COMMERICAL IN CONFIDENCE

NOT FOR PUBLICATION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 3 February 1984 at Market Towers.

Present: Professor R W Gilliatt (Chairman) Dr Sir John Badenoch
Dr P E M Fine Dr J Barnes
Professor A A Glynn Dr R Covell
Professor D Hull Dr M Graveney
Dr B W McGuinness Dr R H Raynes
Dr C Miller Dr M E Duncan (Medical Assessor)
Professor D Miller Dr D Zutshi (Medical Assessor)
Dr D Reid Mr J Grimshaw
Dr J W G Smith Mr H M Morgan (Secretary)
Dr S J Wallace Mr T J Kirkley
Miss S Draper

1. CONFIDENTIALITY AND ANNOUNCEMENTS

The Chairman reminded members that the proceedings, papers and information before them were confidential and should not be disclosed.

The Chairman paid tribute to the work done by Professor Dudgeon, Dr Richards, Dr Wilson and Dr Pollock who had served as members of ARVI since January 1980, they retired on 31 December 1983. Professor Gilliatt on behalf of ARVI congratulated Sir John Badenoch, Chairman of the JCVI, on being awarded a Knighthood in the Queen's New Year's Honour's List. The Chairman welcomed the following new members of the Sub-Committee; Dr Fine, Dr Christine Miller, Dr Wallace and Dr McGuinness. He also informed the meeting that another new member, Professor Banatvala, would be joining the Sub-Committee in the Autumn. Professor Gilliatt welcomed the new Secretary of CSM Mr Grimshaw and the new Secretary of JCVI Mr Cunningham. He also welcomed Dr Graveney from the Office of the Chief Scientist.

The Chairman welcomed Dr W Orenstein from the Centres for Disease Control, Atlanta, USA who was attending the meeting as an invited guest.

2. APOLOGIES FOR ABSENCE

Apologies for absence had been received from Professor Lloyd and Dr Bussey.

3. MINUTES OF THE MEETING HELD ON 28 OCTOBER 1983

The Sub-Committee agreed the following corrections;

paragraph 5.2 - the last line should read

"unreliable and that the Haef Test or Mantoux Test was preferable", 

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paragraph 5.3 - second line

after "vaccination" insert "and described the International Classification".

Several minor typographical errors were also corrected.

The minutes were then agreed and signed by the Chairman as a correct record of the meeting.

4. MATTERS ARISING FROM THE MINUTES

4.1 Adverse Reactions to BCG Vaccine

The Chairman reported that the 1960 College of General Practitioners Report gave the background rate of first convulsions in children aged 10-14 as 0.5 per 1000 children per annum. This would be equivalent to a rate of 1 per 100,000 per week. If 500,000 children between the ages of 10 and 14 years had been vaccinated with BCG in any one year, then 5 children could be expected to have a fit during the course of a given week. It was noted that the number of convulsions reported to the CSM for the week after BCG vaccination was only a fraction of that expected from the background rate. The Committee therefore concluded that convulsions after BCG vaccination were not a problem.

With regard to local reactions, Dr Christine Miller drew attention to 6 nurses recorded in her paper (ARVI/83/28) who were found to be tuberculin negative by the Tine test in spite of a history of vaccination at school and the presence of a scar. They were revaccinated and all six developed troublesome lesions. However, she reported that some authorities, including East and West Suffolk, had dispensed with tuberculin testing prior to BCG vaccination, and had not subsequently experienced an increased number of troublesome lesions.

5. BCG VACCINE

5.1 PHLS Surveillance of B.C.G. Vaccine 1969 - 1983 (ARVI/84/1)

Dr Christine Miller introduced this paper which recorded the results following examination of the BCG vaccination sites and the results of the post-vaccination tuberculin tests 8-12 weeks after vaccination, for 14-20 batches of vaccine annually. Since 1973, the viable count of the batches had ranged from 8-25x10^8/ml. The Sub-Committee noted that there was a suggestion that batches with higher viable counts were more likely to produce lesions with a diameter greater than 10 mm. There was discussion as to whether these larger reactions were at the upper range of size for a normal reaction, or whether they were adverse reactions. Dr Christine Miller said that the injection technique was the crucial factor. If the injection were given in whole or part subcutaneously the resulting abscess would be larger. Further, if the scab were knocked off, the healing process would be delayed. Members asked about the duration of these discharging lesions. Dr Miller said that information was limited to the three month follow up period of the study. However, it was noted that yellow card reports of persistent abscesses had been received by the CSM and noted at previous ARVI meetings.
5.2 The geographical origin of reports to the CSM of injection site disorders following BCG immunisation occurring during 1975 – 1980
(ARVI/84/2)

