UK PUBLIC ASSESSMENT REPORT

Seasonal flu vaccines: no evidence of an increased risk of febrile convulsions in children

December 2010

PLAIN-LANGUAGE SUMMARY

Background

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating medicines and medical devices in the UK. We continually review the safety of medicines and vaccines in the UK, and inform healthcare professionals and the public of the latest updates through several means, including public assessment reports. The following public assessment report discusses the risk of febrile convulsions[a] occurring in children after receiving the seasonal influenza (flu) vaccine.

Flu is a highly infectious disease, characterised by symptoms such as high fever, headache, muscle aches, nausea, sneezing, and dry cough. Most healthy people recover from flu within a few days; however elderly people age over 65 years, and people who have certain underlying medical conditions, may have very severe symptoms or develop complications after flu. Therefore, in the UK, a yearly seasonal flu vaccination is recommended for people in certain 'at-risk' groups. These groups include adults age 65 years and older, and any individuals with serious underlying medical conditions such as asthma or heart disease, including children age 6 months and older with these conditions. Pregnant women are also included in this year's seasonal flu vaccination campaign.

The safety of influenza vaccines is well-established. However, as the use of any medicine or vaccine may cause adverse drug reactions (ADRs; side effects) in some individuals, the MHRA continually monitors safety, and collects information on suspected side effects with all medicines and vaccines (a process known as pharmacovigilance), through an ADR reporting scheme (the Yellow Card Scheme[b]). Recognised adverse reactions are listed in the product information that accompanies medicines and vaccines[c].

Febrile convulsion is listed as a possible side effect in the product information for different brands of influenza vaccines in the UK; however the size or likelihood of this risk is not stated. In Australia, the seasonal influenza immunisation programme for healthy children age less than 5 years was suspended in April 2010 because of an increased risk of febrile convulsions associated with the Fluvax brand of influenza vaccine, manufactured by CSL, in this age group. The risk was estimated to be as high as 1 case per 100 doses. Because of this increased risk, doctors in the UK were advised by the Department of Health not to use CSL's Enzira and CSL Biotherapies brand of influenza vaccine in children age 6 months to less than 5 years (see letter sent to health professionals in July 2010), and were advised to use alternative vaccine brands in this age group.

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[a] A seizure or fit associated with fever that occurs mainly in children age 6 months to 5 years

[b] Suspected adverse drug reactions to any medicine or vaccine in the UK can be reported to the MHRA through our Yellow Card Scheme (www.yellowcard.gov.uk)

[c] See the Electronic Medicines Compendium (product information) website

Although there was no reason to suspect that other influenza vaccines may be associated with an increased risk of febrile convulsions, the MHRA implemented enhanced surveillance, based around the Yellow Card Scheme. The MHRA's strategy for monitoring febrile convulsions with this year's influenza vaccines included the following key aspects:

- Encouraging health professionals to report all cases of febrile convulsion occurring within 72 hours of receiving any influenza vaccine (see article in *Drug Safety Update*[a], *Oct 2010*). On the 13th September 2010, the MHRA issued a letter to healthcare professionals to remind them of this issue, and highlighted that reports could be made either through the Yellow Card Scheme web portal (www.yellowcard.gov.uk) on the MHRA website, or using postal Yellow Card forms.

- Gathering as much data as possible on age-specific vaccine exposure

- Analysing the reported data and historical data to establish if febrile convulsions were reported more frequently after vaccination than might be expected to occur without vaccination.

This report summarises the data obtained on this issue and conclusions drawn from the analysis.

Results

From September 2010 to 17th December 2010, at least 46 000 children age 6 months to 5 years had received a seasonal influenza vaccine in the UK. Up to 17th December 2010, there were two reports of suspected febrile convulsion following seasonal influenza vaccination in children age less than 5 years. The reports were in two different children, both of whom recovered from the convulsion. Analysis of historical data from 2000–2010 shows that seven cases of febrile convulsion would naturally be expected amongst those immunised in this age group; therefore the two suspected reports received are within the expected range.

Conclusions

To date, thousands of young children have received one of the recommended seasonal influenza vaccines and there is no indication of an excess risk of febrile convulsions in children as seen in Australia. It is important to remember that influenza may lead to life-threatening complications in at-risk individuals, which is why they are offered a vaccine against this disease. Influenza vaccines should continue to be given as recommended, since the balance of benefits and risks is clearly favourable.

[a] A monthly bulletin produced by MHRA for healthcare professionals, that provides the latest information and clinical advice on the safety of medicines and vaccines

As with all medicines and vaccines, the MHRA will continue to monitor the safety of influenza vaccines in the UK.

1. INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) is the government agency responsible for regulating medicines and medical devices in the UK. We continually review the safety of medicines and vaccines in the UK, and inform healthcare professionals and the public of the latest updates through several means, including public assessment reports. The following public assessment report discusses the risk of febrile convulsions occurring in children age 6 months to 5 years after receiving the seasonal influenza vaccine.

