MHRA PUBLIC ASSESSMENT REPORT

Swine flu vaccines and antiviral medicines: UK post-pandemic safety review

February 2011

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 all medicines and vaccines in the UK, and inform healthcare professionals and the public of the latest updates through several means, including public assessment reports. This report summarises a review of the safety data on the H1N1v (swine flu) antiviral[a] medicines and vaccines used in the UK during the 2009–2010 swine flu pandemic[b].

In April 2009, a new type of human influenza (flu) virus[c] appeared, known as the H1N1v or 'swine flu' virus, and quickly spread globally. On 11 June 2009, the World Health Organization (WHO) declared an official H1N1v influenza pandemic.

In the UK, from July 2009, anyone with a flu-like illness was offered an influenza antiviral medicine. The antivirals offered were oseltamivir (brand name Tamiflu) which was given as a capsule or liquid to be swallowed, or zanamivir (brand name Relenza), which was inhaled. Then, in October 2009, a mass immunisation campaign with the pandemic H1N1v influenza vaccines, Pandemrix and Celvapan, started across the UK to help prevent future cases of swine flu. The injected vaccines were offered to all frontline health[d] and social care workers, people at increased risk of influenza complications[e], and healthy children.

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 through an ADR reporting scheme (the Yellow Card Scheme[f]). In order to meet the challenges of the pandemic, the MHRA developed an additional strategy to specifically monitor the safety of the H1N1v antivirals and vaccines. This involved development of:

- an on-line 'portal' on the Yellow Card webpage specifically for reporting suspected ADRs to oseltamivir, zanamivir, Pandemrix and Celvapan
- real-time, statistical analysis of the 'observed versus expected' adverse events with the vaccines to detect new safety issues
- weekly publication of the emerging safety profiles (see our swine flu webpage for more information).

On August 10 2010, WHO declared that the swine flu pandemic was over and that worldwide influenza activity had returned to typical seasonal patterns. The MHRA performed a comprehensive post-pandemic review of all suspected ADRs reported with oseltamivir, zanamivir, Pandemrix or Celvapan during the pandemic period, up to

[a] Medicines which kill or suppress the activity of a virus
[b] Outbreak of a disease that spreads over a very wide geographical area and affects a large proportion of the population
[c] A microorganism that invades living cells and causes infections and diseases
[d] Examples of frontline health workers are doctors and nurses
[e] People at high risk of developing flu-related complications include: adults age 65 years and older; pregnant women; those with medical conditions such as asthma or heart disease
[f] 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)

18 June 2010, to outline the UK safety profile of these products. This report summarises the data considered and conclusions of this review.

It is essential to remember that Yellow Card reports to the MHRA relate only to **suspected** ADRs. Therefore, reports may either be true side effects or coincidental events due to underlying or undiagnosed illness that would have occurred anyway in the absence of treatment or vaccination. **The information in this report therefore cannot be considered to represent a list of known side effects of oseltamivir, zanamivir, Pandemrix or Celvapan, or be used to determine the frequency of their occurrence**. The known side effects and their known frequencies are listed in the information accompanying the product[a].

Results

Vaccines

Up to 18 June 2010, more than 6 million doses of Pandemrix, and more than 36 000 doses of Celvapan, were given across the UK. Out of these, there were 3400 reports of suspected ADRs with Pandemrix, and 43 reports of suspected ADRs with Celvapan.

As with many vaccines, the vast majority of the reported reactions related to injection-site reactions and the signs and symptoms of a mild 'flu-like' illness. Despite substantial usage over a very short period, no significant safety issues were identified for either vaccine. Data on reports of Guillain Barre Syndrome[b] (GBS) in particular were examined, as this condition has been reported in the past as a suspected rare side effect of earlier influenza vaccines. However, GBS can also occur following infections, and can develop spontaneously without any obvious cause. There is currently no confirmed evidence to indicate that either the Pandemrix or Celvapan vaccine is associated with an increased risk of GBS. The safety profiles of both vaccines have been very much as expected, and broadly similar to the established profiles for seasonal influenza vaccines.

The UK safety profile of the vaccines is supported by the international experience. It is estimated that at least 30 million and 566,000 people have been vaccinated with Pandemrix and Celvapan, respectively, across Europe during the pandemic and the safety profile mirrors that in the UK.

Antivirals

Up to 18 June 2010, more than 1 million courses of oseltamivir, and more than 14 000 courses of zanamivir, were supplied to patients in the UK. During this time, there were 1100 reports of suspected ADRs with oseltamivir, and 38 reports of suspected ADRs with zanamivir.

The most commonly reported ADRs with both antivirals were consistent with the recognised side effects such as nausea, diarrhoea and headache. The safety profiles of oseltamivir and zanamivir in the UK were broadly in line with the expected profiles, and no new safety issues were confirmed for either antiviral during the pandemic.

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[a] The Summary of Product Characteristics (SPC) and the Patient Information Leaflet (PIL), which can both be viewed on the Electronic Medicines Compendium website: http://emc.medicines.org.uk/

[b] A disorder affecting the nervous system, characterised by a sensation of numbness in the limbs and face, which can lead to loss of feeling and paralysis in affected areas

Conclusions

In July 2010, the Commission on Human Medicines[a] (CHM) considered the MHRA's safety review of the swine flu antiviral medicines oseltamivir and zanamivir, and the swine flu vaccines Pandemrix and Celvapan. The CHM concluded that no new risks have been identified with the extensive use of these products in the UK during the swine flu pandemic, and that the balance of their benefits and risks remains positive. As with all medicines and vaccines, the MHRA will continue to monitor the safety of swine flu antivirals and vaccines in the UK.

[a] An independent body of experts who give advice to UK government Ministers on the safety, quality and efficacy of medicines

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 all medicines and vaccines in the UK, and inform healthcare professionals and the public of the latest updates through several means, including public assessment reports. This report summarises a review of the safety experience in the UK with the H1N1v influenza (swine flu) antivirals and vaccines during the 2009–2010 swine flu pandemic.

Some of the information contained in this report was published in public ADR summaries each week from October 2009 until March 2010 on the MHRA website (http://www.mhra.gov.uk/swineflu).

2. BACKGROUND

2.1 The H1N1v influenza (swine flu) pandemic

In April 2009, a new strain of human influenza H1N1 virus emerged that was genetically unrelated to the human seasonal influenza H1N1 viruses that had been in community circulation since 1977. Following early outbreaks in Mexico, the new virus spread to North America, quickly followed by local and regional outbreaks in several countries around the world. On 11 June 2009, the World Health Organization (WHO) declared an official influenza pandemic (Phase 6) reflecting the global spread of the virus.

Most reported cases in the UK were mild and most people fully recovered from infection. However, the new virus led to patterns of death and severe illness not normally seen in seasonal influenza infections. Most deaths caused by the virus occurred in younger people (ie, age less than 65 years), including some who were otherwise healthy. Pregnant women and people of any age with certain chronic illnesses were at higher risk of severe illness. In the UK, all patients with flu symptoms were offered treatment with one of the influenza antivirals, oseltamivir (brand name Tamiflu) or zanamivir (Relenza) from July 2009. In addition, a mass immunisation programme was implemented in October 2009 using the novel influenza vaccines Pandemrix and Celvapan, which were offered to all frontline health and social care workers, individuals at increased risk of influenza complications, and healthy children.

2.2 The UK antiviral strategy

Oseltamivir given orally was the antiviral of first choice. Zanamivir was the recommended antiviral for treating pregnant women (with uncomplicated illness), as it is inhaled and reaches only very low concentrations in the blood.

Prior to widespread transmission of the virus in the UK, early intervention focused on local, *ad hoc* containment and prophylaxis using oseltamivir and/or zanamivir. As the virus spread more widely in the UK, the national response switched from containment to antiviral treatment only.

Underpinning the antiviral treatment strategy in England was the National Pandemic Flu Service, through which patients could obtain the antivirals without prescription, either on-line or via telephone.

2.3 The UK immunisation programme

Two pandemic vaccines were supplied in the UK from October 2009: Pandemrix and Celvapan. The Joint Committee for Vaccination and Immunisation[a] (JCVI) recommended the following priority groups, in order, for vaccination against swine flu:

(1) individuals age six months to 65 years in the current seasonal flu vaccine clinical at-risk groups; frontline health and social care workers

(2) all pregnant women

(3) household contacts of immunocompromised individuals

(4) people aged 65 and over in the current seasonal flu vaccine clinical at-risk groups

In December 2009, the immunisation campaign was extended to all healthy children age 6 months to less than 5 years.

Pandemrix was the recommended vaccine for most people, given as a single dose. A full dose was given to adults, and a single half-dose to children. Immunocompromised patients were offered two full doses. Celvapan was recommended mainly for individuals who may be hypersensitive to the ingredients in Pandemrix (such as those with confirmed egg allergy).

2.4 The challenges of safety monitoring

2.4.1 Understanding the information contained in this report and the process of pharmacovigilance

The MHRA continually monitors the safety of all medicines and vaccines throughout their marketed life – this is a process known as pharmacovigilance.

Because clinical trials are relatively limited in size, very rare side effects might not be identified until vaccines and medicines have been used on a wide scale in large numbers of people. The swine flu antivirals and vaccines are not unique in this regard and this principle applies to any new medicine or vaccine. We consider medicine and vaccine safety to be of paramount importance and have robust pharmacovigilance systems in place.

The Yellow Card Scheme (www.yellowcard.gov.uk) underpins the safety monitoring of medicines and vaccines in the UK. Through this Scheme, healthcare professionals and members of the public voluntarily submit reports of ***suspected*** side effects to the MHRA. Drug companies also submit such reports as part of their legal requirements.

[a] Independent expert advisory committee who advise UK government ministers on vaccination and immunisation matters

It is important to note that a report of an adverse reaction via the Yellow Card Scheme does not necessarily mean that it has been caused by the named drug or vaccine. We actively encourage reporters to send ***suspected*** adverse reactions; ie, the reporter does not have to be sure that the vaccine or medicine caused the reaction. A Yellow Card report is therefore not 'proof' of a side effect and reports submitted to MHRA for vaccines or medicines may therefore be true adverse reactions, 'psychogenic' reactions related to the process of vaccination rather than to a specific vaccine itself (eg, nervousness or anxiety about needles or vaccination); or they may be purely coincidental events that would have occurred anyway in the absence of the medicine or vaccine (ie, events due to underlying medical conditions). A team of scientists regularly review these data to identify any possible new adverse reactions.

