1 INTRODUCTION

Vaccinations against Meningitis C were introduced in the UK in November 1999 and over the subsequent 16 months virtually the whole population under the age of 18 years was immunised. This paper reports on the work of a group that oversaw safety monitoring during this immunisation campaign.

1.1 Background

Meningococcal meningitis and septicaemia are systemic infections caused by the gram-negative diplococcus *Neisseria meningitidis*. In the UK the Public Health Laboratory Service (PHLS) has estimated that approximately 1500 cases of meningococcal group C disease occurred per annum prior to 1999. The case fatality rate is around 10%, implying that, in the UK, about 150 people died per year as a result of Meningitis C during the 1990s. Infants and teenagers are the most susceptible age groups.

On 1 November 1999, a national immunisation campaign began to vaccinate all individuals under 18 years with one of the new meningococcal C conjugate vaccines. It finished in February 2001 by which time it was estimated that more than 18 million doses of Meningitis C vaccine had been distributed. The overall uptake in children vaccinated in school was 84.6% (data from the PHLS). The campaign led to an 81% reduction in reported cases of meningitis C. Subsequently immunisation with Meningitis C vaccines became part of the routine infant immunisation programme, being given at ages two, three and four months.

1.2 Licensing of Meningitis C Vaccines

Three vaccines were used in the campaign: Meningitec (Wyeth), Menjugate (Chiron) and Neisvac-C (Baxter). Meningitec was authorised in October 1999 and was the first to be indicated for infants aged under one year. Menjugate was authorised in March 2000 and Neisvac-C in July 2000. Meningitec and Menjugate became authorised in other European Member States through the Mutual Recognition procedure in July 2000 with the UK acting as Reference Member State.

When a new medicinal product is to be licensed, the pharmaceutical company has to demonstrate evidence of its safety, efficacy and quality. At the time of licensing, common adverse reactions will have normally been identified during clinical trials. Those that were recognised for Meningitis C vaccines at this stage are listed in Box 1. These reactions were generally short in duration and not severe.
Box 1  ADRs known at the time of licensing of Meningitis C Vaccines

- Injection site reactions (including redness, swelling and tenderness/pain)
- Fever of at least 38.0°C
- Crying (in infants and toddlers)
- Irritability (in infants and younger children)
- Drowsiness (in infants and toddlers)
- Impaired sleeping (in infants and toddlers)
- Anorexia (in infants and toddlers)
- Diarrhoea (in infants and toddlers)
- Vomiting (in infants and toddlers)
- Headache
- Myalgia in adults
- Somnolence in younger children

1.3 Monitoring safety during normal use

Randomised controlled trials conducted before licensing are not usually large enough to identify rare adverse drug reactions. Furthermore, follow-up may be relatively short and the conditions under which the medicine or vaccine is used are carefully controlled. This is why new adverse drug reactions may be identified after any medicine, including vaccines, is used more widely in ordinary practice.

Diverse sources of information are used by the Medicines Control Agency (MCA) and Committee on Safety of Medicines (CSM) to monitor the safety of medicines (Box 2).

Box 2  Key data sources used to monitor the safety of medicines

- spontaneous reports of suspected adverse reactions
- epidemiological studies
- published medical and scientific literature
- further clinical trials
- information from other regulatory authorities
- regular safety updates submitted by pharmaceutical companies

The mainstay of post marketing drug safety monitoring is spontaneous reporting of suspected adverse drug reactions (ADRs). In the UK this is done through the Yellow Card scheme. This voluntary scheme was set up in 1964 and is used to identify possible new concerns about drug safety. It enables doctors, dentists, pharmacists and coroners to report suspected adverse reactions to any medicine, including vaccines. The reporting of a suspected reaction through the Yellow Card Scheme does not necessarily mean that the drug or vaccine caused the reaction. Each report is examined individually to assess whether new adverse reactions or new risk factors for recognised adverse reactions might be emerging. It is well known that not all suspected adverse reactions are reported
through the Yellow Card scheme. The level of under-reporting is influenced by many factors including the length of time a medicine has been available and whether or not awareness is increased by specific concerns about safety. Because of these factors, information from Yellow Cards cannot be used to estimate the incidence of particular adverse reactions. If a significant safety issue is detected, a full investigation is undertaken to assess the risk and identify the appropriate measures to reduce the risk to users. If required, actions such as changes to product information and communication with health professionals and the public are undertaken.

