NOT FOR PUBLICATION ARVI/87/2nd Meeting

COMMERICAL IN CONFIDENCE

COMMITTEE ON SAFETY OF MEDICINES/JOINT COMMITTEE ON VACCINATION AND IMMUNISATION

JOINT SUB-COMMITTEE ON ADVERSE REACTIONS TO VACCINES AND IMMUNISATION

Minutes of the meeting held on 6 July 1987 at 10.30am in Room 1611/12 Market Towers

Present:

Professor J Collee (Chairman)
Sir J Badenoch
Professor A M Breckenridge
Dr C Bowie
Dr N Cavanagh
Dr P Fine
Professor S R Meadow
Professor D Miller
Dr E Miller
Dr D Reid
Dr S Wallace

DHSS:

Dr D Salisbury (Assessor)
Mr K Fowler (Secretary)
Mr J McCracken
Dr R Mann
Dr F Rotblat
Dr A Smithies

1. Confidentiality and Announcements

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 expressed the Sub Committee's thanks for the work of the retiring Chairman, Professor R W Gilliat, who had led the Sub Committee at a time when there had been difficulties in the understanding of adverse reactions to vaccines, especially whooping cough vaccine. It was through Professor Gilliat's efforts that a much clearer appreciation of the specific nature of adverse reactions to vaccines had been gained.

1.3 The Chairman also expressed his thanks for the work of previous members of the Sub Committee who had not been able to accept reappointment because of other work commitments.

1.4 The Chairman welcomed newly appointed members to the Sub Committee, and introduced the secretariat.

1.5 The Secretary, elaborating on the background information which had been sent to newly appointed members, described briefly the function of the Sub Committee, to give advice to both the CSM and JCVI.

1.6 The Secretary informed members about the study of DHSS Medicines Division being carried out at the request of Ministers by Dr Evans and Mr Cunliffe. Members were invited to submit any comments or suggestions they may wish to make by 20 July.

2. Apologies for absence

Apologies had been received from Professor Hull, Professor McDevitt and Dr McGuiness.

3. Minutes of the last meeting

The minutes of the meeting held on 6 February 1987 had been circulated and were agreed by members without amendment. It was noted that they had been seen agreed and signed by Professor Gilliat.

4. Matters arising from the last minutes

The following items were discussed:-

Item 4(a) - Item 5 of the October 1986 meeting ARVI/87/8

This was discussed under Agenda Item 6 - Whooping Cough.

Item 4(b) - Item 6 of the October 1986 meeting ARVI/87/9

The paper on anaphylaxis including Yellow Card reports to the CSM, protocols for treatment of anaphylaxis, dosage regimes and training, was presented. It was felt that reassurance could be derived from the small number of deaths (3) from 212 reports of anaphylaxis, anaphylactoid reactions and allergy. The Chairman suggested that an advisory group should convene to provide advice on anaphylaxis with Professor Hull as Chairman and Professor Breckenridge, Dr McGuiness and Dr Salisbury as members.

Item 4(c) - Item 8 of the October 1986 meeting ARVI/87/10

It was agreed that Dr Smith's letter (ARVI/87/10) should be referred to JCVI with ARVI's endorsement. thought that the previous advice had originally been extrapolation from concerns surrounding tonsillectomy during natural polio epidemics.

Item 5 - MMR vaccine - 5.4 Postpartum Rubella immunisation associated with development of prolonged arthritis neurological sequelae and chronic rubella arthritis Tingle et al. J. of Inf. Diseases (1985), Vol 152: pages 606-612 ARVI/87/11

This paper had been considered at the last meeting of ARVI but had promoted correspondence in the Journal of Infectious Diseases, Vol 154, No. 2, August 1986 from Preblud, Orenstein, Lopez, Herrmann and Hinman from CDC, Atlanta, and a reply from Tingle. The correspondence was submitted for members information. reminded the Committee of an SSPE-like syndrome reported from rubella virus infection and noted the maternal viraemia and transmission of rubella virus in breast milk. reported noted that more than 10,000 women per year received post-partum rubella immunisation and commented on the absence of such cases from the NCES study, when children followed initially to three years were now 10 to 12 years old.

made
has a study of SSPE surveillance and it was thought that none of her cases was associated with rubella. thought the report to which had referred concerned congenital rubella syndrome, not acquired rubella.

