

COMMERCIAL IN CONFIDENCE

COMMITTEE ON SAFETY OF MEDICINES

JOINT COMMITTEE ON VACCINATION AND IMMUNISATION

JOINT SUB-COMMITTEE ON ADVERSE REACTIONS TO VACCINES AND IMMUNOLOGICAL PRODUCTS

Minutes of the meeting held on 6 June 1986 in Room 1611/12, Market Towers.

Present: Professor R W Gilliatt (Chairman)
Sir John Badenoch
Dr A L Bussey ← Prof. Banatvala
Dr P E M Fine ← Prof. Glynn.
Professor D Hull
Dr B M McGuinness
Dr C L Miller
Professor D L Miller
Dr D Reid
Dr S J Wallace

DHSS

Dr J Barnes
Dr J R H Berrie
Dr F Rotblat
Mr K L Fowler (Secretary)
Mr J P Digings

Centers for Disease Control, Atlanta, Georgia, USA

1. Confidentiality and announcements

The Chairman reminded members that the proceedings, papers and information before them were confidential and should not be disclosed. He welcomed from the Centers for Disease Control, Atlanta and Dr Rotblat, to the meeting.

2. Apologies for absence

Apologies were received from Professor Lloyd and Dr J W G Smith.

3. Minutes of the meeting held on 7 February 1986

Item 5. DTP vaccine given to children in the National Childhood Encephalopathy Study within 28 days before the onset of acute neurological illness

It was suggested that the last sentence be amended to read:

"The Sub-Committee suggested that measures should be taken to ensure that health authorities use adsorbed vaccines in preference to plain vaccines."

Item 6.4 Response of pre-term infants to diphtheria/tetanus/
pertussis immunisation-Bern J C et al. Journal of Paediatrics
Vol 107; pages 184-188

It was suggested that the last sentence of this be deleted.

Item 6.5.1 Proposal for the surveillance of severe neurological
disorders in infancy and their relationship to pertussis vaccine

Second paragraph, line 11 - delete '1988' and replace by '1990'.

Apart from typographical amendments, the minutes were agreed and were signed by the Chairman as a true record of the meeting.

4. Matters arising

4.1 Item 5~~A~~ Suspected adverse reactions associated with diphtheria/
pertussis/tetanus vaccine and with Trivax and Trivax AD

_____ said that he wished to comment on this paper which had been submitted to the February meeting when he was unfortunately not able to attend. It was agreed that this paper would be reconsidered at a subsequent meeting.

4.2 Item 8 BCG and keloid scars

_____ reported that the BCG Sub-Committee were writing to plastic surgeons about scars. She also reported that she was following up children with large ulcers encountered in her present study; so far there have been none with progressive enlargement of the ulcer or with continuing discharge after three months.

4.3 Item 10 Cholera and typhoid vaccines

It was agreed to defer consideration of this paper until ^athe subsequent meeting

4.4 Item 5.1 Response to _____ letter

ARVI(86)19

The correspondence with _____ is noted.

4.5 Item 5.3 Sudden Infant Death Syndrome (SIDS) in relation to the
administration of DPT vaccine

4.5.1 Infant deaths associated with vaccination -

ARVI(86)20

Paper by the Department

The Sub-Committee reviewed a paper from the Department giving a seasonal incidence of reported SIDS between December 1984 and May 1986, as well as the interval between vaccination and death. _____ made the point that it was useful to know the date of the Yellow Card report as well as the date of the incident. This enabled one to tell whether the reports were being received as a result of publicity or whether they were part of steady background rate of reporting.

reminded the meeting that the Departmental statistical paper considered at the last meeting suggested an incidence of SIDS occurring within 24 hours of vaccination as being about four to six cases a year. *by chance* had agreed that in spite of the constraints of such a calculation *of* this estimate was ~~in~~ the correct order of magnitude. It was agreed to look at this subject again when the US studies were published. He invited to speak on the American study on SIDS. said that with regard to the NIH study by Hoffman et al, this had been completed and submitted to Paediatrics. The Journal had asked and others at CDC to comment on the paper and they had asked for some changes. He agreed that the results showed vaccination to be slightly less common in the SIDS group than in controls, and that while the study excluded vaccination as a common cause of SIDS, it did not exclude a rare but real association. He added that American bodies representing concerned parents were also making criticisms of the study; one of them was that by its definition of SIDS the study excluded "toxic deaths" in which children developed a vaccine-related illness and then died. For this reason, CDC is looking at all deaths, not merely SIDS.