In December 1999, following requests from nurses responsible for administering Meningitis C vaccines, CSM agreed to accept Yellow Cards from nurses in relation to reports for Meningitis C vaccines during the campaign. These were accepted in addition to those already accepted from doctors, dentists, pharmacists and coroners. This decision was deliberately taken to enhance reporting of possible reactions.

The safety of Meningitis C vaccines was monitored continuously from the time they were licensed in the UK. A detailed safety review was considered by the CSM and its Sub-Committee on Pharmacovigilance in June 2000. Overall, the reported adverse reactions were very rare with no suspected reaction being spontaneously reported at a frequency of greater than 1 in 10,000 distributed doses.

As a result of this review in June 2000 CSM recommended that the following suspected adverse reactions for older children and teenagers be added to product information: headache, nausea and vomiting, rash, dizziness, fants, malaise, lymphadenopathy and allergic reactions including anaphylactoid reactions and seizures. All of these reactions were reported very rarely and reactions were generally short lived. CSM considered that a causal association between seizures (reporting frequency of approximately 1 in 100,000 distributed doses) and Meningitis C vaccination had not been established. However, it recommended that the following precautionary statements regarding seizures be added to product information: “Some of the seizures may have been fants. The reporting rate of seizures was below the background rate of epilepsy in children. In infants seizures were usually associated with fever and were likely to be febrile convulsions.” CSM also advised that the statement ‘Symptoms of meningism such as neck pain/stiffness or photophobia have been reported but as these are not live vaccines there is no evidence that the vaccines cause meningococcal C meningitis’ should be added to product information. The Committee further recommended that a statement relating to continued clinical alertness to the possibility of co-incidental meningitis should be added to product information.

In September 2000, the CSM considered how further review of the safety monitoring of Meningitis C vaccines should be conducted and advised that an Expert Working Group be established.

2 REMIT OF THE EXPERT WORKING GROUP ON MENINGITIS C VACCINES

The remit proposed by the CSM was as follows:
1. To oversee further monitoring of the safety of Meningococcal group C conjugate vaccines, reviewing all spontaneously reported deaths following vaccination and any other areas of concern.
2. To conduct a formal review of the safety of Meningococcal group C conjugate vaccines following completion of the campaign.
3. To consider the need to obtain additional evidence on vaccine safety, including the type of epidemiological studies that could be helpful.
4. To review the current information provision from the MCA to meet the needs of parents, healthcare professionals and the public and advise on how this may be improved.
5. To consider the future strategy for vaccine safety monitoring.

Members of the group are listed in Annex 1. It included members with specialist expertise in the fields of clinical pharmacology, vaccine safety, pharmacovigilance, paediatrics, general practice, nursing, epidemiology and risk communication. The group met three times, on 10 October 2000, 11 November 2000 and 10 April 2001.

3 FINDINGS AND ADVICE

Since 1 November 1999 more than 18 million doses of the three Meningitis C vaccines had been distributed and there had been an 81% reduction in reported cases of Meningitis C [Vaccine 20; 2002: 558 – 567].

3.1 Safety of Meningitis C vaccines

At the first meeting the group agreed to review, in detail, any Yellow Card reports with a fatal outcome. First they adopted a method of causality classification for spontaneous reports based on the methodology set out by Edwards and Aronson [Edwards I, Aronson JK. Lancet 2000; 356: 1255 – 1259] – see Annex 2. Using this classification the group concluded that there was no suggestion that the vaccine had caused any of the reported deaths. This process was undertaken for newly-reported cases at each of the meetings and in total 18 reports with a fatal outcome were reviewed (see below for further details).

