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# Anaphylaxis following single component measles and rubella immunisation

M Erlewyn-Lajeunesse,<sup>1</sup> R Manek,<sup>2</sup> R Lingam,<sup>3</sup> A Finn,<sup>3</sup> A Emond<sup>3</sup>

<sup>1</sup> Southampton University Hospital, Southampton, UK;

<sup>2</sup> Freeman Hospital, Newcastle-upon-Tyne, UK; <sup>3</sup> University of Bristol, Bristol, UK

Correspondence to:

Michel Erlewyn-Lajeunesse, Paediatric Allergy, Immunology and Infectious Diseases, Southampton University Hospital, Tremona Road, Southampton SO16 6YD, UK; [Mich.Lajeunesse@soton.ac.uk](mailto:Mich.Lajeunesse@soton.ac.uk)

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## ABSTRACT

Anaphylaxis as an adverse event following immunisation (AEFI) is a rare occurrence. We report four cases of anaphylaxis following administration of single component measles or rubella vaccine between January 2003 and June 2007. We estimate that the incidence of anaphylaxis to measles and rubella single component vaccines is 18.9 and 22.4 cases/100 000 doses, respectively. These figures are likely to be an underestimate but are higher than expected. Our calculations were hampered by lack of immunisation reporting data from the private sector. We recommend that NHS standards of vaccine data reporting are also applied to private clinics.

Anaphylaxis is a rare adverse event following immunisation (AEFI). The incidence for all vaccines has been estimated at 0.65/million doses based upon five individual cases in over 7 million doses of vaccine.<sup>1</sup> The combined measles, mumps and rubella vaccine (MMR) has been used in the UK since 1988. The best national estimate of the incidence of anaphylaxis for the MMR was 1.4 cases/100 000 doses (two cases of anaphylaxis in 143 000 doses).<sup>2</sup>

In 1998 public confidence in the MMR waned following media speculation about its safety ([www.mmrthefacts.nhs.uk](http://www.mmrthefacts.nhs.uk)), and some parents opted for single component vaccines from private healthcare providers in the belief that this might be safer. Between 2000 and 2002 an estimated 5.2% of

UK children were immunised using single antigen vaccines.<sup>3</sup> These vaccines are not licensed for use in the UK and require an import licence from the Medicines and Healthcare products Regulatory Agency (MHRA). Four cases of anaphylaxis were referred to us following administration of single component measles and rubella vaccines between January 2003 and June 2007, and we estimate the incidence of anaphylaxis to these vaccines. These were the only cases of anaphylaxis following immunisation referred during this period. All met the Brighton Collaboration case definition for anaphylaxis AEFI.<sup>4</sup> Clinical details are given in table 1. We have parental permission to report three cases in detail.

We were unable to establish the actual number of doses of single component vaccines administered in the UK as there is no central reporting. Unlike standard schedule vaccines in NHS primary care, private clinics are under no obligation to report the number of unlicensed vaccines administered. However, information on the number of requests for import was available from the MHRA. Based on the assumption that all imported vaccine was administered, we calculated an incidence of anaphylaxis for measles vaccine of 18.9 cases/100 000 doses (95% CI 5.2 to 68.9) and 22.4 (6.1 to 81.6) for rubella.

These rates appear to be well above those expected for the MMR but are still likely to be an underestimate. We have assumed that these four children were the only cases of anaphylaxis nationally, and that all MHRA requested vaccine was used, when in reality there may have been other cases around the country and only 20–30% of imported vaccine may actually be administered.<sup>5</sup>

Post licensure surveillance requires both active reporting of AEFI by healthcare professionals and comprehensive recording of the number of vaccine doses administered. We add our voices to the recommendation that the Healthcare Commission insists that private clinics are subject to the same standards of vaccine data reporting as are expected of the NHS.<sup>5</sup>

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**Competing interests:** MEL has accepted support to attend and present data at scientific meetings from Wyeth and GlaxoSmithKline, and has received research funding from Sanofi Pasteur MSD, the makers of Rubivax and Priorix MMR. AF has undertaken advisory work for, chaired and spoken at symposia organised by and accepted support to attend scientific meetings from all the major vaccine manufacturers. Payments for these activities have been made to his employer, the University of Bristol and used to pay for research and training materials and activities. RM, RL and AE have no conflict of interest to declare.

