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Surveillance and monitoring for vaccine safety

This chapter describes the process of vaccine safety monitoring in the UK and the reporting of adverse events following immunisation (AEFIs) (see Chapter 8). It also describes the mechanism for the reporting of suspected defects in vaccines or in the devices used for the administration of vaccines.

All vaccines are extensively tested for quality, safety and immunogenicity and/or efficacy before being licensed and used routinely. As not all side effects may have been identified prior to licensing, particularly if they occur very rarely, careful surveillance is required throughout their use. Important information on vaccine safety is routinely collected through the Yellow Card scheme and from other sources, including medical literature, post-marketing safety studies, epidemiological databases and other worldwide organisations.

The Medicines and Healthcare products Regulatory Agency (MHRA) has responsibility for monitoring the safety of all marketed medicines (including vaccines) and medical devices. Suspected adverse events following the use of vaccines, medicines and medical devices should be reported to the MHRA.

The Yellow Card scheme

The Yellow Card scheme is a voluntary reporting system for suspected adverse reactions (ADRs) to medicines, which includes vaccines. AEFIs that are suspected to be vaccine-induced should be reported as ADRs via the Yellow Card scheme. An ADR is an unwanted or harmful reaction following the administration of a medicine, vaccine or combination of vaccines. The ADR may be a known AEFI (see Chapter 8), or it may be previously unrecognised. Spontaneous reports of suspected ADRs are received from UK doctors, pharmacists, dentists, coroners, nurses, midwives, health visitors and patients. There is also a statutory requirement for pharmaceutical companies to report to the MHRA serious suspected ADRs associated with their products.

Reports of suspected ADRs submitted through the Yellow Card scheme are entered onto a computer database operated by the MHRA. The reporter receives an acknowledgement and is supplied with a unique registration number. Reports of suspected ADRs are regularly reviewed, and appropriate investigation and action is initiated if a possible problem is identified. Information relating to the MHRA and the Yellow Card scheme can be found on the MHRA website (www.mhra.gov.uk) and at www.yellowcard.gov.uk. Information on individual patients and reporters submitted to the MHRA is confidential.

The five regional monitoring centres of the Commission on Human Medicines (CHM) work in conjunction with the MHRA in collecting data on ADRs and facilitating local ADR reporting (see end of chapter).

Which ADRs to report

The success of the Yellow Card scheme depends on early, complete and accurate reporting of suspected ADRs. A Yellow Card should be submitted when a causal association is suspected between the product administered and the condition experienced by the patient. The MHRA encourages reporting of suspected ADRs even if there is uncertainty as to whether the vaccine played a causal role.

All suspected ADRs occurring in children should be reported.

Newly licensed vaccine products are subject to enhanced surveillance and are given 'black triangle' status (indicated by an inverted triangle ▼ on the product information). For such products, all serious and non-serious suspected ADRs should be reported, for both adults and children.

For vaccines that have been marketed for two years or more, only serious suspected ADRs should be reported. This applies to all serious reactions, whether or not such reactions have previously been recognised with the suspected vaccine. Serious reactions that should be reported include those that:

- are fatal
- are life-threatening
- are disabling or incapacitating
- result in or prolong hospitalisation
- are medically significant
- lead to congenital abnormalities.

However, a reporter can also state that a case is serious for any reason other than those outlined here.

When submitting a Yellow Card, the vaccine brand name and batch number should be provided. If the brand name is unavailable, the active ingredient or antigen type should be clearly identified, e.g. pneumococcal conjugate vaccine should be clearly distinguished from plain pneumococcal polysaccharide vaccine.

It is important to give as much information as possible about the nature, timing and severity of the suspected ADR, if the patient was hospitalised, what treatment was given and the outcome. Information about other factors, such as immunisation history, concomitant vaccines, underlying disease, allergies or family history, should be provided whenever possible. The provision of additional information, such as test results or relevant hospital correspondence, is always helpful.

Any further information, including where subsequent investigations implicate another possible cause for the condition, should be sent to the MHRA to help in the assessment of the suspected ADR. The Yellow Card registration number, provided to reporters on acknowledgement of receipt of the Yellow Card, should be quoted. The MHRA may also contact the reporter directly if specific information on a suspected ADR is required.

