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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 5 October 1984 at Market Towers.

Present:

Professor R W Gilliatt (Chairman)
Dr P E M Fine
Professor A Glynn
Professor D Hull
Professor J K Lloyd
Dr B W McGuinness
Dr C L Miller
Professor 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 K Fowler (Secretary)
Mr T J Kirkley
Dr A Fenton Lewis

1. ANNOUNCEMENTS AND APOLOGIES

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

1.2 The Chairman introduced and welcomed Dr Fenton Lewis who was attending for the BCG paper, and Mr Fowler the new Secretary to the Sub-Committee.

1.3 Apologies were received from Professor Banatvala, Dr Bussey and Mr Murray.

2. MINUTES OF THE MEETING HELD ON 1 JUNE 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 amendments made:-

a. Item 6.1a, page 5, line 8, delete "an immunisation against pertussis" and replace with "a dose of vaccine".

b. Item 6.1b, page 6, line 1, after "analysed" insert "the histories during"; page 6, 2nd paragraph, line 10, delete "vaccination" and insert "dose of vaccine"; page 7, 1st paragraph, delete the two sentences after "had been disabled" and replace with "Professor Miller replied that this aspect was being studied. It was planned to publish a paper in the near future".

3. MATTERS ARISING FROM THE MINUTES

Item 4.1 NCES data for encephalopathy after natural whooping cough: further information concerning long term outcome

The Chairman said that Professor Miller had sent him further information which would be discussed later in the meeting (7.1)

4. BCG VACCINE

4.1 Report of local abscess formation

4.1.1 Dr Fenton Lewis introduced this paper which analysed reports of local abscesses during a school BCG vaccination programme during 1983/84 in a single Health Authority (which had previously reported suspected reactions to CSM). The incidence of abscesses had increased from 0.18% to 1.68% between January 1983 and October 1983 when the programme used the Dermojet. After temporary suspension of the programme the intradermal technique was used but further abscesses occurred. In all, 63 abscesses were noted in the school vaccination programme for 1983/84. The programme was again suspended in mid-February 1984 and the Health Authority sought advice from an expert on the conduct of the programme which was then re-started in April 1984. Since then only two abscesses had been reported. Investigation suggested that a faulty Dermojet was responsible for the earlier reactions and a faulty intradermal technique over a short period for the later reactions.

4.1.2 The members noted that the Memorandum "Immunisation Against Infectious Disease" which was issued in April 1984, advised against the use of jet injectors. The Sub-Committee agreed a draft paragraph describing this report for inclusion in the proposed ARVI paper on adverse reactions to BCG vaccine. The Sub-Committee hoped that the medical staff of the Health Authority would be asked to follow up these children to ascertain the incidence of keloid formation in the abscess scars.

4.2 Adverse reactions to Bacillus Calmette-Guerin (BCG) strain of tubercle bacillus ARVI/84/31

4.2.1 The Chairman introduced this revised draft of the BCG paper seen by the Sub-Committee at their last meeting. The draft paper was considered in detail and a number of corrections and amendments were

suggested.

4.2.2 Contra-indications to BCG vaccine

a. Pregnancy

The Chairman referred to a letter from Professor Hurley which quoted views of Dr Amstey from Clinics in Obstetrics and Gynaecology, 1983 Vol 10 pages 13-15. In this article no firm recommendation was made concerning the administration of BCG vaccine in pregnancy because there was no information about its transplacental passage, fetal infection or maternal response to the vaccine.

b. Skin Disease

The Chairman had received a helpful letter from Dr R J Hay who confirmed that apart from immuno-deficiency states certain other skin diseases might interact with BCG inoculation. These included sarcoidosis, which might lead to a localised sarcoid granuloma, cutaneous tuberculosis, which might be followed by very sever nodular ulcerative reaction. Patients with skin disease which tend to koebmerise, such as psoriasis, might develop local reactions to the disease in the scars. In addition to these rare contra-indications he considered that generalised erythroderma also constituted a contra-indication. The Sub-Committee felt there was still some uncertainty in relation to patients with eczema and Dr Zutshi was asked to seek further information.

4.2.3 The Sub-Committee agreed that the amended paper should be presented to the parent committees, in particular it should be submitted to the next meeting of the JCVI, and also to the BCG Sub-Committee of the JCVI.

