ITEM
14.1

NOT FOR PUBLICATION ARVI 86/3rd Meeting

COMMERCIAL IN CONFIDENCE

COMMITTEE ON SAFETY OF MEDICINES

JOINT COMMITTEE ON VACCINATIONS AND IMMUNISATION

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

Minutes of the meeting held on 3rd October 1986 in Room 1611/12, Market Towers.

Present: Professor R W Gilliatt (Chairman)
Sir John Badenoch
Professor Banatvala
Dr P E M Fine
Professor Glynn
Professor D Hull
Professor J K Lloyd
Dr B M McGuinness
Dr C L Miller
Professor D L Miller
Dr D Reid
Dr J W G Smith
Dr S J Wallace

DHSS

Dr J Barnes
Dr J R H Berrie
Dr F Rotblat
Dr S Wood
Mr K L Fowler (Secretary)

1. Confidentiality and annoucements

The Chairman reminded members that the proceedings, papers and information before them were confidential and should not be disclosed. He welcomed Mrs Jane Wadsworth and Dr S Wood to the meeting.

2. Apologies for absence

Apologies were received from Dr Covell.

3. Minutes of the meeting held on 6 June 1986

Page 8 Item x. Suspected adverse reactions to housemite desensitising agent and grass pollen vaccines. Penultimate and last lines delete 'the treatment of' replace with 'the problem of'. Apart from this, subject to minor correction of wording and grammatical errors, the minutes were signed as a correct record.

4. Matters arising

Item 4.1 which referred to Item 5 of a subject discussed in a meeting of February 1986 - suspected adverse reactions associated with diphtheria/pertusis/tetanus vaccine and with id reminded members of caution concerning this paper at the last

meeting. said that there was a proviso that the National Childhood Encephalopathy Study (NCES) did not ask the question as to whether a vaccine was absorbed or plain. Therefore it was necessary to contact the manufacturer to obtain this information and the information was not complete. reminded the meeting that in his paper* had found systemic and local reactions less with adsorbed vaccine.

It was agreed to review the figures in this paper at a future meeting.

Item 10 Frequency of true adverse reactions to measles-mumps-rubella vaccine

(Peltola and Heinonen, Lancet 1986 i 939)

Sub-paragraph a. said that the reply he had received from indicated that he could not immediately provide the information requested.

Sub-paragraph b. introduced his review of the Peltola and Heinonen paper which described the reactogenicity of MMR vaccine in children in the age range 14 months to 6 years. The paper indicated that the vaccine was well tolerated; however, some of the children in the survey had presumably experienced natural infection with these viruses. Therefore it would be helpful if the subjects could be classified by age. This would provide some idea of the likelihood of immunity at the time of vaccination. Serological examinations on these children would be helpful. The meeting observed that little or no adverse reactions to MMR vaccine had been reported in the United States. Members emphasised the importance of obtaining as much knowledge as possible regarding the safety of MMR vaccine. observed that measles was prevalent in Finland just before this study commenced. It was agreed to write again to asking if an age classification of the trial subjects could be provided together with an indication as to the zygosity of the twins. Such information could perhaps be incorporated in a letter to the Lancet.

Item 11 Summary of suspected adverse reactions to vaccines.

Sub-paragraph i. Suspected adverse reactions to DPT, last two lines - pointed out that if post-mortem revealed an interstitial broncho-pneumonia, death could not be attributed to the sudden infant death syndrome.

Item 12 Any other business - Vaccination policy with regard to symptomless HTLV-III carriers. reported that US policy had now been published in the US Mortality Morbidity Weekly Return No 38, 26 September 1986, Volume 36 Pages 595-606, and also that the subject would be discussed at the next meeting of the JCVI.

5. Report of a Working Party on Pertussis Vaccine Injury

At the February 1986 meeting ARVI had received a report prepared by a panel of the AMA (JAMA 1986, 254, 3083). Its object had apparently been to provide information for legislators as to what type of vaccine-associated event might require compensation, if Federal compensation for presumed vaccine injury were to be introduced in the United States. In attempting to produce simple guidelines the panel had drawn on previously published work and had made some assumptions of their own. No sources were given in the report and ARVI had viewed it with some concern.

* T M Pollock et al - Symptoms after primary immunisation with DTP and DT vaccines. Lancet: 1984 Vol ii pages 146-149.

