JCVI CSM/DH (Committee on the Safety of Medicines/ Department of Health) Joint Committee on Adverse Reactions Minutes 1986-1992

Last modified date: 29 October 2010

JCVI (Joint Committee on Vaccination and Immunisation) adverse reaction minutes 1986-1992.

Question

Can I have full JCVI adverse reactions from 1986-1992.

Response

Disclosable information is contained in the documents in Portable Document Format below, which include the JCVI CSM/DH adverse reaction minutes as requested.

The information you request has been provided, however the documents have been edited as some of the information is being withheld as it falls under exemption in section 40 and 43 of the Act.

The last meeting of this Committee was held in September 1990 and therefore there are no minutes from 1991-1992.

- Download minutes: February 1986 (PDF, 630K)
- Download minutes: June 1986 (PDF, 521K)
- Download minutes: October 1986 (PDF, 531K)
- Download minutes: February 1987 (PDF, 435K)
- Download minutes: July 1987 (PDF, 440K)
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NOT FOR PUBLICATION

ARVI 86/1st Meeting

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

SEHD

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 He said that Dr Duncan had been replaced by Dr Jenkins who was not able to attend the meeting and he therefore welcomed Dr Mary Glen-Bott who was attending in his place.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 — ARVI(86)1
Letter from [redacted]

The Committee reviewed [redacted]'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 [redacted] 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

[redacted] 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 [redacted]. The Chairman suggested that the points on page 2 of [redacted] response should be answered by reference to [redacted] 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

[redacted] 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 [redacted] 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

[redacted] stated that this paper, which had been prepared by [redacted], 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). [redacted] 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

[redacted] 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
Bernbaum J C et al. J Paediatrics, vol 107; pages 184-188 — ARVI(86)10

[redacted] said that this paper confirmed the view of a previous paper presented to the JCVI by [redacted] that prematurity was not a contra-indication to commencing the basic immunisation programme at the usual date. [redacted] reported that it was proposed to publish a letter to this effect. [redacted] 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
Sub-Committee of the CDVIP of the MRC — ARVI(86)11

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

[redacted] 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 [redacted] to speak to the paper produced on this subject.

[redacted] 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. [redacted] 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.

[redacted] 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. [redacted] 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 [redacted] 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 [redacted] 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

[redacted] 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

[redacted] 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. [redacted] observed that some of these reactions were unlikely to be associated with use of measles vaccine and were more

likely to be temper tantrums. [redacted] said that in reporting suspected adverse reactions a degree of credibility was attached to each assessment. [redacted] 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 [redacted] asking if ARVI would reconsider its previous recommendation that there should be some monitoring of keloid scars after BCG. [redacted] made the point that there were some new data from [redacted] 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 [redacted] 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 PHLS 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, [redacted] 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

[redacted] 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.

[redacted] 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. [redacted] 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.

NOT FOR PUBLICATION

ARVI 86/2nd Meeting

COMMERCIAL IN CONFIDENCE

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 6 June 1986 in Room 1611/12, Market Towers.

Present: Professor R W Gilliatt (Chairman)
Sir John Badenoch
Dr A L Bussey ← Prof. Banatvala
Dr P E M Fine ← Prof Glynn.
Professor D Hull
Dr B M McGuinness
Dr C L Miller
Professor D L Miller
Dr D Reid
Dr S J Wallace

DHSS

Dr J Barnes
Dr J R H Berrie
Dr F Rotblat
Mr K L Fowler (Secretary)
Mr J P Digings

Centers for Disease Control, Atlanta, Georgia, USA

Dr W A Orenstein

1. Confidentiality and announcements

The Chairman reminded members that the proceedings, papers and information before them were confidential and should not be disclosed. He welcomed Dr Orenstein from the Centers for Disease Control, Atlanta and Dr Rotblat, to the meeting.

2. Apologies for absence

Apologies were received from Professor Lloyd and Dr J W G Smith.

3. Minutes of the meeting held on 7 February 1986

Item 5. DTP vaccine given to children in the National Childhood Encephalopathy Study within 28 days before the onset of acute neurological illness

It was suggested that the last sentence be amended to read:

> "The Sub-Committee suggested that measures should be taken to ensure that health authorities use adsorbed vaccines in preference to plain vaccines."

5/5

Item 6.4 Response of pre-term infants to diphtheria/tetanus/pertussis immunisation-Bern J C et al. Journal of Paediatrics Vol 107; pages 184-188

It was suggested that the last sentence of this be deleted.

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

Second paragraph, line 11 - delete '1988' and replace by '1990'.

Apart from typographical amendments, the minutes were agreed and were signed by the Chairman as a true record of the meeting.

4. Matters arising

4.1 Item 5 Suspected adverse reactions associated with diphtheria/pertussis/tetanus vaccine and with Trivax and Trivax AD

[redacted] said that he wished to comment on this paper which had been submitted to the February meeting when he was unfortunately not able to attend. It was agreed that this paper would be reconsidered at a subsequent meeting.

4.2 Item 8 BCG and keloid scars

[redacted] reported that the BCG Sub-Committee were writing to plastic surgeons about scars. She also reported that she was following up children with large ulcers encountered in her present study; so far there have been none with progressive enlargement of the ulcer or with continuing discharge after three months.

4.3 Item 10 Cholera and typhoid vaccines

It was agreed to defer consideration of this paper until a subsequent meeting.

4.4 Item 5.1 Response to [redacted]s letter ARVI(86)19

The correspondence with [redacted] was noted.

4.5 Item 5.3 Sudden Infant Death Syndrome (SIDS) in relation to the administration of DPT vaccine

4.5.1 Infant deaths associated with vaccination - Paper by the Department ARVI(86)20

The Sub-Committee reviewed a paper from the Department giving a seasonal incidence of reported SIDS between December 1984 and May 1986, as well as the interval between vaccination and death. [redacted] made the point that it was useful to know the date of the Yellow Card report as well as the date of the incident. This enabled one to tell whether the reports were being received as a result of publicity or whether they were part of a steady background rate of reporting.

The Chairman reminded the meeting that the Departmental statistical paper considered at the last meeting suggested an incidence of SIDS occurring by chance within 24 hours of vaccination as being about four to six cases a year. [redacted] had agreed that in spite of the constraints of such a calculation this estimate was of the correct order of magnitude. It was agreed to look at this subject again when the US studies were published. He invited [redacted] to speak on the American study on SIDS. [redacted] said that with regard to the NIH study by Hoffman et al, this had been completed and submitted to Paediatrics. The Journal had asked [redacted] and others at CDC to comment on the paper and they had asked for some changes. He agreed that the results showed vaccination to be slightly less common in the SIDS group than in controls, and that while the study excluded vaccination as a common cause of SIDS, it did not exclude a rare but real association. He added that American bodies representing concerned parents were also making criticisms of the study; one of them was that by its definition of SIDS the study excluded "toxic deaths" in which children developed a vaccine-related illness and then died. For this reason, CDC is looking at all deaths, not merely SIDS.

4.5.2 Immunisation and SIDS - Summary of a paper by [redacted] ARVI(86)21

The meeting noted this abstract and the Chairman asked [redacted] to obtain the complete paper in due course together with the work done by Emery at Sheffield. Professor Hull observed that these were unexpected deaths which are slightly different from SIDS as usually defined.

4.6 Poliovaccine for families of immuno-suppressed patients

At the end of matters arising [redacted] raised the question of the use of live and killed poliomyelitis vaccine in families in which there was an immuno-deficient or immuno-suppressed child. She had raised this matter at a previous meeting and was now asking what had happened. The Chairman agreed to raise this matter with the Joint BPA/JCVI Working Group.

5. AMA Panel Report on Pertussis Vaccine Injury (JAMA 1985 Vol 254, pages 3083 - 3084)

5.1 [redacted] said that this report had been prepared in a form which might be helpful to Congress when considering possible compensation for vaccine injury. The report identified severe irreversible vaccine reactions and the criteria for attributing such reactions to DPT vaccine and, second, severe reversible DPT reactions. The report used the known relative risk of the vaccine to estimate the probability that an event was caused by the vaccine. [redacted] then gave the Committee the basis of some of the numerical calculations in the report.

5.2 Encephalopathy

The definition of this condition was a very conservative interpretation of the NCES but with an onset within 72 hours. The report used the NCES estimation of relative risk of 3:1, it was estimated that one third of such cases have permanent handicap one year from their onset (as derived from the NCES).

5.3 Complex Febrile Convulsions

These were defined as being of more than 10 minutes duration, or repetitive over 24 hours, or of a focal nature. In such cases convulsions are thought to be due to fever and there is no other demonstrable cause. Vaccine could cause such seizures and it was believed that 10 per cent of such complex seizures could result in permanent handicap (there was no ~~reference to~~ source given for this but this belief was the impression of the Panel).

5.4 Afebrile convulsions

To be pertussis vaccine related these seizures must develop within 72 hours of administration in a patient with no evidence of pre-existing neurological damage. (If such convulsions develop within 24 hours of vaccination, then they might be regarded as encephalopathy.) There was uncertainty as to whether or not these could be caused by pertussis vaccine at all. More than two thirds of cases are likely to have aetiologies other than the vaccine.

5.5 Simple febrile convulsions

These are defined in the report as convulsions lasting less than 10 minutes and which occurred within 24 hours of the administration of DPT vaccine. It was the opinion of the Panel that the 'probability' of simple febrile convulsions being the result of pertussis vaccine is 100 per cent and that there would be no persistent sequelae. The Panel considered that if no other cause could be found 100 per cent of these reactions were ~~associated with~~ attributable to vaccine and that sequelae were unlikely.

5.6 Shock and Collapse

Signs of vascular collapse, muscular hypotonicity and unresponsiveness for 10 or more minutes with or without fever but without paralysis or seizure. This condition is not a specific pertussis vaccine related event and has been reported with other vaccines. It was considered that the probability was that the DPT could cause 100 per cent of these reactions and that Cody et al had reported complete recovery following these reactions.

5.7 In the general discussion which followed, some members of the Committee felt that the report not only accepted the fact that vaccine damage was a real phenomenon but implied (by the way it was written) that it was commoner than was believed to be the case in the UK. It was agreed that a small Working Party should prepare a position paper taking into account recent proceedings in court in this country, and the AMA Panel Report. [redacted], [redacted], [redacted] and the Chairman agreed to serve on the Working Party. The Chairman asked [redacted] to prepare a position paper relating to the National Childhood Encephalopathy Study. [redacted] asked when the final report on the NCES was to be published.

6. Litigation and pertussis vaccination

6.1 [redacted] referred to the June issue of the American Journal of Diseases of Childhood. He said that between 18 and 22 million doses of DPT were manufactured annually in the United States prior to the difficulties concerning whooping cough vaccine and litigation.

)84 the uptake of the vaccine totalled less than 16 million d
a shortage of vaccine. There are annually 3.7 million births i
efore the shortfall in the provision of DPT indicates that there
) an increase in uptake of diphtheria and tetanus vaccine.

ice 1985, the price of the vaccine has risen from 40 cents per dose to $
r dose in 1986 and it is expected to rise to $11 per dose. Litigation cla
r year have risen from virtually nil in 1978/79 to over 219 in 1985, claimi
billion US dollars, and litigation suits per million doses follow a similar
attern. The total amount claimed has likewise increased greatly.