For this reason, **this report is not a list of known or proven adverse reactions to oseltamivir, zanamivir, Pandemrix or Celvapan, and must not be interpreted and used as such**. A list of the recognised adverse reactions to these drugs is provided in the product information for healthcare professionals (Summary of Product Characteristics) and patients (Patient Information Leaflet).

2.4.2 Expectations of safety

The safety profile of the antivirals was largely established before the pandemic, and was based on their extensive usage in seasonal influenza – more than 9 million courses of Relenza and more than 50 million courses of Tamiflu had been used before the pandemic, mainly in Japan and the US. However, usage of the antivirals in the UK prior to the 2009 pandemic was relatively limited. Furthermore, due to the novel methods of supply of antivirals (ie, without prescription via the National Pandemic Flu Service), it was critical to have a robust strategy in place to monitor their safety in the UK.

Prior to the pandemic, safety experience with the vaccines was limited to clinical trials with several thousand patients which used H5N1 (bird flu) versions of the same vaccines. As the structure and composition of the pandemic vaccines may increase their reactogenicity (ie, the frequency, and possibly severity, of common local and systemic non-serious ADRs observed in clinical trial settings) compared to seasonal flu vaccines, a stringent strategy to monitor the safety of the pandemic vaccines was put into place by the MHRA.

As with any vaccine, the swine flu vaccines were expected to cause side effects in some people. Up to 12 million people in the priority groups were to be offered the swine flu vaccines in the UK during the pandemic. Drawing from recent experience with immunisation campaigns, MHRA expected to receive up to 18,000 suspected ADR reports with this level of possible exposure.

As with most vaccines, we expected to see the following broad categories of suspected side effects reported following vaccination with Pandemrix or Celvapan:

- Most commonly: injection site reactions
- Other common expected side effects: symptoms of a mild flu-like illness (e.g. headaches, dizziness, muscle aches, mild fever and fatigue).
- Less commonly: mild allergic-type reactions (eg mild rashes, localised/generalised itching). Serious allergic reactions (such as anaphylaxis) were expected to be very rare.

- As with any other vaccine, immediate events which are not due to the vaccine itself, but due to fear or anticipation of the needle injection, were expected. We call these ‘psychogenic’ events and they can typically involve fainting and associated symptoms.

A final category of suspected ADRs included either new side effects or coincidental medical conditions which are not due to the vaccine (see below).

Distinguishing potential real side effects from coincidental medical events

Most of the millions of people offered the vaccine had serious and/or chronic underlying medical conditions which put them at greater risk of developing serious flu-related complications or even death. This is why it was so beneficial for these people to be vaccinated as a priority. Over the course of the immunisation campaign, it was expected that many of these patients would naturally experience progression of their existing illness or develop other medical conditions, especially those that can be caused by other circulating pathogens.

Inevitably, as so many people were vaccinated, and at a time when swine flu was also causing illness, some people would develop these medical conditions not long after receiving the vaccine. This temporal association in itself does not mean that the vaccine caused the condition. The key challenge we therefore faced was to distinguish these ‘background’ events from those that may have been caused by the vaccine. The ‘observed versus expected’ analysis described below is one of the tools that helped us to make this distinction.

Example – Guillain Barre Syndrome

Guillain Barre Syndrome (GBS) is a very rare, neurological condition that can cause paralysis. It naturally occurs at a frequency of around 1 case per 100 000 people every year in the UK. It can occur in healthy individuals, either spontaneously or after certain infections. Studies have shown that flu-like illness can also cause up to an 16-fold increase in the risk of developing GBS[1].

GBS was an identified risk with swine flu vaccines used in the United States in 1976 – it is thought that 1 extra case of GBS occurred with every 100,000 doses of vaccine. The exact reason why the 1976 vaccines caused GBS remains unknown and modern flu vaccines have not been found to cause GBS. There was no reason to suspect that the current swine flu vaccines would cause GBS but, obviously, we closely monitored this.

With the normal background frequency of GBS outlined above, for every 6 million people vaccinated over the immunisation campaign we would expect around 10 cases of GBS to occur naturally within one month of vaccination. A proportion of these cases were likely to be reported to the MHRA as suspected side effects, even if the vaccine played no role in causing the GBS. Indeed, although modern seasonal flu vaccines are not thought to cause GBS, the MHRA has received more than 90 reports of GBS as suspected side effects to seasonal vaccines over the past 20 years. These were likely to be coincidental ‘background’ events.

Using the GBS example, we also expected to see, by chance, large numbers of serious medical events caused by underlying illness (e.g. heart attack, cardio-

respiratory arrest, stroke etc) amongst the vaccinated priority population, and also many coincidental fatalities.

Frequency of side effects

Although we intended to analyse the data reported to us in the context of the number of people vaccinated, the nature of the data we collect would not allow us to determine the exact frequency at which side effects were occurring. This is because suspected side effects may not actually have been caused by the vaccine, and for those which may be true side effects, all cases may not be reported to us.

2.5 The MHRA Pandemic Pharmacovigilance Strategy

To meet the challenges above, there were three key elements to the MHRA pharmacovigilance strategy for the swine flu antiviral medicines and vaccines: (i) enhanced passive surveillance; (ii) active surveillance; and (iii) proactive communications. The processes in place to deliver these elements are described below.

2.5.1Enhanced passive surveillance

The Swine Flu ADR webportal

The 'Swine Flu Adverse Reaction (ADR) Portal' was a special on-line interface of the Yellow Card Scheme set up to receive reports of suspected ADRs to the swine flu antivirals and vaccines. The portal was accessed via www.mhra.gov.uk/swineflu, and provided a simple and quick way of getting this information into the MHRA's safety monitoring system. Leaflets and other written material made available to patients and health professionals via the NHS to provide information on the antivirals and vaccines encouraged use of the swine flu ADR portal to report any suspected ADRs. For those without internet access, postal Yellow Card reports were still accepted.

The Swine Flu ADR Portal allowed the MHRA safety scientists to access suspected side effect reports in real-time, which in turn allowed us to identify any possible new risks as soon as they emerged. As well as analysing data from the Portal, the MHRA staff reviewed safety data from all available sources including those from other countries.

'Observed vs expected' analysis

The MHRA analysed all the data collected via the Portal on an ongoing basis. For particular[a] events of interest, we employed a method known as 'observed versus expected' analysis to establish quickly if certain medical events were being reported more frequently after vaccination than might be expected to occur in the population without vaccination.

[a] MHRA had a list of certain medical conditions that were kept under close review using this 'observed vs expected' analysis – this was continually updated as new data emerged

Possible safety signals[a] were identified by comparing the number of reported cases of suspected ADRs (i.e. the 'observed') against the normal background rates of these conditions that usually occur naturally (the 'expected'). Making adjustments for possible levels of under-reporting of such events, these analyses give an indication if the vaccines may carry any excess risk. Observed versus expected analyses were also used in the MHRA's HPV vaccine pharmacovigilance strategy (see the MHRA HPV 2-year safety Public Assessment Report).

Two different 'observed versus expected' methods were used: a statistical sequential test method called the Maximised Sequential Probability Ratio Test (MaxSPRT), which is used for weekly analyses to compare the observed number of reports (relative to data on vaccine usage) with the expected; and a 'snapshot' method which uses a risk period of 42 days post-vaccination to calculate an expected number of cases, based on the number of people vaccinated and the background incidence rate.

To calculate the 'expected', age- and gender-stratified background incidence rates for a range of 'ADRs of interest' were derived using 10 years of historical data from the General Practice Research Database (GPRD; the world's largest computerised database of anonymised patient records).

2.5.2 Active surveillance

As part of the UK pharmacovigilance strategy for the vaccines, the MHRA worked with the two pharmaceutical companies who would supply the vaccines to the UK to ensure that active surveillance was in place. This was achieved via a study using up to 90 GP practices within the Medical Research Council (MRC) General Practice Research Framework. Due to the nature of the eventual UK immunisation policy (i.e. Pandemrix was the recommended vaccine for most people), it was only feasible for this study to be carried out using Pandemrix vaccine.

This type of 'active' surveillance ensures 'follow-up' of a specific group of subjects to discover what, if any, adverse events may have occurred at certain time points after vaccination. This allows the frequency of adverse events to be calculated, which can then be compared with the frequency in the absence of vaccination in other groups. This active surveillance protocol included around 9,000 vaccinated people.

2.5.3 Proactive communications

A key aspect of the MHRA strategy was to proactively publish a weekly public report of the safety data for the swine flu antivirals and vaccines on the MHRA website (see our webpage on swine flu).

The MHRA also provided a briefing to the media in advance of the vaccination campaign. This was to 'set the scene' for what we expected to be reported as suspected side effects, to ensure the media understood the nature of the data we intended to publish each week, to educate how we assess causality, and to encourage balanced reporting of such data.

[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

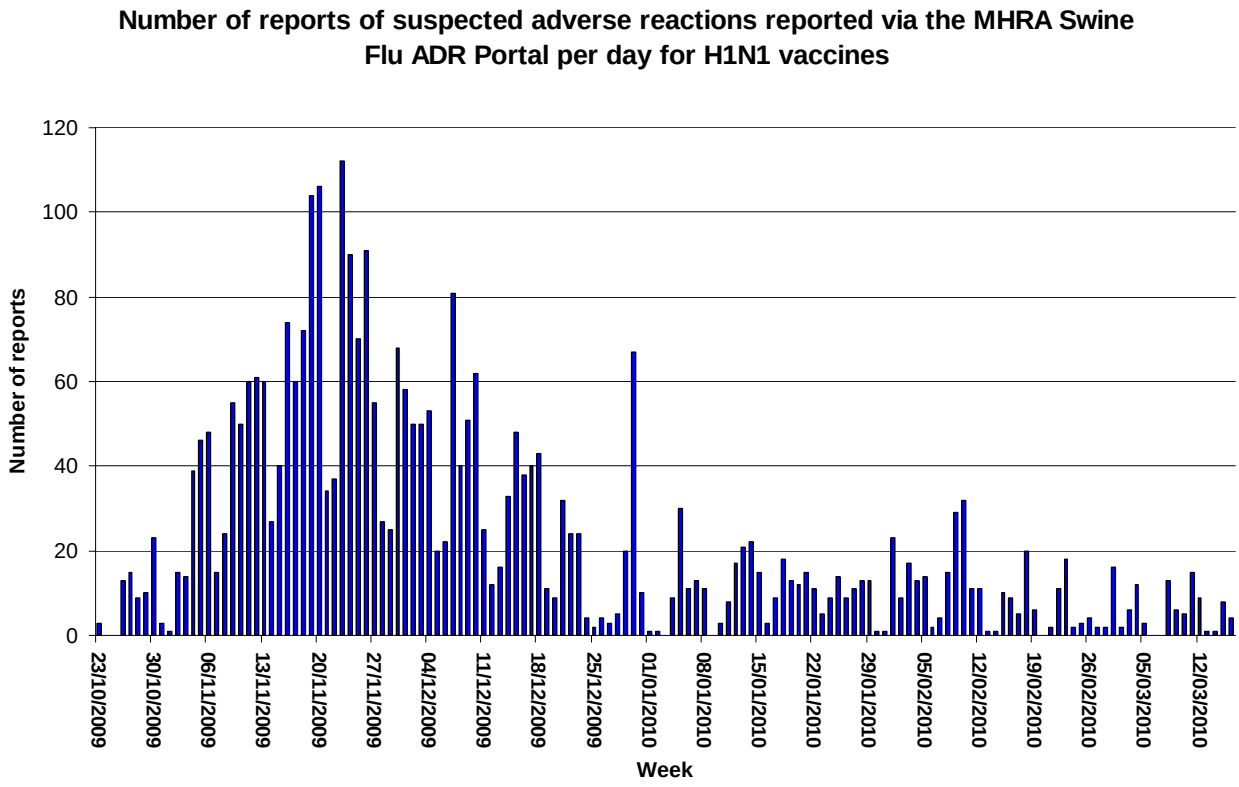
3. VACCINE SAFETY DATA (UK)