4.3 Osteitis associated with BCG vaccination

Professor Miller reported that his Department had continued a search for reports of this condition. This included examination of the records from the Hospital Activity Analysis (HAA) in five districts in the North West Thames Region. This had revealed 25 cases of osteomyelitis in infants but it had not been possible to determine if any of these were associated with recent BCG vaccination. Two districts in the survey undertook BCG vaccination of neonates. The Sub-Committee recorded its interest in this study.

5. SUMMARY OF SUSPECTED ADVERSE REACTIONS ASSOCIATED WITH VACCINES REPORTED ON YELLOW CARDS AND REGISTERED DURING THE PERIOD 1 MAY 1984 to 20 AUGUST 1984

5.1 Dr Zutshi said that during this period 258 reports of suspected adverse reactions had been registered.

5.2 These included 87 reports of suspected adverse reactions to triple vaccine administered with or without oral poliovaccine. There were 10 children with convulsions; five of these occurred the same day as vaccination, three the following day, one at 17 days and one one month after vaccination. Infantile spasms were reported in a 6-month old boy with onset 11 days after vaccination. These reports will be followed up. Members commented on the report of ipsilateral ptosis with facial weakness following DTP and OPV. They agreed the time of onset, 18 hours after vaccination, was not appropriate for a poliomyelitis vaccine adverse reaction and that it was a most unusual reaction to be associated with DTP vaccine. The report of infantile spasms was also difficult to assess. There was a possibility of an intracranial haemorrhage at birth and that the child did not develop normally. Further, there was asphyxia at birth and the EEG was not typical of infantile spasms.

5.3 There were 76 reports of suspected adverse reactions to DT vaccine given with or without OPV. These included one child aged three months who had died on the fourth day after vaccination. There was one report of a convulsion in a four year old boy who developed a febrile convulsion after a booster dose of DT. There was also one report of anaphylactic shock.

5.4 Eighteen reports of suspected adverse reactions to tetanus vaccine had been registered. These included a 21 year old woman who developed polyarthralgia a week after immunisation which was followed by sensory loss in the right hand and right foot drop with sensory loss. A 40 year old woman who had a history of cervical spondylosis developed pain over the left deltoid region which persisted for two weeks. A 16 year old boy who was given tetanus vaccine following a dirty penetrating wound

developed acute transverse myelitis.

5.5 Nineteen suspected adverse reactions were reported to measles vaccine; these included 8 patients who developed convulsions. Members considered that in four of these cases the convulsions were unlikely to be due to measles vaccine owing to the time relationship, either too early or too late.

5.6 There were four reports of suspected adverse reactions to rubella vaccine, including one patient who developed arthritis of the small joints of the hands 22 days after immunisation.

5.7 There were three reports of suspected adverse reactions following administration of hepatitis B vaccine; all were of a non-serious nature.

5.8 Oral poliomyelitis, yellow fever, cholera and pneumococcal vaccine were each associated with one suspected adverse reaction. The cervical and inguinal lymphadenopathy which followed a pneumococcal vaccination was not considered to be causally related.

5.9 There were three reports of suspected adverse reactions to influenza vaccine including one patient who developed the Guillain Barré Syndrome (GBS).

5.10 There were two reports of injection site abscesses following BCG vaccination and four suspected adverse reaction reports associated with grass pollen vaccine.

5.11 A patient who had received a dose of rabies vaccine developed a coronary thrombosis the following day.

5.12 There was one suspected adverse reaction report to anthrax vaccine. This was a 25 year old woman who received a first dose of anthrax vaccine in January 1979 in her left arm and subsequent doses in her right arm. The first injection was followed a day later by pain and swelling at the site. The pain and stiffness gradually improved but an

itchy lump remained for over a year. Although it has gradually got smaller, every four to six weeks this area became painful, red and swollen. In November 1983 the skin and subcutaneous tissue was removed and histology showed a granulomatous reaction similar to that seen following DTP vaccination.

5.13 There were 36 reports of suspected adverse reactions to typhoid vaccine, of which 34 were following the use of monovalent typhoid vaccine. These included one report of Guillain Barre Syndrome in a patient who had received typhoid and tetanus vaccine; one report of the Stevens-Johnson Syndrome; one of polyarthralgia; three of syncope and two of anaphylaxis; most of the remaining reports were either fever or constitutional symptoms following typhoid vaccination.