5.2 [redacted] said that out of court settlements had not been included in these figures. It was difficult to protect manufacturers against such heavy compensation claims. The situation had been aggravated by an organisation called 'Dissatisfied Parents Together'. The Hawkins Congressional Commission suggested that claimants might go into a system with a Panel and if accepted would be given an award of $1 million or alternatively accept a court settlement. There was also a Bill before the American Government which suggested that the punitive damages be done away with and that damages for pain and suffering only be awarded.

Acellular Vaccines

7.1 [redacted] reported that a team from the United States had visited Japan to assess the efficacy of Japanese acellular vaccines and acquire data on adverse reactions. He said that studies on acellular vaccines had been carried out in Japan, Sweden and the USA and that vaccines were being developed in France and the United Kingdom. With regard to adverse reactions, he made the point that only the Japanese had used the new vaccines for long enough to have information about serious reactions.

7.2 In Japan prior to 1975, whole cell vaccines were routinely administered as three doses commencing at three months of age with a booster dose at 18 months. In 1975, two deaths occurred within 24 hours of vaccination and the vaccine was withdrawn; this was followed by a major epidemic of whooping cough in the late 1970s. Whole cell vaccines were reintroduced in the late 1970s but the age of commencement of vaccination was raised to two years. In September 1981, acellular vaccines were introduced for routine use in two year old children and now 82 per cent of children get acellular vaccine.

7.3 Serious adverse reactions with sequelae and deaths had an incidence of 2.47 per million doses during the period 1970 to 1974 - when immunisation commenced at three months of age. The rate of serious reactions fell to 0.4 per million doses during the period 1975 to 1980 when the administration of whole cell vaccine commenced after the age of two years. During the period 1981 to 1984, the incidence of severe adverse reactions was 0.25 per million; during this period acellular vaccine was used. There appears to be little difference in the rate of serious adverse reactions to whole-cell vaccine (0.4 per million) given at 24 months compared with acellular vaccine (0.25 per million doses) also given at 24 months. The comparable incidence for less serious reactions without sequelae was 1.46 per million doses for the period 1975 to 1980 and 0.64 per million doses for the period 1981 to 1984. [redacted] said that the Japanese were now considering whether or not to lower the age at which vaccination should be commenced.

8. Do seizures in children cause intellectual deterioration? ARVI(86)22
Jonas H Ellenberg, Deborah G Hirtz and Karin B Nelson
New England Journal of Medicine; Vol 314, Pages 1085-1088

The Chairman said that the data for this study had been taken from a very large cohort of children, the Collaborative Perinatal Project of the National Institute of Neurological and Communicative Disorders and Stroke (NCBP). The IQ at seven years in children with seizures did not differ significantly from those in controls matched for IQ (as determined at a four year assessment), sex, race and socio-economic status. The study concluded that non-febrile seizures were not associated with a significant change in full-scale IQ.

9. Pertussis vaccine and whooping cough as risk factors in acute neurological illness and death in young children ARVI(86)23
D Miller, Jane Wadsworth, Judith Diamond and E Ross
Proceedings of the Fourth International Symposium on Pertussis
Joint IABS/WHO Meeting, Geneva, Switzerland, 1984.
Develop. Biol. Standard Vol 61, pages 389-394

The Chairman remarked that this paper had been seen in draft by the Committee.

10. Frequency of true adverse reactions to measles-mumps-rubella vaccine ARVI(86)24
A Double-blind Placebo-controlled Trial in Twins
Heikki Peltola and Olli P Heinonen
The Lancet, 26 April 1986, page 939

The meeting noted that vaccination had been carried out between the ages of 14 months to six years with no preliminary screening for immunity, therefore, one might expect 50 per cent of the trial population to be immune. [redacted] pointed out that the zygosity of twins was not defined. The Committee agreed that: (1) [redacted] should ask [redacted] to write a short review of this paper; (2) that the authors be asked to provide information on the history of measles, rubella and zygosity in children having reactions except the minor ones described as nausea, vomiting and coryza.

11. Summary of suspected adverse reactions to vaccines: ARVI(86)25
Reports on Yellow Cards registered during the period
15 January 1986 to 12 May 1986 - Paper by the Department

[redacted] introduced this paper:

i. Suspected adverse reactions to diphtheria, tetanus and pertussis vaccine (DPT) given alone or with oral poliovaccine (OPV)

During the current period 52 adverse reactions were reported. These included:

a. Two sudden infant deaths in (i) 160227 a four-month old girl who was given her first dose of triple vaccine on 7 January 1986. She died two hours later. A subsequent autopsy revealed no significant findings. (ii) 161923 a 10-month old boy who received his third dose of DPT on 14 April 1986, and was found dead on 15 April 1986. Post-mortem revealed an interstitial broncho-pneumonia. ~~Death was attributed to SIDS.~~

b. 160915 One case of meningitis in a seven-month old fem
received a dose of DPT and OPV on 24 January 1986. On admissi
hospital her CSF was found to have an increased cell content and
observed to be drowsy and to have twitching. A diagnosis of asepti
meningitis was made. The Committee asked for more details about this
patient.

ii. Suspected adverse reactions to Monovalent pertussis vaccine

a. Cot Death

156659 An eight month old male who died 12 days after receiving a dose of monovalent pertussis vaccine. Diagnosed as cot death.

b. Encephalitis

157274 A two year old girl who two days after vaccination was febrile, irritable and screaming. She was diagnosed as encephalitis.

c. 157861 Convulsion in a 22-month old girl after her third dose of pertussis vaccine.

iii. Suspected adverse reactions to diphtheria, tetanus vaccine given with or without OPV

During the current period 61 reports were registered; 58 of these were after booster doses and the majority were injection site disorders.

iv. Suspected adverse reactions to tetanus vaccine

Ninety-three reports were registered during the period; these included 67 injection site disorders and one report of Guillain Barré syndrome in a 15 year old boy who was vaccinated on 24 October 1985 and developed symptoms on 8 November 1985. He was reported to have recovered.

v. Suspected adverse reactions to measles vaccine

Twenty-eight reports were received. These included:

a. 157602 A death in an 18-month old boy who was vaccinated against measles on 16 December 1984. Death occurred 10 days after vaccination. The patient gave a history of two previous episodes of febrile convulsions and although on the occasion of his death no convulsions were noted he was extremely hot and had a temperature of 38°C half an hour after death.

The Committee asked if a brother who was a SIDS case was a blood relation or adopted. Also, did the patient receive measles immunoglobulin or anti-convulsants?

b. There were reports of six suspected convulsions after vaccination.

vi Suspected adverse reactions to rubella vaccine

During the period 11 reports were received. These included:

157976 One patient who developed pruritic rash and broncho-spasm after vaccination.

vii Suspected adverse reactions to BCG

Twenty-four reactions were reported. These included:

Nineteen injection site disorders.

viii. Suspected adverse reactions to influenza vaccine

Ten reactions were reported. These included:

a. Two reports of Guillain Barré syndrome.

i. 157596 A 70 year old man who developed transverse myelopathy, and four days after vaccination, he was reported to have made only a minimal recovery.

ii. 157822 An 86 year old woman who developed GBS in November following vaccination in October. She is stated to be recovering.

The Committee asked what interval had occurred between vaccination and onset of GBS.

b. 154706 A major fit in a 21 year old female

Nine hours after vaccination this patient was already taking anti-convulsants.

c. Encephalopathy

159686 One case of encephalopathy in a 61 year old male patient, who developed illness one week after vaccination was reported. The Committee asked for further details of examination of this patient's CSF.

ix. Suspected adverse reactions to typhoid and cholera vaccines given singly or together

There were 11 reports including one convulsion which is to be followed-up.

x. Suspected adverse reactions to house mite desensitising agent and grass pollen vaccines

Seventeen reports were made during the period including one patient with fatal anaphylaxis occurring two minutes after injection. In addition there were three reports of anaphylactoid reactions occuring shortly after vaccination and two reports of bronchospasm. The Committee suggested that a paper on the treatment problem of anaphylaxis be prepared for the next meeting.

12. Any other business

[redacted] discussed vaccination policy in relation to symptomless HTLV-III carriers. He considered that inactivated vaccines could be used safely. The possibility that they might make the patient's lymphocytes more susceptible to the spread of HTLV-III virus was considered to be a theoretical risk only. One hundred and thirty six children who were carriers as a result of perinatal infection had received one or more doses of DPT and OPV without severe reactions and this was reassuring. There was some evidence, however, that their antibody responses were

sub-normal. There was one case of generalised vaccinia in a symptomless sero-positive army recruit after smallpox vaccination. Dr Orenstein considered that the use of IPV in place of OPV would be wise in sero-positive children. Members noted that the JCVI were due to reconsider this subject at their next meeting.

13. Date and time of next meeting

The next meeting is to be held on Friday 3 October, at 11 am.

ITEM 14.1

NOT FOR PUBLICATION

ARVI 86/3rd Meeting

COMMERCIAL IN CONFIDENCE

COMMITTEE ON SAFETY OF MEDICINES

JOINT COMMITTEE ON VACCINATIONS AND IMMUNISATION

JOINT SUB-COMMITTEE ON ADVERSE REACTIONS TO VACCINES AND IMMUNOLOGICAL PRODUCTS

Minutes of the meeting held on 3rd October 1986 in Room 1611/12, Market Towers.

Present: Professor R W Gilliatt (Chairman)
Sir John Badenoch
Professor Banatvala
Dr P E M Fine
Professor Glynn
Professor D Hull
Professor J K Lloyd
Dr B M McGuinness
Dr C L Miller
Professor D L Miller
Dr D Reid
Dr J W G Smith
Dr S J Wallace

DHSS

Dr J Barnes
Dr J R H Berrie
Dr F Rotblat
Dr S Wood
Mr K L Fowler (Secretary)

1. Confidentiality and annoucements

The Chairman reminded members that the proceedings, papers and information before them were confidential and should not be disclosed. He welcomed Mrs Jane Wadsworth and Dr S Wood to the meeting.

2. Apologies for absence

Apologies were received from Dr Covell.

3. Minutes of the meeting held on 6 June 1986

Page 8 Item x. Suspected adverse reactions to housemite desensitising agent and grass pollen vaccines. Penultimate and last lines delete 'the treatment of' replace with 'the problem of'. Apart from this, subject to minor correction of wording and grammatical errors, the minutes were signed as a correct record.

4. Matters arising

Item 4.1 which referred to Item 5 of a subject discussed in a meeting of February 1986 - suspected adverse reactions associated with diphtheria/pertusis/tetanus vaccine and with Trivax and Trivax AD. The Chairman reminded members of [redacted] caution concerning this paper at the last

meeting. [redacted] said that there was a proviso that the National Childhood Encephalopathy Study (NCES) did not ask the question as to whether a vaccine was absorbed or plain. Therefore it was necessary to contact the manufacturer to obtain this information and the information was not complete. [redacted] reminded the meeting that [redacted] in his paper* had found systemic and local reactions less with adsorbed vaccine.

