

# 23a

## Pandemic influenza A(H1N1)v 2009 (swine flu)

### The disease

Influenza pandemics happen when a new influenza virus, to which the population has little or no immunity, emerges and starts to spread. There were three influenza pandemics in the twentieth century, in 1918-19, 1957 and 1968. The influenza pandemic of 1918-19 was the most severe with an estimated global death toll of 40-50 million people over the course of the two years. In June 2009, the World Health Organization (WHO) announced the start of a new pandemic caused by the influenza A(H1N1)v 2009 virus (commonly known in the UK as 'swine flu').

Influenza is an acute viral infection of the respiratory tract. There are three types of influenza virus: A, B and C. Further subtyping of the haemagglutinin (H) and neuraminidase (N) surface proteins of the virus is used to compare strains causing disease. This influenza pandemic is caused by a novel variant of an influenza A (H1N1) virus that emerged during 2009 (usually denoted influenza A(H1N1)v). The incubation period for influenza A(H1N1)v can be up to seven days but is most likely to be between two and five days.

The symptoms of influenza A(H1N1)v are similar to the symptoms of human seasonal influenza namely fever, chills, headache, muscle and joint pains, fatigue, loss of appetite, cough, and sore throat. Gastrointestinal symptoms (vomiting and diarrhoea) have been reported more commonly with influenza A(H1N1)v than with seasonal flu (see Green Book chapter 19). Like seasonal flu, infection with influenza A(H1N1)v may be sub-clinical or cause an unpleasant but self-limiting disease. The median duration of illness is estimated at seven days, with a further 25 per cent of people needing up to ten calendar days to recover and 25 per cent of people having symptoms for more than ten calendar days.

As with all influenza, the virus may cause severe illness in a minority of people. The illness may be complicated by bronchitis or viral or secondary bacterial pneumonia. Other complications can include otitis media, tonsillitis, septic shock, meningitis and encephalitis. The groups that are most at risk of

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hospitalisation and death are those with underlying medical conditions and pregnant women (CDC, 2009; Jamieson *et al.*, 2009). Children with neurodevelopmental problems are at particularly high risk (CDC, 2009). Complications in pregnant women, based on available information in relation to seasonal flu, include pneumonia and cardio-respiratory complications (Kort *et al.*, 1986; Neuzil *et al.*, 1998). Pregnant women are also at increased risk of influenza-related hospital admission compared with non-pregnant women and this risk increases with increasing length of gestation (Neuzil *et al.*, 1999; Jain *et al.*, 2009).

## History and epidemiology of the disease

A new influenza A(H1N1)v virus was first identified in the US in April 2009 and retrospectively in cases in Mexico (CDC, 2009). The virus is a new subtype of influenza affecting humans which contains segments of genes from pig, bird and human influenza viruses. The first illness caused by the new influenza A(H1N1)v virus was confirmed in the United Kingdom on 27 April 2009. Since then the virus has become much more common in both the UK and across the world with the World Health Organization declaring a pandemic on 11 June 2009. Unlike seasonal influenza, high rates of disease due to a pandemic virus may occur throughout the year.

As of 20 September 2009, human infections with the new virus have occurred in 191 countries worldwide including the UK (WHO, 2009). In the UK, the number of reported cases increased rapidly in June and early July 2009 with the first wave peaking in late July 2009 (Figures 1 and 2). The number of cases then fell although the level remained above the summer norm. In September 2009, the number of cases started to increase again. Figure 2 shows the number of GP consultations for influenza-like illness (ILI) per 100,000 population in England, Wales, Scotland and Northern Ireland. Rates are expected to increase further over the winter months of 2009-10.

Children and young adults appear to be most susceptible to clinical infection with the highest incidence in 5-9 and 10-14 year olds (Figure 3) with a smaller number of cases in adults older than fifty years of age (born before 1957). The low number of cases seen in those aged over fifty is thought to be due to previous exposure in this age group to similar strains of H1N1 that circulated between 1918 and 1957 (Hancock *et al.*, 2009). This pattern is confirmed amongst the deaths from confirmed influenza A (H1N1)v infection. By 7 October 2009, 88 per cent of deaths (n=69) reported in the UK had been in patients less than 65 years of age, with 85 per cent of these (where information was available) reported to have an underlying risk factor (Source: HPA).