5. Suspected adverse reactions to vaccines: Reports on Yellow Cards registered during the period 27 Janaury to 4 June 1987 ARVI/87/13

5.1 presented this paper drawing members attention to some of the difficulties distinguishing adverse reactions, adverse events and reports where there was little relationship to immunisation. The paper entitled "Further information on certain suspected adverse reactions associated with vaccines" was presented. ARVI/87/13A

5.2 Fifteen suspected adverse reactions to DPT

The last sentence should be deleted as immunisation is probably a temporal, not causative association with infantile spasms. This summary was produced after reports had been obtained from doctors notifying CSM of "neurological" reactions to vaccines. Scrutiny of the original reports reveals that they were not necessarily all vaccine-related and the follow-up reports were frequently superficial. There was then considerable discussion on the preparation of the Yellow Card data and the form of its submission to ARVI. commented on the need for speed of provision of information with awareness of cost-effectiveness of the work involved. suggested the use of PTMOs for follow-up of adverse reactions and noted that developmental assessment was an essential component of long-term follow-up of neurological reactions in children, and PTMOs employed for this task would need such skills.

5.3 The paper "Netherlands Report on Adverse Reactions to Vaccines in the National Vaccination Programme 1985 Agenda 91 (ARVI/87/19) was discussed at this point. In Holland a paediatrician is employed solely for the follow-up of adverse reactions to vaccination and after the receipt of such reports interviews the vaccinator and the parents, examines the child, and then provides the long-term follow- up. posed the dilemma of the provision of huge lists of adverse reactions or of a distillate and commented that it was bad policy to collect useless information but changes in incidence of reactions were important as was the awareness of permanent or long-term sequelae from vaccination. commented on the need for precise definition of adverse reactions. commented that the reporting system was anecdotal and it was difficult to use such evidence epidemiologically but there could be an alert to the possibility of rare events, which when put together, assume significance. There should be serial presentation of frequency of change with awareness of the basic epidemiology. Longer periods of time and the summation of data were needed. Follow-up was needed to establish permanence of damage and severity, or transience, and to separate temporal associations from aetiological relationships.

5.4 felt that this would be an ideal research project for one four-month cohort to be studied intensively with detailed scrutiny and examination of each report to provide a yardstick for further comparison. PTMOs might be used to eliminate minor reactions and then

significant reactions could be referred to a secondary tier of specialist expertise. felt that this would eliminate many reports as irrelevant and informed the meeting that the yellow card data was to be computerised with a new system over the next few months.

felt that definition of terms was essential and that adverse events should be separated from adverse reactions. The "events" could be excluded with concentration on the reactions.

felt this could be difficult with the quality of information available at present. asked that the numbers of vaccines given the study time period should be estimated to provide an indication of risk of reaction.

6. Whooping cough

6.1 In conjunction with Tabled Paper 1 and an unnumbered agenda paper the Secretary summarised the present position regarding the Loveday litigation for the benefit of new members. He explained that in February the CSM had called for ARVI's advice about updating the statement made in the 1981 report on Whooping Cough (HMSO) about a possible link between DTP immunisation and serious neurological illness. It had been hoped that by this means 'discovery' of all the relevant JCVI, CSM and ARVI documentation on whooping cough vaccine could be avoided. However, by the time could report a revised statement to CSM (see minutes of February 1987 meeting) it was already clear that nothing could be done to avoid 'discovery'. Subsequently, the Chairman of CSM had asked ARVI to keep a watching brief on the situation, and to let the Main Committee know if at any time it was thought possible to modify further the statement.

6.2 spoke to paper ARVI/87/8 which related to NCES data discussed at the meeting on 3 October 1986. It was suggested that under-reporting or selective reporting of vaccine-related cases might give a false estimate of risks. It was not possible to over-report vaccine associated cases but under-reporting was possible on non-vaccine associated cases.

These circumstances would require failure of notification of 500 cases in order to over-estimate vaccine associated risk to produce the NCES data. It was questioned that the ratio of convulsions to encephalopathy was the same in the vaccine and non-vaccine associated cases. The ratio of convulsions to encephalopathy in the vaccine associated cases was compared with the ratio in non-vaccine associated cases and the proportion was identical. Therefore, the vaccine associated convulsions were not over-reported compared to the encephalopathies. The relationship between the dose of vaccine and convulsions was discussed. If convulsions were selectively reported, because they were vaccine associated, then there would be more associated with later doses of vaccine, particularly when convulsions were more common. This was not supported by the evidence. Were doses given at the same ages in children with convulsions as in children with convulsions who were not vaccinated? The median ages were very similar for vaccine assoicated convulsions with no evidence of age distribution of selective reporting. In Item 2, the age distribution of vaccine associated and non-vaccine associated convulsions was considered. There was a falling proportion of vaccine associated convulsions and therefore, vaccine associated convulsions were not being reported because of expectation, if so, the percentage would have been constant. Were vaccine associated severe convulsions benign? Two of 14 vaccine associated

convulsions in previously normal children were associated with impairment 12 months later; this was the same proportion as the non-vaccine associated convulsions.