6. FURTHER INFORMATION ON CERTAIN SUSPECTED ADVERSE REACTIONS ASSOCIATED WITH VACCINES ARVI/84/33

Dr Zutshi described the following reports:

6.1 Sub-acute focal encephalitis associated with DTP immunisation

Follow-up 12 months later showed that this patient was progressing normally and that the only persisting abnormality was a slightly abnormal gait.

6.2 Tonic convulsions following DTP immunisation

Follow-up showed that this patient had no problems 18 months later.

6.3 Convulsion followed by a hemiplegia after DTP immunisation

This patient was reported to be well 16 months later and to have made a complete recovery.

6.4 Four children who had convulsions after DTP immunisation

Follow-up showed that all were satisfactory 15 to 18 months later.

6.5 Myoclonus associated with DTP immunisation

The myoclonus had been controlled and developmental progress six months later was 'pleasing' but the diagnosis was uncertain.

6.6 A five-month old girl who six hours after her second dose of DTP and OPV had developed uncharacteristic screaming

Follow-up showed that the third dose of diphtheria/tetanus vaccine and OPV and measles vaccine had been given without adverse reaction. However the child has repeatedly scratched the area of the left thigh where the second DTP immunisation was given and an urticarial wheal intermittently appeared at this site. In answer to the father's question as to whether this urticarial reaction had been caused by pertussis vaccine induced local histamine release, members considered this possibility was very remote.

6.7 Follow-up of several girls who had all felt unwell, dizzy and were pale and sweating after rubella vaccination revealed that they were now well. The Casualty Officer who saw them soon after the immunisation noted that they either felt well or were much better and they were all allowed to go home after a period of observation.

6.8 Three patients who had articular symptoms following rubella immunisation had been followed up 11 months to 4 years later and it was found that none of them had any further articular symptoms.

6.9 A patient who had Bell's Palsy associated with rubella vaccination was found to still have a mild weakness of the lower face six months later. A neurologist considered that her recovery would not be complete.

7. PERTUSSIS VACCINE

7.1 NCES data for encephalopathy after natural whooping cough: further information concerning long term outcome

7.1.1 Professor Miller said that he had studied 30 cases of neurological illness temporally associated with pertussis vaccine, together with 20 cases of neurological illness following natural pertussis infection, included in the NCES study. The frequency of long term sequelae following neurological illness was similar both in the vaccinated and in the natural pertussis groups but the relative risk of neurological illness was much higher in the latter group. Professor Miller further said that clinical evaluation of these cases was necessary before the

data could be published. He said that he hoped to mount a study to determine the outcome of neurological illness in the NCES, with a follow-up of children between the ages of 6 and 10 years.

7.1.2 Professor Miller informed the Sub-Committee that at the Fourth Symposium on Whooping Cough, recently held in Geneva, he had presented a revised attributable risk for neurological illness after a dose of pertussis vaccine irrespective of outcome but excluding cases of infantile spasms; this was 1:140,000. The attributable risk for previously normal children of developing permanent handicap after vaccination was now 1:330,000. Professor Miller agreed to provide a paper giving this information for the next meeting of the Sub-Committee.

7.1.3 Professor Miller said he had also presented data at Geneva on deaths which could be related to natural whooping cough. Examination of deaths among infants under the age of one year from respiratory disease showed that there was an excess of some 300 deaths over the expected number since 1978. Professor Hull said that if it could be shown that the number of reports of Sudden Infant Death Syndrome (SIDS) varied directly with the number of respiratory deaths each year; this would support the proposition that natural whooping cough was responsible for a significant proportion of the excess deaths.

7.2 Professor G T Stewart's Final Report

7.2.1 Comments on Professor G T Stewart's Final Report to the Office of the Chief Scientist to DHSS on his study of data on suspected adverse reactions to pertussis vaccine, entitled "Whooping Cough and Pertussis Vaccine" ARVI/84/34A

Members noted that on page 8, third paragraph, line 6, 'unvaccinated' should read 'vaccinated'. It was agreed that this report should form part of the collection of reports on adverse reactions to vaccines to be issued to the JCVI and ARVI.

7.2.2 Extract from CSM Minutes - June 1984 ARVI/84/34B

Members noted the comments of the CSM.

7.3 Pertussis Vaccine: "Is the Policy Right?" - an article by Professor Stewart in World Medicine, Sept. 1984 ARVI/84/35

The Sub-Committee noted this paper and agreed not to spend further time listing its inaccuracies. They concurred with Dr Barnes' concern about the misleading use of figures derived from awards made under the Vaccine Damage Payments Scheme.