3.1 Summary overview of safety for Pandemrix and Celvapan

Summary of ADR reports received for Pandemrix and Celvapan through the Swine Flu webportal and the Yellow Card Scheme

From the start of the UK vaccination campaign in mid-October 2009 until closure of the Swine Flu ADR Portal in mid-March 2010, the MHRA received 3316 reports of suspected ADRs via the Portal and the Yellow Card Scheme in association with both Pandemrix and Celvapan vaccines (Figure 1). Between closure of the portal and 18 June 2010, MHRA received a further 127 reports of suspected ADRs for these vaccines via the Yellow Card Scheme. Therefore in total, 3443 reports of suspected ADRs were received for the swine flu vaccines up to 18 June 2010.

Figure 1. Number and time profile of ADR reports for Pandemrix and Celvapan vaccines



Discussion of summary data

Prior to the start of the pandemic, MHRA anticipated receiving up to 1 suspected ADR per 1,000 doses of vaccine administered. This expectation was based on prior experience with several other major vaccine campaigns in the UK (e.g. MenCC vaccine, HPV vaccine) and because the MHRA had proactively encouraged ADR reporting for the swine flu vaccines. Over 6 million doses of Pandemrix and Celvapan

had been administered by 18 June 2010, therefore the number of reports received over this time (3443) was below this expectation.

As expected, the vast majority of suspected ADR reports related to Pandemrix, due to the much higher usage of this vaccine (Table 1). 13% of all ADR reports related to an unspecified vaccine brand – it was assumed that the vast majority of these reports occurred following Pandemrix because of its higher usage. The data for these vaccines are therefore combined in this paper.

The total reporting rates ranged from approximately 0.6 reports per 1000 doses for Pandemrix, to 1.2 reports per 1000 doses for Celvapan (tables 1 and 2). The highest reporting rates were in adolescent and middle-age groups (table 2). As the nature of Yellow Card data do not allow firm conclusions to be drawn on the relative safety of the vaccines in different age groups, it is only possible to speculate on the explanation for such differences. This may reflect increased vaccine reactogenicity in such age groups. However, this could also be due to non-vaccine factors such as better access to the internet for on-line ADR reporting (compared to younger and older groups) and the possibility that daily activities of these more physically active working groups are more likely to be affected by injection site reactions and flu-like illness (but not necessarily that they are more likely to experience such reactions).

Most reports were for women (69% for Pandemrix; 65% for Celvapan); however, there is no evidence to suggest that the safety profile of the vaccines is different between men and women. Given the focus on optimising patient/carer ADR reporting, it is very encouraging that up to 35% of all reports were reported directly by this group (Table 3).

Table 1. Total number of reports of suspected adverse reactions for Pandemrix and Celvapan*

	Pandemrix and unknown H1N1v vaccine			**Celvapan**		
	ADR reports (% total)	**Exposure (doses)**	**Reporting rate/1,000 doses**	**ADR reports (% total)**	**Exposure (doses)**	**Reporting rate/1,000 doses**
Total	**3400**	**6 214 208**	**0.55**	**43**	**36 916**	**1.16**

*At the time of preparing this analysis, exposure data only from England (ImmForm system), Wales and Northern Ireland were available. The total exposure data therefore represent a minimum estimate of the UK-wide exposure.

Table 2. Number of reports of suspected adverse reactions for Pandemrix and Celvapan according to patient age*

	Pandemrix and unknown H1N1v vaccine			**Celvapan**		
Age range (years)	**ADR reports (% total)**	**Exposure (doses)**	**Reporting rate/1000 doses**	**ADR reports (% total)**	**Exposure (doses)**	**Reporting rate/1000 doses**

0–4	251 (7)	683 787[a]	0.37	8 (19)	5373[a]	1.49
5–14	186 (5)	304 143[b]	0.61	6 (14)	4375[b]	1.37
15–44	1461 (43)	971 752[c]	1.50	13 (30)	6432[c]	2.02
45–64	1089 (32)	1 653 622[d]	0.66	10 (23)	6991[d]	1.43
65+	271 (8)	1 969 295[e]	0.14	4 (9)	7292[e]	0.55
Unknown	142 (4)	-	-	2 (5)	-	-
Total	**3400**	**5 582 599[f]**	**0.61**	**43**	**30 463[f]**	**1.41**

*At the time of preparing this analysis, exposure data only from England (ImmForm system), Wales and Northern Ireland were available. The total exposure data therefore represent a minimum estimate of the UK-wide exposure.
ADR=adverse drug reaction

Table 3. Source of suspected adverse drug reaction reports for Pandemrix and Celvapan

Reporter type	Pandemrix and unknown H1N1v vaccine	% total	Celvapan	% total
Patient	1173	35	11	26
Nurse	525	16	10	23
GP	465	14	8	19
Parent/Carer	315	9	3	7
Other healthcare professional	267	8	5	12
Hospital doctor	176	5	3	7
Hospital nurse	123	4	-	-
Pharmacist	108	3	1	2
Hospital healthcare professional	79	2	-	-
Hospital pharmacist	61	2	-	-

[a] Exposure data cover patients age 6 months to under 5 years
[b] Exposure data cover patients age 5 years to under 16 years
[c] Exposure data cover patients age 16 years to under 45 years; includes 50% of healthcare worker exposure
[d] Exposure data cover patients age 45 years to under 65 years; includes 50% of healthcare worker exposure
[e] Exposure data cover patients age 65 years and over
[f] Total exposure figure differs from that in Table 1 as this was based only on datasets in which age-specific exposure was available.

Physician	23	1	1	2
Community pharmacist	10	0	-	-
Total	**3325***	**100**	**43***	**100**

*Excludes reports direct from industry

3.2. Pandemrix safety review

As outlined above, for the purpose of this safety review and on the basis of exposure data, it was assumed that H1N1v vaccine ADR reports where the brand was not specified related to Pandemrix vaccine.

As expected, the vast majority of suspected ADR reports (approximately 60%) with Pandemrix related to those categorised as 'general disorders', 'nervous system disorders', 'musculoskeletal disorders', 'gastrointestinal disorders', 'skin disorders' and 'respiratory disorders'. These mostly related to known side effects such as injection-site reactions, nausea, vomiting, headaches, dizziness, muscle aches, mild allergic reactions, mild fever, fatigue and other 'flu-like' symptoms.

3.2.1 General disorders

2731 reports of suspected ADRs for Pandemrix (31% of the total reactions) were categorised as 'general disorders'. Most of these reports were injection-site reactions such as pain, swelling, and redness, and other events such as 'flu-like illness, fatigue, chills, malaise and fever. These types of event are recognised side effects and do not raise any specific safety concerns.

3.2.2 Nervous system disorders

1500 reports of suspected ADRs (17% of the total) were categorised as nervous system disorders. The vast majority of these reports related to lethargy, dizziness, headache and paraesthesia, which are recognised side effects. The reports of paraesthesia (133; mainly reported as pins and needles and skin tingling), and hypoaesthesia ('numbness'; 52) were generally transient and localised to the injection site or to the injected limb. A smaller number of cases of generalised paraesthesia have been reported; in most cases this condition was transient. There were also several reports of syncope (fainting) and loss of consciousness which were mainly psychogenic responses to the injection process.

Myasthenia gravis
Two reports of myasthenia gravis (MG) were received. However, when the reports were followed-up for further information a diagnosis of MG was excluded for one of the reports. The reports of suspected MG are discussed further in section 3.3.2.

Convulsions/Seizures
Forty-two reports of seizure disorders were received, twelve of which were reports of febrile convulsions (fever fits) in children. These reports are discussed further in section 3.2.10. Afebrile convulsions (reports of convulsions without reference to raised body temperature) are not currently a recognised risk of H1N1v swine flu vaccines. Two reports of afebrile convulsions with Pandemrix were associated with a fatal outcome. However, there is no clear indication from these ADR reports that the vaccine caused or directly contributed to the death of these patients and an

unpublished study has shown that the vaccine does not increase the likelihood of a convulsions occurring. Cases of afebrile convulsions after the vaccine are therefore probably coincidental.

'Nerve Injury'
There were two reports of 'nerve injury'. One report appeared to be related to the injection technique and was associated with sensory loss and a 'pins and needles' sensation along the vaccinated arm. The second report was of dizziness and head pressure, and described a 'nervous' state (ie, anxiety) rather than physical nerve damage.

Neuropathies, paralysis and paresis
Twelve suspected reports of paralysis, hemiplegia, hemiparesis, monoplegia or diplegia were reported. These were short-lasting events and are not indicative of paralysis of neurological origin or any serious neuromotor disease. The initial assessment of the reports of 'paralysis' was that these represented impaired mobility of the injected limb that was probably due to pain and stiffness, rather than a paralysis of neurological origin.

There was one report of polyneuropathy that was described as pins and needles and numbness in injected arm. Reports of neuralgia and facial neuralgia were generally localised to the face and/or injected limb, were transient, and not associated with any serious neurological outcome.

There were also reports of trigeminal nerve paresis (1), facial palsy (7) and facial paresis (2). In the reports of facial palsy the time to onset, where known, was 2–4 days. In one report, the event resolved within 45 minutes of onset in a patient with a history of herpes infection in the lips. In another report, facial palsy was reported as a symptom of Guillain Barre Syndrome (GBS) which is discussed in further detail below.