4.5.2 Immunisation and SIDS - Summary of a paper by

ARVI(86)21

The meeting noted this abstract and asked to obtain the complete paper *in due course* together with the work done by Emery at Sheffield. observed that these were unexpected deaths which are slightly different from SIDS as usually defined.

4.6 Poliovaccine for families of immuno-suppressed patients

At the end of matters arising raised the question of the use of live and killed poliomyelitis vaccine in families in which there was an immuno-deficient or immuno-suppressed child. She had raised this matter at a previous meeting and was now asking what had happened. agreed to raise this matter with the Joint BPA/JCVI Working Group.

5. AMA Panel Report on Pertussis Vaccine Injury (JAMA 1985 Vol 254, pages 3083 - 3084)

5.1 said that this report had been prepared in a form which might be helpful to Congress when considering a possible compensation for vaccine injury. The report identified severe irreversible vaccine reactions and the criteria for attributing such reactions to DPT vaccine and, second, severe reversible DPT reactions. The report used the known relative risk of the vaccine to estimate the probability that an event was caused by the vaccine. then gave the Committee the basis of some of the numerical calculations in the report.

5.2 Encephalopathy

The definition of this condition was a very conservative interpretation of the NCES but with an onset within 72 hours. The report used the NCES estimation of relative risk of 3:1, it was estimated that one third of such cases have permanent handicap one year from their onset (as derived from the NCES).

5.3 Complex Febrile Convulsions

These were defined as being of more than 10 minutes duration, or repetitive over 24 hours, or of a focal nature. In such cases convulsions are thought to be due to fever and there is no other demonstrable cause. Vaccine could cause such seizures and it was believed that 10 per cent of such complex seizures could result in permanent handicap (there was no ~~reference~~ ^{source given for} to this but this belief was the impression of the Panel).

5.4 Afebrile convulsions

To be pertussis vaccine related these seizures must develop within 72 hours of administration in a patient with no evidence of pre-existing neurological damage. (If such convulsions develop within 24 hours of vaccination, then they might be regarded as encephalopathy.) There was uncertainty as to whether or not these could be caused by pertussis vaccine at all. More than two thirds of cases are likely to have aetiologies other than the vaccine.

5.5 Simple febrile convulsions

These are defined in the report as convulsions lasting less than 10 minutes and which occurred within 24 hours of the administration of DPT vaccine. It was the opinion of the Panel that the 'probability' of simple febrile convulsions being the result of pertussis vaccine is 100 per cent and that there would be no persistent sequelae. The Panel considered that if no other cause could be found 100 per cent of these reactions were ~~associated with~~ ^{attributable to} vaccine and that sequelae were unlikely.

5.6 Shock and Collapse

Signs of vascular collapse, muscular hypotonicity and unresponsiveness for 10 or more minutes with or without fever but without paralysis or seizure. This condition is not a specific pertussis vaccine related event and has been reported with other vaccines. It was considered that the probability was that the DPT could cause 100 per cent of these reactions and that Cody et al had reported complete recovery following these reactions.

5.7 In the general discussion which followed, some members of the Committee felt that the report not only accepted the fact that vaccine damage was a real phenomenon but implied (by the way it was written) that it was commoner than was believed to be the case in the UK. It was agreed that a small Working Party should prepare a position paper taking into account recent proceedings in court in this country, and the AMA Panel Report.

_____ and _____ agreed to serve on the Working Party. The Chairman asked _____ to prepare a position paper relating to the National Childhood Encephalopathy Study. Professor Hull asked when the final report on the NCES was to be published.

6. Litigation and pertussis vaccination

6.1 _____ referred to the June issue of the American Journal of Diseases of Childhood. He said that between 18 and 22 million doses of DPT were manufactured annually in the United States prior to the difficulties concerning whooping cough vaccine and litigation.

1984 the uptake of the vaccine totalled less than 16 million a. a shortage of vaccine. There are annually 3.7 million births before the shortfall in the provision of DPT indicates that there is an increase in uptake of diphtheria and tetanus vaccine.

Since 1985, the price of the vaccine has risen from 40 cents per dose to \$1.10 per dose in 1986 and it is expected to rise to \$1.11 per dose. Litigation claims have risen from virtually nil in 1978/79 to over 219 in 1985, claiming a billion US dollars, and litigation suits per million doses follow a similar pattern. The total amount claimed has likewise increased greatly.

