COMMERCIAL IN CONFIDENCE ARVI/84/3rd Meeting

NOT FOR PUBLICATION

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 Friday 1 June 1984 at Market Towers

Present: Prof R W Gilliatt (Chairman)
Dr A L Bussey
Dr P E M Fine
Prof J K Lloyd
Dr C L Miller
Prof D L Miller
Dr D Reid
Dr J W G Smith
Dr S J Wallace
Sir John Badenoch

DHSS
Dr J Barnes
Dr M E Duncan (Medical Assessor)
Dr D W Zutshi (Medical Assessor)
Mr J Griffiths (Secretary)

Scottish Home and Health Dept
Dr R Covell

1. APOLOGIES AND ANNOUNCEMENTS

1.1 The Chairman reminded members that the papers and proceedings were confidential and should not be disclosed.

1.2 Apologies were received from Professor Hull and Professor Glynn.

1.3 The Chairman introduced Mr Griffiths who had taken over as Secretary to the Sub-Committee.

2. MINUTES OF THE MEETING HELD ON 3 FEBRUARY 1984

The Chairman signed the minutes as a true record of the meeting after a number of typographical errors had been corrected and the following two amendments made:-

a. Item 1, second sentence was amended to read:
"The Chairman paid tribute to the work done by Professor Dudgeon, Dr Pollock, Dr Richards and Dr Wilson who had served since January 1980 as members of ARVI; they retired on 31 December 1983."

b. Item 5.1, line 4 - after "vaccine" insert "annually".

3. MATTERS ARISING FROM THE MINUTES

3.1 BCG: Further Studies - this item was taken later with Item 6.

3.2 Professor Breckenridge's study on the possible interaction of influenza vaccine with drugs (Item 11).

said that Professor Breckenridge's study was still in progress, but results so far suggested that while there was an effect of vaccination on blood levels of theophylline, it was doubtful whether this would prove to be of clinical significance. drew attention to a paper by Kremer et al, in Clinical Pharmacology and Therapeutics 1984, Vol 35, page 416, reporting an 81 year old patient receiving warfarin who had problems with anticoagulants following influenza vaccination. The authors had carried out a prospective study on eight patients and found that prothrombin times were increased after vaccination. However in a second study on volunteers no significant effect on warfarin metabolism had been observed after vaccination; the half life of warfarin remained unchanged.

The Sub-Committee noted that more data would be forthcoming on the question of the possible effect of influenza vaccination on

liver function but did not consider that any immediate action was necessary.

4. ADVERSE REACTIONS TO DIPHTHERIA AND TETANUS VACCINE (ARVI/84/13)

The Chairman reported that this paper had been presented to the CSM and the JCVI. Both committees had been pleased to receive this paper which they observed brought together various important sources of information.

5. BCG VACCINE

5.1 Adverse Reactions to BCG Vaccine (ARVI/84/14)

This draft paper was considered in detail and a number of corrections and amendments were suggested. agreed to prepare a redraft of the description of the vaccine and agreed to provide further information relating to the earlier years of the Public Health Laboratory Service surveillance of BCG vaccine. Members observed that it would be helpful if the paper could include a comment on the evidence on which the contraindications to vaccination during pregnancy and in the presence of septic skin lesions and eczema were based.

The Sub-Committee noted that this paper contained their recommendation for further studies on BCG vaccine. It was agreed that if the BCG Sub-Committee of the JCVI met before the next meeting of ARVI it would be advantageous for the BCG Sub-Committee to see a draft of the paper. In that event the draft would be first circulated to members of ARVI for comment.

5.2 BCG Vaccination as a cause of osteomyelitis and subcutaneous abscess - Peltola H, Salmi I, Vahvanen V and

Ahloqvist J, Archeol of Diseases of Childhood 1984, Vol 59, pages 157-161 (ARVI/84/15)

The Sub-Committee noted this paper.