Myelitis/demyelination
There were four reports of transverse myelitis, which is consistent with the expected background incidence of this condition amongst the number of people vaccinated. One report of multiple sclerosis aggravated 4 days after vaccination with H1N1v vaccine (brand unknown) was also reported.

Encephalopathy
Two reports of encephalopathy were recieved with onset times of 1 and 4 days, respectively, after vaccination. No further details were available on these reports.

Guillain Barre Syndrome (GBS)
The MHRA's pharmacovigilance strategy for the pandemic vaccines included active follow-up of any reports of suspected GBS to assess diagnostic certainty against the Brighton Collaboration criteria[a] and a real-time 'observed vs expected analysis' of any reports (see section 3.3.1).

Fifteen reports of suspected GBS were submitted to MHRA in the UK for both H1N1v vaccines (14 for Pandemrix/H1N1v vaccine brand unknown; one for Celvapan). Only two of the 14 reports for Pandemrix met at least one of the Brighton Collaboration diagnostic criteria for a definition of GBS.

Comments:

[a] A standardised set of case definitions of Adverse Events Following Immunization - www.brightoncollaboration.org

As with most vaccines, the most common ADRs we expected to be reported were headaches, dizziness, lethargy, and 'psychogenic' events (eg, fainting). It is therefore not unexpected that nervous system disorders constitute almost 17% of all ADR reports. The ADRs reported in this category raise no new safety concerns.

There is no indication that Pandemrix vaccine may be a cause of any serious neurological adverse events.

3.2.3 Musculoskeletal disorders

There were 1294 reports (15% of the total) of suspected ADRs categorised as musculoskeletal disorders. The vast majority of these related to arthralgia, muscle stiffness, myalgia, other types of limb pain or discomfort and sore arm. Such conditions may be associated with a 'flu-like illness' or may be secondary to an injection-site reaction, and are listed as very common side effects in the Summary of Product Characteristics (SPC). There were 24 reports of arthropathies which, when analysed, were found to be within the expected range. The reports in this category raised no new safety concerns.

3.2.4 Gastrointestinal disorders

1011 reports of suspected ADRs (11% of the total reports) were categorised as gastrointestinal disorders; most of these related to diarrhoea, vomiting, nausea and abdominal pain. These are all recognised as uncommon side effects in the SPC. Several reports related to possible allergic reactions such as lip and tongue swelling. There were reports of oral paraesthesia and oral hypoaesthesia (n=34) that were most likely secondary to possible allergic or psychogenic events. The reports in this category raised no new safety concerns.

3.2.5 Skin disorders

There were 587 suspected ADRs (7% of the total reports) in the skin disorders category. The majority of these reports related to hyperhidrosis (sweating), generalised skin reactions (rashes, redness, itching) and possible allergic reactions. These reports raised no safety concerns.

There were two reports of Stevens Johnson Syndrome, however, other drugs may have been responsible for these events. There was one report of toxic epidermal necrolysis that was fatal, which may have been due to underlying infection.

3.2.6 Respiratory disorders

431 reports of suspected ADRs (5% of the total reports) were categorised as respiratory disorders. The majority of the suspected ADRs in this category related to dyspnoea, cough, asthma and wheezing.

Comments:

As a large proportion of the vaccinated population would have had an underlying respiratory condition when they were vaccinated, or received the vaccination at a time when H1N1v was at peak levels (and therefore possibly have had recent/concurrent infection), it is likely that many of the cases of respiratory disorders will relate to coincidental, underlying conditions.

A generalized flu-like illness is one of the most commonly-reported adverse events following Pandemrix which is possibly due to a non-specific cytokine response to immunisation. In theory, this non-specific event could trigger an exacerbation of asthma. However, a controlled study has found no evidence that (seasonal) influenza vaccination can trigger an asthma attack in asthmatic patients[2]. There is no evidence that Pandemrix causes or is associated with this risk, or any other respiratory adverse event.

3.2.7 Blood and lymphatic disorders

There were 10 case reports of idiopathic thrombocytopenic purpura (ITP) which occurred in five children and five adults (age range 38– 93 years). One of the adults had a history of ITP. There was also one report of autoimmune thrombocytopenia and one report of autoimmune haemolytic anaemia.

The number of reports in the UK is within the range of what would be expected to have occurred coincidentally. There is no clear signal based on reported data that Pandemrix vaccine may cause any blood disorders.

There were 74 cases of lymphadenopathy, which is already listed as a common side effect in the Pandemrix product information.

3.2.8 Immune system disorders

There were 58 reports of immune system disorders with Pandemrix use, most of which were for possible allergic reactions. Anaphylaxis is a known, although very rare, immune system risk with any vaccine and is generally thought to occur at a frequency of between 1–10 cases per million doses of vaccine given. The product information for Pandemrix warns of the possible risk of anaphylaxis, and states that appropriate medical treatment and supervision should always be readily available in case of a rare anaphylactic event.

For many of the reports of suspected anaphylaxis, the available clinical information did not allow the diagnosis to be confirmed. There was also insufficient information to determine if individuals had existing allergies to any of the vaccine ingredients. However, where clinical information was available, it suggested in several cases that the allergic reaction reported was less severe than a true anaphylactic reaction.

There were also two reports of graft dysfunction, and one report of transplant rejection.

Comment:

Patients with immunosuppression, including those on immunosuppressive therapy, were a key priority group for immunisation with H1N1v vaccine. This is because infections such as swine flu can be clinically severe in immunosuppressed patients. The role of an adjuvant in enhancing the immune response in such patients is important.

The available literature on a possible role of influenza vaccination (seasonal) in transplant rejection has been reviewed[3]. The authors of the review suggest that the infectious agent, more than the inactivated vaccine, is a cause of rejection, and that effective immunisations may actually be protective.

The case reports alone are insufficient to determine whether Pandemrix may be a trigger for transplant rejection. This issue will remain under close review.

3.2.9 Safety in pregnancy

Pregnant women, especially those in their 3rd trimester, are at an increased risk of developing severe illness due to influenza and were therefore one of the key priority groups to be offered the swine flu vaccine.

The majority of suspected ADRs reported for pregnant women with Pandemrix involved reactions for the pregnant woman only (ie, without adverse effects to the developing baby). These reports were mostly non-serious and already recognised side effects of all vaccines including Pandemrix, such as injection site reactions and flu-like illness.

There was one report of GBS in a pregnant woman who received H1N1v vaccine (brand unknown; see section 3.2.2). GBS is discussed further in section 3.3.1.

During the time period of this report, at least 500 000 pregnant women were vaccinated with H1N1v vaccines across Europe, including at least 104 000 pregnant women in the UK. The background rate of intra-uterine death/stillbirth in the UK is estimated to be around 5 stillbirths per 1000 pregnancies. The number of intra-uterine deaths and stillbirths reported in the UK (as well as across Europe) in association with swine flu vaccines (n=7) does not exceed what would be expected based on natural background population rates of these events in the absence of vaccination. Miscarriage in early pregnancy is very common and it was therefore inevitable that some cases of miscarriage would occur coincidentally following vaccination without the vaccine playing any causal role in the event. Reported rates of miscarriage following vaccination (n=29), as well as the numbers seen through active surveillance, are well-within the rate expected naturally. There is currently no evidence to suggest that H1N1v vaccines are associated with any risks to pregnancy.

3.2.10 Safety in children

There were almost 450 reports of suspected ADRs to Pandemrix in children age younger than 16 years. The majority of these reports were either for non-serious, recognised side effects of many vaccines including the swine flu vaccines, or were attributed to the process of vaccination rather than the vaccine itself. These reactions include injection-site reactions, fever, flu-like illness, myalgia, rash, headache, dizziness, nausea, vomiting, diarrhoea and psychogenic reactions such as tachycardia and fainting. There were two reports of Kawasaki disease which were consistent with being coincidental events; see section 3.3.2).

Fever and febrile convulsions
There were 12 reports of febrile convulsions (seizures) in children – nine with Pandemrix, three with H1N1v vaccine brand unknown. These data do not allow a robust evaluation of the risk of febrile seizures in children following vaccination, however, a reporting rate of 12 cases out of 643,905 children age less than 4 years who were vaccinated (1.9 cases/100 000 doses) does not in itself raise any concern of excess reporting.

Data from clinical trials showed that a second dose of Pandemrix (half the adult dose) in children age 6 months to 3 years is associated with greater reactogenicity

compared to the first dose. In particular, rates of fever are higher after the second dose compared to the first dose, which is likely to increase the risk of febrile convulsion. However, other than the risk of higher rates of fever after a second dose, there is no indication of any new or specific safety concerns in children. Product information for Pandemrix was amended in December 2009 to warn of the risk of fever, and the possibility of febrile seizures, and to allow for either one or two doses to be given to children. The UK Joint Committee on Vaccination and Immunisation (JCVI) subsequently recommended that only one dose of Pandemrix should be given to children in the UK (for immunocompromised children the policy remained two doses).

3.2.11 Fatal events

As most people offered the vaccine had serious and/or chronic underlying medical conditions which put them at greater risk of developing serious flu-related complications or even death, it was inevitable that many natural events with a fatal outcome would be reported. There were 34 suspected ADRs with a fatal outcome following administration of Pandemrix; in the majority of these, the patients had underlying medical conditions which could have caused the fatal outcome. There is no clear indication from these ADR reports that the vaccine caused or directly contributed to the death of these patients.

3.3 Proactive 'observed versus expected' analyses for Pandemrix

As part of the strategy outlined in section 2.5, background incidence rates for a range of 'ADRs of interest' (calculated using 10 years of historical data from the General Practice Research Database [GPRD]) are used to estimate the expected number of reports on a continuous cumulative basis. The 'observed versus expected' analyses help to determine if a certain proportion of events would anyway have occurred in the age-group being vaccinated, even without the vaccination programme.

A statistical sequential test method, the Maximised Sequential Probability Ratio Test (MaxSPRT) is used to compare the observed number of reports (relative to data on vaccine usage) with the expected. 'Observed versus expected' analyses for Pandemrix were conducted weekly from 2009–2010.

3.3.1 Observed versus expected analyses conducted for Guillain Barre Syndrome (GBS)

Rationale for focus on GBS

Guillain-Barre syndrome (GBS) is a rare autoimmune disease occurring naturally in the population at an overall incidence of ~1 case per 100,000 persons per year. It is considered to result from a spontaneous generation of autoimmune antibodies and/or inflammatory cells which attack the myelin sheath around the axons of nerves. It is characterised by various degrees of weakness, sensory abnormalities, and autonomic dysfunction due to damage to peripheral nerves and nerve roots. Patients typically experience progressive limb weakness, most often beginning in the legs and progressing to the arms and bulbar muscles. GBS is often preceded by a respiratory or gastrointestinal illness. Flu-like illness is a known risk factor.