It was agreed that a small working party ,) should review this report and prepare comments for the October meeting. In view of some questions about the National Childhood Encephalopathy Study (NCES) which had been raised in recent court proceedings, it was agreed that the working party should also review these and make any comments that seemed appropriate.

The working party met on July 31st at St Mary's Hospital, where it had the help of two members of team.

5.1 The following points relating to the NCES were discussed.

1. Queries had arisen in relation to the numbers of cases in the study, which had varied slightly in different publications, as late follow-up rsults came through. The working party had established that the final number of cases in the NCES was 1,167. 39 cases had received triple vaccine in the week prior to the onset of their neurological illness (9 with infantile spasms, 18 with convulsions, and 12 with encephalopathies). These vaccine-associated cases included 5 patients (4 with convulsions and 1 with infantile spasms) who had a history of neurological events before immunisation which indicated possible prior abnormality. These numbers differed from those published in the 1981 Whooping Cough Report (HMSO).

2. A query had been raised over the accuracy of dates. It was accepted that it was sometimes difficult for the NCES team to decide the day of onset of a neurological illness. If there was conflict between information from different sources the team normally took the information from the paediatrician's admission record. Professor Miller also made it clear that day 0 was always the day of vaccination, regardless of the time of day of vaccination.

3. The question of selective reporting by paediatric units to the NCES team was discussed. It was not thought that this would have been a problem in respect of children admitted to hospital with encephalopathy. The reporting of children admitted to hospital with convulsions was a different matter, since many more children would have been admitted than the few who fulfilled the NCES criteria for reporting. In considering whether a convulsion was more likely to be reported because it was known that the patient had received triple vaccine within a few days, the following points were made:

a. It was emphasised that to account for the observed increase in relative risk for all cases after the vaccine, under-reporting of similar cases in unvaccinated children would have to have involved at least 500 reports.

b. The ratio of convulsions to encephalopathies was similar in the vaccine-associated group to that in the unvaccinated group.

c. Although the exact ages at which different doses of vaccine were given were not known for the whole population, in the NCES there were 7 convulsions reported within one week of the first dose of DPT, compared with 5 after the second dose, and 6 after the third. This ratio was not what would have been expected if doctors had merely been reporting chance associations. In the latter case, one would expect many more convulsions after the third dose, since febrile convulsions are commoner in the general population at the end of the first year of life than at

three or six months.

From the above there is reason to believe that the increased relative risk of prolonged convulsions after DPT was a real one.

4. Suggestions had been made that post-pertussis vaccine convulsions were benign and that they did not give rise to bad outcomes. was asked for information on sequelae after both vaccine associated and non-vaccine associated convulsions in children of comparable age.

5. Queries had been raised with regard to long-term sequelae after vaccine-associated encephalopathy. The working party had reviewed the methods of assessment of handicap, which had been refined by team during the course of their work. Among 12 children with encephalopathy there were 2 deaths, and 5 children with impairment of varying severity at 1 year. The relative risk for an acute vaccine-associated illness (convulsions or encephalopathy) was 3.3, and was similar irrespective of degree of impairment.

6. Questions had been asked about the inclusion among the vaccine-associated cases of those in which a possible alternative cause for the encephalopathy had been put forward. It was, however, accepted by ARVI members that cases should not be removed from the calculation of risk in an epidemiological study of this kind, because an alternative diagnosis was possible. The numbers were in any case small, and the removal of cases of possible Reye's syndrome, or possible viral encephalitis, from both vaccine-associated and unassociated groups did not alter the relative risk, but only affected the confidence limits due to the reduction in numbers.

At the end of the discussion, commented that ARVI members had now had a chance to appreciate the difficulties inherent in this type of study.

5.2 The AMA Panel Report on Pertussis Vaccine Injury

(JAMA, 1985, 254 3083-4)

Turning to the AMA panel report, ARVI members noted that this had been prepared with the particular intention of providing information for legislators as to what type of vaccine-associated event might require compensation, if Federal compensation for presumed vaccine injury were to be introduced. It was therefore the intention of the panel to suggest simple guidelines for which "stringent proof for causation by the vaccine was not required". ARVI members commented that they were not aware of all the sources used; while some appeared to be from the NCES, others clearly were not. Furthermore, it was agreed that the document contained a number of assertions which could not be accepted. It was not a scientific statement of the position. Indeed, the AMA Panel itself frequently acknowledged that its conclusions were based upon impressions and opinions, rather than upon established evidence.

