

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 7 FEBRUARY 1986

Present: Professor R W Gilliatt (Chairman)
Dr P E M Fine
Professor D Hull
Dr B M McGuinness
Dr C L Miller
Dr D Reid
Dr S J Wallace

DHSS

Dr J Barnes
Dr A M Glen-Bott
Mr K L Fowler (Secretary)
Mr J P Digings

PHLS, CDSC

Dr N D Noah

SHHD

Dr R Covell

1. Confidentiality and announcements

The Chairman reminded members that the proceedings, papers and information before them were confidential and should not be disclosed. He told members that Dr Mary Duncan had retired and that the Committee would wish to record thanks to Dr Duncan for the services that she had provided for the Sub-Committee. He said that Dr Duncan had been replaced by Dr Jenkins who was not able to attend the meeting and he therefore welcomed Dr Mary Glen-Bott who was attending in his place. The Chairman said that Dr Norman Noah of the Communicable Disease Surveillance Centre (CDSC) of the Public Health Laboratory Service (PHLS) would be attending for the item concerning surveillance of adverse reactions to the new whooping cough vaccine.

2. Apologies for absence

Apologies were received from Sir John Badenoch, Professor Banatvala, Professor Lloyd, Professor Miller and Dr J W G Smith.

Dr Zutshi was also absent due to illness, and the Sub-Committee wished to send him their best wishes.

3. Minutes of the meeting held on 4 October 1985

Following some minor amendments, and corrections of a number of typographical errors, the Chairman signed the minutes as a true record of the meeting.

4. Matters arising from the minutes

Item 4.1 BCG Immunisation and Osteomyelitis
Letter from Dr K Citron

ARVI(86)1

The Committee reviewed Dr Sutherland's data from the MRC Survey of Tuberculosis carried out in 1983; in this there were 11 cases where a vaccination history was known. None of the cases suggested BCG as a causative factor, but it was noted that there were no comparable data for children given BCG in infancy.

It was agreed to ask Dr Citron if there could be an on-going surveillance of neonatal children for the presence of osteitis and that this subject should go before the next meeting of the BCG Vaccination Sub-Committee.

Item 5.1 ARVI's comments on Mrs Fox's paper
"Whooping cough disease, vaccination,
vaccine damage"

ARVI(86)2

Dr Wallace deprecated the use of the term 'brain damage' which the public might consider as a permanent entity. The public may not also understand the significance of febrile convulsions. After discussion it was agreed that a cautious but courteous reply should be sent to Mrs Fox. The Chairman suggested that the points on page 2 of Mrs Fox's response should be answered by reference to Professor Miller's paper which included information on all cases of encephalitis following natural pertussis. This paper was to be published in the proceedings of a Symposium on Whooping Cough held in Geneva in 1984. This response was agreed.

Item 5.2 Deaths of Scottish twins temporally associated
with DPT immunisation, report from the
Scottish Home and Health Department

Dr Covell confirmed that these twins were not identical.

Item 5.3 Suspected adverse reactions associated with diphtheria/pertussis/tetanus vaccine and with Trivax and Trivax AD

The Sub-Committee discussed two sets of comments on the DHSS paper (received at its previous meeting) calculating the likelihood of a chance association between DPT and the Sudden Infant Death Syndrome (SIDS). It was not felt that further studies were required at present, particularly in the light of Dr Fine's paper, which indicated that the DHSS calculations were of the correct order of magnitude in spite of the assumptions which had been made in the course of the calculations. It was also agreed that the whole subject of DPT and SIDS would be reviewed by the Committee when the final report of the American case control Study became available.