It was agreed to review the figures in this paper at a future meeting.

Item 10 Frequency of true adverse reactions to measles-mumps-rubella vaccine

(Peltola and Heinonen, Lancet 1986 i 939)

Sub-paragraph a. [redacted] said that the reply he had received from Dr Peltola indicated that he could not immediately provide the information requested.

Sub-paragraph b. [redacted] introduced his review of the Peltola and Heinonen paper which described the reactogenicity of MMR vaccine in children in the age range 14 months to 6 years. The paper indicated that the vaccine was well tolerated; however, some of the children in the survey had presumably experienced natural infection with these viruses. Therefore it would be helpful if the subjects could be classified by age. This would provide some idea of the likelihood of immunity at the time of vaccination. Serological examinations on these children would be helpful. The meeting observed that little or no adverse reactions to MMR vaccine had been reported in the United States. Members emphasised the importance of obtaining as much knowledge as possible regarding the safety of MMR vaccine. [redacted] observed that measles was prevalent in Finland just before this study commenced. It was agreed to write again to [redacted] asking if an age classification of the trial subjects could be provided together with an indication as to the zygosity of the twins. Such information could perhaps be incorporated in a letter to the Lancet.

Item 11 Summary of suspected adverse reactions to vaccines.

Sub-paragraph i. Suspected adverse reactions to DPT, last two lines - [redacted] pointed out that if post-mortem revealed an interstitial broncho-pneumonia, death could not be attributed to the sudden infant death syndrome.

Item 12 Any other business - Vaccination policy with regard to symptomless HTLV-III carriers. [redacted] reported that US policy had now been published in the US Mortality Morbidity Weekly Return No 38, 26 September 1986, Volume 36 Pages 595-606, and also that the subject would be discussed at the next meeting of the JCVI.

5. Report of a Working Party on Pertussis Vaccine Injury

At the February 1986 meeting ARVI had received a report prepared by a panel of the AMA (JAMA 1986, 254, 3083). Its object had apparently been to provide information for legislators as to what type of vaccine-associated event might require compensation, if Federal compensation for presumed vaccine injury were to be introduced in the United States. In attempting to produce simple guidelines the panel had drawn on previously published work and had made some assumptions of their own. No sources were given in the report and ARVI had viewed it with some concern.

* T M Pollock et al - Symptoms after primary immunisation with DTP and DT vaccines. Lancet: 1984 Vol ii pages 14[redacted]9.

It was agreed that a small working party ([redacted], [redacted] and the Chairman) should review this report and prepare comments for the October meeting. In view of some questions about the National Childhood Encephalopathy Study (NCES) which had been raised in recent court proceedings, it was agreed that the working party should also review these and make any comments that seemed appropriate.

The working party met on July 31st at St Mary's Hospital, where it had the help of two members of [redacted] team.

5.1 The following points relating to the NCES were discussed.

1. Queries had arisen in relation to the numbers of cases in the study, which had varied slightly in different publications, as late follow-up rsults came through. The working party had established that the final number of cases in the NCES was 1,167. 39 cases had received triple vaccine in the week prior to the onset of their neurological illness (9 with infantile spasms, 18 with convulsions, and 12 with encephalopathies). These vaccine-associated cases included 5 patients (4 with convulsions and 1 with infantile spasms) who had a history of neurological events before immunisation which indicated possible prior abnormality. These numbers differed from those published in the 1981 Whooping Cough Report (HMSO).

2. A query had been raised over the accuracy of dates. It was accepted that it was sometimes difficult for the NCES team to decide the day of onset of a neurological illness. If there was conflict between information from different sources the team normally took the information from the paediatrician's admission record. [redacted] also made it clear that day 0 was always the day of vaccination, regardless of the time of day of vaccination.

3. The question of selective reporting by paediatric units to the NCES team was discussed. It was not thought that this would have been a problem in respect of children admitted to hospital with encephalopathy. The reporting of children admitted to hospital with convulsions was a different matter, since many more children would have been admitted than the few who fulfilled the NCES criteria for reporting. In considering whether a convulsion was more likely to be reported because it was known that the patient had received triple vaccine within a few days, the following points were made:

a. It was emphasised that to account for the observed increase in relative risk for all cases after the vaccine, under-reporting of similar cases in unvaccinated children would have to have involved at least 500 reports.

b. The ratio of convulsions to encephalopathies was similar in the vaccine-associated group to that in the unvaccinated group.

c. Although the exact ages at which different doses of vaccine were given were not known for the whole population, in the NCES there were 7 convulsions reported within one week of the first dose of DPT, compared with 5 after the second dose, and 6 after the third. This ratio was not what would have been expected if doctors had merely been reporting chance associations. In the latter case, one would expect many more convulsions after the third dose, since febrile convulsions are commoner in the general population at the end of the first year of life than at

three or six months.

From the above there is reason to believe that the increased relative risk of prolonged convulsions after DPT was a real one.

4. Suggestions had been made that post-pertussis vaccine convulsions were benign and that they did not give rise to bad outcomes. [redacted] was asked for information on sequelae after both vaccine associated and non-vaccine associated convulsions in children of comparable age.

5. Queries had been raised with regard to long-term sequelae after vaccine-associated encephalopathy. The working party had reviewed the methods of assessment of handicap, which had been refined by [redacted] team during the course of their work. Among 12 children with encephalopathy there were 2 deaths, and 5 children with impairment of varying severity at 1 year. The relative risk for an acute vaccine-associated illness (convulsions or encephalopathy) was 3.3, and was similar irrespective of degree of impairment.

6. Questions had been asked about the inclusion among the vaccine-associated cases of those in which a possible alternative cause for the encephalopathy had been put forward. It was, however, accepted by ARVI members that cases should not be removed from the calculation of risk in an epidemiological study of this kind, because an alternative diagnosis was possible. The numbers were in any case small, and the removal of cases of possible Reye's syndrome, or possible viral encephalitis, from both vaccine-associated and unassociated groups did not alter the relative risk, but only affected the confidence limits due to the reduction in numbers.

At the end of the discussion, the Chairman commented that ARVI members had now had a chance to appreciate the difficulties inherent in this type of study.

5.2 The AMA Panel Report on Pertussis Vaccine Injury

(JAMA, 1985, 254 3083-4)

Turning to the AMA panel report, ARVI members noted that this had been prepared with the particular intention of providing information for legislators as to what type of vaccine-associated event might require compensation, if Federal compensation for presumed vaccine injury were to be introduced. It was therefore the intention of the panel to suggest simple guidelines for which "stringent proof for causation by the vaccine was not required". ARVI members commented that they were not aware of all the sources used; while some appeared to be from the NCES, others clearly were not. Furthermore, it was agreed that the document contained a number of assertions which could not be accepted. It was not a scientific statement of the position. Indeed, the AMA Panel itself frequently acknowledged that its conclusions were based upon impressions and opinions, rather than upon established evidence.

5.3 Paper by [redacted] et al: A major role for viruses in acute childhood encephalopathy

(Lancet 1986 Vol 1 pp 989-991)

ARVI members received for information the paper on viral encephalitis by [redacted]. While it was accepted that intensive studies of the kind described in this paper could lead to the identification of a viral cause in a much higher proportion of children with encephalitis than had been possible a few years ago, it was noted that few of the children were, in fact, in the age group relevant to the NCES.

5.4 The Chairman drew the attention of the meeting to the paper:- Cause and Prevention of Post-Infectious and Post-Vaccinal Neuropathies in light of a new theory of auto-immunity (Fred C Westholl and Robert Rott-Bernstein The Lancet 2nd August 1986). Members reported that the paper was interesting although it was correctly categorised under hypothesis. References quoted were sometimes out of context and were of differing intrinsic worth.

6. Review of the Safety and Efficacy of Densensitizing Vaccines
ARVI/86/29 (a), (b) and (c)

Dr Wood introducing this paper said that the adverse reactions section of Medicines Division had for some time been worried about serious anaphylactoid reactions associated with the densensitizing agents, and that this concern had been heightened this year by fatal anaphylactic reactions in two young females after receiving these agents. Medicines Division had reacted accordingly, and together with information provided by manufacturers had produced a paper on these vaccines. Dr Wood explained that because of the concern over adverse reactions and the need to bring this matter to the main committee, timing of meetings had made it necessary to discuss this paper with other sub-committees and the CSM before ARVI.

With regard to the paper Dr Wood said that there were difficulties in standardisation of these products and specifying the content of allergen. The evidence as to efficacy was both controversial and poor, especially with regard to house dust mite preparations. There had been initially difficulty over collating the adverse reactions since the data from manufacturers and that supplied to the CSM on yellow cards were not altogether compatible; however, it had now proved possible to combine these two soures of ADR data and to estimate the incidence of reactions. Anaphylaxis had occurred with these products even at low allergen concentrations. The US FDA review of these vaccines was confused because of legal restraints in the reclassification of the products. In Sweden doctors who administer these products have to be specially licensed.

The Biologicals Sub-Committee had made recommendations on these products as had also SEAR. The CSM had recommended that a letter should be sent to all doctors, dentists and pharmacists warning about the risk of anaphylaxis following treatment with densensitizing agents. The advice included in this warning would include a recommendation that the administration of these agents should only take place where facilities for full cardio-respiratory resuscitation are immediately available, and that patients should be kept under medical observation for at least 2 hours after treatment. The main committee (CSM) had amended the recommendations of its sub-committee slightly by recommending that the warning be given in the form of a letter rather than a 'yellow peril' warning leaflet.

In addition a CSM update article on desensitizing vaccine was to be published and this would appear in the British Medical Journal of the 11 October 1986. It was hoped to obtain agreement with the relevant pharmaceutical companies regarding alteration of data sheets and a decision was to be taken as to who in the DHSS should undertake future prospective monitoring of these products. Dr Smith said that the recommendations of the Biological Sub-Committee differed slightly from those of the CSM in as much that [redacted] had advised that the recommendation that these agents should not be used in asthma should not be brought forward. However doctors were warned that patients with asthma appeared to be particularly susceptible to the development of severe anaphylaxis with the agents.

The Sub-Committee in considering the 'Dear Doctor letter' and other papers advised that as far as possible the word 'vaccines' should not be associated with these products because of the adverse affect that such publicity might have on the JCVI's efforts to promote immunisation of young children in the routine childhood immunisation programme. It was suggested that a future procedure for updating ARVI on adverse reaction reports to these products should be agreed.

Treatment of Anaphylaxis [redacted] said that this paper had been produced as the basis for the section in the Memorandum "Immunisation Against Infectious Disease". Sir John Badenoch said that this particular subject should be treated with caution as it might prove too much of a disincentive towards vaccination. Dr Reid and other members said that the section as it stood at the moment only described drug treatment and did not provide a comprehensive guide as to how anaphylaxis should be managed. In particular, [redacted] pointed out that treatment did not include aminophylline, and that cue-cards should appear in treatment rooms in the surgery.