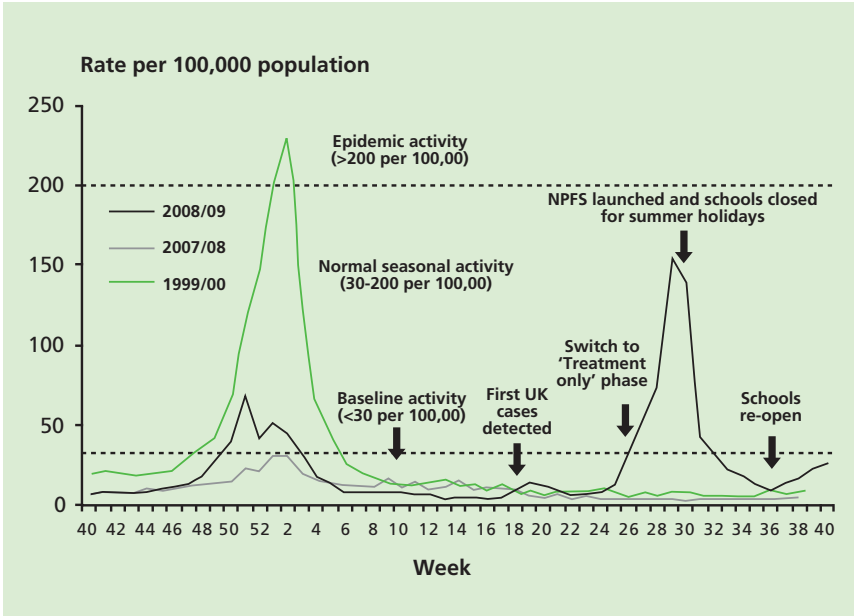


Figure 1 Weekly incidence of ILI/100,000 in England (source: RCGP/HPA)

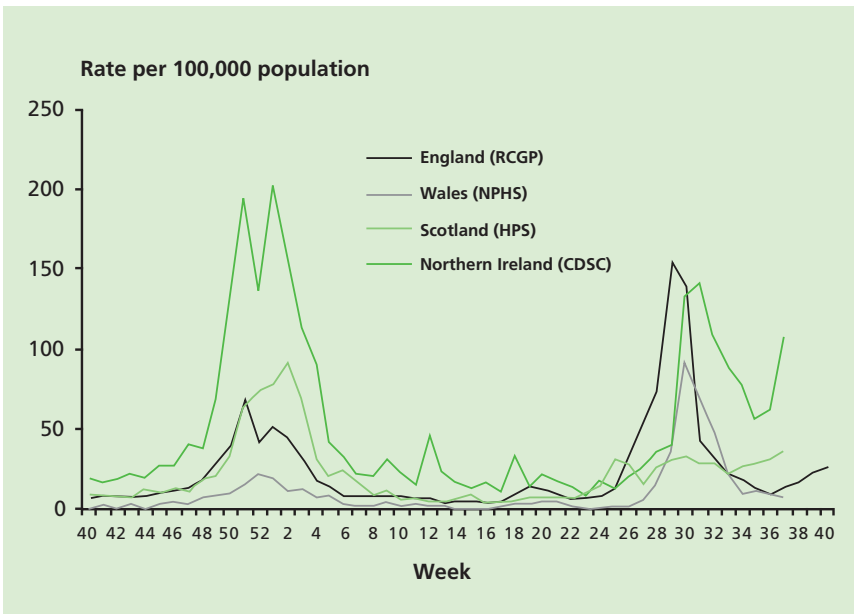


Figure 2 GP weekly consultation rates for influenza/ILI in the UK national sentinel influenza schemes, 2008/09.

