Inactivated Influenza Vaccines

Otfried Kistner

Summer School on Influenza, 2nd Edition

July 16 – 20, 2012, Siena, Italy

Theme 5 – Influenza Vaccines
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1933 – Start of Hunting the Flu Virus

YOICKS! AND TALLY HO!!

Yoicks! and Tally ho!!
It is reported that, with the timely aid of ferrets, our doctors have unearthed the 'flu germ at last.
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1933</td>
<td>Discovery of Influenzaviruses by successful isolation and inoculation of ferrets</td>
</tr>
<tr>
<td>1940</td>
<td>Successful replication of Influenzaviruses in the allantoic fluid of embryonated hens’ eggs</td>
</tr>
<tr>
<td>1941</td>
<td>Discovery of hemagglutination of red blood cells resulted in successful purification of Influenzaviruses by adsorption to red blood cells and subsequent elution</td>
</tr>
<tr>
<td>1943</td>
<td>Clinical trials with more than 12,000 US soldiers with a trivalent (!) Influenza vaccine demonstrate an efficacy of 70%</td>
</tr>
<tr>
<td>1945</td>
<td>Mass Immunizations of the US Army demonstrate the benefit of influenza vaccination</td>
</tr>
</tbody>
</table>
1945

First Licenced Influenza Vaccine in the USA

12 years after discovery of Influenza viruses as the cause of Influenza
1947  Major setback in Influenza vaccine development by failure of the vaccine – but: the analysis of the new isolated viruses and the vaccine strains resulted in the detection of the **Antigen Drift**: the appearance of new strains by mutations of the viral surface proteins hemagglutinin (HA) and neuraminidase (NA)

The **Influenza Surveillance System** is introduced by WHO (World Health Organization); today a network of 138 National Influenza Centers (NIC) in 108 countries and 6 **Collaborating Centers (CC)** in Australia, China, Japan, UK, and USA, until May 24, 2011 known as **GISN (Global Influenza Surveillance Network)**
Milestones of the Development of Influenza Vaccines (V)

Change of Network name
(after adoption of WHA 64.5 on 24 May 2011)

GISN
(WHO Global Influenza Surveillance Network)

GISRS
(WHO Global Influenza Surveillance and Response System)
138 National Influenza Centers (NIC) in 108 countries

http://gamapserver.who.int/mapLibrary/Files/Maps/GISRS_20120426_1.png
<table>
<thead>
<tr>
<th>Year</th>
<th>Milestone</th>
</tr>
</thead>
<tbody>
<tr>
<td>1964</td>
<td>Improvement of the vaccine in terms of reduction of reactogenicity (adverse side reactions) under retaining neutralizing activity by ether treatment of the influenza vaccine strains = Split (Virus) Vaccine</td>
</tr>
<tr>
<td>1966</td>
<td>Introduction of zonal centrifugation (continuous flow centrifugation)</td>
</tr>
<tr>
<td>1975</td>
<td>Development of SRD (Single Radial Immunodiffusion) assay</td>
</tr>
<tr>
<td>1980</td>
<td>First licensure of a Subunit Vaccine; i.e. an influenza vaccine, containing only the 2 purified surface glycoproteins, Hemagglutinin (HA) and Neuraminidase (NA) for additional improvement of tolerability</td>
</tr>
<tr>
<td>2001</td>
<td>Licensure of the first MDCK cell culture influenza vaccine (Solvay, NL)</td>
</tr>
<tr>
<td>2002</td>
<td>Licensure of the first VERO cell culture influenza vaccine (Baxter, A)</td>
</tr>
</tbody>
</table>
Key Points

- Different types of inactivated vaccine (whole, split, subunit, virosomal)
- Year round influenza vaccine timetable and limitations
- Trivalent inactivated vaccine composition – Use of A high growth reassortants for influenza A and B
- Egg-based versus cell-based influenza vaccine production
- Serological criteria for influenza vaccine licensure
- Immunogenicity of seasonal influenza vaccines in different age groups
- Immunogenicity of pre-pandemic vaccines in different age groups
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- Inactivated vaccines against A(H1N1)pdm09 virus – Different global approaches
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Types of Influenza Vaccines

