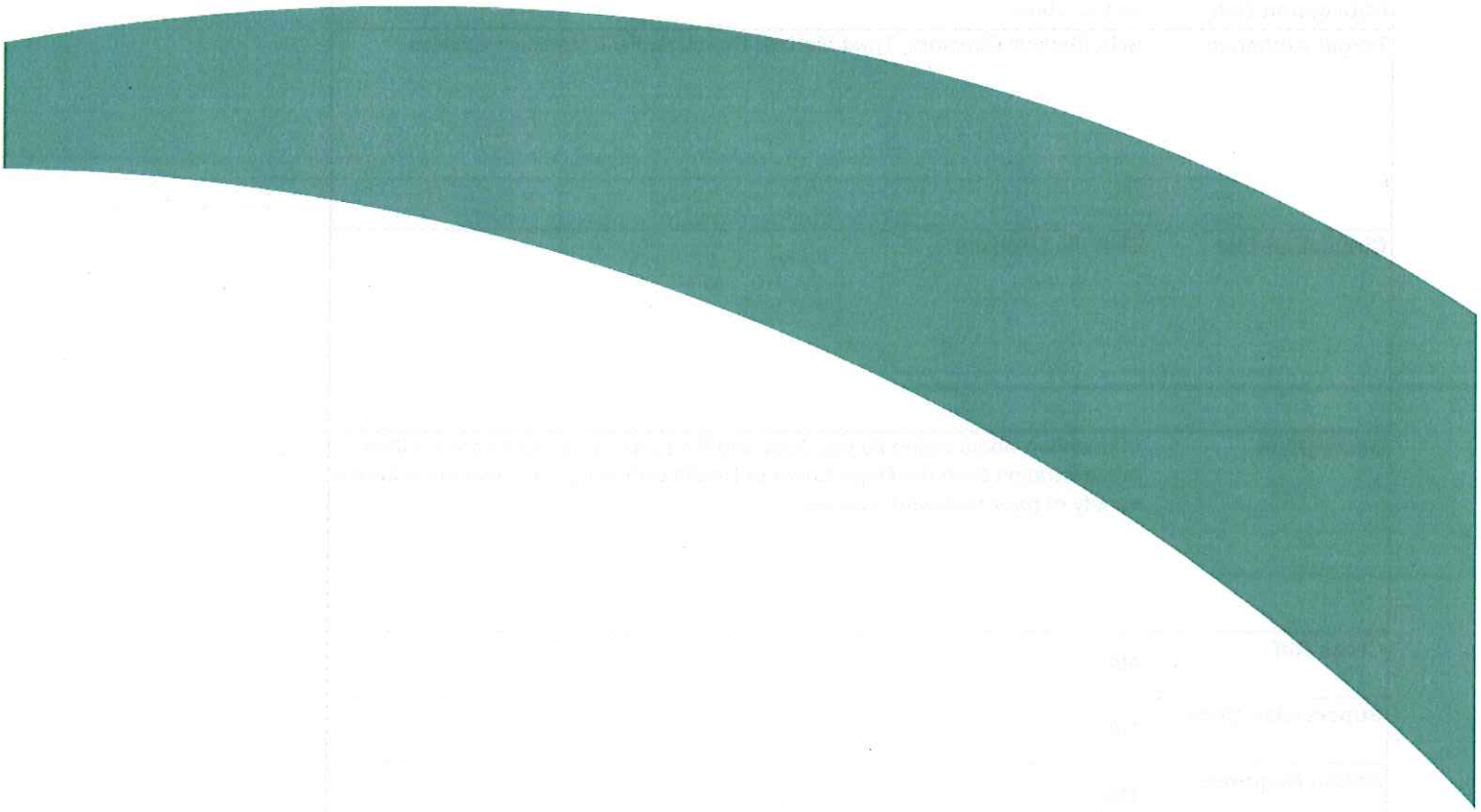

Clinical Professionals Brief on Swine Flu Vaccination

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Clinical Professionals Brief on Swine Flu Vaccination

I encourage all clinical staff to consider carefully the evidence for swine flu vaccination in order to protect their patients, colleagues, families and themselves. This is particularly important at a time when demand on clinical services within the NHS may be high. Vaccination of frontline healthcare workers against swine flu remains a key aspect of the NHS swine flu resilience plan.

