

## Current topics

# The whooping-cough immunisation controversy

R J ROBINSON

*Department of Paediatrics, Guy's Hospital Medical School, London*

Few subjects in child health have caused so much uncertainty and controversy in recent years as whooping-cough immunisation, its benefits and its dangers. A set of reports<sup>1</sup> from the Committee on the Safety of Medicines and the Joint Committee on Vaccination and Immunisation (JCVI) give the best information so far on this difficult subject, and provide definite answers to at least some of the questions. In summary, they show firstly beyond reasonable doubt that in the few days after pertussis immunisation a child is more likely than at other times to develop an acute neurological illness which may leave permanent neurological handicap. However, this complication of pertussis immunisation is rare, and most acute neurological illnesses of early childhood have other causes. Secondly, the reports suggest that the recommended contraindications to pertussis immunisation are genuine and important because children immunised in spite of contraindications are more likely to suffer neurological complications. Thirdly, the experience of the whooping-cough epidemic in the UK in 1977–79, after the dramatic fall in immunisation rates, leaves no doubt that pertussis immunisation does protect the child against the disease.

The reports have already been commented upon.<sup>2–4</sup> Here we discuss the aspects which are of most concern to paediatricians.

### Two retrospective assessments of pertussis vaccine damage

The first two reports are those of two separate advisory panels set up by the Committee on the Safety of Medicines to examine the data about patients believed to have suffered neurological damage from pertussis immunisation. Both panels worked under the same handicaps as all the other retrospective studies on this subject. There is no specific syndrome which follows pertussis immunisation and which does not occur in unimmunised children. Without figures on the background incidence of acute neurological disorders in child-

hood it is therefore impossible to be certain whether an apparent connection with immunisation is genuinely causal or merely coincidental. The first panel, chaired by Professor J A Dudgeon, examined 50 cases selected on the grounds that the medical information was fairly good. The second panel, chaired by Dr T W Meade, examined 229 case records of children said to have suffered serious events after pertussis immunisation in the period 1970–74. For the reasons already given, neither panel could reach firm conclusions, but the picture emerging from both reports is very similar. It is of children developing fits or acute encephalopathies within a very short period—often less than 24 hours—after any of the 3 doses of pertussis immunisation, and having subsequent severe neurological handicap with mental deficit. In children who developed infantile spasms after immunisation the timing was more difficult to establish because the onset of the disorder is often not clearly recognised, and the causal link was more uncertain. The Meade panel conclude that the data are very unsatisfactory from the epidemiological point of view, but ‘the series gave the panel the very strong impression that diphtheria, tetanus, and pertussis (DTP) vaccine was often responsible for the neurological events that followed.’ This view must be shared by many doctors who have assisted the Vaccine Damage Payments Scheme, and who have studied numerous case records of the kind seen by the Dudgeon and Meade panels. It makes it easy to understand the strength of conviction behind the campaign of the Association of Parents of Vaccine Damaged Children. Nevertheless, strong impressions are not scientific proof, and the subject would still rest in this unsatisfactory state but for the National Childhood Encephalopathy Study.

### National Childhood Encephalopathy Study

To establish whether or not pertussis immunisation can *cause* acute neurological disorders, rather than simply being associated with them by chance, required a study with controls, so that the risks in

immunised and unimmunised children could be compared. This was the purpose of the National Childhood Encephalopathy Study (NCES). The research project was a difficult one both in terms of the scale of organisation and the methodological problems. The research team at the Middlesex and Central Middlesex Hospitals are to be congratulated on the quality of the study and the excellence of their report, but all UK paediatricians (as well as neurosurgeons and infectious disease consultants) can take some share of the credit, because the success rested on their monthly notifications of acute neurological disorders in young children from 1976 to 1979.

The study was a case-control one. All young children with acute neurological disorders (including encephalitis and encephalopathy, prolonged or complicated convulsions, infantile spasms, and Reye's syndrome) were to be reported to the study group irrespective of their immunisation histories, which were later compared with those of control children (two for each case).

The crucial finding is that the 'relative risk'—that is the ratio of the incidence of serious neurological illnesses in immunised to that in unimmunised children—was significantly higher in the 7 days after DTP immunisation, and particularly in the first 72 hours, than in control children of exactly the same age. The magnitude of the relative risk depended on factors such as the age of the child, whether the date of apparent onset of the disorder or of admission to hospital was used for comparison with the controls, and the nature of the neurological disorder (the risks were highest for convulsions and encephalopathy), but in rough general terms children were between two and five times more likely to have an acute neurological disorder in the few days after vaccination than at any other time. A useful extra control is that there was no significant excess of such disorders after diphtheria and tetanus immunisation without pertussis. This finding indicates that it was the pertussis component of the vaccine which was responsible for the neurological reactions, and it also increases confidence in the validity of the findings. There was an increased risk of acute neurological illness in the period from 7 to 14 days after measles vaccination, the relative risks being of the same order of magnitude as for DTP. This finding has occasioned much less comment than the effects of pertussis immunisation, but it is reasonably reassuring that no child had serious lasting neurological damage from measles vaccination.