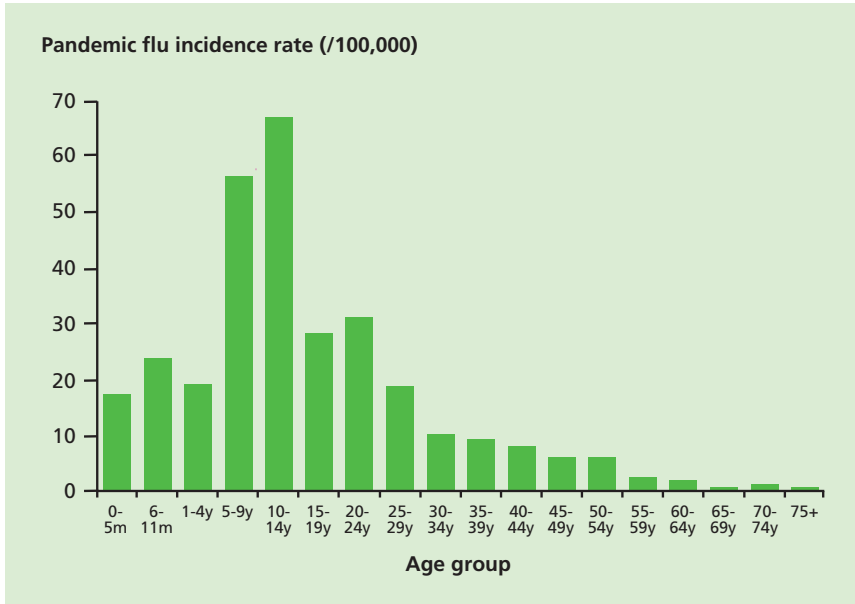


Figure 3 Age-specific incidence of confirmed pandemic H1N1 cases in England, April-30 July 2009 (Source: HPA/Fluzone)

### The influenza A(H1N1)v vaccination

As the strain that will cause a pandemic cannot be predicted, influenza vaccines against a new pandemic virus cannot be produced until the specific virus strain has started to circulate. Prior to this pandemic, however, vaccine manufacturers had developed and tested new types of influenza vaccines that could be adapted when a pandemic arose. These monovalent (i.e. single strain) vaccines were developed with antigen from H5N1 influenza viruses - a virus to which most people have no immunity. The influenza A(H1N1)v vaccines are, therefore, the same as these H5N1 vaccines except that the virus antigen comes from the WHO pandemic declared strain A/California/07/2009.

There are two influenza A(H1N1)v vaccine products available for use in the UK. Pandemrix<sup>®</sup>, manufactured by GlaxoSmithKline, is a split virion, inactivated, adjuvanted vaccine. It is a monovalent vaccine containing 3.75 micrograms of antigen. The antigen used is A/California/07/2009 (H1N1)v-like strain (X-179A), propagated in fertilised hens' eggs. The vaccine contains an adjuvant (AS03) to help boost the immune response. AS03 adjuvant is composed of squalene, DL- $\alpha$ -tocopherol and polysorbate 80.

Celvapan<sup>®</sup>, manufactured by Baxter Healthcare, is a whole virion, inactivated, vero cell derived vaccine containing 7.5 micrograms of antigen. The antigen used is the wild-type A/California/07/2009 H1N1 strain. The whole virion is inactivated both by formaldehyde and UV-irradiation. It does not contain an adjuvant.

Both vaccines are inactivated, do not contain live viruses and cannot cause flu.

Pandemrix<sup>®</sup> is supplied in multi-dose vials (see below) and contains five micrograms of thiomersal as a preservative. This is added to prevent bacterial contamination occurring during the preparation and subsequent storage and use of the vaccine.

There is no evidence of risk from thiomersal-containing vaccines, including for children, pregnant women and their offspring. In 2003, the Committee on Safety of Medicines (CSM) concluded that the balance of benefits and risks of thiomersal-containing vaccines remains overwhelmingly positive (CSM, 2003). In 2004, the European Agency for the Evaluation of Medicinal Products (EMA) also concluded that studies show no association between vaccination with thiomersal-containing vaccines and specific neurodevelopmental disorders (EMA, 2004). A more recent study has also shown no association between neuropsychological functioning at the age of seven to ten years and exposure to mercury during the prenatal period, the neonatal period and the first seven months of life (Thompson *et al.*, 2007).