5. Type of DPT vaccine given to children in the National Childhood Encephalopathy Study (NCES) within 28 days before the onset of acute neurological illness

ARVI(86)6

Dr Barnes stated that this paper, which had been prepared by Professor Miller, concluded that severe acute neurological illness was no more likely to be associated with plain DPT vaccine given within 28 days of onset of the illness than with adsorbed vaccine. The meeting noted this fact but also observed that according to papers published by Pollock et al and others that local reactions, eg crying, screaming and fever were more likely to be observed after immunisation with plain vaccine than with adsorbed vaccine; this emphasised the non-neurological nature of screaming. The Sub-Committee ^{suggested that} measures should be taken to ensure that health authorities used adsorbed vaccines in preference to plain vaccines.

6. Whooping Cough Vaccine

6.1 Pertussis vaccine injury - AMA PANEL Report, JAMA 1985; vol 254: pages 3083-3084

ARVI(86)7

The Sub-Committee noted the Panel Report published in the Journal of the American Medical Association and suggested inviting a representative from the Centers for Disease Control to a future meeting. This expert might be able to place this Panel Report in context.

6.2 History of convulsions and the use of pertussis vaccine, Harrison C Stetler et al, Journal of Paediatrics 1985; vol 107: pages 175-179

ARVI(86)8

The Chairman said that this draft paper had already been seen by ARVI and commented upon in the minutes of the meeting of June 1984 (ARVI 84/20). Dr C L Miller said there was a low incidence of pertussis in the United States, therefore it was possible to delay pertussis vaccination in children with a history of convulsions so that vaccination could be reconsidered later. The Chairman reported that this matter would be discussed at the June Meeting of the Joint BPA/JCVI Liaison Group.

6.3 DPT vaccination, visit to Child Health Centre and SIDS. Solverg L K, Oslo Health Council 1985 ARVI(86)9

Dr Barnes reported that this small study indicated that there was no evidence of association of SIDS with DPT vaccination.

6.4 Response of pre-term infants to diphtheria/tetanus/pertussis immunisation ARVI(86)10
Bernbaum J C et al. J Paediatrics, vol 107:
pages 184-188

Dr Barnes said that this paper confirmed the view of a previous paper presented to the JCVI by Dr J W G Smith that prematurity was not a contra-indication to commencing the basic immunisation programme at the usual date.

Dr C L Miller reported that it was proposed to publish a letter to this effect. Professor Hull observed from the paper quoted that the level of antibodies to pertussis received by new-born children from their mothers was weak and that in pre-term infants there was a poorer response to the first injection of whooping cough vaccine.

6.5 Progress report of work on the improved whooping cough vaccine ARVI(86)11
Sub-Committee of the CDVIP of the MRC

The Chairman welcomed Dr Norman Noah of CDSC who was to speak to the second part of this item. First he invited Dr Reid to inform the members of the progress so far of work undertaken by the Whooping Cough Vaccine Sub-Committee.

Dr Reid reported that the Sub-Committee had met on several occasions to discuss preliminary work, these were:

(a) Developing a serological test which would reliably demonstrate immunity to infection with Bordetella pertussis either derived from the natural disease or from vaccination.

(b) Vaccines; at the moment five component vaccines were available or in course of preparation. These comprised a US vaccine which was derived from the Japanese vaccine (originally reported on), a Canadian vaccine produced by the Connaught laboratories, a vaccine developed by CAMR at Porton (it was hoped to test this vaccine on adults soon for toxicity), together with a French vaccine manufactured by Merieux and a vaccine proposed by a manufacturer in this country.

(c) Surveillance of any new vaccines which might be introduced for adverse reactions. In discussion it appeared that it might be difficult to set up full clinical trials for any new whooping cough vaccine or vaccines in time for the peak of the current epidemic.

6.5.1 Proposal for the surveillance of severe neurological disorders in infancy and their relationship to pertussis vaccine

The Chairman invited Dr Noah to speak to the paper produced on this subject.