6. PERTUSSIS VACCINE

6.1 Professor G T Stewart's final report to the Office of the Chief Scientist, DHSS, on his study of the data on suspected adverse reactions to pertussis vaccine.

a. Draft comments by the ARVI Working Party (ARVI/84/16)

The Chairman reported that the working party consisting of Sir John Badenoch, Professor Miller, Dr Smith, Dr Barnes, Dr Zutshi and himself had prepared draft comments on Professor G T Stewart's report to the Office of the Chief Scientist. These had been accepted by the JCVI and that committee was willing for this commentary to go forward to the Committee on Safety of Medicines providing that ARVI did not see the necessity for any major changes. The commentary stressed the autobiographical nature of Professor Stewart's report and its analysis of retrospective data. A large part of the data in Professor Stewart's report had been previously considered by the Meade Panel in 1981 with significantly different interpretations; examples of these were quoted. There was selective use of evidence from other countries and little understanding of the expected outcome when an effective whooping cough vaccine is used in a population with a high acceptance rate for pertussis vaccine. The Working Party found several contradictions and inaccuracies in the report together with errors of fact relating to published statistics and reference to the work of others.

report also failed to recognise that in natural whooping cough the causative organism is only isolated in a proportion of serologically positive cases. The Working Party's commentary also included Professor Miller's recent observation that the attributable risk of severe neurological disease associated with recent whooping cough was at least ten times more than that associated with an immunisation against pertussis. In the appendix to the commentary the Working Party had made detailed comments for use by Ministers, Departmental officers and committee members on the conclusions Professor Stewart had presented in his summary of his report. Many of these conclusions could not be substantiated either from published literature or from Professor Stewart's own report.

The Sub-Committee considered the Working Party's commentary in detail and approved it, with a number of minor alterations, recording its appreciation of the Working Party's detailed analysis of Professor Stewart's report.

b. <u>National Childhood Encephalopathy Study - Infectious Disease in the month preceding neurological illness</u>

(ARVI/84/17)

Professor Miller said that the paper had been prepared with a view to comparing the risk of serious neurological illness after natural infection and after vaccination against whooping cough and measles. When the temporal relationship between the occurrence of infectious disease and the onset of neurological illness (or preceding the

reference date in controls) was analysed, the six months before the onset of neurological illness and the six months after were remarkably similar except for the month prior to the onset of neurological illness. During this month there was a significant excess of measles and whooping cough amongst cases compared with controls. There was a smaller but non-significant excess for mumps and no excess for chickenpox and rubella.

The relative and attributable risks were calculated in the paper. The attributable risk depended on assumptions regarding the completeness of notification of measles and whooping cough. Dr Fine's determinations on the efficiency of notification were applied to these data and it appeared that notification efficiency was not a critical factor in the estimation of attributable risk. There was convincing evidence that the risk of neurological illness following whooping cough was at least ten times that following a vaccination, although in a population with very high vaccination uptake (therefore with a low incidence of disease) the ratio might become less.

observed that it was interesting that the efficiency of notification did not appear to affect the attributable risk rates. It was possible that the efficiency of notification had changed over the years. Dr Zutshi asked if the relative risk rates quoted in the paper would apply to all age groups. replied that the rates would only be applicable to ages included in the NCES (two months to three years of age). It was pointed out that the risk of encephalitis following measles increased with age. asked if any of the affected children

had been disabled. replied that there were only one or two minor disabilities reported and said that it was planned to publish the paper in the near future.

c. External scientific referees' comments on Professor G T Stewart's report (ARVI/84/18)

Dr Zutshi briefly introduced the comments of the four external referees on the Stewart report. These were noted by members.

6.2 Immunisation of neurologically disabled and developmentally delayed children

a. Comments from the meeting of the JCVI held on 27 April 1984

Dr Zutshi reported that the JCVI had received the comments that ARVI had made on this subject at its last meeting. The JCVI had noted that ARVI would be considering this question further in relation to children with tuberous sclerosis and Down's syndrome. He reported that it was proposed to set up a joint working party of members of the British Paediatric Association and the JCVI to consider the problems of immunisation, including those relating to the indications for and contra-indications against vaccination.

b. Supplementary statements of contra-indications to receipt of pertussis vaccine - recommendations of the Immunisation Practices Advisory Committee (ACIP) - MMWR 33,13 (ARVI/84/19)

The Sub-Committee noted with interest this supplementary ACIP Statement of Contraindications to the receipt of pertussis vaccine.

c. Should a personal or family history of convulsion be a contraindication to receipt of pertussis vaccine? Preliminary draft of a paper by Statler HC et al

(ARVI/84/20)