In the vaccine associated encephalopathy group, the outcome was worst but the proportion identical to the non-vaccine associated encephalopathy group. The estimate of relative risk of vaccine associated illness was 3.3, increasing slightly with more severe levels of impairment; outcomes were no less severe for vaccine associated cases than for non-vaccine associated cases.

6.3 CSM Advice ARVI/87/14
Letter from Chairman of CSM

The letter from , Chairman of CSM to was noted.

Abstracts prepared by of papers submitted to CSM were presented and commented that Paper 2 (Cody et al) included children with an age range two months to six years but with no age breakdown. There were five convulsions in children aged more than 18 months and one in a child who had measles; there were therefore three vaccine associated convulsions in the first year. In Paper 7 (Pollock et al) 14,000 DTP immunisations were given; there were 15,752 reported in the Cody paper. therefore, challenged supposition that small numbers had been studied and that numbers were adequate to assess risk of convulsions when compared with the Cody paper.

6.4 JCVI's revised contra-indications to pertussis vaccine ARVI/87/15

The Chairman stated that JCVI had produced more permissive guidance on contra-indications to pertussis immunisation and that the revised contra-indications, shortly to appear in the next version of the Memorandum 'Immunisation against Infectious Disease' would not conform with the manufacturers data sheet. This might lead to confusion for general practitioners and other vaccinators and there might be legal problems. commented that both the JCVI and the JCVI/BPA Working Party had tried to improve guidelines to give specific contra-indications but an attempt should be made to reconcile these with data sheets and product licences. Delay in the new Memorandum might be worthwhile in order to obtain manufacturers agreement to changes in data sheets and also to allow the BNF opportunity to change its advice. agreed with and welcomed the clearer advice from JCVI on pertussis contra-indications which he endorsed. commented that there was no need for JCVI advice to change but there should be awareness of the implications of change. suggested a meeting with manufacturers to discuss the changes in an attempt to seek common ground. commented that it was not ARVI's responsibility to dismantle other groups instructions. noted that ARVI had responsibilities to both JCVI and CSM and asked that the pertussis section of the revised Memorandum should be submitted to the CSM for endorsement and then to the Licensing Authority to discuss with manufacturers so that data sheets and the Memorandum would be compatible. suggested that advice should be followed and that members should submit their comments in writing to the Chairman. hoped that there could be informal discussion with the manufacturers of areas of agreement or debate

and noted that the new pertussis guidelines would be produced at a time of continuing pertussis litigation. asked if there was likely to be a change in pertussis vaccine in the near future as this might promote difficulties if the contra-indications to pertussis vaccine were also to change. agreed that the pertussis section should be sent to CSM but commented that the new guidance was a rationalisation of the old contra-indications, some of which had no significance scientifically. offered his firm support of the new changes which were not weakening the old recommendations but making clearer existing guidance.

7. Measles Vaccination and MMR Vaccine ARVI/87/18

reported on the present position of the change to the introduction of measles, mumps and rubella vaccine in place of single antigen measles vaccine. At the May 1987 meeting of JCVI, the use of measles specific immunoglobulin had been discussed. It was felt that this practice was a disincentive to measles immunisation and whilst justified in the early days of measles vaccination, may not be necessary with newer measles vaccines. There was concern that the immunoglobulin might interfere with sero-conversion to the rubella and mumps components of MMR promoting further problems with its use. If there was to be a catch-up campaign for MMR, with this vaccine being given to four to five year olds prior to school entry, then at this time, the number of children considered requiring immunoglobulin on the basis of previous convulsions would be very much higher, as 95 per cent of febrile convulsions would have occurred before this age. JCVI had recommended that the administration of measles specific immunoglobulin should stop with the introduction of MMR vaccine. commented that on such matters ARVI would accept the advice of the referring Committee and reminded the Committee that the new edition of the Memorandum would offer an alternative to measles immunoglobulin with other measures for the avoidance of temperature associated convulsions.

8. Immunsation and AIDS ARVI/87/

reported to the meeting that JCVI and EAGA had produced advice concerning immunisation in HIV positive individuals and the summary of the advice, that live vaccines may be used in HIV positive individuals if asymptomatic (except BCG and smallpox) and that symptomatic HIV sufferers should not receive live vaccines would be the basis of a CMO/CNO letter. The guidance on Yellow Fever was being concluded.

9. For Information

9.1 Netherlands Report on Adverse Reactions to Vaccines in the National Vaccination Programme 1985 ARVI/87/19

This was discussed earlier in the meeting (see item 5.3).

10. Any other business

There was none.

11. Date of the next meeting

The next meeting will be held on Friday 2 October 1987 at 10.30am.