7.4 Symptoms after primary immunisation with DTP and with DT vaccine. Pollock T M et al Lancet 1984 ii. 146-149 ARVI/84/36

The Chairman reminded members that they had seen a draft of this paper at a previous meeting. The Sub-Committee noted this paper.

7.5 Reactogenicity of fluid compared with adsorbed diphtheria-pertussis-tetanus vaccine. Mattias R G Can. Med. Assoc. J. 1984 130: 1561-1565 ARVI/84/37

Dr Zutshi said that this study indicated that the risk of a local reaction was higher with the use of fluid (plain) DTP vaccines compared with adsorbed DTP vaccines. Dr Smith said that this observation was in conformity with previous studies.

7.6 Letter from Dr Allsop: Should a history of maternal eclamptic convulsions be a contra-indication to pertussis immunisation ARVI/84/38

The Chairman said he had taken advice from Dr Baraitser, senior lecturer in genetics at the Institute of Child Health. It was agreed that eclamptic convulsions did not indicate a genetic tendency to epilepsy and did not constitute a contra-indication to pertussis immunisation in the child. This did not, of course, apply to convulsions occurring at other times during pregnancy or the puerperium.

8. INFLUENZA VACCINE AND THE GUILLAIN BARRE SYNDROME

8.1.1 Lack of association of A-New Jersey/76 (Swine Flu) Immunisation and Polymyositis, Transverse Myelitis, Brachial Plexopathy, Multiple Sclerosis and Encephalitis. Kurland L T, Beghi E, Mulder D W, Wiederholt W C and Kirkpatrick J W - Abstracts Amer. Acad. Neurol. April 1984 (Neurology 34, p.242-243) ARVI/84/40

This paper was noted.

8.1.2 Guillain-Barré Syndrome (GBS) and Swine Flu Vaccination, 1976: A re-assessment. Wiederholt W C, Kurland L T Abstracts: Amer. Acad. Neurol. April 1984 (Neurology 34 p. 242-243) ARVI/84/41

The Chairman said that this paper questioned the association of GBS with administration of the A-New Jersey strain of influenza vaccine. Dr Fine drew the attention of the meeting to two papers in the American Journal of Epidemiology confirming the association of GBS with this vaccine. The Sub-Committee expressed a wish to see these articles at the next meeting.

8.2 Guillain-Barré Syndrome and Influenza Vaccine. Winer J B et al Lancet 1984: 2: p. 1182 ARVI/84/42

8.3 Letter from Dr J Winer with clinical data on four cases of the Guillain Barre Syndrome with a history of immunisation other than influenza ARVI/84/43

Dr Zutshi introduced these two related papers. He said that the letter in The Lancet reported the occurrence of GBS in two patients who had previously received influenza vaccine at the end of 1983. These cases had been reported to the CSM and reviewed by ARVI. In discussion Dr Barnes reported that 1.3 million doses of influenza vaccine had been distributed during 1983, not 300,000 as stated in the paper. The committee agreed that the finding of a history of influenza vaccination preceding the development of GBS was therefore quite likely to be due to chance. However there were uncertainties here, including the geographical area in which the cases found by Dr Hughes' group and Dr Warlow's group had occurred; the question of the seasonal incidence of GBS was raised since vaccine in distributed during the summer. The second letter reported an apparent temporal cluster of four cases of GBS following other immunisations. The Sub-Committee decided to invite Dr Winer and Dr Hughes to the next meeting of ARVI to speak about the survey of cases of acute ideopathic neuropathy they were conducting within the four Thames Regions.

9. POLIOMYELITIS VACCINE

Fetal damage after accidental polio vaccination of an immune mother. Barton A E et al. Journal of the RCGP 1984: 34: p. 390-394 ARVI/84/44

Dr Smith observed that the termination of the pregnancy at 20 weeks in this case report was not related to the administration of oral poliovaccine (OPV).

However, the foetus was reported to have signs of infection with poliovirus in the nervous system although no similar event had been previously seen after vaccination. He further observed that the fluorescent antibody test used to detect poliovirus sometimes gave cross-reactions and lacked specificity. Members decided that the conclusions drawn by this paper were not convincingly demonstrated. After detailed discussion it was the view of the Sub-Committee that inadvertent administration of OPV was not an indication for termination of pregnancy.