It was agreed that a small group should be drawn up to advise the JCVI. This group would consist of [redacted], [redacted] from Nottingham and [redacted], with the representatives from Scotland.

7. Summary of Suspected Adverse Reactions to Vaccines

Reports on yellow cards registered during the periods 13th May 1986 to the 11th September 1986.

ARVI/96/28

[redacted] introduced this paper

a. Suspected adverse reactions to diphtheria, tetanus and pertussis vaccines (DTP) given alone or with oral polio vaccine (OPV).

During the current period 95 suspected adverse reactions were reported. These included:

i. Death 151828. A 16 month old girl who two days after her first dose of DTP in mid-July 1985 was found to have a fever and a possible upper respiratory tract infection. Two days later she had a major fit and was admitted to hospital where further convulsions occurred. Further fits occurred at the end of July 1985 and she died on the 1st August probably from pneumococcal septicaemia. This patient had a family history of idiopathic epilepsy. This case has been reported to previous meetings of ARVI.

ii. There were 8 reports of convulsions following vaccination including 165236, a patient who was in status epilepticus within hours

of receiving her third dose of triple vaccine. There had been two previous known febrile convulsions.

b. Suspected adverse reactions to monovalent pertussis vaccine.

Five reports had been received including one alleged convulsion which on investigation appeared to be a rigor.

c. Suspected adverse reactions to oral polio vaccine. A six month old girl who developed recipient vaccine-associated poliomyelitis 30 days after receiving her first dose of oral polio vaccine.

d. Suspected adverse reactions to diptheria/tetanus vaccine given with or without OPV.

During the period 283 reports were registered. These included 266 children with injection site disorders. The majority of these reports were among five year old children who had received a boosting dose of vaccine of similar batch number and where the report had come from different geographical locations. [redacted] pointed out that these reports had first of all come to the notice of the Defect Reporting Centre and the Chairman expressed concern that yellow card reports had been initiated by persons other than doctors.

It appeared that these had originally come to the CSM as product defect reports sent in by pharmacists; CSM had then contacted doctors and had obtained the yellow card reports. It was felt that reports from pharmacists, acting on hearsay, were an unsatisfactory source of information. ARVI memebrs asked if yellow card reports originating in this way could in future be distinguished from those which a doctor, who had seen the patient, was the primary source of information. [redacted] observed that follow up by NIBSC had revealed no defect in the vaccine, therefore, apart from a fault in administration of the vaccine there was no reason why these injection site disorders were observed in clusters.

e. Suspected adverse reactions to tetanus vaccine 47 reports were registered. These included 31 injection site disorders with or without fever.

f. Suspected adverse reactions to measles vaccine. These included

i. 154755. A reported encephalitis in a 12 year old girl who was vaccinated on the 20th August 1985 with what seems to have been rubella vaccine and who on the 12th September 1985 developed an encephalitis which had a positive serology of the measles virus. Dr Barnes undertook to carry out a follow up of this report.

ii. 165850. A report of a cerebellar disorder in a 15 months old girl who, two weeks after vaccination developed an acute cerebellar-like ataxia preceded by a febrile cold. Her unsteadiness was so marked that she was admitted to hospital. Examination of the CSF revealed an excess of protein but no increase in the number of cells. EEG and CT scan (with and without contrast) were normal. The consultant concluded that this patient had suffered a demyelinating reaction to either measles vaccine or to some other viral infection. Dr Barnes was asked to follow this patient up at 6 months.

iii. 8 patients with convulsions were reported. In 164808 convulsions were thought to be due to an attack of acute tonsillitis.

163111. This patient had convulsions 8 days after vaccination, which were thought to be caused by otitis media. It was requested that an amendment be made as to the degree of culpability of these reactions. [redacted] was requested to follow up the other six reports at six months.

g. Suspected Adverse Reactions to Rubella Vaccine. 8 such reports had been received including two patients with arthralgia.

h. Suspected Adverse Reactions to BCG. 12 reactions were reported, these included two patients with keloid scarring.

j. Suspected adverse reactios to Monovalent Typhoid Vaccine. There had been seven reports during the period including one anaphylactic reaction.

k. Suspected adverse reactions to cholera vaccine. 4 reports had been made during the period.

l. Suspected adverse reactions to hepatitis B vaccine. 14 reports of relatively minor reactions had been received.

m. Suspected adverse reactions to pneumococcal vaccine. 1 report of an injection reaction had been received. [redacted] requested details of the manufacture of the vaccine.

8. Any Other Business

a. The Chairman reported that the last meeting of the BPA/JCVI Working Party had asked whether the recommendation on Page 29, Paragraph 6.5.4 of the Memorandum "Immunisation Against Infectious Disease" which stated that "it is advisable to allow at least 3 weeks to elapse between undergoing tonsillectomy or oral surgery and the administration of OPV." was still appropriate. [redacted] undertook to check this recommendation.,

b. [redacted] reported that a symposium on the new pertussis vaccines had been recently held at Bethesda in the USA.

9. Date of the Next Meeting

The date of the next meeting would be the 6th February 1987.

CFB/1971L/1

NOT FOR PUBLICATION

ARVI 87/1st MEETING

COMMERCIAL 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 February 1987 in Room 1611/12 Market Towers

Present: Professor R W Gilliatt (Chairman)
Sir John Badenoch
Professor Banatvala
Dr P E M Fine
Professor D Hull
Dr B M McGuinness
Dr C L Miller
Professor D L Miller
Dr D Reid

DHSS

Dr J Barnes
Dr D M Salisbury
Mr K L Fowler (Secretary)
Miss A Simkins

1. Confidentiality and Announcements

The Chairman reminded members that the proceedings, papers and information were confidential and should not be disclosed. He welcomed Dr Salisbury who will be taking over duties as Medical Assessor. The Chairman announced that Mr Digings, administrative assistant to the Committee, had moved to work in Mr Hale's office; he recorded the thanks of ARVI for the assistance given by Mr Digings.

2. Apologies for Absence

Apologies for absence had been received from Professor Lloyd, [redacted] and [redacted]. The Chairman announced that Professor Lloyd had written to him resigning from the Committee because of pressure of other work. He recorded the thanks of the Committee for the work that she had done for ARVI.

3. Minutes of the Last Meeting

Several corrections were made to the draft minutes of the October meeting. It was decided that these should be retyped to incorporate the comments and that the agreed version should then be circulated to members.

4. Matters Arising from the Minutes

Item 4.1 - Adverse reactions to Trivax and Trivax D - six lines from the bottom

[redacted] said that only seven cases and six controls had been given plain vaccine within twenty-eight days of onset of their neurological illness and only two cases and no controls within seven days. It was agreed that these figures were not large enough to justify any firm conclusions.

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Item 4.1 - the last sentence should read:

"[redacted] reminded the meeting that Dr Pollock in his paper had found both local and systemic reactions less with adsorbed vaccines."

Item 5.1 - [redacted] agreed to provide further details in relation to 5.1(3)c and 5.1(4).

Item 6 - Review of the safety and efficiency of desensitising vaccines.

The Chairman enquired about future procedure for up-dating ARVI on adverse reaction reports to desensitising agents. [redacted] reported that Yellow Cards concerning adverse reactions to these products were being coded now by another section of Medicines Division; it has been agreed to supply ARVI with future information on these reports on an annual basis.

Also in Item 6 - Treatment of anaphylaxis:

[redacted] had received papers from Dr McGuinness and [redacted] but unfortunately it had not been possible to arrange a meeting to finalise a paper to enable advice to be prepared for the Memorandum 'Immunisation Against Infectious Disease'. Members discussed the difficulty of distinguishing, fainting attacks from true anaphylactic reactions.

[redacted] demonstrated a portable oxygen machine which could be used in conjunction with a portable resuscitator.

It was agreed to prepare a paper for the next meeting.

Item 8 - Any Other Business - Report on Tonsillectomy and oral surgery as contra-indication to the administration of oral poliovaccine.

The Chairman said that unfortunately [redacted] was unable to attend this meeting and it was agreed to ask [redacted] to report on this matter to the Spring meeting of the JCVI. Members agreed that there appeared to be a hypothetical risk of recipient poliomyelitis associated with these surgical procedures.

Item 7c - Yellow Card Reports
Product Defect Reports by Pharmacists.

[redacted] reported that there was now greater selection with regard to Yellow Card Reports rendered by pharmacists. Where a pharmacist suspected that there was an adverse reaction he was encouraged to get the doctor who did the vaccination to make a report.

5. Proposed Introduction of Combined Measles, Mumps and Rubella (MMR) Vaccine. A Paper by the Department

ARVI/87/2

[redacted] introducing the paper, said that at its November meeting the JCVI had proposed to change from the policy of administering measles vaccine preferably during the second year of life to one of administering measles, mumps and rubella (MMR) vaccine to both sexes. No decision had yet been reached on 'catch-up' vaccination of children of more than two years of age and the schoolgirl rubella vaccination programme would remain unchanged.

MMR vaccine was now used in nine European countries, also in the USA and Canada. Using this vaccine there was a benefit of increasing the uptake of measles vaccine. It was proposed to carry out trials of MMR vaccine in Hertfordshire, Somerset and Fife this year and these studies would be coordinated by the Communicable Disease Surveillance Centre (CDSC). It was also proposed to carry out serological surveillance of mumps and rubella and consideration would be given to making these diseases notifiable. Surveillance would also be undertaken of adverse reactions to MMR in these studies. [redacted] ended by saying it was hoped that adverse reactions to rubella vaccine might be reduced by giving this vaccine to a younger age group.

[redacted] asked if the Department was aware of other studies of MMR taking place, notably in Nottingham and in Oxford. [redacted] confirmed that the Department knew of these studies.

The Chairman asked the Committee to consider the published papers which had accompanied the Departmental paper on MMR vaccine.

5.1 Rubella Vaccine - 'how reactogenic is it'?
G V Griffin and K A Bryett
J Ind Med Res (1986) 14, p 316 ARVI/87/3

[redacted] noted that this study had no control group and that the two rubella vaccines which were compared were derived from the same strain of vaccine virus. He remarked that joint pains were much less common among children than in adults after rubella vaccine.

5.2 Diffuse Retinopathy following measles, mumps and rubella vaccination - Gary S Marshall et al: Paediatrics Vol 76 p 989 (1986) ARVI/87/4

This paper described a diffuse retinopathy following vaccination with MMR. The Chairman suggested that yellow card reports be searched for similar reactions and he agreed to take neuro-ophthalmological advice about the specificity of this syndrome.

5.3 Rubella-associated arthritis I comparative Study of joint manifestation associated with natural rubella infection and RA 27/3 rubella immunisation - Tingle, Allen et al, Annals of the Rheumatic Diseases (1986), vol 45, pages 110-114 ARVI/87/8

[redacted] observed that this paper demonstrated that joint manifestation following rubella vaccination were much more likely to be transitory compared with those which follow natural rubella infection.