At its second meeting the group also considered proposals from the Marketing Authorisation holder for Meningitec (Wyeth) for changes to the safety section of the product information. The group recommended that further changes to the product information for all Meningitis C vaccines should be made. Annex 3 provides details of all of the changes made to the safety sections of the product information during the campaign together with comments on the evidence supporting these changes.

At its last meeting the group considered a detailed review of all relevant safety data available at the end of the campaign. Since 1 November 1999 more than 18 million doses of the three Meningitis C vaccines had been distributed. By the end of the campaign on 28 February 2001, 12,880 reports of suspected adverse reactions had been received through the Yellow Card Scheme for Meningitis C vaccines, approximately half from nurses. The safety profile of the three products was very similar. Detailed consideration was given to reported cases of sudden infant death syndrome (SIDS) and convulsions. In addition three new safety signals were considered in detail: purpura/petechiae, serious
skin reactions and peripheral ischaemia. The findings and advice of the group in relation to the main safety issues considered are summarised below.

Where outcome was reported, the majority of suspected adverse reactions were non-serious and reversible. Serious reactions are defined as those that are fatal, life-threatening, disabling, incapacitating or which result in or prolong hospitalisation and/or are medically significant. Meningitis C vaccines were associated with proportionally fewer serious ADRs than would be expected from the overall proportion of serious to non-serious adverse reactions for all drugs on the Yellow Card database. This may in part reflect the fact that reporting of all suspected reactions was strongly encouraged, rather than just serious reactions as requested for older drugs. However, many of the non-serious suspected ADRs received during the campaign were newly identified, thus highlighting the importance of post-marketing surveillance.

Overall, the group considered that the potential risks associated with Meningitis C vaccines are far outweighed by their benefits.

It should be noted that this report focuses on suspected adverse reactions associated with Meningitis C vaccines and not the consequences of vaccine failures. Vaccine failures are monitored by PHLS who follow up all cases of confirmed or probable meningococcal C infection in England and Wales in the age groups eligible for Meningitis C vaccination. Previously this was under 20 years but has since been extended in light of the recent recommendation to vaccinate up to 25 year olds. As vaccinated cohorts age, the upper limit of the age group followed up will be incremented. Meningitis C vaccination history, including batch number, is obtained via the consultant in communicable disease control or GP. Annex 4 provides the latest information on the number of vaccine failures identified to end March 2002

3.1.1 Suspected ADRs with a fatal outcome: As part of the end of campaign review the group further considered in detail all these cases using the previously agreed causality classification (Annex 2). Following this evaluation, the group concluded there was no sound reason to suggest that the Meningitis C vaccines had caused any of the 18 reported deaths. The final categorisation of all the cases with a fatal outcome was unlikely (15 cases), unlikely/possible (2) and possible (1). It was noted that in many cases non-vaccine related causes of death could clearly be identified.

3.1.2 Sudden Infant Death Syndrome (SIDS): The group considered a detailed review of sudden infant death syndrome (SIDS) and childhood vaccination in general. The literature showed that vaccinated children appear to have a reduced risk of SIDS. This apparent reduction could reflect the possibility that children brought for vaccination would be less likely to have concurrent illnesses. If adjustment is made for non-associated but concurrent illness at the time of vaccination, this effect is reduced. An analysis of expected cases of SIDS compared with reports of SIDS following Meningitis C vaccination received through the Yellow Card scheme was presented. In total 8 cases of SIDS were reported. For cases of SIDS occurring 1-2 days after vaccination, it would be expected that Yellow Card reporting is near complete but as time from vaccination increases, the level of reporting should fall. Within 1-2 days of vaccination, the observed number of reports was slightly less than the expected number following which the
numbers decreased as expected. These results therefore followed a pattern which would be expected if there were no association between Meningitis C vaccination and SIDS. The group therefore concluded that the available data provide no evidence that Meningitis C vaccination is associated with an excess of SIDS.