5.3 Paper by Kennedy et al: A major role for viruses in acute childhood encephalopathy

(Lancet 1986 Vol 1 pp 989-991)

ARVI members received for information the paper on viral encephalitis by Kennedy et al. While it was accepted that intensive studies of the kind described in this paper could lead to the identification of a viral cause in a much higher proportion of children with encephalitis than had been possible a few years ago, it was noted that few of the children were, in fact, in the age group relevant to the NCES.

5.4 drew the attention of the meeting to the paper:- Cause and Prevention of Post-Infectious and Post-Vaccinal Neuropathies in light of a new theory of auto-immunity (Fred C Westholl and Robert Rott-Bernstein The Lancet 2nd August 1986). Members reported that the paper was interesting although it was correctly categorised under hypothesis. References quoted were sometimes out of context and were of differing intrinsic worth.

6. Review of the Safety and Efficacy of Densensitizing Vaccines
ARVI/86/29 (a), (b) and (c)

introducing this paper said that the adverse reactions section of Medicines Division had for some time been worried about serious anaphylactoid reactions associated with the densensitizing agents, and that this concern had been heightened this year by fatal anaphylactic reactions in two young females after receiving these agents. Medicines Division had reacted accordingly, and together with information provided by manufacturers had produced a paper on these vaccines. explained that because of the concern over adverse reactions and the need to bring this matter to the main committee, timing of meetings had made it necessary to discuss this paper with other sub-committees and the CSM before ARVI.

With regard to the paper said that there were difficulties in standardisation of these products and specifying the content of allergen. The evidence as to efficacy was both controversial and poor, especially with regard to house dust mite preparations. There had been initially difficulty over collating the adverse reactions since the data from manufacturers and that supplied to the CSM on yellow cards were not altogether compatible; however, it had now proved possible to combine these two soures of ADR data and to estimate the incidence of reactions. Anaphylaxis had occurred with these products even at low allergen concentrations. The US FDA review of these vaccines was confused because of legal restraints in the reclassification of the products. In Sweden doctors who administer these products have to be specially licensed.

The Biologicals Sub-Committee had made recommendations on these products as had also SEAR. The CSM had recommended that a letter should be sent to all doctors, dentists and pharmacists warning about the risk of anaphylaxis following treatment with densensitizing agents. The advice included in this warning would include a recommendation that the administration of these agents should only take place where facilities for full cardio-respiratory resuscitation are immediately available, and that patients should be kept under medical observation for at least 2 hours after treatment. The main committee (CSM) had amended the recommendations of its sub-committee slightly by recommending that the warning be given in the form of a letter rather than a 'yellow peril' warning leaflet.

In addition a CSM update article on desensitizing vaccine was to be published and this would appear in the British Medical Journal of the 11 October 1986. It was hoped to obtain agreement with the relevant pharmaceutical companies regarding alteration of data sheets and a decision was to be taken as to who in the DHSS should undertake future prospective monitoring of these products.
said that the recommendations of the Biological Sub-Committee differed slightly from those of the CSM in as much that had advised that the recommendation that these agents should not be used in asthma should not be brought forward. However doctors were warned that patients with asthma appeared to be particularly susceptible to the development of severe anaphylaxis with the agents.

The Sub-Committee in considering the 'Dear Doctor letter' and other papers advised that as far as possible the word 'vaccines' should not be associated with these products because of the adverse affect that such publicity might have on the JCVI's efforts to promote immunisation of young children in the routine childhood immunisation programme. It was suggested that a future procedure for updating ARVI on adverse reaction reports to these products should be agreed.

Treatment of Anaphylaxis said that this paper had been produced as the basis for the section in the Memorandum "Immunisation Against Infectious Disease". said that this particular subject should be treated with caution as it might prove too much of a disincentive towards vaccination.
and other members said that the section as it stood at the moment only described drug treatment and did not provide a comprehensive guide as to how anaphylaxis should be managed. In particular, pointed out that treatment did not include aminophylline, and that cue-cards should appear in treatment rooms in the surgery.

It was agreed that a small group should be drawn up to advise the JCVI. This group would consist of from Nottingham and , with the representatives from Scotland.

7. Summary of Suspected Adverse Reactions to Vaccines

Reports on yellow cards registered during the periods 13th May 1986 to the 11th September 1986.

ARVI/96/28

introduced this paper

a. Suspected adverse reactions to diphtheria, tetanus and pertussis vaccines (DTP) given alone or with oral polio vaccine (OPV).

