COMMERCIAL 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NOT FOR PUBLICATION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, 29 October at Market Towers.

Present: Professor R W Gilliatt (Chairman) Dr J Badenoch
Dr D Reid Dr Morris
Professor D Miller Dr Cherry
Dr A L Bussey Dr Duncan
Dr M H J Richards Dr Zutshi
Dr T M Pollock Miss Purves
Dr J Barnes (Medical Assessor) Miss Horridge
Miss Z Spencer (Acting Secretary)

1. CONFIDENTIALITY AND ANNOUNCEMENTS

1.1 The Chairman reminded members that the proceedings and information before them were confidential and should not be disclosed. He welcomed Dr Jean Morris who was attending for item 7.

1.2 The Sub-Committee considered reducing the number of meetings in 1983 from three to two but felt that their workload would necessitate three meetings.

1.3 The Chairman reminded members that the dates of meetings for 1983 were as follows:

4 March, 1 July, 28 October.

2. APOLOGIES FOR ABSENCE

Apologies for absence had been received from Professor Dudgeon, Professor Glynn, Professor Hull, Dr Smith, Dr Young, Dr Wilson.

3. MINUTES OF THE MEETING HELD ON 25 JUNE 1982

These were agreed and signed by the Chairman as a correct record, subject to minor typographical amendments.

4. MATTERS ARISING FROM THE MINUTES

4.1 Minute 5.1 There was nothing new to report on the proposed research into the interaction between influenza vaccine and warfarin.

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4.2 Minute 5.3 Infantile Spasms. The Sub-Committee enquired about progress towards publication of this work. Professor Miller said that he would be submitting it soon for publication. The Chairman emphasised the importance of this paper being published at the earliest possible instance. Professor Miller also reported that a paper on whooping cough and vaccination written by his colleagues and himself had been published in a recent edition of the Epidemiological Review. It was agreed that this latter paper was of interest both to members of ARVI and to the JCVI and should be circulated to these committees.

4.3 Minute 6.3.3 Experimental Model of Post Pertussis Immunisation Encephalopathy: Linkage to the major histocompatibility complex. Paper by Steinman Zanvil, Waldol and Lim. It was reported that this was to be published in Nature.

4.4 Minute 6.3.1 Correspondence arising from the "NICHD Co-operative Epidemiological Study of Sudden Infant Death Syndrome Risk Factors (Paper ARVI/82/17). The Sub-Committee noted an additional study described by Dr Elizabeth Taylor and Professor Emery in a letter to the Lancet of 25 September 1982, and that it supported the findings of the NICHD study. The Committee considered on the basis of the present evidence that there was no association between Pertussis immunisation and Sudden Infant Death Syndrome.

5. ADVERSE REACTION TO RUBELLA VACCINE (ARVI/82/18)

The Sub-Committee noted that the CSM had endorsed their recommendation on the data sheet on Almavax, but that the company did not wish to accept part of the comment on the position on juvenile rheumatoid arthritis.

6. ADVERSE REACTIONS TO POLIOMYELITIS VACCINE (ARVI/82/19–22)

The Sub-Committee welcomed the draft report (ARVI/82/19) prepared by the Chairman and Dr Barnes, noted the comments sent by Dr Smith (ARVI/82/22), and made the following general comments:

1. Page 3, sub paragraph (d) - It was suggested that the end of the sentence should read "unless there are compelling reasons".

2. In the section on adverse reactions to oral polio vaccine, less prominence should be given to the unpublished data of Dr Chamberlain, and more to published papers. There were some problems about her criteria in categorising cases, which differed from previous studies and made in difficult to compare her results with earlier papers. It was agreed that the data should follow discussion of the published papers.

3. The paper should explain the problems of assessing the risk of these vaccines, including the problem of distinguishing cases caused by vaccine and those caused by a wild virus, and whether the risk should be calculated as confined to the first dose.
4. Throughout the paper, cases of paralytic or non-paralytic poliomyelitis should be said to be "associated" with the vaccine rather than "attributable" to it.

5. The Sub-Committee discussed whether the second paragraph on page 15 was within the brief of the committee. Dr Pollock pointed out that it was not practicable in fact to go over to IPV in this country, but Professor Miller said that he felt it was reasonable to look at the relative risks of the two options. It was agreed to leave it to the drafting committee to decide whether this paragraph should be included.