Thirty-five children had acute neurological illnesses in the 7 days after DTP immunisation, of whom 3 were previously abnormal. We can expect from the risk ratios that in some (perhaps about one-third) the

association was coincidental but that in the remainder there was a causal connection. Of the 32 previously normal children, 21 recovered completely, 2 died, and 9 were neurologically handicapped 1 year later.

Case-control studies do not normally permit calculations of 'attributable risk', which in this study is the part of the incidence of serious neurological illness which is actually caused by pertussis vaccination. However, tentative estimates could be made from the NCES since the study was based on a whole population in which the proportion immunised and the total incidence of acute neurological disorder were known with reasonable accuracy.

With italicised cautions that the figures are not precise, the authors estimate that the attributable risk of a serious neurological disorder after pertussis immunisation is 1 in 110 000 immunisations (injections), and of lasting neurological damage the risk is 1 in 310 000. Assuming a full course of 3 immunisations the risk of lasting neurological damage per immunised child is about 1 in 100 000.

Of the possible sources of error discussed in the report, two should be mentioned. The more serious is that consultants—who all knew the purpose of this study—may have been more likely to notify cases if there was a recent history of immunisation. If there had been important bias of this kind in notifications, the conclusions of the study could be false. However, the authors give reasonable grounds for believing this did not happen. The other possible error is that the study assumed that all children with neurological disorders of the kind attributed to pertussis immunisation would be admitted to hospital. This is almost certainly not true. The Meade report suggests that during 1970–74—a few years earlier than the NCES—up to one-third of such cases were not admitted. The major conclusions about relative risk would not be affected by missing these cases, but the calculations for attributable risk would be too low.

#### **Magnitude of the risk**

The tentative estimate from the NCES is that previously normal children having a full course of DTP vaccination have a risk of about 1 in 100 000 of developing a disorder leading to persistent neurological damage as a result of the vaccination.

Tentative calculations of risk were also made by the Meade panel for the years 1970–74 and these suggested that the frequency of neurological events, after DPT immunisation, which caused persistent brain damage in previously normal children was about 1 in 155 000 injections and about 1 in 53 000 children. In spite of the Committee on the Safety of Medicines' reservations about this figure, it is not vastly different from that of the NCES. If one

assumes that the NCES figure may underestimate the risk, because some patients with neurological reactions to pertussis vaccine were not admitted to hospital, and that the Meade figure may be an overestimate because some of the disorders apparently caused by the vaccine will have been coincidental, the two estimates would become very close.

Previous estimates of the incidence of serious neurological complications have varied from greater than 1 in 10 000 to 1 in 180 000. The best current figures therefore put the risk somewhere between these extremes.

#### **Importance of contraindications to pertussis vaccination**

The contraindications to pertussis vaccination which have been repeatedly emphasised by the DHSS and the JCVI are 'a history of seizures, convulsions or cerebral irritation in the neonatal period. A history or family history of epilepsy or other diseases of the central nervous system.\* Children with neurological defects. Any febrile illness, particularly respiratory, until the patient is fully recovered. Any severe local or general reaction to a preceding dose'. There has been some uncertainty as to whether the presence of one of these contraindications actually makes the child more likely to react adversely to pertussis vaccination, or whether the recommendation is a defensive one in the sense that children whose history has one of the contraindications are at somewhat increased risk of convulsions or other neurological disorders regardless of immunisation, and that these might be incorrectly blamed on immunisation.

The Dudgeon and Meade reports strongly suggest that the contraindications have a sound medical basis. Forty-nine per cent of the cases of serious neurological disorder which the Meade panel regarded as likely to be caused by pertussis immunisation had at least one contraindication to this immunisation, and in the smaller number of cases examined by the Dudgeon panel there was also a significant number in whom the relevant immunisation had been contraindicated. From the purely medical, as well as the medico-legal, point of view it is of the utmost importance to observe the contraindications strictly.

#### **Vaccine Damage Payments Scheme**

The Vaccine Damage Payments Act of 1979 provided for a lump sum of money to be paid to those who

\*The family history contraindication sometimes causes difficulty. It is reasonable to take into account only a family history in parents or siblings, and to ignore any condition which is clearly irrelevant to the child's risk of an adverse reaction to immunisation.

were severely disabled as a result of any of the routine childhood immunisations. The scheme and its operation have been criticised.<sup>5</sup> Many paediatricians were unhappy about the concept of special provision for one small group of handicapped children, believing that help should be based on need rather than cause. However, the Act, which had all-party support, was clearly in line with public opinion. Certainly the ethical issues are complex, because it is arguable that a child undergoing pertussis immunisation does so partly for his own benefit but partly also for the benefit of the community. In any case, the time for arguing the merits of the scheme ended when Parliament had passed the Act, and though some paediatricians and paediatric neurologists have been unwilling to assist in its operation, many others have done so by advising the Vaccine Damage Payments Unit of the DHSS on case records, and by sitting on Vaccine Damage Appeals Tribunals.