Dr Zutshi introduced this paper which analysed injection site disorders associated with BCG immunisation reported to the CSM between 1975 and 1978 according to the geographical location of the reporting physician. Of a total of 283 reports, 127 occurred in Bolton. This incident had been reported in Community Medicine (1980) 2, 312-317, with the conclusion that the vaccine had been administered subcutaneously instead of intradermally. A further 53 reports had been received from Manchester where the vaccine was administered by a jet injector. The Sub-Committee noted that the method of administration recommended by the JCVI had always been by syringe and needle. The advice to be published shortly in the revised Memorandum "Immunisation Against Infectious Disease" would specifically state that the use of jet injectors is not recommended. The Sub-Committee was grateful to Dr Zutshi for making it clear that the increase in reporting of injection site disorders in the years 1975-1978 was due in part to incorrect immunisation technique in certain health authorities.

5.3 Further consideration of previously circulated papers concerning BCG
(ARVI/83/27 to ARVI/83/32)

Dr Zutshi reported that he had discussed with Dr Christine Miller and Professor David Miller the possibility of identifying and quantifying the rarer complications of BCG immunisation (osteitis and osteomyelitis, disseminated BCG infection and dermatomyositis). Professor Miller said that he had carried out a preliminary examination of the literature and confirmed that the highest incidence of osteitis and osteomyelitis was in Scandinavia, which was probably related to their higher vaccination rate of young children and awareness of these adverse reactions. He suggested that a retrospective case control study should be undertaken to establish whether such cases occurred in this country. It was noted, however, that cultures of the organism might not always be undertaken in patients with osteitis and osteomyelitis; nevertheless Professor Glynn undertook to examine the PHLS records to see if they included any such cases. It was agreed that Professor Miller should examine further the possibility of mounting a study along the lines he had outlined. It was further agreed that a start should be made on drafting a report for parent committees by the Chairman, Dr Christine Miller, Professor Miller, with Dr Zutshi and Dr Raynes. In view of Professor Hull’s interest, he agreed to comment on this draft at an early stage.

6. ADVERSE REACTIONS TO DIPHTHERIA AND TETANUS VACCINATION
(ARVI/84/3)

The draft report was reviewed and some minor grammatical changes were made. The section concerned with the PHLS Hertfordshire study was further discussed. In view of the possible inconsistency between Tables 3 and 4 concerning the incidence of local adverse reactions, and uncertainty as to whether these reactions were cumulative with successive doses, it was decided to exclude these tables and to simplify the accompanying text.
7. SUMMARY OF SUSPECTED ADVERSE REACTIONS TO VACCINES REPORTED ON YELLOW CARDS AND REGISTERED DURING THE PERIOD 16.9.83 TO 16.12.83 (ARVI/83/4)

There had been 45 reports of suspected adverse reaction to DTP including 7 cases of convulsions, 1 of encephalitis and 1 of the sudden infant death syndrome. Members felt that there was some doubt about the diagnosis in the case of encephalitis. Only one report of a suspected adverse reaction following monovalent pertussis vaccine had been received. This had occurred in a girl who developed an eczematous reaction after the first dose and then a pruritic rash after the second dose.

There had been 27 reports of adverse reactions associated with diphtheria/tetanus vaccine; 2 of fever and 25 of injection site disorders. 11 suspected adverse reaction reports associated with tetanus vaccine had been received, all of these being injection site disorders, 2 of which were accompanied by pyrexia. There were 16 suspected adverse reaction reports to measles vaccine. Four of these were of convulsions, 3 accompanied by pyrexia; in one case otitis media was also present. There was one report of a coagulation disorder. Dr Zutshi said he would be following up this report of a haematological disorder as well as the patients who had neurological disorders.

Five adverse reaction reports following rubella immunisation had been received. These included the report of a pregnant woman who had been in contact with rubella and was immunised against rubella at 8 weeks gestation. The baby was born with a missing left hand. The rubella immunity status of the baby was not yet available.

Five suspected adverse reactions to BCG had been reported. 3 of these were abscesses which had occurred 6, 7 and 9 months respectively after immunisation. There was one report of meningismus and pyrexia occurring in a 22 year old man on the day of immunisation.