**Table 1** Case summaries

| Case                           | 1                                  | 2                                      | 3                                                                               |
|--------------------------------|------------------------------------|----------------------------------------|---------------------------------------------------------------------------------|
| Age                            | 15 months                          | 18 months                              | 20 months                                                                       |
| Vaccine                        | Measles (Rouvax, Merck)            | Rubella (Rudivax, Aventis Pasteur MSD) | Rubella (Rudivax, Aventis Pasteur MSD)                                          |
| Time to onset of symptoms      | <15 min                            | <5 min                                 | <5 min                                                                          |
| Diagnostic likelihood*         | Level 1                            | Level 1                                | Level 1                                                                         |
| Severity grade†                | III                                | III                                    | II or IV‡                                                                       |
| Cardiovascular                 | —                                  | —                                      | (Shocked)‡                                                                      |
| Respiratory                    | CYANOSIS                           | STRIDOR                                | WHEEZE                                                                          |
|                                | TACHYPNEOA                         |                                        | Cough                                                                           |
| Dermatological                 | ANGIOEDEMA                         | ERYTHEMA                               | (Flushed)                                                                       |
| Gastrointestinal               | —                                  | Vomiting                               | Vomiting                                                                        |
| Treatment                      | IM adrenaline<br>PO chlorphenamine | IM adrenaline<br>IM chlorphenamine     | Nebulised salbutamol<br>IM adrenaline<br>PO chlorphenamine<br>IV hydrocortisone |
| Previous non-schedule vaccines | Rubella                            | Typhoid/hepatitis A                    | Measles                                                                         |

\*Diagnostic likelihood was confirmed using the Brighton Collaboration case definition for anaphylaxis AEFI.<sup>4</sup> Level 1 is the most specific case, while level 3 is most sensitive. CAPITALS indicate a MAJOR Brighton diagnostic criterion, while lowercase letters are for minor criteria. Symptoms in brackets are non-contributory. †Mueller's standard grading system is used for reaction severity but is not in itself diagnostic.<sup>6</sup> Grade I is mild and IV severe. ‡Case 3 would be regarded having grade IV severity if shock had been described in greater clinical detail and was in keeping with circulatory failure.

**Patient consent:** Obtained.

**Contributors:** MEL is the guarantor for this paper. MEL and RM wrote the paper. RL provided background research for the paper. All authors were involved in developing and editing the manuscript.

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## Calling European Paediatric Research Networks

The European Medicines Agency (EMA) is fully committed to facilitating a “virtual” European Network through linking all existing national and European networks, investigators and centres with specific expertise in the performance of paediatric studies. This commitment is grounded in the Paediatric Regulation EC No 1901/2006, as amended (Article 44), which has the objectives:

- ▶ to ensure that medicinal products used to treat children are subject to ethical research of high quality and are appropriately authorised for use in the paediatric population
- ▶ to improve the information available on the use of medicinal products in the various paediatric populations
- ▶ to achieve the above without subjecting the paediatric population to unnecessary clinical trials

Clinical trials in the paediatric population require specific expertise, specific methodology and, in some cases, specific facilities. They should be performed by appropriately trained investigators.

The EMA European Network aims are:

- ▶ to identify, coordinate and link together existing networks, existing national and community initiatives and study centres in order to build the necessary competences at community level
- ▶ to ensure efficient, timely communication and exchange of information between networks
- ▶ to be a source of information and expertise for health professionals
- ▶ to provide a forum for scientific discussion related to paediatric clinical trials with all stakeholders, where necessary
- ▶ to take account of community and third country data
- ▶ to help facilitate cooperation
- ▶ to avoid unnecessary duplication of studies

This network will:

- ▶ provide a central source of information and expertise for industry
- ▶ contribute to strengthening the foundations of the European research area in the context of community framework programmes for research, technological development and demonstration activities
- ▶ benefit the paediatric population

An implementing strategy was adopted 26 January 2008 by the EMA management board.

<http://www.emea.europa.eu/pdfs/human/paediatrics/54352307en.pdf>

There are many advantages to joining the network:

- ▶ be visible as a potential site for externally sponsored clinical trials
- ▶ be at the forefront of medicinal development
- ▶ be consulted for your expert opinion when paediatric investigation plans in your field of expertise are discussed and developed
- ▶ share the skills and expertise of other national and European networks
- ▶ shape and influence future development in paediatric research

Joining the network is easy; contact us with your details via [enpremea@emea.europa.eu](mailto:enpremea@emea.europa.eu).

Contact details will allow the EMA to set up an initial mailing list of networks, who will be invited for an implementation meeting to be held at the EMA in London, planned for February 2009.

The meeting will:

- ▶ discuss and agree mandate and objectives
- ▶ define scientific and operational quality standards and recognition criteria
- ▶ implement coordinating group