This document provides details of the swine flu vaccines, as well as the vaccination programme and explores some of the surrounding issues which may be of particular interest to clinicians.

Wherever possible, the sources of the information have been referenced so that those who wish to explore the evidence further can do so.

Please circulate this document as widely as possible among the clinical professionals within your organisation.

Additional information about the swine flu vaccination programme can be found on the Department of Health website:
http://www.dh.gov.uk/en/Publichealth/Flu/Swineflu/InformationandGuidance/Vaccinationprogramme/index.htm

Professor Sir Bruce Keogh
NHS Medical Director
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Contents

Introduction

This paper aims to provide clinicians with further information about the swine flu vaccination programme. It combines information about the vaccines and the proposed programme for their administration from the Department of Health with evidence from a variety of peer-reviewed sources. Should you have any further queries, please contact your Trust flu lead who should be able to direct you further.

Influenza A H1N1v (swine flu)

The first cases of swine flu emerged in Mexico in April 2009. The first cases were reported in the UK later that month. On 11th June 2009 the WHO declared a pandemic[1]. This is a new strain of influenza, different from any strain previously affecting humans. For this reason, the majority of people will not have immunity to it[2].

The role of swine flu vaccination

Vaccinating healthcare workers is a key aspect of the NHS swine flu resilience plan[3]. It is estimated that, in addition to the usual winter pressures faced by the NHS, up to 5% of the NHS workforce may be unable to work because of swine flu in the peak weeks of a surge[4]. With high uptake of vaccination it is likely that this proportion can be reduced.

Healthcare workers as a target population

Healthcare workers, with their high levels of exposure, are at high risk of occupationally acquired infections[5]. The Government has therefore decided that frontline health and social care staff should be offered the swine flu vaccination. The definition of which healthcare staff are included is the same as those who are offered the seasonal flu vaccine. Advice on this is set out in the Green Book[6]. Frontline healthcare workers who provide direct patient care will be offered swine flu vaccination at the same time as the priority groups[7].

As well as this personal risk, healthcare workers may transmit infections to vulnerable patients. Patients with existing co-morbidities (those who would be routinely offered seasonal flu vaccine) are at increased risk from swine flu. As of 1st October 2009, across all age groups, 81% of those who have died in England from swine flu had an underlying health condition[8]. Flu- Clinical Information Network (FLU-CIN) data suggest that across all age groups 60% of those hospitalised with swine flu have at least one co-morbidity[8]. This rate is high as 85% in some age groups. There are an estimated 9.36 million people in England whose health status makes them a priority for vaccination[9].

Composition of the vaccines

The UK has contracts for the supply of vaccine from two different manufacturers. The core characteristics of the vaccines are outlined in Table 1 below:

Table 1: Characteristics of the swine flu vaccines[10] [11]

Manufacturer	**GlaxoSmithKline (GSK)**	**Baxter**
Brand name	**Pandemrix®**	**Celvapan®**
Vaccine type	Inactivated, split virion	Inactivated, whole virion
Viral valency	Monovalent	Monovalent
Virus strain	A/California/07/2009 (H1N1)v-like strain (X-179A)	Wild-type A/California/07/2009 H1N1
Antigen quantity (µg)	3.75	7.5
Production method	Egg based	Vero cell-derived culture. Inactivated by formaldehyde and UV-irradiation
Adjuvant	AS03 Squalene DL-α-tocopherol Polysorbate 80	None
Thiomersal based Preservative	Yes	No
Other constituents	Octoxynol 10 Sodium chloride Disodium hydrogen phosphate Potassium dihydrogen phosphate Potassium chloride Magnesium chloride Water for injections	Trometamol Sodium chloride Water for injections Polysorbate 80

Potential side effects

Very common side effects for Pandemrix® are likely to include headache, myalgia, arthralgia and injection site pain, redness or bruising. Common side effects are likely to include influenza like illness and lymphadenopathy[10].

Very common side effects for Celvapan® are likely to include injection site pain. Common side effects are likely to include headache, myalgia, arthralgia dizziness, vertigo, and nasopharyngitis[11].