6. Dr Pollock pointed out that the paper did not mention poliomyelitis-like illness caused by other enteroviruses, nor the validity of marker tests to determine whether a poliovirus was vaccine-like or wild. In addition no indication was given of the number of recipient cases associated with first doses compared with booster doses.

The Sub-Committee agreed that the drafting group should prepare a further draft of the paper, in the light of comments made at the meeting and in writing, and Professor Miller agreed to re-write the section pages 4-10.


The Sub-Committee noted that there were problems in comparing information of different reliability from different countries. Nevertheless the results were in general agreement with the findings in the UK and it was interesting that some of the cases were reported to have had immuno-deficiency.

8. The Sub-Committee also noted the letter from Professor Miller (ARVI/82/21) reporting that his NCEs data did not show any clustering of neurological illness between 7th-13th day, following oral polio vaccination ie when such reactions would be reported if OPV were a causal factor.

ADVERSE REACTIONS TO DIPHTHERIA AND TETANUS VACCINES (ARVI/82/23)

Dr Barnes said that this was a preliminary draft, and he would be grateful for the Committee's views on how to proceed. It was particularly difficult to get clear information, because the vaccines were often given with pertussis and polio.

The paper described diphtheria and tetanus vaccines, their recommended use, contra-indications and the adverse reactions reported to the CSM on yellow cards. The most commonly reported reactions were injection site disorders and secondary fever. More serious reactions, mostly neurological disorders, had been reported; but it would be difficult to determine which antigen had been the cause of these reactions since most of these occurred when the vaccines had been given in association with pertussis vaccine.
Members observed that a considerable amount of tetanus vaccine had been given in the Armed Services and that enquiries should be made to the Ministry of Defence regarding adverse reactions to tetanus vaccine. It was also suggested that information be sought from the North West Thames Survey, and the NCES. The Chairman said that there were isolated reports in the literature of neurological reactions to diphtheria and tetanus vaccines. It was agreed that a fuller report should be assembled for the next meeting of the Committee.

8. **MANIFESTATIONS OF REACTIONS FOLLOWING VACCINATION IN THE NORTH WEST THAMES REGION - A SEVEN YEAR SURVEY - (FROM THE PHLS EPIDEMIOLOGICAL RESEARCH LABORATORY AND SPECIALISTS IN COMMUNITY MEDICINE CHILD HEALTH) (ARVI/82/24)**

Dr Pollock introduced this paper, which was a report of an intensive study carried out in the New Thames RHA, and which would be published soon. He said that they had changed their methodology during the study in an attempt to counteract the effect of intensive newspaper publicity which appeared to be distorting the number of voluntary reports received on DTP as opposed to DT. The Hospital Activity Analysis section of the work was intended to resolve this problem, and in general the conclusions were reassuring.

Professor Miller welcomed the study and said that he agreed that the HAA analysis resolved the problem of selective reporting, and that it was a most important conclusion that neither this study nor the NCES had found evidence of severe brain damage associated with pertussis vaccine. The shifting background rate for febrile convulsions at different ages in children made it very complicated to calculate any association with vaccination. He felt it was important that the paper made it clear that there should be no concern that there appeared to be an increased incidence of febrile convulsions after the third dose of DTP, which coincided with the natural peak incidence.

In response to a question, Dr Pollock confirmed that the diagnoses made in the Hospital Activity Analysis survey could be considered reasonably reliable. Each case in the study was checked so that the initial diagnosis was used just as a filter to identify more serious neurological reactions. It was possible that some cases might be missed if the primary diagnosis was different from those they were looking for, but this was unlikely, and in any case would apply to both groups.

It was suggested that the discussion section of the paper should perhaps start with the third sentence, rather than the present first sentence.

The Sub-Committee felt that the paper should be seen by the JCVI before publication.

