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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 28 October 1983 at Market Towers.

Present: Professor R W Gilliatt (Chairman) Dr J Badenoch
Dr A L Bussey Dr R Covell
Professor J A Dudgeon Miss Z Spencer
Professor D Hull Dr M Duncan (Medical Assessor)
Professor D Miller Dr D W Zutshi (Medical Assessor)
Dr D Reid Mr H M Morgan (Secretary)
Dr M H J Richards Mr T J Kirkley

Dr K M Citron and Dr R H Raynes attended the meeting for item 5 on the Agenda only.

1. CONFIDENTIALITY AND ANNOUNCEMENTS

The Chairman reminded members that the proceedings and information before them was confidential and should not be disclosed. He welcomed Dr Citron and Dr Raynes who would be attending for item 5. He also welcomed Dr Covell from the Scottish Home and Health Department.

2. APOLOGIES FOR ABSENCE

Apologies for absence had been received from Professor Lloyd, Dr Pollock, Dr Smith and Dr Wilson.
3. **MINUTES OF THE MEETING HELD ON 1 JULY 1983**

Subject to the correction of a number of grammatical and minor
typographical errors these minutes were agreed and signed by the Chairman
as a correct record of the meeting.

4. **MATTERS ARISING FROM THE MINUTES**

4.1 **Wasp and Bee Sting Desensitization (ARVI/83/23)**

Dr Zutshi had written to Dr Atkinson conveying ARVI's advice
concerning the place and period of observation considered advisable
for patients undergoing desensitization to wasp and bee venom. The
Company had agreed to amend the statement in the package insert
concerning the period of observation following injection so that it
was in line with the advice given in the data sheet.

5. **BCG VACCINE**

5.1 **Adverse Reactions to BCG Immunisation (ARVI 83/27)**

5.1.1 Dr Raynes introduced the first five paragraphs of this paper
and gave a brief history of BCG vaccination.

5.1.2 The Sub-Committee noted that a Medical Research Council
Working Party was assessing the benefit in epidemiological
terms of the routine programme of BCG vaccination. The
Working Party would be completing its collection of data by
the end of 1983 and making a preliminary report in the
Spring or Summer of 1984. It had been previously calculated
that naturally acquired tuberculin sensitivity was falling by
10% per annum in schoolchildren.
The total number of notifications of tuberculosis was also falling steadily. It was therefore possible that a recommendation might be made that the BCG programme should not be continued except in certain specified groups eg health professionals, immigrants, etc. In 1981 some 575,000 school children and about 28,000 babies were recorded as having been immunised. The number of neonates vaccinated varied from region to region depending upon the immigrant population. Members commented that the number of doses of BCG vaccine supplied each year (1,700,000) was well in excess of the number of immunisations.

5.1.3 In discussing the Redbridge Report, members considered whether the recommendations were, in fact, realistic.
Dr Citron said that by far the most important one was that related to the proper training of health professionals involved in the BCG vaccination programme.

5.1.4 The subsequent sections of ARVI 83/27 were introduced by Dr Zutshi who discussed those adverse reactions that had been reported to the Committee on Safety of Medicines. Professor Hull made the point that BCG immunisation was bound to identify infants who had a severe combined immune deficiency syndrome, most of whom were destined to die of an intercurrent infection. It was therefore doubtful if disseminated BCG tuberculosis and subsequent death should be regarded as a complication of vaccination in the ordinary sense.
It was noted that a small number of convulsions associated with BCG immunisation had been reported to CSM. The Chairman undertook to check whether these exceeded the expected background rate of first convulsions in children aged 13 or 14.

With regard to local reactions, the point was made that if preliminary tuberculin testing was not done, some vaccinees would be expected to get violent local reactions. It was known that at least one authority did not carry out preliminary tuberculin testing prior to immunisation. It was also noted that although the vaccine had been altered in 1975 the number of viable units being increased, its potency had remained unchanged since then. It was difficult to explain why the increase in local adverse reactions occurred mainly in 1975 to 1978. It seemed possible that a small number of "Redbridge Type" incidents and subsequent publicity could have been responsible for this increase. Dr Zutshi undertook to ascertain if these adverse reactions were reported predominantly from localised areas of the country.

Throughout the discussion of adverse reactions to BCG the likelihood of under-reporting was emphasised; for example only one non-fatal case of adenitis had been reported to CSM during the past 20 years.
5.2 Adverse Reactions to BCG Vaccine reported to the North West Thames Regional Study ARVI/83/28

Dr Christine Miller's letter describing the adverse reactions noted in the N.W.T. Regional Study and subsequently reported to the CSM and her paper given at the Harrogate Seminar on Vaccination and Immunisation in May 1983 were considered by the Sub-Committee. In addition to the data from the N.W. Thames Region, the PHLS had data from a BCG surveillance scheme which included the examination of some 12,000 lesions. The numbers still discharging at 3 months had always been small. No case of adenitis had been reported since 1969. The Sub-Committee decided it would welcome further information on the BCG surveillance scheme. It was noted that the Tine test could be unreliable and that the Heaf or Mantoux test was preferable.