There were 25 reports of suspected adverse reactions to influenza vaccine, 3 with a fatal outcome. A man aged 70, who was receiving Warfarin, 18 days after immunisation developed spontaneous bleeding and died four days later. Another man aged 70 and a woman aged 100 who both had long standing cardiac problems collapsed and died two days and 23 days after immunisation respectively. Two reports were received from the same neurologist of Guillain Barre syndrome occurring in a 70 year old and a 73 year old man 10 days after immunisation. The other reports included 3 with vertigo.

Six adverse reaction reports following monovalent typhoid immunisation were received, including 2 of convulsions. Five reports were registered associated with the administration of monovalent typhoid and cholera vaccine which included one of anaphylaxis.

There were one report of a suspected adverse reaction following hepatitis B vaccine, two following rabies vaccine, one following a tuberculin test and one following cholera vaccine; all of a non-serious nature. There was one report of a suspected adverse reaction to yellow fever vaccine of a man who 24 days after immunisation was found to have moist ulceration in the left axilla preceded by general febrile illness with myalgia.

8. FOLLOW-UP OF CERTAIN SUSPECTED ADVERSE REACTIONS ASSOCIATED WITH VACCINES (ARVI/84/5)

Dr Zutshi said that he had received further information of 5 additional patients who had articular symptoms following rubella immunisation. 4 of these did not appear to have had any subsequent unexplained articular
symptoms following the initial suspected adverse reaction. In the fifth, intermittent hip pain had persisted for a period of 8 months.

Further information had been received concerning a baby who was born with flaccid limbs and "a bulbar palsy reminiscent of poliomyelitis", and whose mother had received oral poliomyelitis vaccine before she missed her first period. The consensus of the Sub-Committee's opinion was that the administration of poliomyelitis vaccine was unrelated to the baby's illness and subsequent death. However, a closer analysis of the brain and brainstem as well as knowledge of the birth weight would have provided helpful information. The Sub-Committee noted that the occurrence of congenital abnormalities following maternal poliomyelitis immunisation had not been reported in previous studies.

The Committee considered the immunisation history of a 17 year old boy who experienced irritability with each dose of DTP and finally a convulsion with screaming attacks. However, subsequent immunisations, including a dose of monovalent pertussis, had not caused any adverse effect except for an episode of pyrexia following measles vaccine. The Committee felt it did not have sufficient information to answer the reporting physician's question as to whether pertussis vaccine was more likely to cause reactions when it was given in triple vaccine and whether it might be wiser to give pertussis vaccine separately even though this would necessitate more injections.

9. **PERTUSSIS VACCINE**

**9.1 Pertussis: Should we immunise neurologically disabled and developmentally delayed children?** - Miles RN and Hosking GP, BMJ 30 July 1983 Vol 287 p 318-320 (ARVT/84/6)

The Chairman introduced this paper which suggested that the risk of serious neurological handicap after pertussis immunisation was small and that there was little evidence to support the view that underlying neurological disease predisposed a child to increased risk.

It was agreed said that while the question posed in the title of the paper was an interesting one, the conclusions drawn from their study were open to criticism since -

i the vaccination records of their 400 handicapped children and 400 controls had not been checked and reliance had been placed on the parents' account many years after the event,

ii it was uncertain whether children attending general paediatric clinics could be regarded as satisfactory controls,

iii there was no information about deaths; to that extent the population studied was a biased one,

vi no information was obtained about the frequency of adverse reactions to vaccination in the handicapped group.

The Sub-Committee was therefore unwilling to accept the conclusions of this study.
9.2 A review of problems associated with pertussis immunisation in children with a neurological disorder

Professor David Hull introduced his paper which considered the reasons why doctors and health visitors might be reluctant to advise immunisation and made a number of recommendations which might clarify the problem.

9.3 Sequelae in children with previous neurological abnormality given Diphtheria, Tetanus and Pertussis vaccine or Diphtheria and Tetanus vaccine

Professor David Miller tabled abstracts of case histories from the National Childhood Encephalopathy Study of 5 previously neurologically abnormal children who had vaccination reactions. It was felt that the number of cases was too small to provide statistically relevant information. The Chairman reported there were 4 similar cases studied by the Dudgeon Panel, but that the data were equally unsatisfactory.