In 1976, a swine flu immunisation campaign in the US to protect the public against a possible pandemic was stopped due to an excess reporting of cases of GBS following vaccination. The vaccines used in the US were not used in any other country. Subsequent epidemiological studies confirmed that the US vaccines were associated with up to a10-fold increased risk of GBS in the 6-week period following vaccination. The exact reason why the 1976 vaccines caused GBS remains unknown. There has been speculation that manufacturing quality may have been a factor but this has not been confirmed.

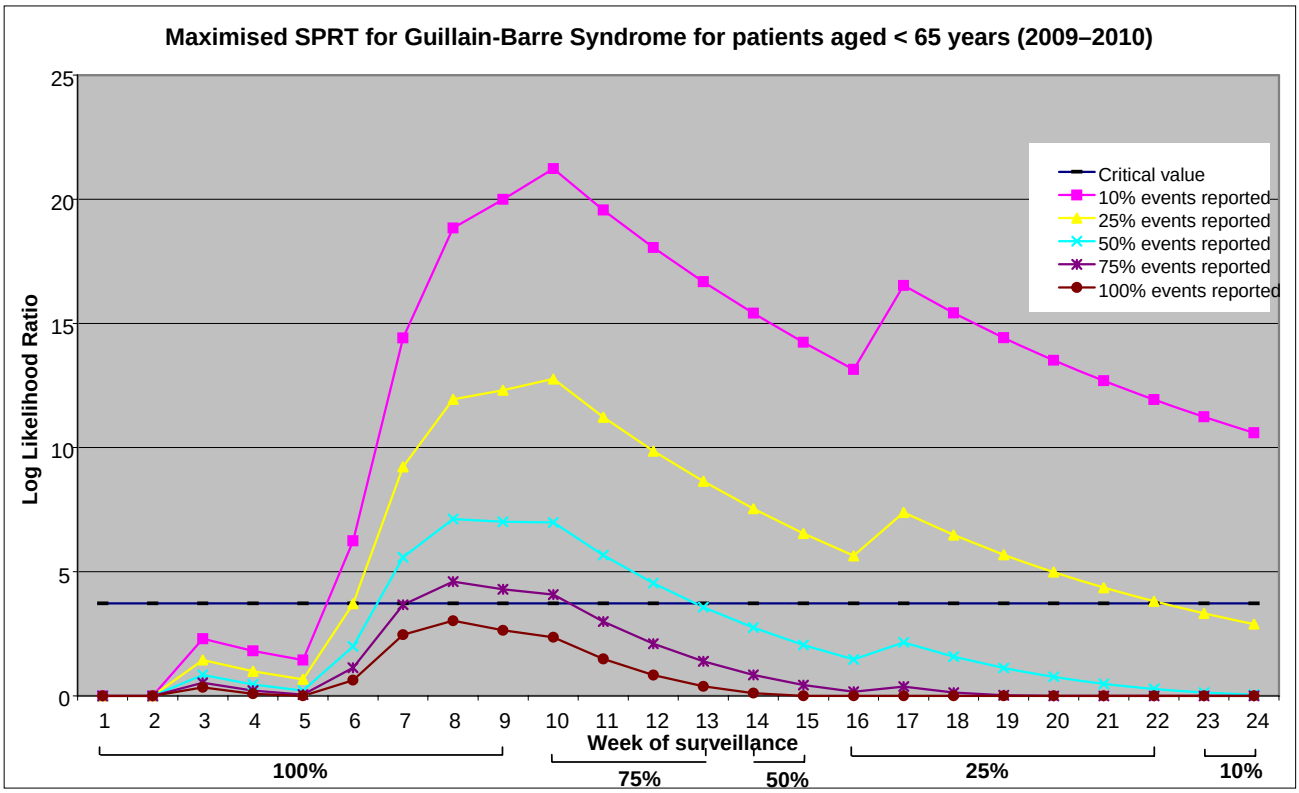
There was no specific reason to suspect that the current swine flu vaccines may increase the risk of GBS. However, given that GBS occurs naturally (due to various infections including flu-like illness) and as we were vaccinating millions of people, we anticipated receiving reports of GBS in close temporal association with swine flu vaccines during the swine flu immunisation campaign. Reporting of GBS following vaccination in the current pandemic therefore remained under intense scrutiny.

Results of 'observed versus expected' analyses for GBS reports

The observed vs expected analysis for GBS was stratified by age (<65 years and 65+ years), as the incidence of GBS increases considerably with age. Based on the number of people in each age groups immunised, the analysis indicated that within 6 weeks of vaccination we would expect 8-9 incident cases amongst the <65 years vaccinated cohort and around 6 incident cases amongst the 65+ years vaccinated cohort by chance alone.

At the time of the data analysis in 2010, the MHRA had received two reports of GBS in the 65+ years age group which were well within the expected range of incidence. There were 12 reports in the <65 years which exceeds the expected number, although this does not reach statistical significance (standard morbidity ratio: 1.46 [95% CI 0.75–2.55]. The MaxSPRT analysis for the <65 years age group shows that all under-reporting scenarios regardless of time since vaccination, except 100%, indicate an excess above the critical threshold (Figure 2).

Figure 2. The Maximised Sequential Probablility Ratio Test (MaxSPRT) for reports of Guillain-Barre Syndrome (GBS) with Pandemrix vaccine



European review of GBS data

Similar analyses carried out by Germany and Sweden also indicated that the observed number of cases of GBS were close to, equal to, or slightly exceeded the expected national rate.

Because of these findings, an expert meeting, including neurologists and epidemiologists, was convened by the European Medicines Agency in March 2010 to discuss the available data. The key points agreed in the meeting were as follows:

- An analysis of worldwide data is reassuring and there is no sign of a risk of GBS with the pandemic vaccines of a similar magnitude as that found in the pandemic situation of 1976.
- A possible association between the pandemic vaccines and GBS cannot be completely excluded given the uncertainties in the current information. However, even if an association exists, it would probably translate to a very small increase in the risk.
- Factors limiting interpretation of the data include an uncertainty regarding the completeness of reporting of adverse reactions by physicians; the variability of the underlying risk of GBS measured in different age groups of the general population; incomplete vaccination statistics in several countries; and a lack of knowledge of the numbers of vaccinated people in different age categories.

Comments:

Observed versus expected analyses are useful tools for evaluating a possible association between a vaccine and a reaction. However, the limitations of the current analyses include: uncertain diagnostic certainty of reports (and therefore possible 'over-reporting' of cases); possible under-reporting of cases; lack of robust data on age-specific vaccine exposure; and the unknown effect of the pandemic itself on the background incidence of GBS during the immunisation programmes.

It was evident from our analyses early in the vaccination programme, including similar analyses across the EU, that there was no indication of a large increased risk of GBS similar to that seen with swine flu vaccines in the US in 1976. To date, there remains no confirmed evidence to indicate that Pandemrix, or any H1N1v vaccine, is associated with any increased risk of GBS.

However, flu-like illness is known to increase the risk of GBS, and the possible role of swine flu infection, including asymptomatic infection, prior to immunisation is one of several uncertainties in interpretation of GBS reports. Due to the rarity of GBS as a condition, evaluation of much smaller levels of risk is associated with more uncertainty. As with seasonal flu vaccines, although there is no proven association with 2009/10 swine flu vaccines, a slightly elevated risk of GBS (in the order of 1 case for every million doses given) following swine flu vaccines cannot be completely ruled out yet. The benefits of vaccination would still outweigh any small vaccine-attributable risk of GBS. Epidemiological studies are ongoing in Europe to further assess this possible association.

3.3.2 Analyses conducted for myasthenia gravis, facial palsy, transverse myelitis, thrombocytopenia, and Kawasaki disease.

Other 'ADRs of interest' with Pandemrix including myasthenia gravis, facial palsy, transverse myelitis, thrombocytopenia, and Kawasaki disease were assessed using similar 'observed versus expected' methods. The observed number of reports of these conditions did not exceed the expected number.

3.3.3 Narcolepsy

Since the time period covered by this report, the MHRA has led on a European review of reports of narcolepsy (a sleep disorder characterised by sudden and uncontrollable episodes of deep sleep) in temporal association with Pandemrix vaccine. Narcolepsy is a rare, natural illness, with around 10 new cases per million people every year.

Most reports of narcolepsy after exposure to Pandemrix vaccine came from Finland and Sweden. In September 2010, the European review concluded that the available evidence was insufficient to confirm a link between Pandemrix and narcolepsy, and that further studies were necessary to fully understand this issue. No restrictions on use of the vaccine were recommended.

After use of more than 6 million doses of Pandemrix vaccine in the UK, we have received 4 unconfirmed reports of narcolepsy following vaccination. These were received after the reports from Finland came to light. The reports so far in the UK are no more than we would expect to see by coincidence after vaccination.

After review of all of the available information, the case remains that a link between Pandemrix vaccine and narcolepsy has not been confirmed. Epidemiological studies are ongoing to further evaluate this.

3.4 Celvapan safety review

There was relatively limited usage of Celvapan in the UK during the pandemic period due to the policy of limiting its use to those with a confirmed egg allergy (or who were otherwise intolerant of Pandemrix). It is therefore not possible to gain a robust picture of the relative safety profile of Celvapan in the UK, compared to Pandemrix.

However, based on the few reports received in association with Celvapan, the type of suspected ADRs reported are broadly similar to those associated with Pandemrix – i.e. mainly mild gastrointestinal ADRs, 'flu-like illness', myalgia/arthralgia and mild allergic reactions. There was one report of suspected GBS. No fatal events were reported in association with Celvapan. Following administration of at least 566,000 doses of Celvapan across the EU, no significant safety issues have arisen (www.ema.europa.eu/influenza/updates).

4. ANTIVIRAL SAFETY DATA (UK)

4.1 *Summary overview of safety for oseltamivir and zanamivir*

This section summarises the safety experience with the antivirals, oseltamivir (brand name Tamiflu) and zanamivir (Relenza), from 1 April 2009 until mid-March 2010.

Due to the varying ways and circumstances in which antivirals were supplied in the different UK regions at different stages in the pandemic period, it is difficult to obtain a precise estimate of actual exposure. The estimated quantities of the two antivirals supplied via the National Pandemic Flu Service (NPFS) in England from 23 July 2009 to 9 February 2010 are summarised below. Although the figures below represent the vast majority of courses supplied during the entire pandemic in the UK, these are an underestimate of UK-wide exposure. The ADR reporting rates listed below are therefore an over-estimate of the true rates.