### Storage

Both vaccines should be stored in the original packaging at +2°C to +8°C and protected from light. All vaccines are sensitive to some extent to heat and cold. Heat speeds up the decline in potency of most vaccines, thus reducing their shelf life. Effectiveness cannot be guaranteed for vaccines unless they have been stored at the correct temperature. Freezing may cause increased reactogenicity and loss of potency for some vaccines. It can also cause hairline cracks in the container, leading to contamination of the contents.

Pandemrix<sup>®</sup> must be used within 24 hours after mixing, storing it either in a fridge or at a room temperature (see below for details).

Celvapan<sup>®</sup> must be used within three hours once the vial has been removed from the fridge (even if the bung has not been pierced).

Both vaccines should be administered as soon as possible after withdrawal from the vial.

## Presentation

### Pandemrix®

The outer box of Pandemrix® contains three inner boxes. Inside you will find one large box containing 50 multidose vials of vaccine antigen suspension and two smaller boxes, each containing 25 vials of adjuvant emulsion. The two vials (one vaccine antigen and one adjuvant) need to be mixed prior to administration.

Instructions for mixing Pandemrix® (see Figure 4) are:

1. Mark the larger vial containing the vaccine antigen with the date, time and the initials of the immuniser immediately before mixing the vaccine. Return the boxes to the fridge.
2. Let both vials (one vaccine antigen and one adjuvant) reach room temperature before mixing. This should only take a few minutes.

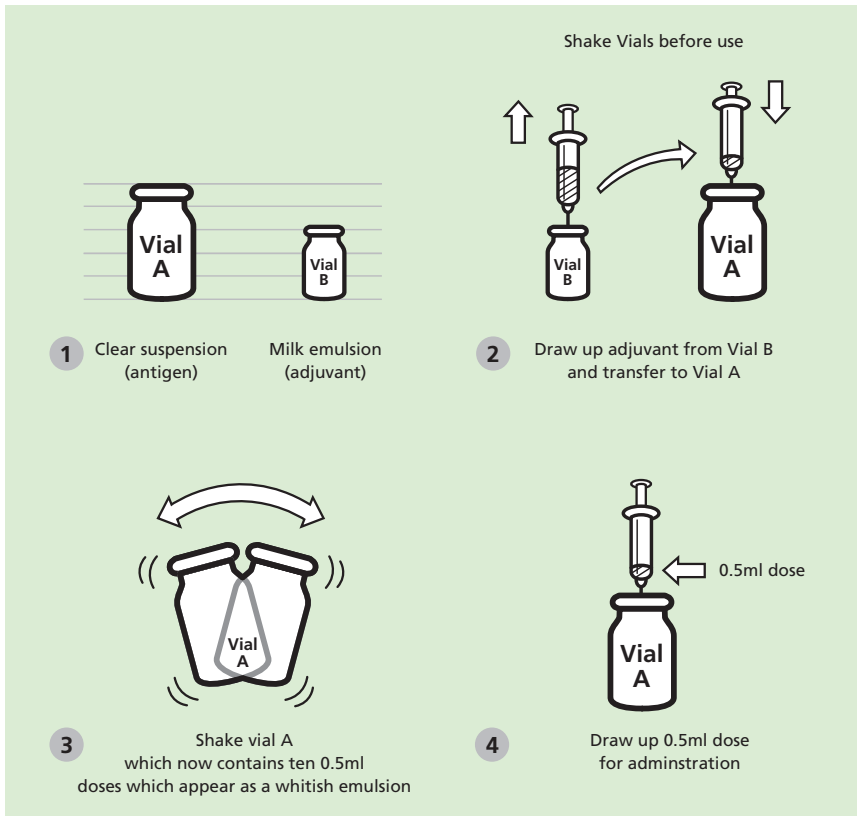


Figure 4 How to mix Pandemrix® vaccine prior to administration.