2. BACKGROUND

In April 2010, the seasonal influenza immunisation programme for healthy children age less than 5 years in Australia was suspended, because of an increased risk of febrile convulsion associated with a particular seasonal influenza vaccine - Fluvax, manufactured by CSL. The available data suggest that CSL's Fluvax vaccine may carry a risk of febrile convulsions of up to 1 case per 100 doses in children age less than 5 years. It is apparent that this adverse reaction (ADR) is a product/brand-specific risk, and there is no indication that other brands of influenza vaccine are associated with this risk.

Two similar vaccines manufactured by CSL and marketed by Pfizer, Enzira and CSL Biotherapies generic influenza vaccine, have been supplied to the UK for use in the current seasonal influenza immunisation programme. Because of the febrile convulsion issue in Australia with vaccines from CSL, Enzira and CSL Biotherapies generic influenza vaccine are not licensed for use in children age less than 5 years in the UK this year. A letter was sent by the Department of Health to UK health professionals in July 2010 advising them not to use Enzira/CSL vaccines in children age less than 5 years because of the increased risk of febrile convulsion. Children age 6 months to less than 5 years in clinical risk-groups should still receive seasonal influenza vaccination, but health professionals are advised to use the alternative vaccines recommended by the Department of Health.

The MHRA is closely monitoring the safety of all influenza vaccines used in the UK during the current vaccination campaign and requested health professionals in the UK to promptly report any occurrence of febrile convulsion within 72 hours of receiving an influenza vaccine (see article in *Drug Safety Update, Oct 2010*).

MHRA Pharmacovigilance Strategy

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The MHRA's proactive pharmacovigilance strategy for monitoring febrile convulsions with influenza vaccines this year is based around enhanced, passive surveillance, the key aspects of which are:

- To encourage health professionals to report all cases of febrile convulsion occurring within 72 hours of receiving any influenza vaccine. On the 13th September 2010, the MHRA issued a letter to healthcare professionals to remind them of this issue, and highlighted that reports could be made either through the Yellow Card Scheme web portal (www.yellowcard.gov.uk) on the MHRA website, or using postal Yellow Card forms.

- To gather as much data as possible on age-specific vaccine exposure

- To evaluate historical data from the General Practice Research Database (GPRD; the world's largest computerised database of anonymised patient records) to establish the age-specific 'expected' or background rate of febrile convulsions amongst children immunised with influenza vaccine

- To use 'observed versus expected' analysis to establish if febrile convulsions were reported more frequently after vaccination than might be expected to occur in the population without vaccination.

    - Possible safety signals[a] were identified by comparing the number of reported cases of febrile convulsions against the normal background rate that was expected to occur by chance (calculated from GPRD data), to determine if the vaccines carried any excess risk.

[a] An indicator or reported information suggesting that a drug may be associated with a previously unrecognised ADR, or an existing ADR that is different from current expectations

3. ASSESSMENT OF DATA

From September 2010 to 17th December 2010, at least 46 000 children age 6 months to 5 years had received a seasonal influenza vaccine in the UK. Up to 17th December 2010, there were only two cases of suspected febrile convulsion reported in association with seasonal influenza vaccines, via the Yellow card Scheme, in this age group. The reports were in two different children, both of whom recovered from the convulsion.

Observed versus expected analysis

Background rates of febrile convulsion within 72 hours following vaccination with seasonal influenza vaccine were calculated over a 10 year period from 2000/01 – 2009/10 using GPRD data. Additionally, rates of febrile convulsion following H1N1v (swine flu) vaccination in the 2009/10 season were also calculated using GPRD data.

Background ('expected') rates of febrile convulsions were higher following seasonal influenza vaccine than following H1N1v vaccination: two cases per 10 000 children who received seasonal influenza vaccine versus 1.4 case per10 000 children who received H1N1v vaccine (all children age 1–4 years).

Some previous studies have found no evidence of an increased risk of febrile convulsions following influenza vaccination. Others have found a small excess risk (~ 1 occurrence of febrile convulsion per 10 000–20 000 doses).[1,2,3] It was therefore assumed for the 'expected' calculations that there is no influenza vaccine-attributable risk of febrile convulsions (i.e. the 'expected' rate was based on febrile convulsion due to any cause in this age group).

The rates following H1N1v vaccination were used in the 'observed versus expected' analysis in order to provide a conservative estimate of the expected number of events (ie, using the lower 'expected' rate gives greater sensitivity to detect an increased risk after vaccination).

Based on the vaccine exposure data currently available in the UK, it was estimated that seven cases of febrile convulsion would normally be expected to have occurred within 72 hours of receiving an influenza vaccine among children age up to 5 years.

The observed versus expected ratio for children age less than 5 years (observed number of cases = 2) is **0.30** (95% confidence interval [CI] 0.04–1.07).