During this period, 1100 reports of suspected ADRs were reported to MHRA via the Swine flu webportal and the Yellow Card Scheme (see section 2.5.1) in association with oseltamivir. There were 38 reports in association with zanamivir. Most reports for both drugs came from patients age 15–44 years (table 4), and were mostly from females.

Table 4. Number of reports of suspected adverse reactions for oseltamivir and zanamivir according to patient age

	Oseltamivir (Tamiflu)			**Zanamivir (Relenza)**		
Age range (years)	**ADR reports (% total)**	**Exposure (courses)***	**Reporting rate/1,000 courses**	**ADR reports (% total)**	**Exposure (courses)***	**Reporting rate/1,000 courses**
0	31 (3)	-	-	-	-	-
1–4	123 (11)	98 535	1.25	-	-	-
5–14	190 (17)	189 022	1.01	1 (3)	561	1.78
15–44	473 (43)	628 093	0.75	26 (68)	12 123	2.14
45–64	181 (16)	196 471	0.92	1 (3)	1475	0.68
65–74	31 (3)	24 799	1.25	-	357	-
75+	29 (3)	9371	3.09	-	191	-
Unknown	42 (3)	-	-	10 (26)	-	-
Total	**1100**	**1 146 291**	**1.38**	**38**	**14 707**	**1.54**

*Only covers the number of treatment courses of antivirals (both oseltamivir and zanamivir) supplied via the National Pandemic Flu Service (NPFS) in England from 23 July 2009 to 9 February 2010. These figures do not cover courses given in Scotland, Ireland and Wales, or individual prescriptions from GPs.
ADR=adverse drug reaction

Figure 3. Time profile of suspected adverse drug reaction reports for oseltamivir and zanamivir

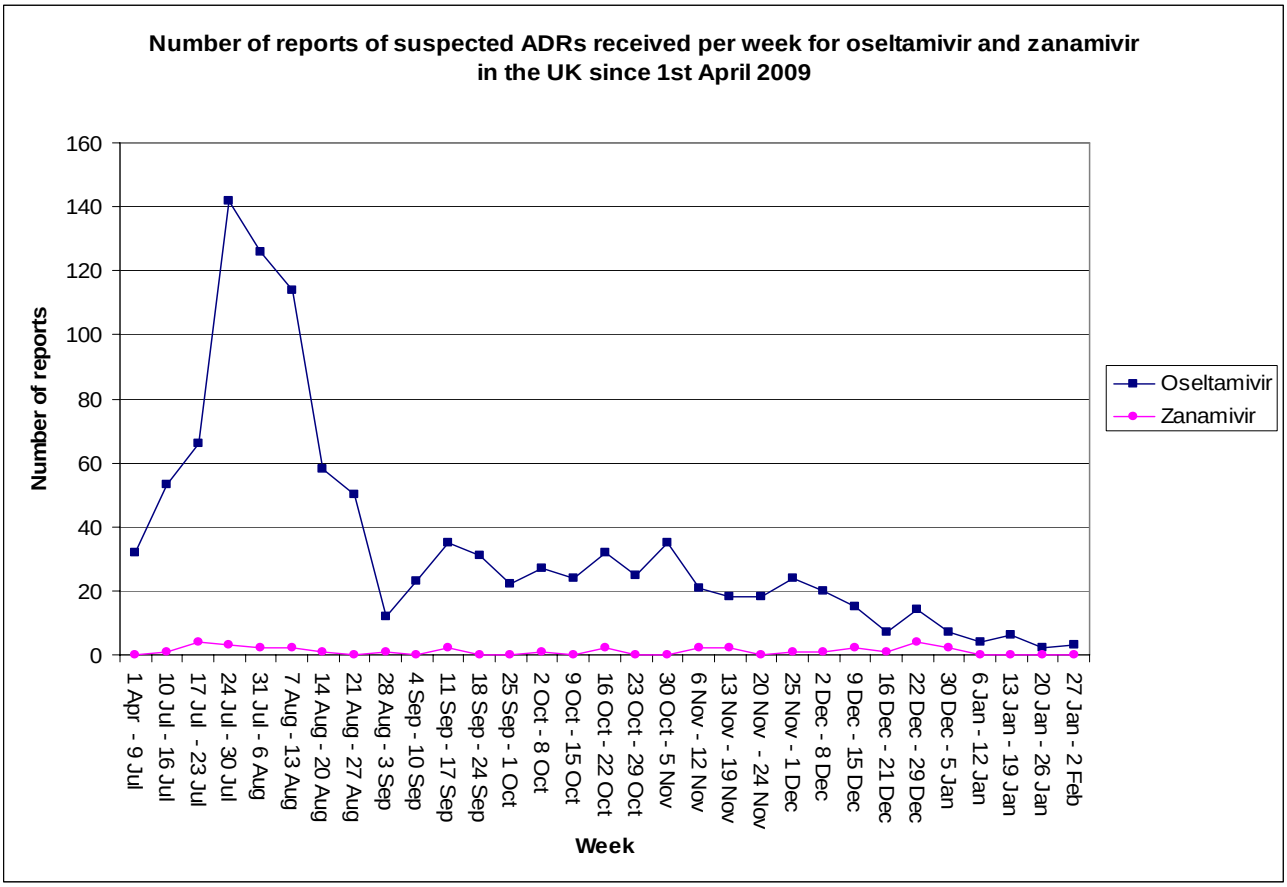


Figure 4. Time profile of oseltamivir ADR reports relative to oseltamivir supply

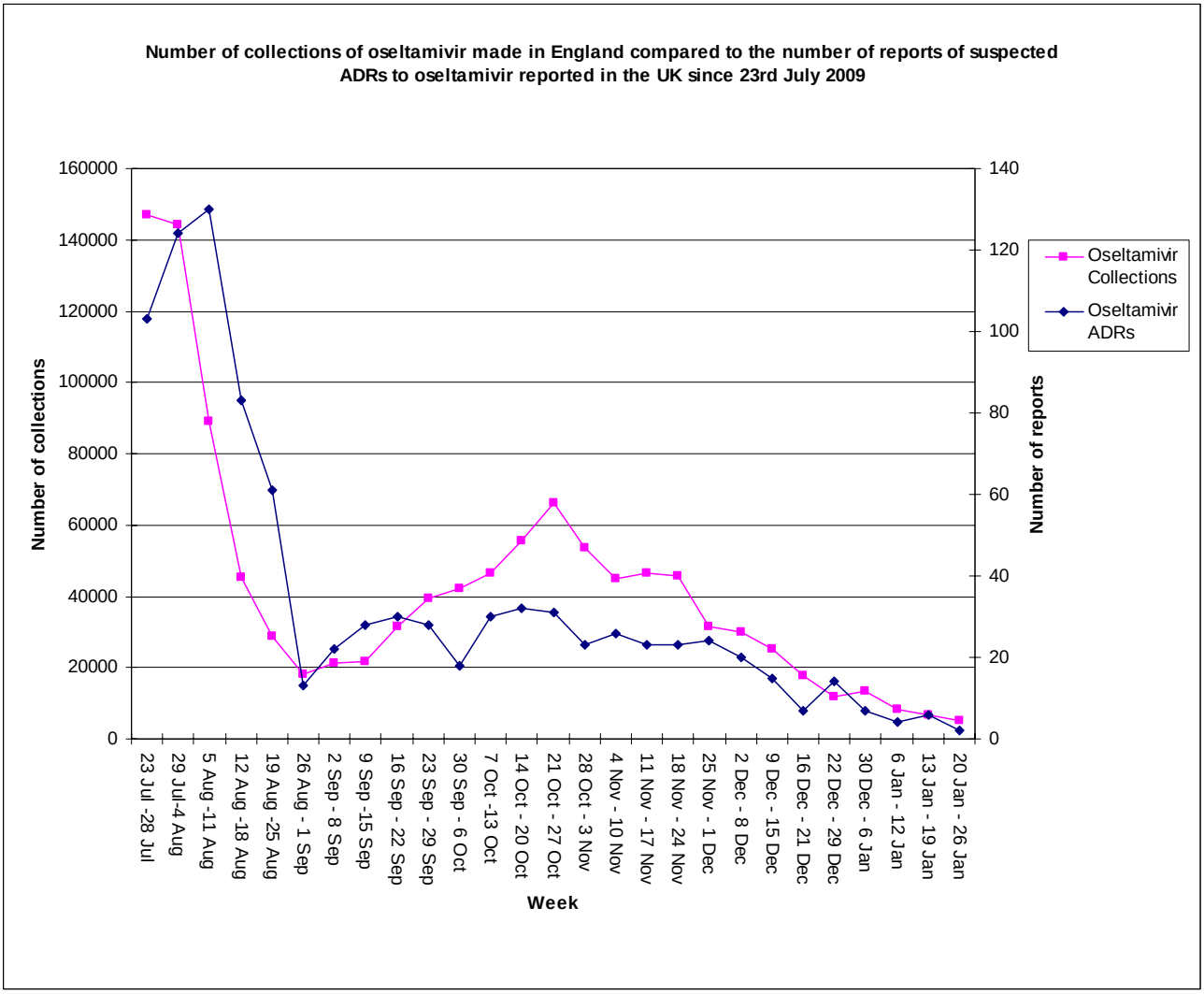

Number of collections of oseltamivir made in England compared to the number of reports of suspected ADRs to oseltamivir reported in the UK since 23rd July 2009
Number of collections
160000
140000
120000
100000
80000
60000
40000
20000
0
Number of reports
140
120
100
80
60
40
20
0
Oseltamivir Collections
Oseltamivir ADRs
23 Jul -28 Jul
29 Jul-4 Aug
5 Aug -11 Aug
12 Aug -18 Aug
19 Aug -25 Aug
26 Aug - 1 Sep
2 Sep - 8 Sep
9 Sep -15 Sep
16 Sep - 22 Sep
23 Sep - 29 Sep
30 Sep - 6 Oct
7 Oct -13 Oct
14 Oct - 20 Oct
21 Oct - 27 Oct
28 Oct - 3 Nov
4 Nov - 10 Nov
11 Nov - 17 Nov
18 Nov - 24 Nov
25 Nov - 1 Dec
2 Dec - 8 Dec
9 Dec - 15 Dec
16 Dec - 21 Dec
22 Dec - 29 Dec
30 Dec - 6 Jan
6 Jan - 12 Jan
13 Jan - 19 Jan
20 Jan - 26 Jan
Week

Table 5. Source of suspected adverse drug reaction reports for Pandemrix and Celvapan*

Reporter type	Oseltamivir (number of reports [% total])	Zanamivir (number of reports [% total])
Patient/Parent/Carer	421 (39.1)	8 (28.6)
GP	372 (34.5)	10 (35.7)
Hospital doctor	68 (6.3)	5 (18)
Other healthcare professional	50 (4.6)	2 (7)
Pharmacist	44 (4.1)	-
Hospital pharmacist	38 (3.5)	1 (3.5)
Nurse	34 (3.2)	-
Hospital healthcare professional	17 (1.6)	1 (3.5)
Community pharmacist	14 (1.3)	-
Physician	13 (1.2)	1 (3.5)
Hospital nurse	6 (0.5)	-
Total	**1077***	**28***

* This table excludes reports direct from industry as reporter type is not known

Discussion of summary data

It is estimated that at least 22 million people were given a course of oseltamivir across the whole of the EU during the pandemic (see www.ema.europa.eu/influenza/updates). Over 1 million course of oseltamivir, and over 14,000 courses of zanamivir, were given out in the UK. Prior to the start of the pandemic, the MHRA anticipated receiving at least one suspected ADR report per 1,000 antiviral courses administered. The overall reporting rate – 1/1000 for oseltamivir and 1/500 for zanamivir – does not indicate any specific safety concern. It is encouraging that up to 40% of all reports were reported directly by patients and carers, as the MHRA focussed on optimising patient/carer reporting with the swine flu antivirals and vaccines.