5.4 Postpartum Rubella Immunisation: Association with development of prolonged arthritis, neurological sequelae and chronic rubella viraemia - Tingle, Chartler et al. The Journal of Infectious Diseases (1985) Vol 152, pages 606-612 ARVI/87/9

This paper described six women who developed joint problems and neurological manifestations (paraesthesiae) following rubella vaccination. Rubella virus was also demonstrated in the breast milk of one of these patients nine months post-vaccination. [redacted] pointed out that this paper described no denominator and he mentioned that

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there had been a response from the Centres for Disease Control (Atlanta) to this particular paper.* It was agreed to circulate this response to members.

6. Vaccine Related Poliomyelitis in Non-Immunised Relatives and Household Contacts - D E Bateman, G Elrington, P Kennedy, M Saunders
BMJ (1987) Vol 294, pages 170-171

ARVI/87/5

[redacted], introducing this paper which described two contact vaccine-associated cases of poliomyelitis, said that it was unfortunate that the paper strongly recommended the vaccination of unprotected parents and other household contacts of infants receiving oral poliovaccine for the first time; he said that the JCVI would wish to change this advice because the risk of contact vaccine-associated poliomyelitis was replaced by an almost equal risk of recipient vaccine-associated poliomyelitis. What was now recommended was the washing of hands after changing babies napkins. Members suggested that a response should be made to the British Medical Journal concerning this article. It was agreed that the changes in the Memorandum 'Immunisation Against Infectious Disease', agreed by the JCVI at their October meeting, should come to the next meeting of ARVI.

7. Whooping Cough and Whooping Cough Vaccine

7.1 Whooping cough vaccine - CSM advice

[redacted] said that the CSM had been asked to obtain the advice of ARVI concerning the statement made in paragraph 1.14 in the blue book (Whooping Cough, HMSO 1981, page 4).

The statement read:

> "No scientifically unassailable link has been established between DTP immunisation and serious neurological illness but we have come to the conclusion, on the basis of all present evidence, that there is a prima facie case that such a link may exist. We would also agree that the evidence suggests that the vaccine causes convulsions in some children."

The Committee were asked whether or not they remained content with this statement.

In the ensuing discussion it was noted that this extract was taken from the CSM statement contained in the 1981 Blue Book and was made at a time when vaccine hazards were receiving more scrutiny than natural pertussis. ARVI suggested that the statement be updated to read:

> "Although there is no scientifically unassailable proof that DTP vaccination causes serious neurological illness we are still of the view that a link may exist. However, such an association is an exceedingly rare event. We would also agree that the evidence suggests that the vaccine can precipitate convulsions in some children."

* J Inf Dis (1986) Vol 154 under correspondence Preblud S R et al, pages 367 and 368. Reply by Tringle A J pages 368 and 369.

7.2 MRC Sub-Committee on Whooping Cough Vaccine

[redacted] reported that development of the acellular whooping cough vaccine in this country had received several setbacks. Initially it was hoped to carry out the trials with a Clinical Trial Exemption Certificate however the organisers had now been told that a full Clinical Trial Certificate would be needed. A controlled trial in Sweden had discovered three deaths among children taking part in the trial, although the number of these events did not reach statistical significance the findings had caused the organisers some concern. Finally the diphtheria component in one of the vaccines to be used in the British trial had failed its NIBSC test and therefore a replacement vaccine had to be sought.

7.3 A personal and family history of seizures among persons reporting neurologic adverse events following immunisation with DTP or measles-containing vaccines. Presentation to the Immunization Practices Advisory Committee
John R Livengood - October 6 1986
(This draft paper was provided by [redacted] (Secretary of the Canadian National Advisory Committee on Immunisation.)

Members asked [redacted] to provide the published version of this paper.

7.4 History of convulsions and use of pertussis vaccine - editorial Journal of Paediatrics 1985 Vol 107 pages 244 and 245

This paper was provided for information.

8. Effect of Influenza Vaccine in Patients Receiving Long-Term Warfarin Therapy -
Weibert, Lorentz, Norcross, Klauber and Jagger (1986)
Clinical Pharmacy, Vol 5 June 1986 ARVI/87/7

[redacted] said that the Sub-Committee had for some time been interested in the possible effect of influenza vaccine on the metabolism of warfarin. The paper demonstrated that in patients on warfarin therapy influenza vaccine did tend to influence the prothrombin-time but that no untoward events were observed.

9. Suspected Adverse Reactions to Vaccines: The Reports on Yellow Cards Registered During the Period 12 September 1986 to 26 January 1987
ARVI/87/1

[redacted] Introduced this paper.

(a) suspected adverse reactions to DTP vaccine given alone or with OPV.

During the current period sixty-nine suspected adverse reactions were reported. These include:

i. eight patients with reported convulsions including one, 170519, whose seizures were associated with pneumococcal meningitis.

ii. 169110, a nine-month old female who developed angio-oedema two minutes after being injected with DTP.

iii. 175296, a seven-month old female who developed thrombocytopenia the day after immunisation.

(b) Suspected adverse reactions to oral polio vaccine.

A patient (not reported on a yellow card) aged three-months who two weeks after receiving OPV developed lower motor neurone lesions of of the arms together with upper neurone lesion signs in the legs. Some sensory loss was noted. The patient developed difficulty in breathing and swallowing and died six weeks later. The final diagnosis was respiratory failure and poliomyelitis. Members expressed some doubt as to the diagnosis in this patient because of the presence of sensory symptoms and upper motor neurone signs.

(c) Suspected adverse reactions to diphtheria/tetanus vaccine.

During the period fifty-four reactions were reported, fifty of these included a mention of injection site disorder.

(d) Suspected adverse reactions to tetanus vaccine.

During the period twenty-three reports were registered; they consisted mainly of injection site disorders.

(e) Suspected adverse reactions to measles vaccine.

Eighteen reports were received during the period and included a report of sudden infant death syndrome. 170520, a fifteen-month old patient who died two to three days after measles vaccination. Autopsy revealed infection of the respiratory tract. The cause of death was described as:

(1) SIDS

(2) Possible upper respiratory tract infection.

ii. Convulsions

Four patients with convulsions were reported and one case (175708) of convulsions associated with otitis media.

iii. There were two reports of anaphylactic reactions and these should be associated with seven similar reports observed since February 1986 of reactions occurring within minutes of vaccination and all associated with vaccine from one manufacturer. It was suggested that the advice of [redacted] be sought over these reactions.

(f) Suspected adverse reactions to rubella vaccine.

During the period there were three reports, one of syncope, one report of arthropathy and one girl who had a major convulsion within eight minutes of receiving the vaccine.

(g) Suspected adverse reactions to BCG.

There were three reports of injection site disorder.

(h) Suspected adverse reactions to influenza.

There were nineteeen reports of adverse reactions during the period all were of a relatively mild nature except in one case of non-fatal but severe anaphylaxis.

(i) Suspected adverse reactions to hepatitis vaccine.

There were thirteen reports during the period and these included one death.

170927, an Asian baby born to a mother who was a carrier of hepatitis B who was given BCG and hepatitis B vaccine at brith. One week later the child developed unexplained drowsiness, fits and then died. Autopsy revealed no abnormality apart from cerebral oedema. It was suggested that details of the histological examination of this patient might be obtained.

(j) Suspected adverse reactions to typhoid vaccine.

There were twelve reports, including two patients who had convulsions after vaccination.

(k) Suspected adverse reactions to cholera vaccine.

Two reports were received during the period.

10. Any Other Business

[redacted] informed members that Professor Gilliat was retiring from his Chairmanship of the ARVI Sub-Committee to take up the post of visiting scientist at NIH Bethesda. Members of the Sub-Committee expressed their gratitude to Professor Gilliat for his invaluable work as Chairman since the formation of ARVI in 1980, and wished him well in his new post.

11. Date of the Next Meeting

The next meeting is to be held on Friday 5 June 1987.

D.X200 J.X1144.1

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 [redacted], [redacted] and [redacted]

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. [redacted] suggested that an advisory group should convene to provide advice on anaphylaxis with [redacted] as Chairman and [redacted], [redacted] and [redacted] as members.

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

It was agreed that [redacted] letter (ARVI/87/10) should be referred to JCVI with ARVI's endorsement. [redacted] thought that the previous advice had originally been extrapolation from concern 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. [redacted] 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. [redacted] noted that more than 10,000 women per year received post-partum rubella immunisation and [redacted] 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.

[redacted] made has a study of SSPE surveillance and it was thought that none of her cases was associated with rubella. [redacted] thought the report to which [redacted] 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 [redacted] 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. [redacted] commented on the need for speed of provision of information with awareness of cost-effectiveness of the work involved. [redacted] suggested the use of PTMOs for follow-up of adverse reactions and [redacted] 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. Sir John Badenoch 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. [redacted] commented on the need for precise definition of adverse reactions. [redacted] 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 [redacted] 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. [redacted] felt that this would eliminate many reports as irrelevant and [redacted] informed the meeting that the yellow card data was to be computerised with a new system over the next few months. [redacted] 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. Sir John Badenoch felt this could be difficult with the quality of information available at present. [redacted] 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 Professor Gilliat 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 [redacted] 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
Letter from Chairman of CSM — ARVI/87/14

The letter from [redacted], Chairman of CSM to Professor Gilliat was noted.

Abstracts prepared by Professor Gilliat of papers submitted to CSM were presented and [redacted] 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. [redacted] therefore, challenged Professor Gilliat's 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

[redacted] 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. Sir John Badenoch 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. [redacted] agreed with Sir John and welcomed the clearer advice from JCVI on pertussis contra-indications which he endorsed. [redacted] commented that there was no need for JCVI advice to change but there should be awareness of the implications of change. Sir John suggested a meeting with manufacturers to discuss the changes in an attempt to seek common ground. [redacted] commented that it was not ARVI's responsibility to dismantle other groups instructions. [redacted] 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. [redacted] suggested that [redacted] advice should be followed and that members should submit their comments in writing to [redacted]. Sir John Badenoch hoped that there could be informal discussion with the manufacturers of areas of agreement or debate

and [redacted] noted that the new pertussis guidelines would be produced at a time of continuing pertussis litigation. [redacted] 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. Sir John Badenoch 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. [redacted] 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

[redacted] 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. [redacted] commented that on such matters ARVI would accept the advice of the referring Committee and [redacted] 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/

[redacted] 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.

NOT FOR PUBLICATION ARVI/87/3rd Meeting

COMMERCIAL 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 Friday 2 October 1987 at 10.30 am in Room 1611/1612 Market Towers

Present:

Professor J Collee (Chairman)
Sir J Badenoch
Dr N Cavanagh
Dr P Fine
Dr B McGuiness
Professor S R Meadow
Dr C Miller
Dr D Reid
Dr S Wallace

DHSS

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

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 welcomed Dr Scott who had recently joined Medicines Division and was attending his first meeting of ARVI.

2. Apologies for absence

Apologies had been received from Professors Banatvala, Breckenridge, Hull, Miller and Dr Bowie.