3.1.3 Convulsions: Overall there were 291 reports of convulsions, a reported rate of around 1 case per 60,000 doses. It was noted that in many of the reports, Meningitis C was given with another vaccine known to be associated with a febrile response (e.g. DTP Hib with convulsions in the first 72 hours and MMR with convulsions at 9 – 10 days). Most of the reports of suspected convulsions following Meningitis C vaccines occurred on the first day and the number of reports rapidly decreased over subsequent days. The group considered that these early reports were probably explained by mis-reporting of faints as convulsions, together with some unrelated (non-causally associated) events. However, it was considered that some reports might reflect febrile convulsions. Sixty of the reports of convulsions (21%) were associated with a past medical history or a family history of convulsions. The group considered whether this might simply reflect convulsions being more likely in individuals with a past history, reporting bias, or an increased risk of convulsions in susceptible individuals following Meningitis C vaccination. They concluded that the evidence available did not support a particular risk of convulsions following Meningitis C vaccination in individuals with a past history of convulsions. The group proposed that the issue of convulsions should be subjected to further review when an analysis of linked hospital episodes statistics and vaccination records by PHLS is available (see section 3.2). The group advised that the current wording relating to convulsion in product information adequately reflected the evidence available (see Annex 3).

3.1.4 Purpura and petechiae: It was noted that these are very common signs in children and that the small number of reports received on Yellow Cards relative to overall vaccination rates (purpura – 57; petechiae 114) suggests that these were likely to be unrelated events rather than adverse reactions. The group therefore advised that purpura and petechiae should not be added to product information as recognised adverse reactions to Meningitis C vaccines.

3.1.5 Serious skin reactions: It was considered that, since more than 18 million doses of vaccine were distributed, the absolute number of cases (e.g. erythema multiforme - 24; Stevens Johnson Syndrome – 2) reported was very low. On reviewing the individual reports the group advised that, although causal association has not been completely established, serious skin reactions should be added to product information as possible very rare ADRs.

3.1.6 Peripheral ischaemia: The group advised that the 53 reports, which mainly related to temporary coolness and pallor of the limbs were most likely to be related to the injection process rather than the vaccine. The group considered that these reports were already adequately covered by warnings in product information.

3.2 Need for additional evidence
Determining whether or not there is a causal relationship between a medicine and a suspected adverse reaction on the basis of spontaneous data alone can be problematic and sometimes more formal studies are required to decide on causality.

At each of its meetings the group considered which safety issues might warrant further study using epidemiological techniques. The group identified the need for formal epidemiological study of seizures following Meningitis C vaccination. Following this recommendation PHLS prepared a protocol for a record linkage study. This study will link vaccination records with hospital admissions in the Thames region. Work on the study is in progress and it is expected that the results will be available in 2002.

Another area identified by the group for possible epidemiological study was serious skin reactions. Initial exploratory work on the feasibility of using record linkage methodologies to investigate this potential drug safety signal is therefore being conducted by PHLS.

### 3.3 Provision of information

The group considered assessment reports on communications about Meningitis C vaccine safety at its second and third meetings. The group recommended the following:

- Communications about vaccine safety should be more pro-active – making more information about the safety of the vaccines available to health professionals and the public.

- Messages about the safety of vaccine should be clear and risks should be balanced against benefits in terms of diseases prevented.

- Different audiences have different requirements for information on vaccine safety. However, the existing model of two forms of information, one for healthcare professionals and one for users of medicines is too simplistic. It was recommended that layers of information of increasing detail were produced with no distinction as to who could access these different layers. The first layer would be a very brief summary of the key points about the safety of the vaccine together with information about the benefits of the vaccine. The second layer of detail would be a detailed summary of the benefits of the vaccine together with explanation of all of the recognised safety issues. The third level of detail would be aggregated, anonymised data from the UK Yellow Card database together with a detailed explanatory note on how to interpret these data.