5.3 Complications of BCG Vaccination ARVI/83/30

Dr Citron introduced his paper reviewing the complications of BCG vaccination and described the International Classification. He drew attention to the bone and joint lesions which had occurred, particularly in Scandinavia with the use of the Gothenberg strain. Osteitis was related to the type of vaccine used, and was associated mainly with neonatal vaccination in the gluteal region. This complication was rarely seen in the UK since the Gothenberg strain was not used here. He considered that local adverse reactions were the most important ones in the UK and that incorrect technique was the main causal factor. Dr Citron said that keloid scars often took 3 to 4 years to appear. In answer to a question regarding the possibility of a relationship between BCG and malignancy Dr Citron said that Dr Rosenthal in a matched case control study in Hungary had found that the incidence of Hodgkin's disease and tumours occurring under the age 20 had been reduced by neonatal BCG immunisation.
5.4 BCG Vaccine: Systemic Adverse Reactions  ARVI/83/31

Professor Gilliatt's literature review was discussed with Dr Citron's paper. Published reports of reactions appeared to include; local injection site reactions, disseminated skin lesions, lymphadenitis, osteitis and osteomyelitis, disseminated tuberculosis (BCG -osis) and increased risk of malignancy. The reactions seen after other forms of vaccination (anaphylaxis, nervous system complications) seemed to be rare but dermatomyositis was the subject of several reports. Professor Gilliatt again emphasised the presence of under-reporting. He drew attention to a case of generalised tuberculosis following BCG immunisation published in the Journal of the Royal Society of Medicine which was not included in the cases reported to the CSM.

5.5 BCG Vaccination: Armed Forces Experience  ARVI/83/32

The Sub-committee noted that the Ministry of Defence did not have records of any serious scars from BCG vaccinations in service personnel, even among Gurkhas.

5.6 In general discussion the Sub-Committee agreed that in order to reduce the incidence of adverse reactions it was of crucial importance that the vaccinators should be educated to use the correct technique of immunisation. Sub-Committee members were also of the opinion that some form of surveillance was needed to establish the incidence of rarer adverse reactions. Even if the national programme were to be abandoned, vaccination would still be offered to limited groups; it was estimated this might involve 75,000 vaccinations per annum. Under these circumstances surveillance might be easier. Professor Hull raised the question of osteitis and osteomyelitis which occurred in
Scandinavia with an incidence of one in 15,000 following neonatal immunisation with the Gothenberg strain. Although the Gothenberg strain was not used in the UK, the possibility that osteomyelitis occurred in the UK could not be ruled out. Cases of osteitis might not be attributed to BCG since it could occur a relatively long time after immunisation. The Sub-Committee agreed that Dr Zutshi should consult with Dr Christine Miller and Professor David Miller about the feasibility of a study which might establish the incidence of the rarer complications of BCG immunisation.

6. **DIPHTHERIA AND TETANUS VACCINE  ARVI/83/33-34**

Minor amendments to the draft (83/33) were agreed. The Sub-Committee considered Professor Miller's further analysis of the NCES data (83/34), which now incorporated all cases. It noted that the number of children with the onset of severe neurological reactions within seven days of DT vaccination was greater than expected by comparison with controls. However data were not yet available for the subsequent 3 weeks in which there might be a corresponding deficit. Professor Miller was also asked to provide data on the incidence of reactions in children who were not neurologically normal before immunisation. This could be particularly important information in view of the current advice that diphtheria/tetanus immunisation can be safely carried out in children with a previous history of convulsions or neurological disease. It was agreed that the drafting committee should meet before the next meeting of ARVI to consider these data and to redraft the final conclusion of the paper.
7. **SUMMARY OF SUSPECTED ADVERSE REACTIONS ASSOCIATED WITH VACCINES**

**REPORTED ON YELLOW CARDS AND REGISTERED DURING THE PERIOD 11 JUNE 1983 TO 15 SEPTEMBER 1983**

ARVI/83/35

Dr Zutshi reported that there had been 56 reports of suspected adverse reactions to DTP including 5 cases of convulsions. There had been 3 reports of suspected adverse reactions to monovalent pertussis vaccine, 2 of fever and 1 of bronchospasm in a boy with a past history of bronchitis.

There had been 38 reports of adverse reactions associated with diphtheria/tetanus vaccine; 34 of these were injection site disorders.

There were 15 reports associated with tetanus vaccine, mostly of a minor nature. There was 1 report of a man aged 53 who developed tinnitus 3 days after immunisation.

There were 33 suspected adverse reaction reports to measles vaccine, including those of 6 patients who had convulsions with pyrexia. One patient developed an acute hemiplegia 6 days after immunisation.

Nine adverse reaction reports following rubella immunisation had been received including 1 report of arthritis and another of a Bell's palsy 5 days after vaccination.

There had been 6 reports of suspected adverse reactions to oral poliomyelitis vaccine. These comprised of 1 cot death a few days after the first dose of oral polio vaccine, a case of partial paralysis of the left tibialis anterior muscle 7 days after a booster dose and four reports of a minor nature.
Four suspected adverse reactions to BCG had been reported, 3 of these were abscesses which had occurred 6 months, 8 months and 3 years respectively after immunisation.