6.2 said that out of court settlements had not been included in these figures. It was difficult to protect manufacturers against such heavy compensation claims. The situation had been aggravated by an organisation called 'Dissatisfied Parents Together'. The Hawkins Congressional Commission suggested that claimants might go into a system with a Panel and if accepted would be given an award of \$1 million or alternatively accept a court settlement. There was also a Bill before the American Government which suggested that the punitive damages be done away with and that damages for pain and suffering only be awarded.

Acellular Vaccines

7.1 reported that a team from the United States had visited Japan to assess the efficacy of Japanese acellular vaccines and acquire data on adverse reactions. He said that studies on acellular vaccines had been carried out in Japan, Sweden and the USA and that vaccines were being developed in France and the United Kingdom. With regard to adverse reactions, he made the point that only the Japanese had used the new vaccines for long enough to have information about serious reactions.

7.2 In Japan prior to 1975, whole cell vaccines were routinely administered as three doses commencing at three months of age with a booster dose at 18 months. In 1975, two deaths occurred within 24 hours of vaccination and the vaccine was withdrawn; this was followed by a major epidemic of whooping cough in the late 1970s. Whole cell vaccines were reintroduced in the late 1970s but the age of commencement of vaccination was raised to two years. In September 1981, acellular vaccines were introduced for routine use in two year old children and now 82 per cent of children get acellular vaccine.

7.3 Serious adverse reactions with sequelae and deaths had an incidence of 2.47 per million doses during the period 1970 to 1974 - when immunisation commenced at three months of age. The rate of serious reactions fell to 0.4 per million doses during the period 1975 to 1980 when the administration of whole cell vaccine commenced after the age of two years. During the period 1981 to 1984, the incidence of severe adverse reactions was 0.25 per million; during this period acellular vaccine was used. There appears to be little difference in the rate of serious adverse reactions to whole-cell vaccine (0.4 per million) given at 24 months compared with acellular vaccine (0.25 per million doses) also given at 24 months. The comparable incidence for less serious reactions without sequelae was 1.46 per million doses for the period 1975 to 1980 and 0.64 per million doses for the period 1981 to 1984. said that the Japanese were now considering whether or not to lower the age at which vaccination should be commenced.

8. Do seizures in children cause intellectual deterioration? ARVI(86)
Jonas H Ellenberg, Deborah G Hirtz and Karin B Nelson
New England Journal of Medicine; Vol 314, Pages 1085-1088

said that the data for this study had been taken from a very large cohort of children, the Collaborative Perinatal Project of the National Institute Neurological and Communicative Disorders ^{and Stroke} (NINCDS). The IQ at seven years in children with seizures did not differ significantly from those in controls matched for IQ (determined at a four year assessment), sex, race and socio-economic status. The study concluded that non-febrile seizures were not associated with a significant change in full-scale IQ.

9. Pertussis vaccine and whooping cough as risk factors in acute neurological illness and death in young children ARVI(86)2
D Miller, Jane Wadsworth, Judith Diamond and E Ross
Proceedings of the Fourth International Symposium on Pertussis
Joint IABS/WHO Meeting, Geneva, Switzerland, 1984.
Develop. Biol. Standard Vol 61, pages 389-394

remarked that this paper had been seen in draft by the Committee.

10. Frequency of true adverse reactions to measles-mumps-rubella vaccine ARVI(86)2
A Double-blind Placebo-controlled Trial in Twins
Heikki Peltola and Olli P Heinonen
The Lancet, 26 April 1986, page 939

The meeting noted that vaccination had been carried out between the ages of 14 months to six years with no preliminary screening for immunity, therefore, one might expect 50 per cent of the trial population to be immune. [redacted] pointed out that the zygosity of twins was not defined. The Committee agreed that: (1) [redacted] should ask [redacted] to write a short review of this paper; (2) that the authors be asked to provide information on the history of measles, rubella and zygosity in children having reactions except the minor ones described as nausea, vomiting and coryza.