9. **NATURE AND RATES OF ADVERSE REACTIONS ASSOCIATED WITH DTP AND DT IMMUNISATIONS IN INFANTS AND CHILDREN. (CODY ET AL PAEDIATRICS, VOL 68, PAGES 650-660, 1981) ARVI/82/12d**

The Chairman welcomed Dr James Cherry to the meeting, saying that he had been co-author of the paper which had been considered at the last meeting of ARVI.
Dr Cherry said that the concern in Great Britain, which commenced in 1974, over adverse reactions to whooping cough vaccine had had little impact in the United States. In 1977 it was decided to set up an investigation into adverse reactions to diphtheria, tetanus and pertussis vaccines. Prior to immunisation, consent was obtained from the parents or guardian to conduct surveillance of adverse reactions. Parents were given a questionnaire and were asked to record the child’s temperature at 3, 6, 24 and 48 hours and any of the following reactions that occurred within the 48 hours: redness, swelling or pain at the injection site, drowsiness, fretfulness, vomiting, anorexia, persistent or unusual crying, convulsion, or a hypo-responsive episode. Only reactions occurring within 48 hours of immunisation were reported. The study was conducted in the greater Los Angeles area and was divided into three parts: unblind DTP recipients (confined to private clinics); unblind DT recipients, and double-blind DTP versus DT recipients (the latter two studies were carried out in County Clinics). During the period 1 January 1978 to 15 December 1979, 15,752 DTP and 784 DT immunisations given to children up to the age of six years were prospectively studied for reactions occurring within 48 hours. Follow-up was by post, telephone or home visits. The vaccines used were all adsorbed. Results showed that local reactions such as redness and swelling were much more common following DTP compared with DT. Fever in excess of 38°C was observed in 47 per cent of children receiving DTP compared with 9 per cent of children receiving DT. Systemic reactions such as abnormal crying, drowsiness, vomiting and anorexia were also observed more frequently after DTP. Local reactions and fever were more frequent with increasing immunisation series number. No such series dose relationship was seen with other systemic reactions. Apart from these less serious reactions, nine children were reported with convulsions and nine with a shock-like state. On follow-up none of these children appeared to have suffered permanent handicap.

In the ensuing discussion Dr Pollock, speaking to a tabled paper, said that an unpublished study of 803 children followed up for 24 hours after DTP or DT showed that DTP is more likely to provoke an increase of temperature within 24 hours than an injection of DT. He observed that the infrequency and the mildness of fever observed after DTP and DT were in marked contrast to the study by Cody and his colleagues. Fever occurred more frequently between 20 to 24 hours after vaccination and not at 4 hours. However fever was more frequently observed after the third dose. Dr Cherry observed that it had been his experience that if post-immunisation fever was to be detected it should be measured within 4 hours after immunisation. It was noted that in Dr Pollock’s study the axillary temperature was used to assess fever. Members were reassured that this method of measurement of temperature was reliable.

10. SUMMARY OF ADVERSE REACTIONS TO VACCINES REPORTED ON YELLOW CARD DURING THE PERIOD FROM 31 MAY TO 30 SEPTEMBER 1982 (ARVI/82/24)

1. Dr Barnes in presenting this paper tabled three extra cases of suspected adverse reactions to monovalent pertussis vaccine. The reports on adverse reactions to Diphtheria/Tetanus and Diphtheria/Tetanus given with OPV, had been divided as requested into those occurring with the primary course and with the booster.
2. It was noted that injection site disorders were more frequent following booster doses of diphtheria and tetanus vaccine and it was agreed that information on this subject should be incorporated in the ARVI Report. The four reports of encephalopathy following measles vaccine were also noted.

3. Members emphasised the importance of follow up of the more serious reactions, such as encephalopathy. Professor Miller agreed that the follow up of such adverse reactions was of value although it could not replace a structured controlled study.

4. The Sub-Committee discussed what reasons might lie behind the apparently higher incidence of neurological reactions to measles vaccine experienced in the UK compared to the USA. The types of vaccine used were considered and the possibility that adverse reactions were reported less frequently in the USA. The Sub-Committee queried whether a study of the American vaccine in the UK might be indicated if neurological reactions to the British vaccine continued to be reported at the current rate.

5. Dr Barnes drew attention to the four fatal adverse reactions to grass pollens. It was noted that anaphylaxis could occur if the vial was not shaken properly on each occasion.

11. ANY OTHER BUSINESS

There was none.

12. ITEMS FOR INFORMATION

MLX 143 was circulated to members for information.

13 DATE OF THE NEXT MEETING

The date of the next meeting is Friday, 4 March 1983.