3. Minutes of the last meeting

The minutes of the meeting held on 6 July had been circulated and members amendments were noted. They were signed by

[redacted]

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4. Matters arising from the last minutes

The following items were discussed:

Item 6.2 It was felt that the second paragraph of this heading failed to reflect [redacted] views and [redacted] has therefore been asked to submit a summary of Paper ARVI(87)8 relating to the NCES data discussed at the meeting on 3 October 1986.

Item 6.3 "Therefore" (para 2, line 5) to be deleted.

Item 6.4 JCVI's Revised Contra-indications to Pertussis Vaccine

[redacted] reported that the discrepancy between JCVI recommendations and manufacturers product licenses had been discussed at CSM who had upheld JCVI's right to issue advice to the profession.

Sir John Badenoch reported that a meeting was shortly to be held with the Pharmaceutical Industry to find common ground on issues such as this. [redacted] stated that DHSS Solicitors views of this discrepancy had been sought and had been advised that there was no obligation on JCVI's views to conform with the manufacturers product licenses when those views represented the advice of expert medical opinion.

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5. Working Group on Protocols for Treatment of Anaphylaxis

It was agreed that a Group would need to meet quickly to complete these recommendations for the Memorandum or alternatively, to distribute material by post. [redacted] had already provided valuable material for this purpose and [redacted] offered to send examples of the material on anaphylaxis to [redacted]

6. Processing and use of data from the Register of Adverse Reactions

[redacted] described the changes in data processing and on quality control which would follow the introduction of new computing facilities. There would be fewer backlogs and the opportunity for screening of individual reports.
The example printouts of reported reactions were explained and the anticipated future improvements discussed.

7. Suspected Adverse Reactions to Vaccines : Report on Yellow Cards

[redacted] presented a paper which discussed some of the aspects of analysis of the Yellow Card data and identified other epidemiological information which could be considered in association with the adverse reaction reporting.
Sample printouts of summaries and analyses of reactions were available. [redacted] reminded members that the role of ARVI was not to consider the minutiae of vaccine reactions and expressed a wish that there should be summary of data rather than discussion of excess material. [redacted]

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asked if analyses were possible according to manufacturer and [redacted] questioned the delays in reporting and coding. These points were answered by [redacted].

Sir John Badenoch commented that general practitioners should be aware of the need for specificity of vaccine and batch and [redacted] agreed to investigate this.

8. Vaccination and Cot Deaths in Perspective

There was discussion by the Committee of the reports made available on this topic and [redacted] identified the need for the present information, that there did not appear to be a causal relationship between pertussis immunisation and SIDS, to be disseminated and suggested the Foundation for the Study of Sudden Infant Death could promote the present knowledge. [redacted] noted that there was a methodological problem preventing the conclusion that pertussis vaccination was protective against sudden infant death syndrome as those risk factors for sudden infant death syndrome may overlap with the contra-indications for vaccine and this issue had not been dealt with in the submitted papers. [redacted] questioned what risks were common to contra-indications and SIDS and [redacted] mentioned factors such as ill-health and socio-economic issues which inhibited pertussis immunisation.

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9. Investigation of the effects of influenza vaccine on drug metabolism.

This paper and its conclusions were noted. Merieux plan to study the effects of theophyllinewith their influenza vaccine and then submit data.

10. Reactogenicity of Meningococcal A and C Vaccine in a population of United Kingdom school children

This paper was discussed and members noted that meningococcal vaccines still were without product licence. [redacted] described the consequences of the outbreak of Group A meningococcal infection in Mecca, with cases in this country and a huge demand for vaccine. A CMO letter had been sent to all doctors advising them of the approprite use of meningococcal vaccine in September.

11. Dates of Meetings in 1988

It was agreed that the Sub Committee should meet on two occasions during 1988, on Tuesday 8 March, and Friday 2 September, and not as previously notified.

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JOINT SUB-COMMITTEE ON ADVERSE REACTIONS TO VACCINATION AND IMMUNISATION

Minutes of the meeting held on Tuesday 8 March 1988 at 10.30am in Room 1612, Market Towers

Present	Professor J Collee (Chairman)	
	Professor J E Banatvala	
	Dr N Cavanagh	
	Dr J Cameron Bowie	
	Dr P E M Fine	
	Professor D Hull	
	Professor D G McDevitt	
	Dr B W McGuiness	
	Professor S R Meadow	
	Professor D L Miller	
	Dr E Miller	
	Dr D Reid	
DHSS	Dr D M Salisbury	- Assessor
	Mr K Fowler	- Secretary
	Dr R Mann	
	Dr F Rotblat	

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 announced that this was the last meeting of the Sub-Committee which would be attended by Dr Mann, the Medical Assessor of the CSM's Adverse Drug Reaction Section, because he would be retiring at the end of the month. The Chairman and members extended their thanks to Dr Mann for the work and advice he had given the Sub-Committee and wished him well in his retirement.

2. Apologies for Absence

Apologies had been received from Professor Breckenbridge, Sir John Badenoch and Dr Wallace.

3. Minutes of the last meeting

The minutes of the meeting held on Friday 2 October 1987 were signed by the Chairman as a true record of the meeting after adding Professor McDevitt's name to the list of apologies for absence.

4. Matters arising from the Minutes

4.1 Item 6.2 of the minutes of the July 1987 meeting - [redacted] redraft of this paragraph (ARVI/88/1) was agreed by members and replaces the previous draft.

4.2 Item 7 (October 1987 minutes), paragraph 2 - Dr Mann reported about the CSM proposal for a pilot study to involve community pharmacists in the reporting of adverse drug reactions, which he thought would pick up information of the kind required.

4.3 Item 11 - the Chairman brought the attention of members to the date of the next meeting which will be Friday 2 September 1988.

5. Treatment of Anaphylaxis

The section on Anaphylaxis from the forthcoming edition of the Memorandum "Immunisation against Infectious Disease" had been made available to the Committee. The Anaphylaxis section had been written to incorporate the recommendations of [redacted], [redacted] and [redacted]. The Committee recommended that this section should be made available to the British National Formulary who may wish to include it in subsequent editions.

6. Report of Yellow Card Data

There was considerable discussion of the information on reactions to vaccines during 1987. [redacted] commented that this format of the data was more appropriate for the Committee's needs, provided that the Committee's attention could be drawn to any important or unusual reactions. The frequency of adverse reactions to influenza vaccine was noted, perhaps reflecting the age and ill-health of the target recipients and JCVI may wish to consider the specificity of recommendations for appropriate groups. [redacted] asked if information could be made available on the timing of convulsions in relation to immunisation. [redacted] and [redacted] asked for information to be available in the future on reactions to plasma derived or recombinant hepatitis B vaccine. [redacted] cautioned the Committee on interpretations or comparisons when there was a

significant degree of under-reporting. The figures were accepted as being useful for alerting ARVI ~~of~~ to evolving problems.

7. Adverse Reactions Surveillance

[redacted] introduced his paper on adverse reaction surveillance as a spontaneously generated contribution which was not a criticism of present policies. He expressed anxieties that since the loss of public confidence in pertussis vaccine, the public had become far more critical of all vaccines. He recommended consideration of a monitoring system for vaccine reactions which would cope with any vaccine related adverse publicity. There was considerable discussion of this paper which received the widespread support of ARVI. The Committee agreed the following recommendations:-

(a) There was a need for good and adequate reporting of adverse drug reactions with control data where available.

(b) The Committee had reservations about patient generated data often involving event reporting, endorsed the need for doctor generated reporting and noted the resource implications of any new scheme. Existing facilities were acknowledged such as the Red Alert Scheme.

(c) The Committee suggested that a Working Group should be convened involving [redacted] and the

ARVI secretariat who could co-opt other expert advisers to then provide advice for JCVI and CSM.

(d) The District Health Authority Immunisation Co-ordinators were identified as individuals who may have an important role in adverse reaction surveillance at district level and the possible involvement of CDSC/CDC was identified.

(e) [redacted] paper will be submitted to JCVI as soon as possible.

3. Measles, Mumps, Rubella (MMR) Vaccines

(a) [redacted] reported to the Committee on the steps which had been undertaken and were to be implemented in he near future for the introduction of MMR. The District Immunisation Co-ordinators had been identified as essential links in the dissemination of information to all those professionals involved in immunisation in each District. The Co-ordinators were all due to attend a meeting at DHSS on 15 March to discuss the implementation of MMR.

(b) [redacted] spoke on the MMR trials which had been carried out using Health diaries on approximately 5,000 children in Fife, Somerset and North Hertfordshire. There had been no problem in introducing MMR into these districts and there had been a 90 per cent response from patients to

take part. The rate of convulsions in Somerset was two per 1,000, similar to the rate of convulsions after measles vaccine in the original MRC trial. Parotid swelling was noted ~~at~~ in approximately one per 100 children. The peak incidence of fever occurred eight to ten days after immunisation. Professor Hull spoke on the MMR trial in Nottingham and noted local concerns ~~of~~ about the potential infectivity of the mumps component of MMR to susceptible contacts. He was assured that the mumps vaccine virus is not transmissible.

(c) Five cases of mumps encephalitis following MMR have been reported from Canada. Four of these cases definitely followed the use of Urabe 9 mumps virus vaccine containing ~~containing vaccine~~, and the fifth probably did. This corresponded to a frequency of one per 100,000 doses and no sequelae had been reported in the sufferers. [redacted] had discussed the incidence of mumps related complications from MMR with the Communicable Disease Center, Atlanta, whose data were unfortunately only superficial on this issue. In the United States, Jeryl Lynn mumps virus is included in MMR but no data were available on parotitis following MMR and many of the reported neurological complications were clearly related to the measles component. Two manufacturers have applied for Product Licences for the United Kingdom and both their vaccines contain Urabe 9 mumps virus. One manufacturer already had a Product Licence for vaccine containing Jeryl

Lynn mumps virus. After discussion, the Committee felt that the rate of adverse reactions to the mumps component of MMR from Canada was in keeping with that expected from live virus vaccine and endorsed the view that a study of the Jeryl Lynn containing vaccine should be carried out using the same health diaries as the present trial.

9. JCVI Memorandum

The rewriting of the 1988 edition of the Memorandum "Immunisation against Infectious Disease" had been completed and the material submitted to the printers. The publication was expected for mid-April. The Committee recommended that the Memorandum should have the widest possible distribution.

10. MMWR 36 Number 18 "Pertussis Immunisation"

This MMWR article had been distributed to Committee members for information. The ACIP had stated that a family history of convulsions should not be a contra-indication to vaccination with diphtheria and tetanus toxoids and pertussis (DTP) vaccine. In addition, the ACIP believed that antipyretic use in conjunction with DTP vaccination may be reasonable in children with personal or family history of convulsions.

11. Code of Conduct Disclosure of Interests

[redacted] introduced this paper and explained the relevance of the proposed Code to Sub-Committee members. He briefly outlined the changes in the redrafted Code which members were being asked to consider, and which would be re-submitted to Ministers in due course. Some concern was expressed about the proposal to publish members' declared interests in the Committee's Annual Reports, and it was explained that this was the specific request of Ministers. [redacted] invited any members who might have uncertainty about what they should personally declare to contact him or Aileen Simkins, the Secretary to the CSM.