3. Check both vials for any particles. Shake both vials. Then draw up all of the adjuvant emulsion into the syringe. Inject this into the vial containing the antigen suspension.
4. Shake the vial of the mixed antigen and adjuvant again. This vaccine should now resemble a whitish emulsion. In the event of other variation being observed, discard the vaccine.
5. The mixed vial now contains ten (0.5ml) doses of vaccine.
6. Before each dose is administered, the vial should be shaken well.
7. The vaccine should be drawn up into the dose-sparing syringe with fixed needle and should be administered immediately.

### **Celvapan®**

Celvapan® is supplied already mixed in a multi-dose vial. Each vial contains ten (0.5ml) doses.

1. Mark the vial with the date, time and the initials of the immuniser immediately on removal from the fridge. Return the box to the fridge.
2. The vial should be allowed to reach room temperature. This should only take a few minutes.
3. Check the vial for any foreign particles. The vial should be shaken well before each dose is administered. The vaccine appears as a translucent, colourless solution.
4. The vaccine should be drawn up into the dose-sparing syringe with fixed needle and should be administered immediately.
5. Shake the multi-dose vial before subsequent use.

Both Pandemrix® and Celvapan® are manufactured and packaged without the use of latex.

### **Dosage and schedule**

The two vaccine products are not interchangeable and the same vaccine product must be used if a two-dose schedule is being followed.

If available, children aged six months to 18 years should receive Pandemrix® as there are currently no data on the use of Celvapan® in children. Although there are no data on the use of Pandemrix® in children under three years, children aged six months to three years who fall into the clinical at-risk groups should receive Pandemrix®, as it is likely that the immune response will be sufficient to provide some benefit in this high-risk group.

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Age	Dose
	<b>Pandemrix®</b>
Children aged 6 months to under 10 years	Two doses of 0.25ml (i.e. half the normal dose) given at least three weeks apart.
Adults and children aged 10 years and above	A single injection of 0.5ml.
Immunocompromised individuals aged 10 years and above	Two doses of 0.5ml given at least three weeks apart.
	<b>Celvapan®</b>
Adults and children aged 6 months and above	Two doses of 0.5ml given at least three weeks apart.

Pregnant women should be given Pandemrix® since a one-dose schedule with this vaccine appears to give adequate levels of antibodies and thereby confers more rapid protection than would be afforded by a two-dose schedule at a time when pandemic influenza viruses are circulating.

### Administration

The vaccines are given by intramuscular (IM) injection into the upper arm or anterolateral thigh. However, individuals with a bleeding disorder should be given the vaccine by deep subcutaneous (SC) injection to reduce the risk of bleeding.

For IM and SC injections, the needle needs to be sufficiently long to ensure that the vaccine is injected into the muscle or deep into subcutaneous tissue. Studies have shown that the use of 25mm needles can reduce local vaccine reactogenicity (Diggle *et al.*, 2000; Diggle *et al.*, 2006). Fixed 25mm 25G (orange) needles and syringes are supplied and are recommended for administering these vaccines.

The influenza A(H1N1)v vaccine can be given at the same time as other vaccines including seasonal influenza vaccine and other childhood vaccines. Vaccines should be given at separate sites, preferably in different limbs.

Individuals who have had influenza A(H1N1)v infection can safely be vaccinated, however vaccination provides no additional benefit in those who have had laboratory confirmed infection. In the absence of a documented laboratory confirmed diagnosis of influenza A(H1N1)v infection, individuals should be vaccinated.

The site at which each vaccine is given, the vaccine product name and the batch numbers of the vaccines should be recorded in the individual's records and on the patient's appointment card.

### Disposal

Equipment used for vaccination, including used vials, should be disposed of at the end of a session by sealing in a proper, puncture-resistant 'sharps' box, according to local authority regulations and guidance in the Technical Memorandum 07-01 (Department of Health, 2006).