10. MEASLES VACCINE

10.1 PHLS surveillance of reactions to measles vaccine. Paper by Dr C L Miller (July 1984) ARVI/84/85

Dr Miller said that an earlier version of this paper had been seen by the Sub-Committee. This study comparedthe incidence and severity of reactions after measles vaccination in 1326 children who received the Schwarz strain (Mevilin) with those 1371 children who received Moraten strain (Attenuvax) vaccine. The rate and severity of reactions, including convulsions were similar after both strains. Three convulsions had been reported associated with Mevilin and three with Attenuvax in the post-vaccination period. However, two of the three children vaccinated with Mevilin should have also received a small dose of immunoglobulin because of a previous history of fits. One of the children who had been immunised with Attenuvax had a urinary tract infection which could have been the cause of the convulsion rather than the measles vaccine. Dr Miller informed the Sub-Committee that the study was continuing but that another Schwarz strain vaccine recently introduced, Rimevax, was now being studied instead of Mevilin.

10.2 Early onset adverse reactions following measles vaccination ARVI/84/46

10.2.1 Dr Zutshi reminded members that at a previous meeting he had reported a cluster of reports of anaphylactoid and similar reactions occurring within an hour of measles vaccination. These initially appeared to have been associated with a particular batch of the newly marketed Rimevax vaccine. Dr Zutshi reported that similar adverse reactions, which had occurred in Australia mostly in association with

Rimevax, had been termed "early onset reactions" to measles vaccine. The Australian cases first reported in 1981 appeared to be hypersensitivity reactions with a rapid onset and of such a nature that children were taken back to the surgery for advice. Following these reports the Australian Drug Evaluation Committee had recommended that children should be observed for at least 20 minutes following measles vaccination.

10.2.2 Dr Zutshi said that his paper reviewed the published reports of similar adverse reactions from other countries and those reported to the CSM in an attempt to establish whether these reports constituted a new phenomenon and whether a particular period of observation following measles immunisation was necessary as advised in Australia. He reported that in addition to the 18 Australian cases, published between 1981 and 1983, a paper in 1980 had reported six similar reactions which had occurred in 60,000 children immunised with Mevilin in Norway. The licence holder for Rimevax had received reports of two similar reactions from Botswana and three from Belgium in addition to the Australian and British cases.

10.2.3 Dr Zutshi said that he had examined similar reactions reported to the CSM. This type of reaction had not been reported in association with Attenuvax but 15 reports had been received associated with Rimevax and 35 with Mevilin. Many of them were reported or assessed as being anaphylactoid reactions. The time of onset varied between 2 and 30 minutes after vaccination, the majority occurring within 10 minutes. This time interval on average was shorter than that associated with the Australian cases. Extensive investigations of batches of Rimevax vaccine had not revealed any defect in the vaccine. The last report associated with Mevilin had occurred in August 1981.

10.2.4 Dr Zutshi informed the Sub-Committee that the licence holder of Rimevax intended to include this statement in the adverse reactions section of the data sheet: " Allergic type reactions have been reported rarely". The company were also in the process of reformulating the product to reduce the molecular weight of Dextran, which is included as

a stabiliser, since theoretically this could cause an occasional problem.

10.2.5 Dr Smith said that he had asked Dr Bart of CDC Atlanta if similar cases had been seen in the United States but Dr Bart had replied that he was not aware of such adverse reactions. The Chairman observed that the analysis of these reactions suggested they were probably identical with the anaphylactoid type complications originally included in the ARVI report on adverse reactions to measles vaccination. Dr Smith agreed that these recent reactions might possibly have been caused by a difference in the Dextran content of the vaccines. The Sub-Committee decided that it would need to continue to monitor suspected early onset reactions associated with measles vaccines.

11. ITEMS FOR INFORMATION

MLX 152 and 152a
MLX 153
MAIL 40
Statutory Instrument 769
Annual Calendar for 1985

These were noted

12. ANY OTHER BUSINESS

Dr Miller asked whether live poliovaccine be given to the sibs of patients with immuno-deficiency or those on immuno-suppressive drugs? Members agreed that in such cases killed polio vaccine should be used.

13. DATE AND TIME OF NEXT MEETING

The next meeting will be held on Friday 1 February 1985 at 11 am in Rooms 1611-12 Market Towers. Further meetings have been arranged for 7 June and 4 October 1985.