, aggravated responses after second or third injections. These adverse effects cannot be separated from the immunising effect since, at least under experimental conditions, potency is related to the presence of the thermolabile and thermostable toxins.[24–27] The raising of potency levels to above 4 I.U. by international agreement in recent years must therefore increase toxicity. These facts are not stated in manufacturers' literature nor in the advisory and promotional documents sent by the D.H.S.S. to health authorities, doctors, and others. It is stated that adverse reactions may occur, including, very rarely, encephalopathies—without mention of the nature and the symptoms.

A number of cases were brought to my attention by parents and doctors, and they were closely investigated by consultation, by examining records, reports, and letters, and sometimes by referral to colleagues. This investigation is far from complete, but so far the results (table II) indicate that a number of infants and toddlers can be identified as likely victims of the toxic effects. In varying degree, they present a pertussis reaction syndrome with some or all of the following features:

(1) Persistent crying or fits of screaming 4–48 hours after injection.
(2) Marble pallor, rigidity, unresponsiveness, and shock sudden onset within 48 hours of injection, usu within 6–12 hours.
(3) Irritability and interrupted sleep for a few days or lon
(4) Refusal or vomiting of feeds.
(5) Altered response to the parents.
(6) Pareses or localised paralysis.
(7) One or more convulsions with or without pyrexia cyanotic episodes (blue fits).

In some cases, probably the majority, these symptom subside within a few days or weeks. But in other case including at least 65 reported to me, the following sign also appear:

(8) Hyperkinesis.
(9) Infantile spasms extending into convulsions, epileps or salaam fits.
(10) Progressive unresponsiveness to parents.
(11) Flaccid paralysis.
(12) Partial or complete amentia.

Electroencephalograms in such patients may have hypsarrhythmic pattern of random multifocal spikes. In 36 cases in which adverse reactions appeared after a firs or second injection, pertussis vaccine was not given again. In 24 cases, a second or third injection was given and the reaction syndrome recurred in exaggerated forms, and thereafter signs of progressive brain damage ensued. In 40 cases, parents who questioned the safety of the vaccine were assured by their doctors in general practice and in hospitals that there was no connection between their child's condition and the vaccine, but in no case was an alternative diagnosis given. In 17 cases parents were advised that the vaccine might have been responsible for the incident: on review, there were at least 41 cases so classified.

DISCUSSION

These results confirm and extend an inquiry by Bassili and Stewart.[22] The steady decline of whooping-cough between 1930 and 1957 is predictive of linear exponential decay characteristic of a general and progressive lessening in the volume and spread of infection among the susceptible population. With this pattern well established before 1957, there is no evidence that vaccination played a major role in the decline in incidence and mortality in the trend of events. This conclusion does not mean that whooping-cough is no longer a problem. There are residual pockets of infection in Glasgow as elsewhere, in which outbreaks might recur, as in 1970 and 1974, when the epidemic threshold falls as the proportion of newborn susceptible infants rises. The question is: how can susceptibility be reduced in these pockets? The official and orthodox answer is by vaccination during infancy.

The results recorded here show that infants at high risk, with an attack rate of 93%, are not themselves protected. To justify vaccination, it has to be shown therefore, under present conditions, that vaccination of infants produces and maintains immunity in older children, so that they will be less infectious to infants. In the families studied, 70% of "introducers" were themselves fully vaccinated, as were 48% of their contacts. This was a small sample: but it was small mainly because whooping-cough is now an uncommon disease even in a large city in which living conditions in many houses and schools provide ideal conditions for spread. The overall attack-rate of 67% among fully vaccinated children in the family study was close to that in full vaccinated children (61%) in the school study, so it

hat general practitioners are much less likely to whooping-cough in vaccinated children, even the symptoms are typical. The figures may therefore underrate the incidence in vaccinated children.

In this study as in others, vaccination seems to give some protection to children aged 1 year and older. When whooping-cough was much more common, such protection seemed desirable.[28 29] But the present situation in the U.K. is that protection by vaccination is, at best, partial, probably temporary,[30 31] and seldom if ever complete enough to protect the only group which is seriously at risk—namely, infants in crowded homes. Nevertheless, whooping-cough is a distressing disease and even partial protection in children aged 1–10 might be desirable in some situations if vaccination in itself is free from risk. But this is where the main question arises.

Because of the national deficit in epidemiological data and in intelligence, it is impossible to estimate the prevalence of the pertussis reaction syndrome or of subsequent brain damage and mental defect. It is unlikely to be lower than 1 in 60 000, but it might be as high as 1 in 10 000, or, in its transient form, still higher. If it is 1 in 20 000 then at least 30 children will suffer permanent brain damage in the U.K. each year and many more might be started, early in life, on the early stages of an organic dementia which, in its ultimate form, has the features of a demyelinating disease and cerebral atrophy. This risk far exceeds the present risk of death or permanent damage from whooping-cough or even, in some parts of the country, the chance of contracting it.

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WHOOPING-COUGH ADMISSIONS TO A PÆDIATRIC HOSPITAL OVER TEN YEARS

The Protective Value of Immunisation

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Summary 188 children with pertussis were admitted to Derbyshire Children's Hospital over a period of ten years. Fewer immunised children were admitted than would be expected if immunisation were ineffective. Immunisation seemed to decrease the risk of complications and the time spent in hospital. It is suggested that pertussis immunisation is valuable and should perhaps be introduced at an earlier age than is now recommended.

INTRODUCTION

THE value of pertussis immunisation has been questioned continually over recent years, either on the grounds of vaccine inefficiency[1–3] or because of the risk of severe complications due to the vaccine.[4 5] Adverse comment by the mass media is likely to lead to a decrease in pertussis immunisation, unless it can be shown categorically that whooping-cough is still a severe disease and that immunisation protects against it. We therefore decided to look retrospectively at the admissions to Derbyshire Children's Hospital of all children with a diagnosis of whooping-cough over the ten years from January, 1964, to June, 1974.

Derbyshire Children's Hospital serves a population of approximately 50 000 children under five years of age. All children in the area with severe whooping-cough, particularly those with complications, would have been referred to the hospital.

METHOD AND PATIENTS

The case-notes of all admissions classified as pertussis were studied with respect to age, immunisation status, presence or absence of significant lymphocytosis, complications, and time spent in hospital. The diagnosis of whooping-cough was made purely on clinical grounds. Many children had an absolute lymphocytosis, but those children presenting late in the illness, usually because of persistent cough, often did not. Pernasal swabs were not taken routinely, so bacterial isolation could not be used as a criterion for diagnosis.

In Derbyshire, the acceptance-rate for pertussis immunisation has varied: 68% in 1964, 70% in 1965, 74% in 1966, 82% in 1969, and 80% in 1970 and 1971. A figure of 75% has been taken as an approximate average acceptance-rate over the ten years.

Immunisation schedules have also varied over this period. Before 1968, immunisation started at three months of age. From 1968 to 1973, inclusive, it was started at four months. From 1974 onwards, the first injection has been given at six months of age. Hence, when comparing the immunisation status of the children admitted to hospital with that of the general population, those children aged three months or less before 1968, those aged four months or less between 1968 and 1973, and those six months or less when admitted in 1974 were omitted from the calculations, since they were too young to have been offered immunisation.