There had been one report of an anaphylactic reaction following cholera immunisation and a further two following TAB vaccinations. Reports of nine suspected adverse reactions, including four of anaphylactic reactions, had been received associated with typhoid and cholera immunisation. There were 17 reports of suspected adverse reactions to monovalent typhoid vaccine including 2 of grand mal fits, 1 of a febrile convulsion and 1 of a man aged 23 who 10 days after immunisation developed herpes zoster. The Sub-Committee suggested that the development of herpes zoster in this patient was a coincidence and not causally related.

There was 1 report of acute vertigo lasting 10 days which occurred 23 days after immunisation with hepatitis B vaccine.

Two reports, one fatal, had been received of anaphylactic reactions to desensitising agents.

There were 2 reports of suspected adverse reactions to influenza vaccine, one of these was a report of mononeuritis multiplex.

8. FOLLOW-UP OF CERTAIN SUSPECTED ADVERSE REACTIONS  ARVI/83/36

Dr Zutshi said that he had undertaken a follow-up of 53 reported cases of suspected articular reactions after rubella vaccination. Clinical information had been received so far on 22 patients. Nineteen of these patients did not appear to have any subsequent unexplained articular
symptoms following the initial suspected adverse reaction which had occurred during the previous 13 years. Three patients had suffered a further recurrence of articular symptoms but in only 1 was it persistent. Dr Zutshi hoped that information would be forthcoming on a further 24 patients but he said it had proved impossible to obtain information on the 7 remaining patients who had articular symptoms following rubella immunisation. The Sub-Committee felt this follow-up study of suspected arthropathy and rubella was particularly worthwhile and await further information.

Two cases of convulsions suspected of being associated with measles vaccination had been followed-up. One child was apparently well 14 months after the convulsion, the other had had a febrile convulsion 10 months later associated with otitis media but had remained well during the succeeding 6 months.

Follow-up had confirmed the diagnosis of dermatomyositis which had developed in a 15 year old girl 1 week after immunisation with diphtheria, tetanus and poliomyelitis vaccines. She apparently needed quite high doses of corticosteroids to suppress the myositis.

9. PERTUSSIS VACCINE

9.1 Immunisation against whooping cough: A Neuropathological Review – Neuropathology and Applied Neurobiology 1983, 9, 261-270

The Chairman introducing this paper reminded members that Professor Corsellis had attended ARVI's second meeting in 1980 and his paper had now been published.
9.2 Safety of Pertussis Vaccine - Pollock T M
Lancet 1983, 2; 795-796 ARVI/83/38

9.3 Pertussis Vaccine and infantile spasms -
Meade T W, Lancet 1983; 2, 278-279 ARVI/83/39

9.4 "Campaign of Terror" - Barrie H,
The Chairman said that these papers were provided for information.

10. MEASLES, MUMPS AND RUBELLA VACCINES

10.1 Measles vaccine associated encephalitis in Canada
Dr. Zutshi said that on the basis of doses of measles vaccine distributed, the author estimated that the Canadian rate for measles vaccine-associated encephalitis was one-four-hundredth of the rate of encephalitis complicating natural measles infection.

10.2 Mass vaccination programme aimed at eradicating measles, mumps and rubella in Sweden: First Experience:
Dr. Zutshi said this paper was of interest since it showed adverse reactions were more likely to occur when immunisation was carried out at 18 months rather than at 12 years, in particular fever, rash and febrile convulsions. In the 18 month old children, there was a 1 percent incidence of febrile convulsions. Arthralgia was more common in the immunised 12 year old children but was no higher than what would normally be expected during any month in a school population of that age.
10.3 Rubella Vaccination during pregnancy - United States

1971-1983 MMWR : 26 August 1983; Vol 32/No 33 429-432 and 437

The Chairman said that this paper was provided for information.


Dr Zutshi said that this paper raised the interesting possibility that joint symptoms following rubella immunisation might be more common in those patients who had serological evidence of a previous rubella infection. However, the numbers of patients studied were small.

11. ANY OTHER BUSINESS

11.1 The Chairman drew attention to a recent paper by Miles and Hosking - Pertussis : Should we immunise neurologically disabled and developmentally delayed children? (BMJ, 30 July 1983 Vol 287, pages 318-320). ARVI had been asked by JCVI to consider this paper and it was agreed that it would be most helpful if Professor Hull could make some comments from the paediatric point of view on which categories of neurological disorders or handicaps might or might not be considered to predispose to an increased risk of adverse reactions from pertussis immunisation, for the next meeting of ARVI. Professor Miller was also asked if the NCES could produce data on children with pre-existing neurological problems who had either deteriorated abruptly or not deteriorated after immunisation. In the light of these comments and data, the Sub-Committee felt that this matter could then be discussed at the next meeting.
11.2 The Chairman referred to the tabled paper and it was agreed that the dates of meetings of ARVI for 1984 would be 3 February 1984, 1 June 1984 and 5 October 1984.

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

It was confirmed that the next meeting of ARVI would commence at 11.00 am on Friday 3 February 1984.