Deciding whether to report a suspected ADR

It is a matter of clinical judgement whether a suspected ADR should be reported or not. Although a reaction might occur in close temporal association with an immunisation, often it can be very difficult to assess whether there is a causal link. If there is any suspicion that the reaction is vaccine-induced, an ADR should be reported. Many suspected ADRs are actually medical conditions that have occurred spontaneously and coincidentally.

The probability that a vaccine has caused an ADR may be increased if there is biological plausibility for the event. For instance, pyrexial illness occurring five to ten days or parotid swelling occurring three weeks after measles, mumps and rubella (MMR) immunisation would be consistent with the incubation periods for measles or mumps viruses. On the other hand, pyrexia occurring less than three days after MMR vaccination is unlikely to be caused by the immunisation, and an underlying infection is a more likely explanation.

Where to get Yellow Cards

Yellow Cards can be downloaded from the MHRA website (www.mhra.gov.uk) and reports can be submitted electronically (www.yellowcard.gov.uk). Yellow Cards are also available in the back of the *British National Formulary* (BNF), the *BNF for Children*, the *Nurse Prescribers' Formulary*, the Association of the British Pharmaceutical Industry *Compendium of Data Sheets and Summaries of Product Characteristics* and *MIMS for Nurses.*

Yellow Cards can also be obtained by calling the national Yellow Card information service (0800 731 6789) or by writing to the MHRA or one of the five regional centres (see contact details at the end of the chapter).

Causality assessment of potential new vaccine safety signals

Yellow Cards are important in generating possible new signals of safety concerns. When assessing whether a signal generated by Yellow Cards or from other sources is vaccine-induced, all of the available evidence is considered.

Causality assessment often depends on factors that include biological plausibility – an excess of events in a specified post-immunisation period compared with background rates and laboratory evidence.

Formal epidemiological studies are required to strengthen or refute an assessment of causality. Where a causal association is demonstrated, the level of risk should be quantified and the risk factors established. For example, by linking computer records of hospital admissions and MMR immunisation, a positive association was found between MMR and idiopathic thrombocytopenic purpura (ITP). One case of ITP, attributable to vaccine, occurs for every 32,000 doses administered (Miller *et al*., 2001). Using a similar method, the hypothesis that oral live polio vaccine was associated with intussusception was rejected (Andrews *et al*., 2001).

Matters relating to vaccine safety are kept under constant review. The CHM and the Joint Committee on Vaccination and Immunisation (JCVI) are independent, expert scientific committees that advise the Government. The CHM advises on the safety, quality and efficacy of medicines and vaccines,

and the JCVI provides expert advice on immunisation policy. These committees examine carefully any new evidence that relates to vaccine safety, and make recommendations on the subsequent use of a vaccine or the implementation of the immunisation programme.

Action following evidence about vaccine safety

If the available evidence supports a causal association between a vaccine and a reported ADR, the CHM or JCVI may give recommendations for action. These will take into account an assessment of the balance of benefits of vaccination versus the risks.

Regulatory action may be taken by the MHRA on the recommendation of the CHM. This could involve withdrawal of a vaccine but would more often involve an amendment to a vaccine licence (marketing authorisation) in order to ensure that it is used more safely and effectively. Such amendments may include restrictions on usage, refinement of dosage instructions or the introduction of specific recommendations or warnings in the Summary of Product Characteristics (SPC).

Where further evidence to reject a causal association between a vaccine and a condition becomes available, action may include the removal of previous restrictions or a change to the SPC.

Defective vaccines and batch problems

Defects in medicinal products may include errors in the packaging, labels or leaflets, or other product faults, such as particulate contamination of a vaccine. If healthcare professionals suspect that a vaccine is defective, they should not use the product but contact the Defective Medicines Report Centre (DMRC) of the MHRA (see contact details at the end of the chapter). The DMRC assists in the investigation of defective medicines and co-ordinates any action that may need to be taken.