JOINT SUB-COMMITTEE ON ADVERSE REACTIONS TO VACCINATION AND IMMUNISATION

Minutes of the meeting held on Friday 6th October 1989 at 10am in Room 1611/12, Market Towers

Present: Professor J G Collee (Chairman)
Professor J E Banatvala
Dr C Bowie
Dr E Miller
Professor S R Meadow

DH: Dr D M Salisbury (Assessor)
Mrs J F Alderman (Secretary)
Dr S Wood
Dr F Rotblat
Mr P A Whitbourn
Mrs S Thomas
Dr E Rubery

SHHD: Dr O A Thores

1. Confidentiality and Announcements

1.1 The Chairman reminded members of the particular confidentiality of the proceedings of the meeting, as information from companies and patients' clinical details were to be discussed.

1.2 The Chairman welcomed Mrs Alderman, Dr Rubery and Dr Thores.

2. Apologies for Absence

2.1 Apologies had been received from Dr Cavanagh, Dr McGuiness, Dr Fine, Professor Hull, Professor Miller, Professor Breckenridge and Dr Reid.

2.2 Dr Salisbury was asked to write to members pointing out that ARVI depends on representation from its members' wide spread of specialties and knowledge, and their attendance is of real importance to the work of the sub-committee.

3. Minutes of the last meeting

After correction of some typographical errors, the minutes of the meeting held on Friday 3rd March 1989 were signed by the Chairman as a true record of the meeting.

4. Matters arising

4.1 Adverse Reactions Surveillance (item 4.1)- [redacted] advised that active surveillance of MMR vaccine in Somerset had just started.

4.2 Anaphylaxis- JCVI has been reassured by the observation that there were no deaths from anaphylaxis following childhood vaccination over 11 years. [redacted] had approached OPCS to see whether any death certificates over the same time period had mentioned anaphylaxis following childhood vaccination. None had. [redacted] was congratulated on taking this initiative. The next issue of the "Green Book" would appear soon after changes had been approved by JCVI in early November. The removal of the text stating that treatment with chlorpheniramine, hydrocortisone and

adrenaline should be "at doctor's discretion" was endorsed by the meeting.

5. Measles, Mumps and Rubella Vaccine

5.1 Vaccine supply and uptake information

It was noted that distribution of supplies gives a reasonable indication of the use of MMR vaccine, and on this basis (which was justified in discussion) 3 years' worth of vaccine had been used in one year. The meeting felt that the present drive and initiative should be encouraged. The experience from the USA is that vaccination at school age is too late to eliminate measles. It was also noted that the SKF vaccine (containing Urabe mumps strain) has nearly all the UK market share. This might be attributed to the fact that the Wellcome product (made by MSD and containing Jeryl-Lynn mumps strain) hurts at the injection site and has a shorter shelf life at room temperature.

5.2 Neurological reactions

5.2.1 Members attending this ARVI meeting included a Professor of Paediatrics, a senior Epidemiologist, a senior Community Medicine Specialist, a Professor of Virology, and other experienced professional with special interests in this field. The details of 19 cases in or relating to the UK were considered, to the end of September 1989, and these had also been checked by a search of the yellow cards. The following agreed criteria were applied to the assessments: likely association=isolation of mumps virus 15-28 days after vaccination, with an appropriate clinical history; possible=clinical history with or without positive CSF cytology and an acceptable time course; negative=no such evidence. The findings were: 3 likely associations, 9 possibles and 7 negative associations with the mumps component of the MMR vaccines in current use in Britain.

5.2.2 These preliminary conclusions are to be reviewed with reference to further information that may be available. It would be important to follow up certain aspects of virological investigations and other observations relating to the local circumstances in some cases. Further information needed to be sought from Professor Anthony on histopathology in the Exeter case, as the reported pathology had not resembled that of vaccine damage or varicella encephalitis.

5.2.3 The risk, assessed on the basis of the numbers of affected cases from whom mumps virus had been isolated (in relation of the assumed numbers of doses of vaccine given) seems to be of the same order as that accepted for polio vaccine, and in the worst analysis considering the likely and possible cases, the risk would be 1 in 200 000, which is still less than that found in Canada.

5.2.4 Special consideration was given, at the request of SHHD, to a case from Glasgow of July 1989. This was a fiscal case and as such was higly confidential. Doubts were expressed about the cause of death of this child, and while it was not possible to give a clear judgement, it was felt that there was unlikely to have been a causal relationship with the vaccine and that this was an unusual case. The letter from [redacted] had left the matter open, and it would be reasonable to ask for further information as to the family's circumstances, social history, the child's and the family's previous medical history, and for a detailed account of the viral investigation and timecourse in light of the negative virology. The existence of bronchopneumonia of 12-24 hours duration needed to be clarified in the face of the other evidence of sudden death, and anxiet.

was expressed over the retinal haemorrhages. This was difficult to relate to meningoencephalitis in a child of this age. It would be reasonable to ask [redacted] to expand on the view that the cerebral changes were similar to those reported in the paper by Hart and Earle that was cited, especially as the CSF was normal.

5.2.5 [redacted] report had mentioned that the lesions were not destructive and were thought to be minimal. Expert opinion should be sought as to whether minimal cerebral lesions were judged to be compatible with significant effects.

5.2.6 The meeting's further sadness was expressed over the press reports, which could have harmful implications and unneccessarily damage public confidence in vaccines.

5.2.7 Two drafts for suggested statements were tabled and examined, and amendments to the SHHD version were agreed. The amended version is at annex A. Any statement would be issued only with the prior approval of CSM and JCVI, who would be guided by SHHD with reference to the fiscal proceedings.

5.3 Oral report of meeting with NIBSC

NIBSC are now able to sequence mumps virus, to distinguish between wild and vaccine-related strains, and to distinguish between Urabe and Jeryl-Lynn vaccine strains. [redacted] would obtain further samples using saliva from patients with symptoms of wild disease and from those with post-vaccine parotitis. NIBSC were thanked for this most significant advance.

5.4 Death of child:report

The meeting was provided with the details of a child from Clacton who had died 12 days after MMR vaccination. No evidence of either death from meningoencephalitis or from MMR related conditions was found. An echovirus had been identified.

5.5 Material from manufacturers

A summary of the Canadian experience and a paper from Germany were examined, and the paucity of data from the US was noted. The help of SKF was appreciated, and a letter from [redacted] would be sent.

5.6 Publications on MMR

Copies of various manuscripts currently in the press had been made available to members. These were of great use at this stage of the sub-committee's deliberations.

6. Extract from Meyler's Side Effects of Drugs, 11th edition, 1988; Immunobiological Preparations, Dittman S

[redacted] was thanked for this updated extract.

7. Any other business

7.1 [redacted] commented that there should be ongoing evaluation of MMR-related neurological events so that the fullest information is available to set against instances such as those discussed at this meeting.

7.2 The meeting thanked [redacted] and expressed gratitude for his courtesy and efficiency as ARVI Chairman.

8. Date of next meeting

Friday 23rd March 1990, at 10am.

FOR SHHD

ANNEX A

IN CONFIDENCE

REPORT OF DEATH OF 16 MONTH OLD CHILD

In July 1989 a 16 month old child was found seriously ill by his parents and subsequently died. The cause of death was certified as "not ascertained" although there was evidence of bronchopneumonia and aspiration of gastric contents.

The child had received MMR vaccine five days before his death and had apparently been well following vaccination. However, post mortem examination revealed evidence of minimal brain changes of a non specific nature and the possibility was raised that these might have been vaccine-related.

The case was therefore reported to the Subcommittee on Adverse Reactions to Vaccination and Immunisations (ARVI), a group of experts who advise both the Committee on Safety of Medicines (CSM) and the Joint Committee on Vaccination and Immunisation (JCVI). ARVI have considered all available clinical and biological data carefully and do not consider that there is evidence to support a link between MMR vaccine and the cause of death.

25/6

JOINT SUB-COMMITTEE ON ADVERSE REACTIONS TO VACCINATION AND IMMUNISATION

Minutes of the meeting held on Thursday 7th March 1990 at 1.30pm in Room 119 Hannibal House

Present: Professor A Breckenridge (Chairman)
Dr P Fine
Professor A Campbell
Dr E Miller
Professor D Miller
Dr D Tyrrell
Professor D McDevitt
Dr P Minor
Professor F Harris
Dr D Cavanagh
Professor J Banatvala

DH: Dr D Salisbury (Assessor)
Mrs J Alderman (Secretary)
Dr S Wood
Mrs S Thomas
Mr P Whitbourn

Welsh Office: Dr K Richmond

1. Announcements and confidentiality

The Chairman reminded members about the confidentiality of the proceeding of the meeting, and asked that members notify him and the Secretary if they proposed to publish papers of relevance to the work of ARVI.

2. Welcome to new members

Professor Harris, Dr Minor and Dr Tyrrell were welcomed to ARVI.

3. Apologies for absence

Apologies had been received from Drs Bowie, McGuiness, Reid and Kennedy.

4. Minutes of the last meeting

These were agreed, 4.2 being amended so as to read (lines 1-2)...there were no known deaths from anaphylaxis.

5. Matters arising

From 4.1- The surveillance of MMR vaccine in Somerset is unlikely to detect issues of concern Problems exist with under-reporting.

6. Adverse reactions to MMR vaccine

Background paper
3 vaccines are in use in the UK, manufactured by SKF and Merieux (using Urabe mumps strain) and MSD/Wellcome (using Jeryl Lynn strain). The SKF

Urabe mumps virus is grown in chick fibroblast culture, the Merieux mumps virus grown in chick amniotic fluid. It was noted that the SKF product ha most of the market share, for the reasons described at the last meeting. In Canada, the MSD vaccine had been used exclusively. Following the introduction of the SKF product, cases of meningoencephalitis had been reported. When distribution of the SKF vaccine was halted, no further cases of meningoencephalitis were reported. The Merieux product is used extensively in France, but the company have stated that there had been no virologically proven cases occurring there, to date.

It was suggested that, due to different reaction criteria and methods of data collection, reporting in different countries should not be compared.

6.1 Measles notifications to week 7 1990
Notifications of measles have decreased since the introduction of MMR vaccine. It had been anticipated that 1990 would be an epidemic year, but to date 1000-2000 fewer notifications had been received each week than in previous epidemic years.

6.2 Supply of MMR vaccine and ADRs to manufacturer
Graph B- Two cohorts of patients in the 12-15 months and 4-5 years age groups were represented, and 100,000 doses had been supplied per month. I was felt that distribution reflected use. There had been a surplus supply over calculated demand, and this may have represented use in age groups between and above those targetted. It was likely that demand would decrease in the next 6 months.

Graph C- Figures had been obtained from SKF. The progressive distribution of vaccine was noted. The smaller increases in June and July 1989 were attributable to a batch failing at NIBSC. [redacted] asked whether authorities were using MMR vaccine in place of rubella vaccine, but this is not being done, one possible explanation being that MMR is 5 times dearer.