### Recommendations for the use of the vaccine

As with the seasonal influenza programme, the primary objective of the influenza A(H1N1)v immunisation programme is to protect those who are most at risk of serious illness or death should they develop influenza. This includes both the risk of influenza A(H1N1)v infection exacerbating any underlying disease that the patient may have, as well as the risk of serious illness from influenza A(H1N1)v infection. Other objectives include reducing transmission of the infection, thereby contributing to the protection of vulnerable patients who may have a suboptimal response to their own immunisations.

Certain groups of people are at higher risk of developing complications from influenza A(H1N1)v. These include individuals with underlying health conditions who fall into the various clinical at-risk groups shown in Table 1 and pregnant women. It is important these groups receive the vaccine to protect against severe disease. As this is a new virus, most of the UK population have not been exposed to this virus before and will have no immunity and are therefore at risk of infection. A higher proportion of people over 65 years of age appear to have some immunity as a result of exposure to similar viruses in the past (Hancock *et al.*, 2009). For this reason, healthy individuals aged over 65 years are not being prioritised for influenza A(H1N1)v vaccination.

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Immunocompromised individuals may have a suboptimal immunological response to the vaccine. In addition to offering vaccination to these patients, their household contacts should be offered vaccination to reduce the risk of exposure. 'Household contact' is defined as individuals who expect to share living accommodation on most days over the whole pandemic period and therefore continuing close contact is unavoidable. This may include carers.

Frontline health and social care workers should also receive the influenza A(H1N1)v vaccine as they are at increased risk of exposure to the virus and increased risk of transmitting the virus to vulnerable patients and to others including their own family members. Frontline staff are those who have regular clinical contact with patients and who are directly involved in patient care.

Patients should be advised that the influenza A(H1N1)v vaccine will not protect against other types of influenza that may be circulating during the influenza season. Patients who are normally offered the seasonal influenza vaccine (see p.190 of the Green Book) should still be offered the seasonal influenza vaccine.

### Contraindications

There are very few individuals who cannot receive the swine flu vaccine.

The vaccines should not be given to those who have had:

- a confirmed anaphylactic reaction to a previous dose of the vaccine, or
- a confirmed anaphylactic reaction to any component of the vaccine.

Pandemrix<sup>®</sup> should not be given to those who have had:

- a confirmed anaphylactic reaction i.e. marked dyspnoea or hypotensive symptoms (collapse/loss of consciousness) to egg products (as the vaccine is prepared in hens' eggs).

Celvapan<sup>®</sup> is grown in mammalian cells and does not contain egg.

Confirmed anaphylaxis is rare (see chapter 8 for further information). Other allergic conditions such as rashes may occur more commonly and are not contraindications to further immunisation. A careful history of the event will often distinguish between true anaphylaxis and other events that are either not due to the vaccine or are not life threatening. In the latter circumstance, it may be possible to continue the immunisation course. Specialist advice must be sought on the vaccines and the circumstances in which they could be given. The risk to the individual of not being immunised must be taken into account.

Table 1 Clinical risk groups who should receive the influenza immunisation

Clinical risk category	Examples (decision based on clinical judgement)
Chronic respiratory disease, asthma	<p>Chronic obstructive pulmonary including disease (COPD) including chronic bronchitis and emphysema; bronchiectasis, cystic fibrosis, interstitial lung fibrosis, pneumoconiosis and bronchopulmonary dysplasia (BPD).</p> <p>Asthma that requires continuous or repeated use of inhaled or systemic steroids or with previous exacerbations requiring hospital admission.</p> <p>Children who have previously been admitted to hospital for lower respiratory tract disease.</p>
Chronic heart disease	<p>Congenital heart disease, hypertension with cardiac complications, chronic heart failure, individuals requiring regular medication and/or follow-up for ischaemic heart disease.</p>
Chronic renal disease	<p>Chronic renal failure, nephrotic syndrome, renal transplantation.</p>
Chronic liver disease	<p>Cirrhosis, biliary atresia, chronic hepatitis.</p>
Chronic neurological disease	<p>Stroke, transient ischaemic attack (TIA).</p>
Diabetes requiring insulin or oral hypoglycaemic drugs	<p>Type 1 diabetes, type 2 diabetes requiring oral hypoglycaemic drugs, and diet controlled diabetes.</p>
Immunosuppression	<p>Immunosuppression due to disease or treatment. Patients undergoing chemotherapy leading to immunosuppression. Asplenia or splenic dysfunction. HIV infection at all stages. Individuals treated with or likely to be treated with systemic steroids for more than a month at a dose equivalent to prednisolone at 20mg or more per day (any age) or for children under 20kg a dose of 1mg or more per kg per day.</p>