Guillain Barré Syndrome (GBS)

GBS is a rare, immune-mediated disease characterised by acute, rapidly-evolving, bilateral, ascending neuromuscular paralysis. Although it can be fatal, it usually resolves, but may require a period of intensive care[12]. GBS is a naturally occurring condition so it is inevitable that cases may occur and be reported not long after vaccination.

In 1976 in the US a pandemic swine flu vaccine programme was suspended after a significant increase in the number of cases of GBS were reported with concerns about an association with the vaccine[13]. It is thought that one extra case of GBS occurred with every 100,000 doses of vaccine given[14]. The exact mechanism behind this association is not known. Several studies in the US and elsewhere have looked at possible links between influenza vaccines used since 1976 and GBS. No convincing evidence of an increased risk has been demonstrated[15].

A recent UK study that used GP data showed the relative incidence of GBS within 90 days influenza vaccination was 0.76 (95% CI 0.41 to 1.40). The same study concludes that the risk of GBS within 90 days of an influenza-like illness is 7.35 (4.36 to 12.38)[16].

Adjuvants

Adjuvants are substances added to vaccines to improve their immunogenicity and efficacy[17]. They work by promoting a more potent immunological response than would be generated by the antigen alone. There are different types of adjuvants including oil-in-water emulsions and aluminium based compounds.

The main advantages of adjuvants are that they are antigen sparing and that they help to produce broader protection[18]: Adjuvants permit a smaller amount of antigen to be used in each dose of vaccine thus enabling a greater number of doses to be made in a limited time. In trials looking at H5N1 vaccines that used the same adjuvant as in Pandemrix®, the inclusion of the AS03 adjuvant was shown to induce broader, cross-clade protection[19].

A study using H5N1 vaccine (Prepandrix® by GSK) has shown significantly more injection site pain with AS03 adjuvanted vaccine (90%) than non-adjuvanted vaccine (38%) ($P<0.0001$)[19]. Approximately 40,000 people have been vaccinated with AS03 containing vaccines in clinical trials since the late 1990s with no serious adverse events thought to be caused by the vaccine[18].

Squalene

One of the components of the AS03 adjuvant system is squalene. Squalene is a naturally occurring substance that is found in humans, other animals and plants. It is commercially extracted from fish (shark liver) oil. Since 1997, more than 25 million doses of one squalene containing vaccine (FLUAD by Novartis) have been administered[20]. There have been no associated severe adverse events thought to be caused by the vaccine.

It has been postulated that the use of squalene was linked to 'Gulf-war syndrome' as anti-squalene antibodies were identified in some veterans who received anthrax vaccine. It is now known that squalene was not added to the vaccines administered to these veterans, and that there were technical deficiencies in the reports[21].

The WHO Global Advisory Committee on Vaccine Safety (GACVS) has concluded that "The absence of significant vaccine-related adverse events following this number of doses suggests that squalene in vaccines has no significant risk." [22]

Thiomersal

Thiomersal is a mercury containing preservative. Pandemrix® contains small amounts of this[10]. Both the GACVS[23] and the UK Commission on Human Medicines (CHM) have issued statements that there is no evidence of neurodevelopmental adverse effects caused by such levels of thiomersal in vaccines. The CHM goes on to say that "The only evidence of harm due to thiomersal is a small risk of hypersensitivity reactions (that typically include skin rashes or local swelling at the site of the injection). The CHM advises that the balance of risks and benefits of thiomersal-containing vaccines is overwhelmingly positive." [24]

Pregnancy and lactation

Pregnant women are at higher risk of serious consequences of H1N1 infection. A review article by MacDonald *et al.* from this year cites evidence that vaccinating this population against seasonal flu reduces rates of potentially severe influenza and influenza-like illness in both mothers and infants. There is no evidence of increased vaccination-related adverse events in this group[25].

The Summary of Product Characteristics for Pandemrix® states[10]:
"There are currently no data available on the use of Pandemrix® in pregnancy. Data from pregnant women vaccinated with different inactivated non-adjuvanted seasonal vaccines do not suggest malformations or fetal or neonatal toxicity. Animal studies with Pandemrix® do not indicate reproductive toxicity (see section 5.3).

The use of Pandemrix® may be considered during pregnancy if this is thought to be necessary, taking into account official recommendations.