The Chairman introduced this draft paper by Statler et al which had been kindly made available by Dr Orenstein. It indicated that children in the US with a history of previous convulsions or a family history of convulsions appeared to have an increased risk of convulsions following DTP immunisation. Members noted that the size of the family was not documented, nor was it stated whether the family history of convulsions was in a first degree or more distant relative. Members were concerned that the family history of convulsions was not verified. Further, the data on children with a family history of epilepsy could be biased in that relatives would be more likely to recall a positive family history if a child had a convulsion following vaccination. The method of ascertainment, which involved both the ability to read and to recall events, i.e. a double selection, was not considered to introduce any systematic bias which might affect the conclusions of the study. Dr Wallace said that, despite the limitations of the data on family histories, the results of this study were in accord with other studies of family histories of children who had had febrile convulsion

d. Pertussis vaccination of children with previous personal history of convulsions

Table from Livingstone S. Comprehensive Management of Epilepsy in Infancy, Childhood and Adolescence. Springfield, Illinois, Charles C Thomas, 1972, pp159-166 (ARVI/84/20A)

This table was noted by the Committee.

e. Tuberous sclerosis - a survey of 97 cases

1: Seizures, pertussis immunisation and handicap.

A paper by Ann Hunt, Developmental Medicine and Child Neurology, 1983, Vol 25, pp 246-249 (ARVI/84/21)

introduced this study which concluded that there was no evidence that pertussis vaccine caused additional brain damage to children with tuberous sclerosis. She said that the disadvantage of this study was that the immunisation history was not validated. Whilst it was possible that immunisation might act as a trigger for convulsions that herald the onset of tuberous sclerosis the evolution of this condition was not influenced by pertussis immunisation.

6.3 Whooping cough vaccination: a review of the controversy since the DHSS report - paper by Christina M Harding, Child: care, health and development, 1983, vol 9, pp 257-272 (ARVI/84/22)

The Sub-Committee concluded that this review was uncritical and unhelpful.

7. SUMMARY OF SUSPECTED ADVERSE REACTIONS ASSOCIATED WITH VACCINES REPORTED ON YELLOW CARDS AND REGISTERED DURING THE PERIOD 17 DECEMBER 1983 TO 30 APRIL 1984 (ARVI/84/23)

Forty-four suspected adverse reactions associated with DTP had been reported, including one death and three children with convulsions. The death had occurred in a six month old boy, 14 days after immunisation with DTP and OPV, who was found at post mortem to have pneumonia and an atrial septal defect. There had been three reports of suspected adverse reaction following immunisation with monovalent pertussis vaccine, two children with pyrexia and a third who had a convulsion.

There had been 32 reports of suspected adverse reactions following diphtheria/tetanus vaccine including one child with a convulsion. These reports included 32 cases of injection site disorder and one of hypotonia. Members considered that the convulsion was probably due to the presence of tonsilitis. Twenty adverse reaction reports following tetanus vaccination had been received; 19 were injection site disorders, four of which were accompanied by malaise and fever, and

one child had a rash. There were 20 suspected adverse reactions to measles vaccine, including six children with convulsions; there was one report each of anaphylaxis, bronchospasm and apparent vaccine failure.

Sixteen reports of suspected adverse reactions following rubella immunisation had been received. These included two reports of arthritis, one of circulatory collapse and reports of seven school-girls in one school who, half an hour after immunisation, all felt unwell, dizzy and were pale, sweating and had feeble pulses. Two were treated with hydrocortisone and five were sent to the local hospital casualty department for observation. said that he would endeavour to obtain details of their clinical status on arrival at hospital.

One report of a suspected adverse reaction to oral poliomyelitis vaccine had been received, a three month old child who 14 days after immunisation developed meningoencephalitis associated with a lower motor neurone lesion. Following initial improvement and discharge from hospital she was found dead in her pram 32 days after the onset of the illness. There was one report of an influenza-like illness in a 28 year old mother following immunisation with inactivated poliomyelitis vaccine.

Forty-three reports of injection site abscesses occurring one to six months after BCG vaccination were reported; all of these came from one district health authority.

Thirteen reports of suspected adverse reactions to influenza vaccine were received including one report of Guillain-Barré syndrome in a 73 year old man.

There was one report of anaphylaxis following house dust mite desensitising vaccine and another following cholera vaccine.