However, some immunocompromised patients may have a suboptimal immunological response to the vaccine

### Precautions

Minor illnesses without fever or systemic upset are not valid reasons to postpone immunisation. If an individual is acutely unwell, immunisation may be postponed until they have fully recovered. This is to avoid confusing the differential diagnosis of any acute illness by wrongly attributing any signs or symptoms to the adverse effects of the vaccine.

### Pregnancy and breast-feeding

All pregnant women should be vaccinated as they are at increased risk of complications from swine flu. A study of over 2000 pregnant women who received influenza vaccine demonstrated no associated adverse fetal effects (Heinonen *et al.*, 1973). There is no evidence of risk from vaccinating pregnant women, or those who are breast-feeding, with inactivated viral or bacterial vaccines or toxoids (Plotkin *et al.*, 2009).

Pregnant women should be given Pandemrix<sup>®</sup> as this vaccine appears to give adequate levels of antibodies after a single dose thereby conferring more rapid protection than would be afforded with Celvapan<sup>®</sup>.

### Premature infants

It is important that premature infants who have clinical risk factors are protected as early as possible and therefore have their immunisations at the appropriate age. Influenza A(H1N1)v vaccine should be considered after the child has reached six months of age. As there are no paediatric data for Celvapan<sup>®</sup>, it is advised that these children have Pandemrix<sup>®</sup>.

### Immunosuppression and HIV infection

Individuals with immunosuppression and HIV infection (regardless of CD4 count) are at high risk of the complications of influenza A(H1N1)v and should be offered vaccine in accordance with the recommendations above. As these individuals may not make a full antibody response to vaccination, a second dose is recommended and their household contacts should also be offered vaccination (see above).

## Adverse reactions

Current information on the adverse reactions seen following influenza vaccination is based on the reactions observed following vaccination with similar influenza vaccines containing the H5N1 virus and early results from the clinical trials of H1N1v vaccines. Experience with seasonal flu vaccines has shown that changing the strain of virus in a vaccine does not substantially alter the safety profile of the vaccine.

### Pandemrix®

Headache, fever, fatigue, arthralgia, myalgia, induration, swelling, pain and redness at injection site are very common side effects. Other common reactions include lymphadenopathy, increased sweating, shivering, influenza-like illness, and injection site reactions such as ecchymosis, warmth, pruritus.

### Celvapan®

Pain at the injection site was a very common side effect. Other common side effects include nasopharyngitis, headache, dizziness, vertigo, arthralgia, myalgia, pharyngolaryngeal pain, hyperhidrosis, pyrexia, chills, fatigue, malaise, and local injection site reactions such as induration, erythema, swelling and haemorrhage at the site of injection.

As with any new vaccine, rare and very rare side effects may not be identified or be excluded until the vaccines are used in much larger numbers of people in the general population. Robust systems are in place in the UK to identify any rare and serious risks.

A recent study in the UK found that there is no association between Guillain-Barré syndrome (GBS) and seasonal flu vaccines although there is a strong association between GBS and influenza-like illness. The increased risk of GBS syndrome after influenza-like illness, if specific to infection with influenza virus, together with the absence of a causal association with influenza vaccine suggests that influenza vaccine should protect against GBS (Stowe *et al.*, 2009). GBS has been reported very rarely after immunisation with influenza vaccine (one case per million people vaccinated in one US study (Lasky *et al.*, 1998). In 1976, a cluster of GBS cases was reported in association with the swine flu vaccines used in the United States. The exact reason why the 1976 vaccine appeared to increase the risk of GBS remains unknown, but it was estimated that around one extra case of GBS occurred for every 100,000 doses of vaccine given (Schonberger *et al.*, 1979). Surveillance of GBS following

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influenza A(H1N1)v infection and vaccination has been established through the British Neurologists Surveillance Unit (BNSU) and the British Paediatric Surveillance Unit (BPSU). Current data suggest, however, that the benefits of vaccination will outweigh any risk of GBS.