When submitting reports on suspected defective medicinal products to the DMRC, the following information should be provided:

- brand/non-proprietary name
- name of the manufacturer/supplier
- strength and dosage form
- product licence number
- batch number(s)
- expiry date(s)

- nature of the defect
- an account of any action already taken.

Where the defect is noticed after the vaccine has been administered, advice on the management of that patient should be sought from a local immunisation lead or health protection unit.

Adverse reactions to a vaccine may also result from a defective batch of vaccine (programme-related AEFI) and should be reported to the MHRA.

Defective medical devices

Medical devices and equipment are items used for the diagnosis and/or treatment of disease, or for monitoring patients, as well as aids for daily living. This covers a wide range of products used every day in primary and acute care settings, in residential or nursing settings or in the patient's own home, and by school nurses. Examples of devices relevant to the immunisation programme include needles and syringes, vials or ampoules.

Additional information and examples of categories of medical devices can be found on the 'Devices information' part of the MHRA website (www.mhra.gov.uk). The MHRA assesses all reports of adverse incidents involving medical devices and, where appropriate, instigates an investigation, corrective actions and design changes to reduce the risk of recurrence.

Defects in medical devices may occur because of:

- design or manufacture problems
- poor user instructions and training
- inappropriate local modifications
- inadequate maintenance
- unsuitable storage and use conditions.

A defective medical device may cause unexpected or unwanted effects involving the safety of patients, device users or other persons. Any adverse incident involving a medical device should be reported, especially if the incident has led to or could lead to:

- death or serious injury
- medical or surgical intervention or hospitalisation
- unreliable test results (and risk of misdiagnosis).

Minor faults and discrepancies should also be reported, as these can help to demonstrate trends or highlight inadequate manufacturing or supply systems.

Examples of incidents involving immunisation equipment which should be reported include:

- needles that break in use
- needles that leak or disconnect at the hub
- blocked needles
- barbed or blunt needles
- syringe tips, flanges or plungers that break in use
- contaminated products
- missing components
- visible damage (cracked syringe barrels, etc.).

How to report an incident

Defective devices and adverse incidents should be reported at the earliest opportunity, following any local incident-reporting policies. Adverse events involving immunisation equipment (rather than the vaccine itself) should be reported to the medical devices Adverse Incident Centre (AIC) at the MHRA. If in doubt, contact the MHRA about the most appropriate reporting route.

Where possible, reports should be submitted electronically using the medical device online reporting system on the MHRA's website (www.mhra.gov.uk). This provides an immediate acknowledgement and MHRA reference number for each report, and also allows you to e-mail a copy to others within your organisation. However, if necessary, forms may be downloaded from the website or obtained from the AIC and can be e-mailed or faxed to AIC (see contact details at the end of the chapter). Detailed information on reporting adverse incidents with medical devices can be found on the MHRA website, from the AIC or from your local Medical Device Liaison Officer.

Contact details

Yellow Card reports:

Pharmacovigilance Group
Medicines and Healthcare products Regulatory Agency
Market Towers
1 Nine Elms Lane
London SW8 5NQ

Defective medicines:

The Defective Medicines Report Centre
Medicines and Healthcare products Regulatory Agency
Room 1801, Market Towers
1 Nine Elms Lane
London SW8 5NQ
www.mhra.gov.uk

Tel: 020 7084 2574 (weekdays 9am to 5pm)
or 020 7210 3000 (outside normal working hours)

Defective Devices/Adverse Incident Centre:

Adverse Incident Centre
Medicines and Healthcare products Regulatory Agency
2/2G Market Towers
1 Nine Elms Lane
London SW8 5NQ

E-mail: aic@mhra.gsi.gov.uk
Fax: 020 7084 3109
Incident hotline: 020 7084 3080
Text phone: 020 7084 3356

References

Andrews N, Miller E, Waight P *et al*. (2001) Does oral polio vaccine cause intussusception in infants? Evidence from a sequence of three self-controlled cases series studies in the United Kingdom. *Eur J Epidemiol*. **17**(8): 701–6.

BNF for Children www.bnfc.org.

Miller E, Waight P, Farrington CP *et al*. (2001) Idiopathic thrombocytopenic purpura and MMR vaccine. *Arch Dis Child*. **84**(3): 227–9.