Pandemrix® may be used in lactating women."

The Summary of Product Characteristics for Celvapan® states[11]:
"Data from vaccinations with interpandemic trivalent vaccines in pregnant women do not indicate that adverse foetal and maternal outcomes were attributable to the vaccine. Therefore, for pregnant women, administration of the pandemic influenza vaccine is recommended, irrespective of their stage of pregnancy.

The vaccine CELVAPAN® may be used during lactation."

The Joint Committee on Vaccination and Immunisation has advised that pregnant women should be given Pandemrix® since a one-dose schedule with this vaccine confers more rapid protection that would be afforded by a two-dose schedule with Celvapan®. There is no evidence that thiomersal-containing vaccines present a risk to pregnant women or their offspring[26] .

Timeline for vaccination programme

The first deliveries of vaccine arrived in Acute Trusts on 21st October 2009. Vaccine supplies are being delivered to GPs from 26th October 2009. It is likely to take up to "4 weeks to complete the distribution of first supplies to all GP practices"[27]. It is expected that vaccination programmes will begin as soon as deliveries are received.

Vaccination schedule

Following advice from the Joint Committee on Vaccination and Immunisation, the following vaccination schedule is recommended in the UK[26, 28]:

Pandemrix® (manufactured by GSK)

For all children aged from 6 months of age to less than 10 years of age:

- Two half doses (0.25ml) of Pandemrix® should be given with a minimum of three weeks between doses.

For individuals aged from 10 years to less than 60 years of age:

- One dose (0.5ml) of Pandemrix®

For individuals aged 60 years and over:

- One dose (0.5ml) of Pandemrix® (this advice will be reviewed when more data become available).

For immunocompromised individuals aged 10 years and over:

- Two doses (0.5ml) of Pandemrix® should be given with a minimum of three weeks between doses

Celvapan® (manufactured by Baxter)

For children from 6 months of age and adults:

- Two doses (0.5ml) of Celvapan® should be given with a minimum of three weeks between doses.

The two vaccine products are not interchangeable and the same brand of vaccine must be used for both doses if two doses are needed.

This dosage advice may change in the light of new clinical data and any such changes will be made public if and when they are made.

These recommendations are based on initial trials of the vaccines, such as a trial of Pandemrix® that was carried out in Germany. This study of 130 healthy adults aged 18-60 years showed that one dose of adjuvanted vaccine achieved >98% seroconversion at 3 weeks[29].

Seasonal flu vaccine

The seasonal flu vaccine provides immunity against three different strains of influenza. Those people who are eligible for both the seasonal and the swine flu vaccinations (including all frontline healthcare workers) are advised to get both[30]. The two vaccines can be administered at the same time.

Licensing procedure

Within the EU "all medicinal products for human and animal use derived from biotechnology and other hightechnology processes must be approved (by the European Medicines Agency (EMEA))" [31] prior to a marketing authorisation (known as a licence) being issued by the European Commission.

The EMEA assessment of the swine flu vaccines is based on a mock-up dossier process. Vaccines have been developed, tested and licensed so that once a pandemic strain is identified, it can be substituted into a vaccine that is of proven safety and efficacy. Quality and non-clinical data are then assessed prior to a variation to the licence being permitted.

The mock-up dossiers for the swine flu vaccines are based on the H5N1 (avian flu) vaccines that have previously been developed[32].

Monitoring for adverse events

The Medicines and Healthcare Regulatory Agency (MHRA) has developed a specific pharmacovigilance strategy for pandemic vaccines and antivirals[33]. There are three main elements:

- Increased passive surveillance

A separate, parallel, passive reporting system has been in place since 6th July 2009.
The web-based Pandemic ADR reporting Portal is available via www.mhra.gov.uk/swineflu . It is largely based on the existing web-based Yellow Card Scheme.

- Active Surveillance

Two parallel studies will be carried out amongst 9000 individuals of the first vaccinated cohorts for each vaccine.
This process aims to estimate the incidence of any medically-attended adverse events in vaccinated subjects.

- Data mining

GP data and electronic records will be assessed.

Conclusion

It is hoped that the information presented here will reassure individual clinicians about swine flu vaccines and enable them to promote their take up amongst frontline healthcare staff and high risk patients.

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