During the current period 95 suspected adverse reactions were reported. These included:

i. Death 151828. A 16 month old girl who two days after her first dose of DTP in mid-July 1985 was found to have a fever and a possible upper respiratory tract infection. Two days later she had a major fit and was admitted to hospital where further convulsions occurred. Further fits occurred at the end of July 1985 and she died on the 1st August probably from pneumococcal septicaemia. This patient had a family history of idiopathic epilepsy. This case has been reported to previous meetings of ARVI.

ii. There were 8 reports of convulsions following vaccination including 165236, a patient who was in status epilepticus within hours

of receiving her third dose of triple vaccine. There had been two previous known febrile convulsions.

b. Suspected adverse reactions to monovalent pertussis vaccine.

Five reports had been received including one alleged convulsion which on investigation appeared to be a rigor.

c. Suspected adverse reactions to oral polio vaccine. A six month old girl who developed recipient vaccine-associated poliomyelitis 30 days after receiving her first dose of oral polio vaccine.

d. Suspected adverse reactions to diptheria/tetanus vaccine given with or without OPV.

During the period 283 reports were registered. These included 266 children with injection site disorders. The majority of these reports were among five year old children who had received a boosting dose of vaccine of similar batch number and where the report had come from different geographical locations. pointed out that these reports had first of all come to the notice of the Defect Reporting Centre and expressed concern that yellow card reports had been initiated by persons other than doctors.

It appeared that these had originally come to the CSM as product defect reports sent in by pharmacists; CSM had then contacted doctors and had obtained the yellow card reports. It was felt that reports from pharmacists, acting on hearsay, were an unsatisfactory source of information. ARVI memebrs asked if yellow card reports originating in this way could in future be distinguished from those which a doctor, who had seen the patient, was the primary source of information. observed that follow up by NIBSC had revealed no defect in the vaccine, therefore, apart from a fault in administration of the vaccine there was no reason why these injection site disorders were observed in clusters.

e. Suspected adverse reactions to tetanus vaccine 47 reports were registered. These included 31 injection site disorders with or without fever.

f. Suspected adverse reactions to measles vaccine. These included

i. 154755. A reported encephalitis in a 12 year old girl who was vaccinated on the 20th August 1985 with what seems to have been rubella vaccine and who on the 12th September 1985 developed an encephalitis which had a positive serology of the measles virus. undertook to carry out a follow up of this report.

ii. 165850. A report of a cerebellar disorder in a 15 months old girl who, two weeks after vaccination developed an acute cerebellar-like ataxia preceded by a febrile cold. Her unsteadiness was so marked that she was admitted to hospital. Examination of the CSF revealed an excess of protein but no increase in the number of cells. EEG and CT scan (with and without contrast) were normal. The consultant concluded that this patient had suffered a demyelinating reaction to either measles vaccine or to some other viral infection. was asked to follow this patient up at 6 months.

iii. 8 patients with convulsions were reported. In 164808 convulsions were thought to be due to an attack of acute tonsillitis.

163111. This patient had convulsions 8 days after vaccination, which were thought to be caused by otitis media. It was requested that an amendment be made as to the degree of culpability of these reactions. was requested to follow up the other six reports at six months.

g. Suspected Adverse Reactions to Rubella Vaccine. 8 such reports had been received including two patients with arthralgia.

h. Suspected Adverse Reactions to BCG. 12 reactions were reported, these included two patients with keloid scarring.

j. Suspected adverse reactios to Monovalent Typhoid Vaccine. There had been seven reports during the period including one anaphylactic reaction.

k. Suspected adverse reactions to cholera vaccine. 4 reports had been made during the period.

l. Suspected adverse reactions to hepatitis B vaccine. 14 reports of relatively minor reactions had been received.

m. Suspected adverse reactions to pneumococcal vaccine. 1 report of an injection reaction had been received. requested details of the manufacture of the vaccine.

8. Any Other Business

a. reported that the last meeting of the BPA/JCVI Working Party had asked whether the recommendation on Page 29, Paragraph 6.5.4 of the Memorandum "Immunisation Against Infectious Disease" which stated that "it is advisable to allow at least 3 weeks to elapse between undergoing tonsillectomy or oral surgery and the administration of OPV." was still appropriate. undertook to check this recommendation.,

b. reported that a symposium on the new pertussis vaccines had been recently held at Bethesda in the USA.

9. Date of the Next Meeting

The date of the next meeting would be the 6th February 1987.