Dr Noah, reporting on behalf of the Sub-Group of the Pertussis Sub-Committee of the MRC, CDVIP, stated that there would be a time of transition in the early years of introduction of any new whooping cough vaccine or vaccines; this could comprise at least two years of overlap between use of the current vaccine and a new component vaccine. He observed that it might not be possible to institute controlled field trials in time for the peak of the present epidemic of whooping cough and that it might be necessary to await the next epidemic, whose peak was expected in 1990. It was considered unreasonable to ask paediatricians to report for a period of six years. Dr Noah said that the surveillance would cover England, Wales and Scotland and that the revised age range now was two months to two years of age. It was obvious that the study could be subject to several biases which might affect results. A preliminary study of the hospital activity analysis (HAA) indicated that it would be impracticable to use this as a source of information of adverse reactions; therefore reliance must be placed upon clinicians to report serious adverse reactions and this would be via a CDSC/BPA surveillance unit which was already conducting a study of other rare diseases. No attempt would be made to study serious neurological disease arising from pertussis and other infectious diseases.

Dr Noah said that there was difficulty in deciding which cases should be notified to the system. He said that reporting of all cases of non-specific encephalitis might produce too much data and that he had in mind the reporting of cases of unexplained loss of consciousness or behavioural change which could not be associated with a toxic/chemical/neoplastic/bacteriological or viral cause. Dr Noah said that neurological signs which might be reported would include fits lasting more than 30 minutes, coma lasting more than two hours, paralysis or other neurological signs lasting 24 hours or altered behaviour lasting more than 24 hours. It was hoped that all children seen by a consultant paediatrician would be reported, therefore this would include not only inpatient cases but out-patient ones as well. The Chairman observed that this might attract larger numbers of reports than the numbers seen by the NCES.

In the ensuing discussion it was suggested that the study should be more specific with regard to information concerning cases to be reported to the study, ie should specifically note convulsions, loss of consciousness for 12 hours or more and cases of paralysis. It was mentioned that the NCES may have missed cases of severe neurological disease which progressed to handicap among children who were not admitted to hospital. It was suggested that a pilot study should be carried out in specific localities and the Chairman invited Dr Noah to return to ARVI to report progress. The Chairman said he hoped that all cases which were suspected to be associated with vaccination would be reported on a Yellow Card System. He also considered that this proposed study should be brought to the notice of the Joint BPA/JCVI Liaison Group.

It was agreed that the timing of the study was crucial. It was hoped to report back to the Parent Sub-Committee in March and to seek grants for the study and commence by the end of the year.

The Chairman thanked Dr Noah for providing this information for ARVI.

7. Measles Vaccine

7.1 PHLS surveillance of adverse reactions to two measles vaccines (Rimevax and Attenuvax)

ARVI(86)12

Dr C L Miller reported that some more up-to-date data had been obtained since this paper was written in September 1985 and results showed that 70 per cent of children were well after receiving Attenuvax and 61 per cent after receiving Rimevax. If children with mild general reactions were added to those who were apparently well then the numbers associated with Attenuvax were 85 per cent and those with Rimevax 80 per cent. 1.7 per cent of children had a more severe reaction to Attenuvax compared with 0.7 per cent of children who received Rimevax. Three convulsions were reported after Attenuvax and two after Rimevax.

After discussion it was agreed that there was now enough information to stop the study.

7.2 Suspected adverse reactions to measles vaccine : a summary of recent reports to the CSM, June 1983 to September 1985

ARVI(86)13

Dr Barnes said that this paper supplemented the ARVI paper which considered adverse reactions to measles vaccine up to 1981 and observed that about one or two serious adverse reactions were reported on Yellow Cards each year; a similar degree of reporting had been found in this paper. Dr Wallace observed that some of these reactions were unlikely to be associated with use of measles vaccine and were more

likely to be temper tantrums. Dr Glen-Bott said that in reporting suspected adverse reactions a degree of credibility was attached to each assessment. Dr Barnes went on to say that the most important aspect of the present report was 11 cases of early onset reactions to measles vaccine, nearly all of these were associated with Rimevax and could be due to the dextran content of the vaccine.