In general discussion Members considered it was important to distinguish a past history of convulsions which might influence decisions about immunisation, from a history of Down’s syndrome or tuberous sclerosis, for which there was no evidence that the risks of whooping cough vaccination were higher than normal. Dr Wallace referred to a study indicating that the vaccine did not affect prognosis in tuberous sclerosis. Dr Smith noted that contra-indications should be interpreted in the light of the prevailing incidence and severity of the natural disease. Dr Orenstein informed the Sub-Committee that recent American data indicated an increased risk of post-vaccination convulsions in those with a history of febrile convulsions. This data would be considered by the US Advisory Committee on Immunisation Practices in the near future and he would make this information available to ARVI at a later date.

The Sub-Committee concluded that in judging the risks of vaccination, the nature of the pre-existing neurological condition was all-important; different neurological conditions required separate consideration. Professor David Hull informed the Sub-Committee that the British Paediatric Association would be considering this problem in relation to Down’s syndrome.

9.4 Professor G T Stewart’s final report to the Office of the Chief Scientist (OCS) DHSS

Dr Zutshi introduced Professor Stewart’s report to the OCS on suspected adverse reactions to pertussis vaccine, in which he had assembled clinical reports and other data about suspected adverse reactions received from parents, doctors and other sources available to the Department of Community Medicine at the University of Glasgow.

Dr Graveney reported that the Chief Scientist had asked external referees to assess this report. In answer to a question he stated that the OCS would not oppose its publication but could insist that disclaimers were inserted.

Members found that there was much with which they could not agree in the report. Further, there were statements critical of colleagues, Committee members, the Sub-Committee on Complications of Vaccination, JCVI, CSM and DHSS which could not be overlooked without comment, and which must be refuted. Dr Reid said he had been misquoted and Professor Miller said that the NCES had been misreported. It was
decided that in view of the complexity and length of the document, time should be devoted to a detailed review. It was agreed that the report should be reviewed by a small working group consisting of Professor Gilliatt, Professor Miller, Dr Smith and Sir John Badenoch, together with Dr Barnes and Dr Zutshi. Mr Grimshaw said that the Ministers would like to have the views of JCVI and the CSM on Professor Stewart’s report as soon as possible. The Sub-Committee agreed that the working party could present a preliminary report to the next meeting of the JCVI, prior to the next meeting of ARVI.

10. MEASLES VACCINES

PHLS surveillance reactions to measles vaccines (ARVI/84/10)

Dr Christine Miller introduced her paper which reviewed the incidence and severity of reactions to measles vaccines following measles immunisation in Buckinghamshire and Somerset. A total of 1,191 children had been immunised with Mevvin and 1,221 with Attenuvax. 55% were reported to be well after each vaccination and significant reactions occurred in only 1% of children. 6 convulsions were reported in the post-vaccination period, 3 after Mevvin and 3 after Attenuvax. In two of the children who received Mevvin there was a past history of convulsions and according to current recommendations they should have received a dose of specially diluted immunoglobulin at the same time as the measles vaccine. In the third child who received Mevvin, and in one of the other children who received Attenuvax, there were additional possible causes for the convulsions. The Sub-Committee considered that the study was of considerable value and it hoped that it would be continued since the numbers were still relatively small.


Dr Zutshi introduced this paper which reviewed the possibility that influenza vaccination might be associated with severe drug toxicity in patients taking Warfarin or Theophylline. Amongst the data it considered a study of 6,759 nursing home residents in the USA which had suggested that clinically apparent adverse reactions to Warfarin and Theophylline were rare after influenza vaccination and were not more frequent in occurrence than similar reactions in unvaccinated people. The Sub-Committee noted that earlier in the meeting it had considered a report of spontaneous haemorrhage in a man receiving Warfarin some 18 days after immunisation with influenza vaccine. Dr Smith reported that Professor Breckenridge’s study on this subject was proceeding and that no detectable drug interactions had been demonstrated so far. Dr Smith said that he hoped to be able to obtain more information on this study and to report its progress to the next meeting of ARVI.


This paper was received for information.

13. ITEMS FOR INFORMATION

The following items were also received for information

MLX 149 + 149 Corrigendum
MLX 150
14. **ANY OTHER BUSINESS**

   No matters were raised.

15. **DATE AND TIME OF NEXT MEETING**

   It was confirmed that the next meeting on ARVI would commence at 11.0 am on Friday 1st June 1984.