Graph D- The large degree of under-reporting was noted. This graph matche the chart at C.

6.3 Review of MMR ADRs
6.3.1 The following criteria had been applied to the assessments:
Definite=Virus isolated from CSF, time course of 14-28 days;
Possible/probable=Cells isolated from CSF, no virus in CSF, acceptable time course. Symptomatic reports were defined as those mentioning meningoencephalitis with hospital admission. It was considered that increased local awareness had a bearing on the clustering of origin of th reports. It was agreed that, in future report dates, reference number and age of child would be added to the data tables.

6.3.2 One case of bilateral deafness had been reported, and coded as "possible". This was an atypical reaction, and there was no proof as to the presence of meningoecephalitis. The wild mumps disease may cause unilateral deafness, and 2 reports have been received of unilateral deafness following the MSD vaccine. There have been no reports in the medical literature of bilateral deafness following MMR.

6.3.3 A fatality had been reported from Exeter. The histology had not supported varicella or other encephalitis. This case had been discussed a the previous meeting, and it was decided that it should remain classified as "possible".

6.3.4 The case reported from Maidenhead was uncertain. Lymphocytes were present in the CSF, and there was the possibility of the existence of neurological problems, which may have preceded vaccination.

6.3.5 Since the paper was prepared, two more "possible/probable" reaction had been reported on yellow cards, one virus positive case from Oxford, and one reported via the British Paediatric Surveillance Unit.

6.3.6 It was suggested that this information should be publicised more widely, and agreed that JCVI should be provided with this information fro ARVI, with the additional details as mentioned in 6.3.1. JCVI were to publish details relating to frequency of reactions.

6.4 Report from Japanese National Institute of Health

6.4.1 Following introduction of MMR vaccine in Japan, a close study had been made of adverse events. This study received high publicity, which lead to increased reporting. Promotion of the vaccine was then stopped in Japan, although it remains available. Differences in the measles (this is of higher potency) and rubella strains exist between the products used in Japan and the UK, although the same Urabe mumps strain is used, but at a higher dose.

6.4.2 It was noted that the incidence of meningoencephalitis in Japan had been 1 in 100,000 before the increased publicity, whereas afterwards the incidence had risen to 1 in 8000. Clarification was needed as to why this had occurred, and it was suggested that lumbar punctures might have been carried out on all admitted patients including those who were asymptomatic, which would not have been done in the UK.

6.4.3 The Committee agreed that the problem in Japan seemed to be of an increased order of magnitude to that seen anywhere else. This may be due to different reporting/investigating criteria or some local factors. The Committee felt that present surveillance would detect such problems if they were occurring in this country at levels sufficient to produce significant symptoms. The Committee endorsed the present MMR programme an felt that there were not sufficient indications to make changes at present. The situation will require careful monitoring and review.

6.5 MMR surveillance in the UK- BPSU protocol

This information paper was noted. The project is now running, and two report cards had been returned, recording reactions not reported elsewhere, or on yellow cards. This suggested that the study had raised awareness of adverse reactions. It was felt that, at present, a general study relating to all vaccines would not be helpful. Future meetings will be kept fully updated on progress.

6.6 Report from NIBSC

It was noted that NIBSC are able to distinguish between wild and vaccine virus types, and between Urabe and Jeryl Lynn vaccine types.

6.7 Published reports on MMR ADRs

This paper was noted.

6.8 Letter from [redacted]

This was noted.

7. Article [redacted] and letter [redacted] in Lancet

These were noted.

8. Any other business

The new immunisation schedule was due to start in May, and a new edition of the Green Book was to be published shortly.

9. Date and time of next meeting

Members would be sent a list of dates to select the most suitable for the September meeting.

JOINT SUB-COMMITTEE ON ADVERSE REACTIONS TO VACCINATION AND IMMUNISATION

Minutes of the meeting held on Monday 17 September 1990 at 1.30pm in Room 85 Hannibal House

Present: Professor A Breckenridge (Chairman)
Dr Bowie
Dr Cavanagh
Dr P Fine
Professor F Harris
Dr Kennedy
Professor McDevitt
Professor D Miller
Dr E Miller

DH: Dr D Salisbury (Assessor)
Mrs S Thomas (Temporary Secretary)
Dr J Hilton
Dr F Rotblat
Dr E Rubery
Dr P Waller
Mr P Whitbourn

1. Announcements and Confidentiality

The Chairman reminded members about the confidentiality of the proceedings of the meeting.

2. Welcome to New Members

Dr Colin Kennedy, Dr Patrick Waller and Dr Rileen Rubery were welcomed to this ARVI meeting.

3. Apologies for Absence

Apologies had been received from Dr Banatvala and Dr Wood.

4. Minutes of the Last Meeting

Members had only received the minutes at the meeting, so that they were not able to agree them. Members were asked to forward any comments back to Dr Salisbury.

5. Matters Arising

There were none from the minutes.

[redacted] asked whether there had been any feedback on a paper he submitted to JCVI 18 months ago on 'Systems of Surveillance'. Dr Salisbury recalled the paper, but thought that it had just been noted. [redacted] would investigate the matter and convey his findings to [redacted].

6. Adverse Reactions to MMR

There are currently three vaccines in use in the UK, manufactured by SmithKline Beecham and Merieux (using Urabe mumps strain) and MSD, distributed by Wellcome (using Jeryl Lynn strain). It was noted that there had been consistent reductions in the notifications of measles, mumps and rubella since the introduction of the MMR vaccine. This was welcomed.

6.1 Measles, Mumps and Rubella Notifications

Graph A - The notifications of measles have continued to decrease since the introduction of MMR vaccine. Despite anticipations, there had been no epidemic of measles this year and presently notifications were less than three hundred each week.

Graph B - Again, the mumps notifications were declining rapidly. Reporting to the RCGP Sentinel Surveillance Scheme also showed similar reductions. This was found to be a very encouraging sign.

6.2 Supply of MMR Vaccine

It was noted that SKB still held the larger share of the market. The MSD/Wellcome vaccine was found to have lost ground and Merieux have now taken over those lost sales from MSD/Wellcome. There was no backlog in filling orders from health authorities. The type of vaccines supplied was decided upon by the ordering pharmacist within each Regional Health Authority. It was found that the distributors preferred the SKB/Merieux varieties for posting long distances, but for vaccine which was required more locally, the distributors used the Wellcome vaccine. The time out of the fridge that manufacturers allowed for their vaccines was longer for the SKB and Merieux products.

6.3 Review of Cases Reported on Yellow Cards

6.3.1.The following criteria had been applied to the assessments:
Definite=Virus isolated from CSF, time course of 14-28 days;
Possible/probable=Cells isolated from CSF, no virus in CSF,acceptable time course.
It was noted that there were 10 definite cases of meningitis/encephalitis. It was likely that local awareness had a bearing on the clustering of cases in the origin of some of the reports.

6.3.2. One case had been reported from Cambridge. The patient had received the Jeryl Lynn strain of single antigen mumps vaccine. After five weeks the patient was reported to have developed mumps meningitis. No CSF was obtained in this case.

6.3.3. It was considered that the clustering of cases in Crawley was a result of increased local awareness. However, one of those cases had actually been vaccinated in Scotland and had been taken ill in Crawley. The clustering of cases in Kidderminster was also noted. These will be investigated further.

6.3.4. It was noted that the mumps viruses obtained from two out of the three cases from Nottingham were sequenced and shown to be vaccine related. The patients had all been vaccinated from different batches and did not live close to each other. These patients were not severe clinical cases.

6.3.5. One case of bilateral deafness had been reported, and coded as possible. This was an atypical presentation of mumps related deafness, and there was no evidence as to the presence of meningoecephalitis.

6.4 Report from BPSU Study on Neurological Reactions following MMR vaccine.

[redacted] reported on the BPSU scheme for reporting reactions following MMR vaccine. Reporting started in February 1990. There had been 19 cases reported to date of meningoecephalitis associated with MMR vaccine.

It was found that two thirds of the cases reported to the BPSU had also been reported on yellow cards to the CSM. It was agreed that it was important that all of these cases were followed up. [redacted] informed the committee that a Research Fellow was currently in post and all of the reported cases to either CSM or BPSU, were now being investigated.

There are currently four avenues for adverse reaction reporting for ADRs following MMR vaccine; via the Yellow Cards,the BPSU scheme, directly to CDSC and through Laboratory reports. It was

recognised that the use of such data was limited for detailed epidemiological evaluation and in order to further validate vaccine related illnesses, fuller studies would be required.

6.5 Article "Characteristics of live mumps vaccine in current use" J Millstein

This article was noted. In conclusion it was pointed out that the Urabe strain was more reactogenic but also more immunogenic than the Jeryl Lynn strain. This was re-inforced by information from Sweden suggesting only 80% seroconversion using the MSD vaccine.

It was noted that the introduction of mumps immunisation could in theory shift the age specific infection rates to older age groups in whom the complications were greater; nevertheless, the gains from the progressive reductions in mumps illnesses outweighed such concerns. This observation was supported by Prof. Anderson's work on modelling of mumps infections and immunisation.

6.6 Draft article "Aseptic meningitis as a complication of mumps vaccine" A Sugiura et al

[redacted] reminded members that this paper was confidential and not for publication.

This paper highlighted the increased numbers of isolations of mumps viruses from the CSF following the promotion of MMR vaccine in Japan. The paper confirmed information from Japan previously disclosed to ARVI. The Committee found it most reassuring that there had been no sequelae from these cases of meningitis.

6.7 Conclusions

Thus ARVI's conclusions on the present position concerning ADR's to MMR vaccine are as follows:

6.7.a The impact of the MMR programme has been most successful in achieving considerable reductions in the target diseases; mumps elimination is a realistic prospect in the near future.

6.7.b After intense demand for vaccine, and matching frequency of ADRs, (see last ARVI meeting), vaccine distribution is now less, despite three products being available. Each of these incorporates either different mumps viruses, or uses different culture techniques.

6.7.c There has been no increase in the rate of reports of either definite vaccine associated cases or probable/possible cases. Whilst the rate should remain constant, it is anticipated that the number will fall as vaccine use declines to a steady rate.

6.7.d It is likely that the SKB Urabe 9 vaccine is more reactogenic and more immunogenic than the MSD Jeryl Lynn strain. This is supported by anecdotal evidence from Sweden suggesting only 80% seroconversion using the MSD vaccine.

6.7.e The BPSU scheme is providing excellent surveillance to supplement reporting to CSM.

6.7.f This sentence was amended by the committee to read "There should be no change in the present recommendations or supply of MMR vaccine on the evidence available to us at the present time".

7. Review of adverse reactions following hepatitis B Vaccine

This paper was noted.

8. Review of adverse reactions following influenza vaccine

This paper was noted. It was also agreed that there should be no further addition of text to that which already appears in the memorandum "Immunisation against Infectious Diseases 1990".

9. Any other Business

None.

10. Date of Next Meeting

The next meeting would be in six months time. Members were advised that they would be contacted to agree a suitable date.