8. BCG and keloid scars

ARVI(86)14

Item 8.1

The Sub-Committee had received a letter from Dr Citron asking if ARVI would reconsider its previous recommendation that there should be some monitoring of keloid scars after BCG. Dr Citron made the point that there were some new data from Dr Sutherland, seen at the BCG Sub-Committee on 7 February 1985 (Ref: JCVI(BCG)(85)1) showing that in the MRC tuberculosis vaccines clinical trial the incidence of unsightly scars or keloid was approximately 0.25 per cent; the subjects concerned were examined two to seven years after vaccination. While ARVI did not have this information when compiling its report on adverse reactions to BCG, it seems that the MRC trial was carried out in the 1950s and that a case could be made for obtaining more up-to-date information.

Item 8.2

A letter was received from Dr Christine Miller concerning the problem of delayed or long-continued ulceration after BCG. The point was made that her surveillance of school children could not easily be adapted to provide this information. However, ARVI members were concerned that reports of delayed or long-continued ulceration did come up on Yellow Cards, yet we had no idea of their frequency. Furthermore, the PELS Study was concerned with school-children and there was no data at all for those vaccinated in infancy.

In relation to both prolonged ulceration and keloid formation, ARVI accepted that extended surveillance to include these could not be carried out without extra staff and resources, but it was still felt that if the use of BCG in infants was to be continued, some monitoring of its effects was required. With regard to late or prolonged ulceration in school children, Dr Miller thought that she might be able to arrange for some of the large ulcers encountered in her present study to be followed; while not necessarily leading to an incidence figure for late ulceration, this would give some idea of its likelihood in those who developed large ulcers within three months.

9. Summary of suspected adverse reactions associated with vaccines reported on Yellow Cards during the period 19 September 1985 to 15 January 1986

ARVI(86)16

Dr Barnes reported these reactions:

(1) Suspected adverse reactions to DPT vaccine with or without OPV

Ninety such adverse reactions have been registered during the period. These included six patients with convulsions, one a patient with abnormal fever following vaccination and one patient with apparent cerebral irritability; in addition two cot deaths were reported.

(i) Case No. 154043 A three-month old boy who after his first dose of Trivax AD and OPV on 17 September 1985 was found dead 18 hours after immunisation. He was known to be alive 16 hours after vaccination. The results of the post-mortem are awaited.

(ii) Case No. 154080 A three month old girl who received her first dose of Trivax and OPV on the 19 September 1985 and was found dead on the night of 21/22 September 1985. No initial adverse reaction to vaccination was reported and the cause of death was stated as SIDS.

Dr Barnes reported that in addition to these two cases there had been four more deaths of children in association with the administration of DPT vaccine.

(iii) A six-month old girl who was immunised with Trivax AD and OPV on 28 November 1985 was found dead the following morning face-down in the cot.

(iv) An 11-month old child who had severe congenital heart disease and absence of a spleen received a third dose of DPT on 21 November 1985. The child had apparently had two previous doses of DPT without untoward effects. The child remained irritable and niggly for the next 24 hours but slept and fed normally. Twenty-seven hours after the injection the child became very hot, had a temperature of 100°F and during the next couple of hours the temperature continued to rise to 104°F. Apart from known abnormalities post-mortem revealed a white cell count of 27,000 cells per cubic mm although blood cultures were negative. Nevertheless, death was considered to be due to an overwhelming infection.

(v) A four-month old girl who was given her first dose of triple vaccine on 7 January 1986 died two hours later and subsequent autopsy revealed no significant findings. This case was reported as SIDS.

(vi) A healthy infant boy who received a dose of Trivax on 14 January 1986 and was found dead at 6.00am on 15 January. On the previous day he had received a dose of OPV. The results of autopsy are awaited.

In the ensuing discussion it was agreed that timing in relation to death and time of vaccination was critical. Dr Barnes agreed to summarise these deaths which had occurred during this period and the previous period and these reports would be received by the JCVI and no doubt would be considered again by ARVI.