The following adverse events have been reported very rarely after seasonal flu vaccination over the past 30 years but no causal association has been established; neuralgia, paraesthesiae, convulsions and transient thrombocytopenia, vasculitis with transient renal involvement and neurological disorders such as encephalomyelitis and neuritis.

Suspected reactions to the influenza A(H1N1)v vaccines should be reported to the Medicines and Healthcare products Regulatory Authority (MHRA) using the Swine Flu ADR portal which will remain in operation for the duration of the pandemic. This is available at [www.mhra.gov.uk/swineflu](http://www.mhra.gov.uk/swineflu). Suspected adverse reactions to seasonal flu vaccines should also be reported via this Portal. As with the Yellow Card Scheme, the swine flu ADR portal is open to members of the public as well as healthcare professionals. For those without internet access, reports may also be submitted on Yellow Cards.

### Management of suspected cases, contacts, carriers and outbreaks

There are antiviral drugs available which can be used to treat influenza A(H1N1)v and in some circumstances to prevent influenza A(H1N1)v.

Guidance on the treatment of influenza with antiviral drugs is available from the Health Protection Agency (<http://www.hpa.org.uk/HPA/Topics/InfectiousDiseases/InfectionsAZ/1240812234677/#treatment>)

The Department of Health has supplied clinical guidance for healthcare professionals (<http://www.dh.gov.uk/en/Publichealth/Flu/Swineflu/InformationandGuidance/index.htm>)

### Post-exposure prophylaxis

Prophylaxis after contact with a case of pandemic flu needs to be considered in those at highest risk, many of whom will also have been targeted for vaccination (DH, 2009). Please refer to the detailed guidance document available from (<http://www.dh.gov.uk/en/Publichealth/Flu/Swineflu/InformationandGuidance/index.htm>)

Prophylaxis with antivirals should be considered regardless of vaccination status, particularly in immunosuppressed individuals who may have a sub-optimal response to vaccine.

Although post-exposure vaccination is unlikely to be effective within the time period required, consultation following a possible exposure does provide an opportunity to provide longer term protection in those who have not yet been fully vaccinated. Influenza A(H1N1)v vaccine should therefore be offered as soon as possible to anyone in a clinical risk group who has not yet been fully vaccinated.

## Supplies

### Vaccines

- Pandemrix<sup>®</sup> – manufactured by GlaxoSmithKline
- Celvapan<sup>®</sup> – manufactured by Baxter Healthcare

In England, pandemic influenza A (H1N1)v vaccine will be supplied as detailed in the letter issued 30 September by Professor Salisbury, Director of Immunisation ([http://www.dh.gov.uk/en/Publicationsandstatistics/Lettersandcirculars/Dearcolleagueletters/DH\\_106300](http://www.dh.gov.uk/en/Publicationsandstatistics/Lettersandcirculars/Dearcolleagueletters/DH_106300))

In Scotland, pandemic influenza A (H1N1)v vaccine will be supplied as detailed in the letter issued 13 October by Dr. Kevin Woods, Director-General and Chief Executive NHS Scotland.

In Wales, pandemic influenza A (H1N1)v vaccine will be supplied as detailed in the letter issued 16 October by Dr Jewell, Chief Medical Officer; <http://wales.gov.uk/topics/health/ocmo/publications/cmo/cmo09/?lang=en>

In Northern Ireland, pandemic influenza A (H1N1)v vaccine will be supplied as detailed in the latest Chief Medical Officer's letter issued by the Department of Health, Social Services and Public Safety. Details can be found at: <http://www.dhsspsni.gov.uk/>

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