Final decisions have now been reached in over 2000 cases of alleged vaccine damage, and it is possible to make some judgments about the operation of the scheme in the light of the NCES and of the Meade and Dudgeon reports. Is it true that '£6m of public money had been dispensed in a highly arbitrary way'?<sup>5</sup> The decision as to whether an individual child's disability was the result of vaccination is always difficult, for the reasons that have made all retrospective studies of the subject difficult. However, experience of the scheme, and in particular of the vaccine damage tribunals, is that they have applied exactly the same criteria as those used by the Meade panel. In order of importance, these are: Was there a close time relationship between the immunisation and the onset of the suspected reaction? Was there any other explanation for the child's illness or his later disability? Has the history been consistent? It is also helpful if the role of immunisation was questioned at the time of the original events.

Does the number of claims allowed correspond reasonably with the expected number of cases of pertussis vaccine damage? Up to 20 January 1981, 2683 claims had been made, of which 607 had been successful (339 at the first application and 268 after appeal to tribunals).<sup>5</sup> The final number of successful claims from this batch is likely to be about 700. The scheme relates to other vaccinations apart from pertussis: of the first 579 awards, 432 related to vaccines or combinations including pertussis (DHSS, 1981, personal communication). We can therefore expect that the 700 successful claims relating to vaccinations given from 1948 to 1980 will include about 520 where pertussis immunisation was incriminated.

In the years 1958-79 the total number of children

receiving complete courses of pertussis immunisation in the UK was 13 209 212. The expected number of cases of persistent neurological damage from these vaccinations would be 132 applying the NCES figures and 249 applying the Meade figures.

There are three reasons why these calculations underestimate the expected number of successful claims for pertussis vaccine damage. Firstly, they only refer to the years after 1957 when DTP immunisation was nationally recommended. However, it had been used by many local health authorities since the early 1950s. Secondly, the figures refer only to completed courses of 3 immunisations, and about another 10% should be added for children having incomplete courses. Thirdly, and most important, the Vaccine Damage Payment Act lays down that the question as to whether vaccination was responsible for the disability shall be determined on the balance of probability. This means that those making the decision have to be satisfied that there is more than a 50% probability of the vaccine being responsible, not that this is established beyond reasonable doubt. It can be expected that the number of awards made will therefore exceed the number of cases of vaccine damage suggested by rigorous scientific investigation. Taking these three factors into account it seems reasonable to expect that the total number of awards for pertussis vaccine damage so far would be at least double the number calculated from the 1958–79 immunisation figures. The NCES calculation would then suggest 264 and the Meade calculation 498. All these calculations are subject to substantial margins of error, as stressed by NCES and Meade, and the individual decisions made under the Vaccine Damage Payments Scheme are usually difficult. All that could reasonably be hoped is that the number of awards made should look of the right order of magnitude. The actual figure of 520 corresponds remarkably well with an expected 264 to 498, and suggests that those operating the scheme are getting it about right.

#### 1977–79 pertussis epidemic

The reports do not assess numerically the relative risks and benefits of pertussis immunisation but the JCVI reaffirm their advice that the benefits outweigh the risks. The final report in the booklet is an account by the JCVI of the 1977–79 whooping cough epidemic

in the UK and it provides strong evidence of the efficacy of vaccination and of the potential seriousness of the illness.

The acceptance rate for pertussis immunisation in England fell from 79% in 1973 to 31% in 1978. From late 1977 there occurred the largest outbreak of whooping cough since vaccination was nationally recommended. In contrast to previous epidemics the attack rate was far higher in children under 5 (who were less likely to have been vaccinated), and geographically the attack rate was especially high where vaccination acceptance rates had been lowest.

There were at least 28 deaths from whooping cough during the epidemic, which may be compared with 2 deaths from neurological illnesses after DTP (of which one was probably unrelated to immunisation) in the 3 years of the NCES. The JCVI report also indicates that the illness in the 1977–79 epidemic was often protracted and debilitating, usually lasting 10–12 weeks. They estimate that there may have been 5000 hospital admissions, 200 cases of pneumonia, and 83 of convulsions, and point out that the late effects are still unknown.

This experience certainly suggests that pertussis immunisation confers a substantial degree of protection and that the JCVI is correct in recommending that the benefits of pertussis immunisation outweigh the risks provided there is strict attention to the contraindications.

#### References

- 1 Goldberg A, Badenoch J. *Whooping cough. Reports from the Committee on Safety of Medicines and the Joint Committee on Vaccination and Immunization*. London: HMSO, 1981.
- 2 Anonymous. Pertussis vaccine. *Br Med J* 1981; **282**: 1563–4.
- 3 Anonymous. Further contributions to the pertussis vaccine debate. *Lancet* 1981; **i**: 1113–4.
- 4 Anonymous. Vaccination against whooping cough. *Lancet* 1981; **i**: 1138–9.
- 5 Appleyard W J. Vaccine damage payments scheme criticised. In a report on the Joint Consultants Committee meeting, Edinburgh, 7 April 1981. *Br Med J* 1981; **282**: 1333.

Correspondence to Professor R J Robinson, Department of Paediatrics, Guy's Hospital Medical School, St Thomas Street, London SE1 9RT.

Received 18 June 1981