Fifty-three reports of suspected adverse reactions following monovalent typhoid vaccine were received. These included 39 reports of systemic reactions including headache, shivering and vomiting (three reports) in 37 schoolchildren and two teachers; these were associated with a single batch of vaccine used by one health authority. Three different groups of schoolchildren, three doctors and three locations were involved but not all vaccinees at a particular session were affected. The National Institute for Biological Standards and Controls had found no evidence of contamination of this batch.

There were two suspected adverse reaction reports following typhoid and cholera vaccine, two following hepatitis B vaccine, two following tuberculin tests and two following grass pollen vaccine; all of a non-serious nature. There was a report of a 13 year old boy who developed neuromyelitis optica following a dose of pneumococcal vaccine. Dr Zutshi said that the time of onset was between seven and 11 weeks after immunisation. It was agreed that more precise information on this patient should be sought.

8. FURTHER INFORMATION ON CERTAIN SUSPECTED ADVERSE REACTIONS ASSOCIATED WITH VACCINES (ARVI/84/24)

said that he had received further information concerning a four month old boy who had a febrile convulsion five or six hours after a first dose of DTP vaccine. Sixteen months after the vaccination the boy was well and had suffered no sequelae following the convulsion. His gereral practitioner had reported that it was possible that the boy had an epileptic cousin. Another boy,

aged 13, who three days after BCG vaccination had a typical grand mal episode, had a further convulsion eight months later. Subsequent paediatric opinion was that he had idiopathic epilepsy unrelated to the BCG vaccination. Following commencement of valproate therapy, no further convulsions had occurred in this boy during the following five years.

The Sub-Committee also considered further information relating to a four month old girl who developed petit mal six days after her first dose of DTP vaccine. The Sub-Committee noted that the clinical picture, which included the detection of a raised blood pyruvate level, could be compatible with a metabolic disorder. Dr Zutshi reported that had confirmed that the 43 injection site abscesses, which occurred one to six months after BCG vaccination in one district health authority during 1983 and 1984, were almost certainly caused by faulty technique in the administration of the vaccine. The Sub-Committee requested that it should be informed of the occurrence of any further abscesses.

The Sub-Committee noted the published clinical histories of two cases of Guillain-Barré syndrome (previously recorded) which were reported by the same neurologist in two 70 year old men ten days after immunisation with influenza vaccine. The Sub-Committee also considered further clinical and post mortem findings in a three month old girl with type 3 poliovirus meningo-encephalitis associated with a lower motor neurone lesion which occurred two weeks after immunisation with DPT and OPV. She was admitted to hospital and apparently improved sufficiently to be discharged home two weeks later. Apart from a chest infection on the following day, progress seemed uneventful but on the eighteenth day after discharge she was found dead in her pram. observed that the batch of polio

vaccine had been widely used and that the data on its neurovirulence was satisfactory.

9. RUBELLA VACCINES

9.1 Rubella vaccination and pregnancy study - Report from the National Rubella Surveillance Programme (ARVI/84/25)

9.2 Rubella vaccination during pregnancy - United States 1971-1982 (ARVI/84/26)

9.3 Fetal risk associated with rubella vaccine - an update - Bart SW et al, presented at the International Symposium on Prevention of Congenital Rubella Infection, Washington DC, March 13-15 1984 (ARVI/84/27)

The Sub-Committee noted these papers.

10. INFLUENZA VACCINES

Abstracts: Amer. Acad. Neurol. April 1984 (neurology 34 S 242-243)

10.1 Lack of Association of A-New Jersey/76 (Swine Flu) Immunization and: Polymyositis, Tranverse Myelitis, Brachial Plexopathy, Multiple Sclerosis and Encephalitis. Kurland LT, Beghi E, Mulder DW, Wiederholt WC and Kirkpatrick JW. (ARVI/84/28)

10.2 Guillain-Barré Syndrome (GBS) and Swine Flu Vaccination, 1976: A Reassessment. Weiderholt WC and Kurland LT (ARVI/84/29)

The Sub-Committee deferred consideration of these papers until its next meeting.

11. ITEMS FOR INFORMATION

MLX 147A

MAIL 39

STATUTORY INSTRUMENT No 187

The Sub-Committee noted these items for information.

12. ANY OTHER BUSINESS

There was none.

13. DATE AND TIME OF NEXT MEETING

Friday 5 October 1984 at 11.00 am.