Vaccine exposure data were not available for specific brands of influenza vaccine.

4. DISCUSSION

The 'observed versus expected' analysis of suspected febrile convulsions reported in children age less than 5 years after receiving seasonal influenza vaccine does not

indicate an excess number of reports in this age group. Although potential under-reporting of events is a possible limitation of 'observed versus expected' analyses, the expected number has been calculated using conservative background rates and vaccine exposure data.

The large number of children immunised so far in the UK would be sufficient to allow an excess risk of febrile convulsions of a magnitude seen with Fluvax in Australia (up to 1 case per 100 doses) to be identified. Even if a significant level of under-reporting of possible cases via the Yellow Card Scheme is assumed, the observed versus expected analysis gives reasonable confidence that such a large risk is unlikely with the seasonal influenza vaccines currently in use in the UK.

Australian analysis of Fluvax vaccine

The Australian regulatory authority, the Therapeutic Goods Administration (TGA), published a detailed overview of its risk assessment of the Fluvax vaccine and root cause evaluation of the associated febrile convulsion issue, on 8 October 2010. The key points of the overview are:

- The available data suggest that CSL's Fluvax seasonal influenza vaccine may carry a risk of febrile convulsions of up to 1 case per 100 doses in children age less than 5 years
- Analysis of data for two other seasonal influenza vaccines used in children indicate that the risk is specific to Fluvax vaccine
- Detailed laboratory investigations have so far failed to confirm any manufacturing or quality defect which may have contributed to this product-specific issue

5. CONCLUSIONS

To date, thousands of young children have received one of the recommended seasonal influenza vaccines in the UK and there is no indication of an excess risk of febrile convulsions in children as seen in Australia. It is important to remember that influenza may lead to life-threatening complications in at-risk individuals, which is why they are offered a vaccine against this disease. Influenza vaccines should continue to be given as recommended, since the balance of benefits and risks is clearly favourable.

As with all medicines and vaccines, the MHRA will continue to monitor the safety of influenza vaccines in the UK.

6. REFERENCES

1. France EK, Glanz JM, Xu S, et al. Safety of the trivalent inactivated influenza vaccine among children: a population-based study. *Arch Pediatr Adolesc Med* 2004; **158** (11): 1031–1036

2. Hambidge SJ, Glanz JM, France EK et al. Safety of trivalent inactivated influenza vaccine in children 6 to 23 months old. *JAMA* 2006; **296** (16): 1990–1997

3. www.cdc.gov/vaccines/recs/acip/downloads/mtg-slides-jun10/10-8-flu.pdf [Last accessed December 2010]

7. GLOSSARY

Asthma
A condition characterised by narrowed airways, in which patients experience symptoms of cough, wheezing and difficulty breathing

Confidence interval
A statistical method of assessing the true difference in risk between two groups, that usually accompanies ratio values such as odds ratios, hazard ratios and 'observed versus expected' ratios. A 95% CI suggests that there is a 95% chance that the real difference between two groups is within this interval. If a 95% CI does not cross 1, the ratio is regarded as statistically significant

Convulsion
Intense, involuntary muscular contractions

Drug Safety Update
A monthly bulletin produced by MHRA for healthcare professionals that provides the latest information and clinical advice on the safety of medicines and vaccines

Febrile convulsion or seizure
A **convulsion** or **seizure** accompanying a fever

H1N1v
A type of **influenza virus** that caused the **swine flu** global **pandemic** in 2009

Heart disease
A condition where the normal functioning of the heart is impaired

Influenza
An infectious disease caused by a virus, characterised by fever, sore throat, muscle pains, headache and cough. It can lead to serious complications in at-risk patients, such as those age over 65 years, and adults and children with serious underlying medical conditions such as chronic asthma or heart disease

Pandemic
An outbreak of an infectious disease over a wide geographical area that affects a large proportion of the population

Psychogenic
A disorder which has a psychological, rather than a physical, origin

Seasonal influenza
A type of **influenza** that comes to an area every year during a particular range of months (the flu season). In the UK, the most common occurrence is during the winter months (October – April)

Seizure
Uncontrolled electrical activity in the brain which may produce a physical **convulsion**

Swine influenza/swine flu
A highly contagious form of human influenza caused by a virus that is similar or related to a virus that causes a form of influenza in pigs (swine)

Vaccine
A weakened form of a virus that causes a particular disease. It is introduced to the body to stimulate the body's defensive immune response, which provides protection against the disease

Vaccination
The injection of a **vaccine** into the body in order to stimulate the immune system, thereby preventing the disease

Virus
A sub-microscopic infectious agent that is passed from living host to living host and causes disease

Yellow Card Scheme
Suspected adverse drug reactions to any medicine in the UK can be reported to the MHRA through our Yellow Card scheme (www.yellowcard.gov.uk)