(2) There had been three reports of suspected adverse reaction to monovalent pertussis vaccine and three reports of suspected adverse reaction to OPV. None of these were particularly serious.

(3) With regard to suspected adverse reactions to diphtheria/tetanus vaccine given with or without OPV, during the period 26 reports had been registered, 15 of which were injection site reactions associated with booster doses. Details of two patients who suffered convulsions were also reported.

Seventy-two suspected adverse reactions to tetanus vaccine were registered. These included reports of batches of reactions from adjacent schools and it was considered possible that injection technique may have been responsible for these reactions. There was also a report No. 153687 of a 57-year old woman who after a dose of tetanus toxoid and OPV developed diarrhoea and subsequently developed arthralgia.

(4) Suspected adverse reactions to measles vaccine

Eighteen reports were received during the period which included six reports of convulsions, together with two reports of anaphylactoid-type reactions and one report of a rapid onset reaction. The Chairman asked that all reports of rapid onset reactions to measles vaccine be consolidated in a single report.

(5) Suspected adverse reactions to rubella vaccine

Two reports had been received and registered, both of these were fairly minor reactions.

(6) One report of a reaction to BCG vaccine had been received.

(7) Fourteen suspected adverse reactions to influenza vaccine were registered, most of the more serious reactions had occurred in patients who were already ill.

(8) There were eight reports in respect of typhoid vaccine and cholera vaccine, either administered separately or simultaneously. Three of these consisted of rigors associated with fever. One was of erythema multiforme, one was a patient who developed severe muscle pain, occipital headache, bronchospasm and cyanosis and the remaining reactions were a mild allergic response together with two reports of injection site reactions.

(9) There were nine reports of suspected adverse reactions to housemite dust desensitising agents. These comprised: two of bronchospasm, one of urticaria, two of bronchospasm and urticaria, one of purpura, one injection site disorder and two of anaphylaxis.

(10) There were nine reports of suspected adverse reactions to grass pollen vaccines.

(i) 152088 A report of fatal acute anaphylaxis following the last of three injections for hay fever.

(ii) 151259 A report of possible attack of petit mal following the first monthly maintenance dose of alavac-S.

(iii) There were two reports of injection site reactions, two of bronchospasm, one of urticaria, one of palpitations, dizziness and sweating and one of apnoea, rash, parasthesiae and paresis two hours after receiving a ninth injection of an initial course.

(11) Suspected adverse reaction to tuberculin PPD

A 25-year old woman developed a brisk reaction after an intradermal injection of 1 : 10,000 tuberculin PPD. The reaction consisted of malaise, anorexia, vomiting, diarrhoea and fever. She subsequently developed a delayed skin reaction. Tuberculous cervical lymphadenopathy was subsequently confirmed in this patient.

(12) Suspected adverse reactions to hepatitis vaccine

Three reports have been received:

(i) 154433 A 37-year old man who five days after his second dose of hepatitis B vaccine developed symptoms and signs of a right brachial neuritis which persisted for five weeks. He had suffered a similar episode of right-sided brachial neuritis in 1978 for which no cause was found.

(ii) Two reports of injection site reactions.

10. Cholera and Typhoid Vaccines

Damages for stroke after cholera and typhoid vaccination
Lancet 1985, vol 2 : page 1372

ARVI(86)17

It was decided to defer consideration of this item to the next meeting.

11. Influenza Vaccination

Influenza Vaccination, paper by Gomolin I H et al.
J. Am. Geriatric Soc 1985; Vol 33. pages 269-272

ARVI(86)18

Dr Barnes said that this paper failed to support previous reports that influenza vaccine inhibited the metabolism of theophylline or that it enhanced anticoagulation due to interference with the metabolism of Warfarin. Members noted that similar work concerning interference caused by influenza vaccination had been undertaken by the Hammersmith Hospital and enquired if the CSM had received a progress report on this work.

12. Any other business

There was none.

13. Date of the next meeting

The date of the next meeting is to be Friday 6 June at 11.00am.

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