The vast majority of ADR reports for zanamivir were in females due to the preferential use of the drug in pregnant women (safety in pregnancy is discussed below). As there was no differential clinical attack rate of H1N1v in females compared to males and we do not have data on exposure by gender for either antiviral, the higher proportion of oseltamivir ADRs in females is unexplained. These data do not allow conclusions to be drawn on relative safety in females compared to males.

Given the limitations of the data, it is also not possible to draw firm conclusions on the relative safety of the antivirals in different age groups. For oseltamivir, there are trends for higher reporting rates in young children, and especially the elderly. This may reflect a reporting bias, a differential safety profile in each age group, or a combination of both. As the vast majority of ADR reports are associated with treatment for influenza symptoms (prophylaxis strategies ceased early in the pandemic), the clinical manifestation of influenza in different age groups is also a likely factor in the nature of suspected ADR reporting (ie, some reported events will be due to influenza illness).

There were 12 reports of suspected ADRs with a fatal outcome for oseltamivir. However, for the vast majority of these reports, the patients had underlying medical conditions which provide a plausible alternative explanation for the fatal outcome. There is no clear indication that the antiviral contributed to a progression of the underlying illness, or caused or directly contributed to the death of these patients.

There were six reports of suspected ADRs with a fatal outcome for zanamivir. Five of these six fatal reports were associated with an unlicensed intravenous formulation. This was used during the pandemic on a very limited basis in severely ill patients to treat infections which did not respond to other first line treatments (such as oseltamivir or inhaled zanamivir). There is no clear indication from these ADR reports that zanamivir caused or directly contributed to the death of the patients and underlying medical conditions provide a plausible alternative explanation for the fatal outcome.

Analysis of suspected adverse drug reaction reports by category

This section discusses the case reports received in the UK for oseltamivir and zanamivir, which were published in public ADR summaries each week from August 2009 to January 2010 on the MHRA website (http://www.mhra.gov.uk/swineflu).

4.2 Oseltamivir safety review

The vast majority of suspected ADR reports related to those categorised as ‘gastrointestinal disorders’, ‘nervous system disorders’, ‘psychiatric disorders’, and ‘skin disorders’.

4.2.1 Gastrointestinal disorders

There were 642 reports (32% of the total) of suspected gastrointestinal ADRs for oseltamivir. Based on data from clinical trials, it was expected that gastrointestinal disorders would be the most commonly reported ADR in association with oseltamivir. Most of these reports were diarrhoea, nausea, vomiting and abdominal pain and discomfort. These are recognised side effects and no specific safety concerns were raised.

4.2.2 Skin disorders

There were 356 reports (18% of the total) categorised as skin disorders. Of these, 16 were categorised as serious skin reactions including eight reports of Stevens Johnson syndrome, six reports of erythema multiforme, and two reports of toxic epidermal necrolysis.

In a small proportion of the reports of blistering rash, a causal association between oseltamivir and the reported suspected reaction cannot be excluded. These types of skin reactions can also be caused by a number of different factors including viral infections. All of these reactions are listed in the side effects section of the product information for oseltamivir.

4.2.3 Psychiatric and nervous system disorders

203 reports of suspected ADRs (10% of the total) were classified as nervous system disorders. Most of these reports were for headache and dizziness which are recognised side effects of oseltamivir.

There were 26 reports of seizure disorders with oseltamivir. Convulsions (a seizure disorder), along with other neuropsychiatric adverse reactions including delirium (with symptoms such as confusion, abnormal behaviour, hallucinations, agitation, anxiety and nightmares) are listed in the SPC for oseltamivir as possible adverse effects. This is based mainly on data from Japan and the US, which included serious delirious events leading to serious injury and death. However, influenza infection itself can be associated with a variety of neurological and behavioural symptoms including those listed above, sometimes without obvious signs of a serious infection. Some studies have found that these types of events are no more frequent in influenza patients who have taken oseltamivir compared to those who have not taken oseltamivir. It remains unclear whether the neuropsychiatric events are a true side effect of oseltamivir or whether they are due to underlying infection (or a combination of both).

There is no indication from the UK suspected ADRs reported during the pandemic of any serious neuropsychiatric events occurring.

4.2.4 Hepatic disorders

There were 25 reports (1% of the total) of suspected hepatic ADRs for oseltamivir during the pandemic. These include four reports of hepatic failure, one of which resulted in a fatal outcome. In the majority of the UK reports of hepatic ADRs there is insufficient information to assess a possible role of oseltamivir, or plausible alternative explanations exist for the event. There are however a small number of reported cases of liver reactions in which a causal association with oseltamivir cannot be excluded.

Serious adverse effects on the liver including fulminant hepatic failure are included in the SPC for oseltamivir, based on isolated case reports originating from outside the EU.

4.2.5 Possible interaction between oseltamivir and warfarin

The MHRA has closely assessed suspected ADR reports (n=14) of a possible drug interaction between oseltamivir and warfarin which can lead to prolonged coagulation time and increased risk of bleeds (see weekly update on suspected ADRs for swine flu antivirals).

This interaction is not recognised or listed in the SPC and INR values, and blood clotting control can also be affected by infection and associated symptoms of influenza (eg. decreased appetite and anorexia). Therefore, it is difficult to assess whether or not the underlying viral illness, an interaction between oseltamivir and warfarin, or both, is responsible for the changes in clotting times in the reported cases.

This safety issue will remain under review, along with other suspected ADRs, while oseltamivir is used in the management of seasonal influenza.

4.3 Zanamivir safety review

Most of the suspected ADRs reported in association with zanamivir in the UK are consistent with the recognised side effects of the drug as listed in the SPC, or are consistent with the symptoms of underlying flu-like illness or concurrent infection.

As with oseltamivir, although convulsions are listed as a possible side effect in the zanamivir SPC, the information in UK reports was not sufficient to allow this association to be further assessed.

4.4 The safety of influenza antivirals in pregnancy

Pregnant women, particularly those in the 3rd trimester, were at high risk of serious complications of swine influenza. It was therefore essential that pregnant women received appropriate antiviral treatment during the pandemic. In May 2009, the EU Committee for Medicinal Products for Human Use (CHMP) reviewed the available data on the safety of oseltamivir and zanamivir in pregnancy and lactation, with a view to issuing guidance on their use during the pandemic[a].

CHMP concluded that there did not appear to be any evidence to suggest that maternal exposure to oseltamivir or zanamivir was associated with adverse pregnancy or fetal outcomes. Further, CHMP advised that the overall data suggest that the benefit of using oseltamivir or zanamivir in pregnant or breastfeeding women outweighs the risk in the context of a novel influenza (H1N1v) pandemic situation. The MHRA closely monitored the safety of oseltamivir and zanamivir use in pregnancy during the pandemic.

Based upon widespread use in the UK and the rest of the world during the pandemic, there is no evidence to suggest that either oseltamivir or zanamivir carry any risks (maternal, fetal, perinatal or postnatal) when used during pregnancy.

[a] www.ema.europa.eu/humandocs/PDFs/EPAR/tamiflu/28766209en.pdf

5. DISCUSSION AND CONCLUSIONS

5.1 Pandemic vaccine safety

Up to 18 June 2010, more than 6 million doses of Pandemrix vaccine, and more than 36,000 doses of Celvapan vaccine, were given across the UK. Out of these, there were 3400 reports of suspected ADRs with Pandemrix, and 43 reports of suspected ADRs with Celvapan.

On the basis of the safety experience in clinical trials and post-licensing experience with most new vaccines, the MHRA expected the vast majority of suspected ADR reports in association with both Pandemrix and Celvapan to relate to injection-site reactions and the transient signs and symptoms of 'flu-like illness' (ie, headaches, dizziness, muscle aches, fever, fatigue, malaise). Less commonly, the MHRA also anticipated receiving reports of mild allergic-type reactions (eg, mild rashes, localised/generalised itching). It was expected that serious allergic reactions (such as anaphylaxis) would be very rare.

In addition to these possible known side effects, the MHRA also expected a significant number of 'psychogenic' events to be reported (ie, events which are not due to the vaccine itself, but due to fear or anticipation of the injection needle). 'Psychogenic' events typically involve fainting and associated symptoms.

Based on review of the suspected ADRs reported in the UK, the type and nature of the majority of ADR reports are consistent with these expectations. This is the same general ADR reporting profile as seen in other EU countries where Pandemrix and Celvapan vaccine have also been used.

There was relatively limited usage of Celvapan in the UK during the pandemic period due to the policy of limiting its use to those with a confirmed egg allergy (or who were otherwise intolerant of Pandemrix). It is therefore not possible to gain a robust picture of the relative safety profile of Celvapan in the UK, compared to Pandemrix. However, based on the few reports received in association with Celvapan, the type of suspected ADRs reported are broadly similar to those associated with Pandemrix – ie, mainly mild gastrointestinal ADRs, 'flu-like illness', myalgia/arthralgia and mild allergic reactions.

Swine flu vaccines used in the USA in 1976 were associated with a 10-fold risk of Guillain Barre Syndrome (GBS), therefore the issue of GBS following vaccination in the current pandemic campaign was monitored with particular scrutiny. The observed versus expected analysis of GBS gave an early and reassuring indication that the vaccines were unlikely to be associated with the increased risk seen in 1976.