11. Summary of suspected adverse reactions to vaccines: ARVI(86)2
Reports on Yellow Cards registered during the period
15 January 1986 to 12 May 1986 - Paper by the Department

introduced this paper:

- i. Suspected adverse reactions to diphtheria, tetanus and pertussis vaccine (DPT) given alone or with oral poliovaccine (OPV)

During the current period 52 adverse reactions were reported. These included:

- a. Two sudden infant deaths in (i) 160227 a four-month old girl who was given her first dose of triple vaccine on 7 January 1986. She died two hours later. A subsequent autopsy revealed no significant findings. (ii) 161923 a 10-month old boy who received his third dose of DPT on 14 April 1986, and was found dead on 15 April 1986. Post-mortem revealed an interstitial broncho-pneumonia. ~~Death was attributed to SIDS.~~

b. 160915 One case of meningitis in a seven-month old female received a dose of DPT and OPV on 24 January 1986. On admission to hospital her CSF was found to have an increased cell content and she was observed to be drowsy and to have twitching. A diagnosis of aseptic meningitis was made. The Committee asked for more details about this patient.

ii. Suspected adverse reactions to Monovalent pertussis vaccine

a. Cot Death

156659 An eight month old male who died 12 days after receiving a dose of monovalent pertussis vaccine. Diagnosed as cot death.

b. Encephalitis

157274 A two year old girl who two days after vaccination was febrile, irritable and screaming. She was diagnosed as encephalitis.

c. 157861 Convulsion in a 22-month old girl after her third dose of pertussis vaccine.

iii. Suspected adverse reactions to diphtheria, tetanus vaccine given with or without OPV

During the current period 61 reports were registered; 58 of these were after booster doses and the majority were injection site disorders.

iv. Suspected adverse reactions to tetanus vaccine

Ninety-three reports were registered during the period; these included 67 injection site disorders and one report of Guillain Barré syndrome in a 15 year old boy who was vaccinated on 24 October 1985 and developed symptoms on 8 November 1985. He was reported to have recovered.

v. Suspected adverse reactions to measles vaccine

Twenty-eight reports were received. These included:

a. 157602 A death in an 18-month old boy who was vaccinated against measles on 16 December 1984. Death occurred 10 days after vaccination. The patient gave a history of two previous episodes of febrile convulsions and although on the occasion of his death no convulsions were noted he was extremely hot and had a temperature of 38°C half an hour after death.

The Committee asked if a brother who was a SIDS case was a blood relation or adopted. Also, did the patient receive measles immunoglobulin or anti-convulsants?

b. There were reports of six suspected convulsions after vaccination.

vi. Suspected adverse reactions to rubella vaccine

During the period 11 reports were received. These included:

157976 One patient who developed pruritic rash and broncho-spasm after vaccination.

vii Suspected adverse reactions to BCG

Twenty-four reactions were reported. These included:

Nineteen injection site disorders.

viii. Suspected adverse reactions to influenza vaccine

Ten reactions were reported. These included:

a. Two reports of Guillain Barré syndrome.

i. 157596 A 70 year old man who developed transverse myelopathy an four days after vaccination, he was reported to have made only a minimal recovery.

ii. 157822 An 86 year old woman who developed GBS in November following vaccination in October. She is stated to be recovering.

The Committee asked what interval had occurred between vaccination and onset of GBS.

b. 154706 A major fit in a 21 year old female

Nine hours after vaccination this patient was already taking anti-convulsants.

c. Encephalopathy

159686 One case of encephalopathy in a 61 year old male patient, who developed illness one week after vaccination was reported. The Committee asked for further details of examination of this patient's CSF.

ix. Suspected adverse reactions to typhoid and cholera vaccines given singly or together

There were 11 reports including one convulsion which is to be followed-up.

x. Suspected adverse reactions to house mite desensitising agent and grass pollen vaccines

Seventeen reports were made during the period including one patient with fatal anaphylaxis occurring two minutes after injection. In addition there were three reports of anaphylactoid reactions occurring shortly after vaccination and two reports of bronchospasm. The Committee suggested that a paper on the treatment of anaphylaxis be prepared for the next meeting. *problem*

12. Any other business

discussed vaccination policy in relation to symptomless HTLV-III carriers. He considered that inactivated vaccines could be used safely. The possibility that they might make the patient's lymphocytes more susceptible to the spread of HTLV-III virus was considered to be a theoretical risk only. One hundred and thirty six children who were carriers as a result of perinatal infection had received one or more doses of DPT and OPV without severe reactions and this was reassuring. There was some evidence, however, that their antibody responses were

sub-normal. There was one case of generalised vaccinia in a symptomless sero-positive army recruit after smallpox vaccination. considered that the use of IPV in place of OPV would be wise in sero-positive children. Members noted that the JCVI were due to reconsider this subject at their next meeting.

13. Date and time of next meeting

The next meeting is to be held on Friday 3 October, at 11 am.