- The group advised that, wherever possible, Department of Health information on vaccines and vaccine Patient Information Leaflets should be compatible.

- The group recommended that the distribution of Patient Information Leaflets for vaccines be further investigated by the MCA to ensure that these could be made available to parents and older children.
3.4 Future strategies for vaccine safety monitoring

The group considered a review that outlined the current mechanisms of pharmacovigilance (safety monitoring) for vaccines and invited suggestions for enhancing these mechanisms in the future.

The group carefully considered the decision making process of vaccine safety monitoring and acknowledged the importance of keeping separate decision making on safety and on policy. However, it also recognised the need for effective communication between these areas. The group recommended that the MCA should be ready to form vaccine expert groups at short notice on an ad hoc basis using as a model the Meningitis C vaccine group. The expertise on such groups would vary depending on the issue being considered with those participating including individuals with relevant expertise from within or outside of the CSM. It was also agreed that when major new vaccination campaigns are planned careful consideration should be given to the need for such an expert group in advance.

The group advised that, when major new vaccines are introduced, opportunities for enhanced safety monitoring before expanding vaccine coverage nation-wide should be sought. Such opportunities should be focussed on gathering evidence to demonstrate vaccine safety rather than merely detecting previously unrecognised safety issues. The group considered that very large cluster randomised trials might be an important methodology for enhancing safety surveillance when a new vaccine is introduced. Such trials would randomise different vaccinations between regions or would randomly stagger the introduction of new vaccines by area. However, it was acknowledged that much work needed to be done to develop protocols for such trials and the group advised that the MCA consider proactively developing such methodology. The group also noted that the already used linkage of hospital episode statistics to vaccination records and the use of longitudinal patient records held in the General Practice Research Database were both potentially powerful tools in vaccine safety monitoring.

4 OVERALL CONCLUSIONS

The Meningitis C vaccination campaign was one of the largest, most successful and most important public health exercises undertaken in the UK in recent decades. Since 1 November 1999 more than 18 million doses of the three Meningitis C vaccines had been distributed in the UK. There had been an 81% reduction in reported cases of Meningitis C. The very large exposure to the vaccines during a relatively short period generated a large amount of data on safety, particularly through the Yellow Card scheme. The number of reports was further expanded by the valuable addition of nurses as recognised reporters to the Yellow Card Scheme during the vaccination campaign. These data were intensively monitored and all new safety signals were rapidly evaluated. Although new adverse reactions were identified during the campaign, these were generally non-serious and the only actions necessary were updates to product information. The balance of risks and benefits for Meningitis C vaccines was considered to be overwhelmingly favourable. The MCA should be ready to form vaccine expert groups at short notice on an ad hoc basis using as a model the Meningitis C vaccine group.
LIST OF ANNEXES

ANNEX 1 – MEMBERSHIP OF THE EXPERT WORKING GROUP

ANNEX 2 – CLASSIFICATION USED FOR ASSESSMENT OF SUSPECTED ADR REPORTS WITH A FATAL OUTCOME

ANNEX 3 – SUMMARY OF CHANGES MADE TO PRODUCT INFORMATION

ANNEX 4 – SUMMARY OF VACCINE FAILURES
ANNEX 1 : MEMBERSHIP OF THE CSM EXPERT WORKING GROUP ON MENINGITIS C VACCINES

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Department of Health

Dr. David Salisbury
Ms. Arlene Cook
Ms. M. Murray
ANNEX 2 – CLASSIFICATION USED FOR ASSESSMENT OF SUSPECTED ADR REPORTS WITH A FATAL OUTCOME (amended from Lancet 2000; 356: 1255-1259)

Certain

- A clinical event, including a laboratory test abnormality, that occurs in a plausible time relation to drug administration, and which cannot be explained by coincidental or concurrent disease or other drugs or chemicals.

- The response to withdrawal of the drug (dechallenge) should be clinically plausible.