Following substantial usage in pregnant women, there is also currently no evidence, from UK or EU data, to suggest that the swine flu vaccines are associated with any risks to the mother or unborn baby during pregnancy.

The overall safety profile of the swine flu vaccines in the UK during the pandemic has been broadly as expected and no new safety issues have emerged.

5.2 Pandemic antiviral safety

Prior to the pandemic, there had been limited exposure to oseltamivir and zanamivir in the UK. However, there had been significant use of these antivirals for managing seasonal influenza in other countries, especially in Japan and the US. Based on data from clinical trials and ADR reports in those countries prior to the pandemic, the most common side effects of oseltamivir are gastrointestinal, particularly nausea and vomiting. These may occur in approximately 10% of patients.

During the course of the pandemic up to 18 June 2010, more than 1 million courses of oseltamivir, and more than 14 000 courses of zanamivir, were supplied to patients in the UK. During this time, there were 1100 reports of suspected ADRs with oseltamivir, and 38 reports of suspected ADRs with zanamivir.

From the data assessed in this report, the most commonly reported suspected ADRs reported in association with oseltamivir and zanamivir during the pandemic were consistent with the signs and symptoms of flu-like illness (possibly due in part to the infection being treated rather than the drug) or are recognised side effects of the antivirals. These included gastrointestinal disorders (eg, nausea, vomiting, diarrhoea, stomach pains), allergic reactions (including skin rashes), headache, dizziness and non-serious psychiatric events including confusion, hallucinations, nightmares and sleep disturbance.

The oseltamivir and zanamivir SPCs include a warning about the possible risk of neuropsychiatric events including hallucinations, delirium, and abnormal behaviour, in some cases resulting in serious injury and fatal outcomes. These events were reported primarily among paediatric and adolescent patients in Japan and US during use in seasonal influenza and often had an abrupt onset and rapid resolution.

There was no indication from the UK suspected ADRs reported during the pandemic of any serious neuropsychiatric events occurring.

Based upon widespread use in the UK and the rest of the world during the pandemic, there is no robust evidence to suggest that oseltamivir or zanamivir carry any risks to the mother or unborn baby when used during pregnancy.

The overall safety profile of oseltamivir and zanamivir in the UK during the pandemic has been broadly as expected and no new safety issues have emerged. Although a range of suspected ADRs will remain under close review as the antivirals continue to be used in seasonal influenza, and any future pandemic, there was no clear evidence of any new, serious risks emerging with their use during the pandemic period.

5.3 Overall conclusions

In July 2010, the Commission on Human Medicines[a] (CHM) considered the MHRA's safety review of the swine flu antiviral medicines oseltamivir and zanamivir, and the swine flu vaccines Pandemrix and Celvapan. The CHM concluded that no new risks have been identified with the extensive use of these vaccines and drugs in the UK during the swine flu pandemic, and that the balance of their benefits and risks remains positive.

[a] An independent body of experts who give advice to UK government Ministers on the safety, quality and efficacy of medicines

It is estimated that at least 30 million and 566,000 people have been vaccinated with Pandemrix and Celvapan, respectively, across the whole of the EU during the pandemic (refer to www.ema.europa.eu/influenza/updates). The safety experience in other countries mirrors that in the UK.

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

6. REFERENCES

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7. GLOSSARY

Agitation
Emotional state of excitement or restlessness

Allergic reaction
The body's response to sensing a foreign substance (such as a vaccine), which can consist of symptoms such as a rash, itchy skin or breathing difficulties

Anaphylaxis
A life-threatening **allergic reaction**, consisting of swelling around the mouth or eyes, and difficulties in breathing or swallowing

Arthralgia
Severe pain in a joint

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

Autoimmune haemolytic anaemia
A group of blood disorders where the immune system malfunctions and produces antibodies that attack red blood cells

Autoimmune thrombocytopenia
A blood disorder where the immune system malfunctions and specifically attacks the body's own platelet blood cells

Celvapan
Influenza (H1N1v or swine flu) vaccine

Coagulation
To form a blood clot

Control group
In a clinical trial or research study, this refers to a group of participants who receive either a **placebo** or no treatment at all, for comparison with a group who receive an **active treatment**

Convulsion
Intense, involuntary muscular contractions

Cytokine
A small protein released by cells in the immune system that helps the body to generate an immune response to foreign substances

Diplegia
Paralysis affecting symmetrical parts of the body (legs, arms, etc)

Dyspnoea
Difficulty in breathing

Encephalopathy

A syndrome of brain dysfunction

Erythema multiforme
A type of **allergic reaction** that occurs in response to medications, infections or illness. Its symptoms include inflammatory skin eruptions or rashes. There are two forms: a minor form which is not serious, and a major form (also known as **Stevens-Johnson syndrome**) which is more severe

Facial palsy
Paralysis or weakness on one side of the face

Fatigue
Mental or physical tiredness

Febrile illness
A non-specific term for an illness accompanied by fever

Febrile seizure
A **seizure** accompanying a fever

Fetal (or foetal)
Related to a baby developing in the mother's womb

Gastrointestinal
Related to the stomach and intestines

Graft dysfunction
A clinical complication that can occur in patients after a lung transplant operation, which affects the function of the new lungs

Guillain Barre syndrome
A disorder characterised by paralysis and loss of reflexes in the body (without a fever), usually starting in the legs. It can sometimes follow events such as vaccinations, and is thought to be caused by an immune response

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

Haemolysis
The breakdown of red blood cells

Hallucinations
Perception of visions or sounds that are not actually real.

Hemiparesis
Weakness on one side of the body

Hemiplegia
Complete paralysis on one side of the body

Hepatic
Related to the liver

HPV
See **human papillomavirus**

Human papillomavirus (HPV)
A group of viruses, including ones that can cause warts. Some types are associated with tumours of the genital tract, notably cervical cancer

Hypoaesthesia
A loss of sensitivity in the skin to feeling touch or pain

Idiopathic thrombocytopenic purpura (ITP)
A blood disorder where the platelet (a type of blood cell which helps to form clots in injury) count is low, and there is no known cause.

Immunisation
See **vaccination**

Immunosuppression
Reduced effectiveness of the immune system

Influenza
An infectious disease caused by a virus, characterised by fever, sore throat, muscle pains, headache and cough

INR
International normalized ratio which is used to assess the time taken for a blood clot to form

Kawasaki disease
An autoimmune disease seen in children characterised by fever and rash

Lactation
Production of milk by breasts, normally at the end of pregnancy

Lethargy
See **fatigue**

Lymphadenopathy
Enlarged lymph nodes usually associated with disease. Lymph nodes are small structures located along the lymphatic system in the neck, armpit and groin, which filter bacteria and foreign particles out of lymph (fluid derived from body tissues that circulates in the body's lymphatic system)

Malaise
A feeling of fatigue and bodily discomfort

Meningitis
An infectious disease characterised by inflammation of the tissues surrounding the brain or spinal cord. Symptoms include fever, headache, vomiting and sensitivity to light

Miscarriage
Spontaneous loss of a fetus before 24 weeks of pregnancy

Monoplegia

Paralysis of a single limb, muscle, or muscle group

Multiple sclerosis
A chronic disease of the nervous system

Musculoskeletal
Relating to or involving the muscles and skeleton

Myalgia
Muscle pain

Myasthenia gravis
A disorder of the nerve and muscle systems caused by the immune system mistakenly attacking certain receptors in the body. The disease causes **fatigue** and exhaustion of muscles.

Myelitis
Inflammation of the spinal cord

Narcolepsy
A sleep disorder characterised by sudden and uncontrollable episodes of sleep

Nausea
Feeling of sickness or an urge to vomit

Neuralgia
Intense pain caused by irritation or damage to a nerve

Neuropathy
Disease or abnormality of the nervous system

Oseltamivir
An antiviral drug used in the treatment of influenza

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

Pandemrix
Influenza (H1N1v or swine flu) vaccine

Panic attack
An episode of intense fear that develops for no reason, which can trigger severe physical reactions such as rapid heart rate, sweating and shortness of breath

Paraesthesia
Abnormal skin sensations, such as tickling, itching or burning, usually associated with peripheral nerve damage

Paralysis
Loss or impairment of the ability to move a body part

Paresis
Partial **paralysis**

Pathogen
An agent that causes disease, such as bacteria or fungus

Perinatal
The time period immediately before and after birth

Pharmacovigilance
The act of monitoring the safety of medicines and vaccines

Photophobia
Abnormal sensitivity to, or intolerance of, light

Placebo
Inactive dummy treatment given in a **clinical trial** to a particular patient group so their responses can be compared with the group receiving the test medicine

Postnatal
The time period after birth

Post viral fatigue syndrome
A state of fatigue resulting from a viral infection. It is also known as **myalgic encephalomyelitis** or **chronic fatigue syndrome**

Pre-cancerous lesions
Abnormal or diseased change in a bodily organ or tissue

Pre-eclampsia
A disorder that may happen in late pregnancy, characterised by high blood pressure, persistent swelling and protein in the urine. It can lead to complications for both the mother and the developing baby

Primary care trusts
NHS groups responsible for local community health services

Prophylaxis
Prevention of disease

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

Pyrexia
Fever

Relenza
Brand name of **zanamivir**
somnolence
Respiratory
Related to breathing

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

Sensory disturbance
A term used to describe a group of symptoms such as **parasthesia**, numbness, pain and itching, which are caused by injured nerves in the spinal cord

Somnolence

Sleepiness

Stevens-Johnson syndrome
A serious bodywide allergic reaction consisting of a rash on the skin and mucous membranes (also known as **erythema multiforme** major)

Summary of Product Characteristics
Product information available at http://www.medicines.org.uk/emc/

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)

Syncope
Partial or complete loss of consciousness (a faint)

Tachycardia
An abnormal increase in heart rate

Tamiflu
Brand name of **oseltamivir**

Thoracic
Related to the chest

Toxic epidermal necrolysis
A condition where large portions of the skin's outermost layer (the epidermis) detaches from the rest of the skin. It is usually caused by an adverse reaction to a medicine, and can be fatal.

Transient
Temporary

Transplant rejection
A condition where the immune system attacks an organ that has been transplanted into the body

Trigeminal nerve
A nerve that carries information from most areas of the face to the brain

Vaccine
A weakened form of a pathogen 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

Warfarin

An anticoagulant (anti-clotting) medicine given to patients with disorders that cause unwanted blood clots to form

Wheezing
An abnormal whistling sound that accompanies difficult breathing caused by narrowed airways in conditions such as asthma

Zanamivir
An antiviral drug used for the treatment of influenza