- The event must be definitive pharmacologically, using a satisfactory rechallenge procedure if necessary.

Probable/likely

- A clinical event, including a laboratory test abnormality, with a reasonable time relation to administration of the drug, unlikely to be attributed to concurrent disease or to other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge).

- Rechallenge information is not required to fulfil this definition.

Possible

- A clinical event, including a laboratory test abnormality, with a reasonable time relation to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals.

- Information on drug withdrawal may be lacking or unclear.

Unlikely

- A clinical event, including a laboratory test abnormality, with a temporal relation to administration of the drug, which makes a causal relation improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations.

Conditional/unclassified

- A clinical event, including a laboratory test abnormality, reported as an adverse reaction, about which more data are essential for a proper assessment or the additional data are being examined.

Unassessable/unclassifiable

- A report suggesting an adverse reaction that cannot be judged, because information is insufficient or contradictory and cannot be supplemented or verified.
## ANNEX 3 – SUMMARY OF CHANGES MADE TO PRODUCT INFORMATION
Changes to the safety sections of Product Information for the meningococcal group C conjugate vaccines (includes all changes made during the vaccination campaign)

<table>
<thead>
<tr>
<th>ADR</th>
<th>Evidence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>Added at the first review when there were 347 reports relating to various types of rashes.</td>
<td>A third of patients had generalised rashes over their trunk, neck or face, and 20 cases were described as severe.</td>
</tr>
<tr>
<td>Headache</td>
<td>Added at the first review when there were 484 reports. The cases were generally transient and non-serious. However, fifty cases were described by the reporters as being severe.</td>
<td>The Product Information originally only covered headache in adults, this was considered inappropriate given the number of reports in teenagers. Headache was added as a possible ADR for all age groups.</td>
</tr>
<tr>
<td>Nausea</td>
<td>Nausea (number of Yellow Cards = 271).</td>
<td>Originally only covered in Product Information for toddlers. Extended to all age groups following first review.</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Vomiting (number of Yellow Cards = 148).</td>
<td>Originally only covered in Product Information for toddlers. Extended to all age groups following first review.</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Abdominal pain (number of Yellow Cards = 24).</td>
<td>Originally only covered in Product Information for toddlers. Extended to all age groups following first review.</td>
</tr>
<tr>
<td>Urticaria</td>
<td>Urticaria (number of Yellow Cards = 185).</td>
<td>Added to Product Information following the Nov 2000 review.</td>
</tr>
<tr>
<td>Pruritus/urticaria</td>
<td>Pruritus/urticaria (number of Yellow Cards = 185).</td>
<td>Added to Product Information following the Nov 2000 review.</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Dizziness (number of Yellow Cards = 338).</td>
<td>Added to Product Information following the first review</td>
</tr>
<tr>
<td>Faints</td>
<td>Faints (n=163) and collapse (n=15) were also reported.</td>
<td>Approximately 10% of these patients had previously experienced syncope or faintness associated with injections.</td>
</tr>
<tr>
<td>Malaise</td>
<td>Malaise was reported in 89 patients. Somnolence was already covered in the Product Information for younger children.</td>
<td>As only 2 of these reports related to younger children, this adverse reaction was included as a potential adverse reaction for all age groups.</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>In the majority of reports of lymphadenopathy, nodes were axillary in location (i.e. in the drainage area of the injection site), suggesting a likely causal relationship with the vaccine.</td>
<td></td>
</tr>
<tr>
<td>Allergic reactions/</td>
<td>There were 43 reports of bronchospasm and asthma. Eight patients had a previous history of asthma. Four patients had associated urticaria, lip swelling or other features consistent with an allergic reaction. Patients of all age groups vaccinated were affected.</td>
<td>The allergic/hypersensitivity warning was strengthened.</td>
</tr>
<tr>
<td>hypersensitivity reactions</td>
<td></td>
<td></td>
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<tr>
<td>including bronchospasm,</td>
<td></td>
<td></td>
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<tr>
<td>facial oedema and</td>
<td></td>
<td></td>
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<tr>
<td>angioedema</td>
<td></td>
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</tr>
<tr>
<td>ADR</td>
<td>Evidence</td>
<td>Comments</td>
</tr>
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<td>----------------------------</td>
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</tr>
<tr>
<td>Anaphylactoid reactions</td>
<td>Added at the first review when there were 7 Yellow Card reports of suspected anaphylaxis, with symptoms such as dyspnoea and collapse.</td>
<td>It should be noted that the preferred terms for recording such ADRs on the database are as ‘Anaphylactic reaction’, ‘Anaphylactic shock’ and ‘Anaphylactoid reaction’. The ADR is classified/linked on the database as the exact term described by the reporter. A general warning regarding anaphylaxis and vaccines was in the original Product Information. In light of the reports it was considered appropriate to also list anaphylactoid reactions as a possible adverse reaction to Meningitis C vaccines (in addition to the general warning).</td>
</tr>
<tr>
<td>Seizures</td>
<td>Added at the first review when there were 62 Yellow Card reports of convulsions had been received. Age, onset, and past medical history were all considered. Further spontaneous case reports have been insufficient to determine a causal association. Ongoing studies are further evaluating this issue.</td>
<td>A qualifying statement regarding seizures was added to Product Information: “There have been very rare reports of seizures following vaccination; individuals have usually rapidly recovered. Some of the reported seizures may have been fakts. The reporting rate of seizures was below the background rate of epilepsy in children. In infants seizures were usually associated with fever and were likely to be febrile convulsions.”</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>39 Yellow Card reports of hypotonia, 26 were in infants under 2 years.</td>
<td>Added to Product Information following the Nov 2000 review. No age limit included.</td>
</tr>
<tr>
<td>Hypoaesthesia</td>
<td>Hypoaesthesia (121 Yellow Card reports). Onset varied from 5 minutes to 9 days after vaccination but in most onset was within the first few hours.</td>
<td></td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>Paraesthesia (122 Yellow Card reports). Onset varied from 5 minutes to 9 days after vaccination but in most onset was within the first few hours.</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>71 Yellow Card reports. Onset ranged from 10 minutes to 9 days after vaccination. Most of the children affected were teenagers but arthralgia was reported in 9 children under 5 years.</td>
<td></td>
</tr>
<tr>
<td>Serious skin reactions</td>
<td>Yellow Card reports: erythema multiforme (19) and Stevens Johnson syndrome (2).</td>
<td></td>
</tr>
<tr>
<td>including Steven’s Johnson Syndrome and Erythema</td>
<td></td>
<td></td>
</tr>
<tr>
<td>multiforme</td>
<td>Symptoms of meningism</td>
<td>The following warning was added to Product Information. &quot;Although symptoms of meningism such as neck pain/stiffness or photophobia have been reported there is no evidence that the vaccine causes meningococcal C meningitis. Clinical alertness to the possibility of co-incidental meningitis should therefore be maintained.&quot;</td>
</tr>
<tr>
<td>---</td>
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<td>---</td>
</tr>
<tr>
<td></td>
<td>Photophobia (Yellow Card reports = 37), neck stiffness (n=85). 10 cases of both. 3 reports of meningism.</td>
<td></td>
</tr>
</tbody>
</table>

The numbers of cases quoted in this table are those which had been reported at the time the ADR was added to product information.
ANNEX 4 – DATA FROM PHLS ON VACCINE FAILURES

- Six scheduled for routine vaccination
  - one had late single dose, five three doses
- Four scheduled for infant catch-up
  - Two had single dose beyond 12 months of age
  - Two had two doses between 9-11 months of age
- Seven toddlers (55, 167, 246, 342, 413, 420, 736 days)
- One pre-school (91 days)
- Three in primary school (58, 301 days)
- Five in secondary school (280, 289, 304, 320, 572 days)
- Five adolescents (83, 512, 521, 535, 791 days)