- **Inactivated Vaccines**
  - Whole Virus
  - Split Virus
  - Subunit
  - Adjuvanted Vaccine (oil-in-water emulsion or Virosome)

- **Live-attenuated Vaccines**
Influenza Vaccine Types

**Whole virion vaccine:** complete, inactivated virus particles

**Split-particle vaccine:** split particles in a highly purified form

**Subunit vaccine:** purified HA and NA antigens
Characteristics of Egg-Derived Seasonal Influenza Vaccines

- Trivalent, 15 µg HA per strain (A/H1N1; A/H3N2; B)
- Produced in embryonated hens’ eggs
- Inactivated by Formalin or β-Propiroleacton
- Split, subunit, or virosomal formulation
- Non-adjuvanted (exception: one MF-59 adjuvanted vaccine for elderly adults)
- Use of High Growth Reassortants for A strain production provided by WHO Collaborating / Reference Centers such as
  - NYMC (New York Medical College), USA
  - Melbourne / CSL, Australia
  - NIBSC (National Institute of Biological Standards and Controls), UK
# Types of Seasonal Influenza Vaccines


<table>
<thead>
<tr>
<th>Vaccine (route)</th>
<th>Dosage per hemagglutinin antigen</th>
<th>Adult age range (years)</th>
<th>Examples (manufacturer)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactivated, split product, egg-derived (IM)</td>
<td>15 μg</td>
<td>≥18</td>
<td>Fluzone®, Vaxigrip® (Sanofi Pasteur); Fluarix®, Flulaval® (GlaxoSmithKline); Afluria®, Fluvax® (CSL Biotherapies)</td>
<td>Standard vaccine</td>
</tr>
<tr>
<td>Inactivated, subunit, egg-derived (IM)</td>
<td>15 μg</td>
<td>≥18</td>
<td>Agrippal®, Fluvirin® (Novartis); Influvac® (Solvay Pharmaceuticals)</td>
<td></td>
</tr>
<tr>
<td>Inactivated, split product, egg-derived (IM)</td>
<td>60 μg</td>
<td>≥65</td>
<td>Fluzone High-Dose® (Sanofi Pasteur)</td>
<td>Superior immunogenicity compared with standard dose in elderly [23]</td>
</tr>
<tr>
<td>Inactivated, split product, cell culture-derived (IM)</td>
<td>15 μg</td>
<td>≥18</td>
<td>Optaflu® (Novartis); Influvac TC® (Solvay Biologicals)</td>
<td>Uses cell culture (Madin-Darby Canine Kidney) in place of embryonated chicken eggs to grow vaccine virus</td>
</tr>
<tr>
<td>Inactivated, subunit, egg-derived, MF59-adjuvanted (IM)</td>
<td>15 μg</td>
<td>≥65</td>
<td>Fluad® (Novartis), Addigrip® (Novartis)</td>
<td>MF59 adjuvant, modest increase in immunogenicity compared with nonadjuvanted vaccine in some studies [48,49]</td>
</tr>
<tr>
<td>Inactivated, subunit, egg-derived, virosome-adjuvanted (IM)</td>
<td>15 μg</td>
<td>≥18</td>
<td>Inflexal V® (Crucell)</td>
<td>Less injection-site reactogenicity than MF59-adjuvanted vaccine [57]</td>
</tr>
<tr>
<td>Live-attenuated, egg-grown (IN)</td>
<td>10^6.5–10^7.5 FFU</td>
<td>18–49 (USA) 18–59 (Canada)</td>
<td>FluMist® (MedImmune)</td>
<td>Less efficacious compared with inactivated vaccine [21]</td>
</tr>
<tr>
<td>Inactivated, split product, egg-derived (ID)</td>
<td>9 μg</td>
<td>18–59</td>
<td>Intanza® (Sanofi Pasteur)</td>
<td>Subject of this review; noninferior compared with 15 μg of Vaxigrip IM</td>
</tr>
<tr>
<td>Inactivated, split product, egg-derived (ID)</td>
<td>15 μg</td>
<td>≥60</td>
<td>Intanza</td>
<td>Subject of this review; superior immunogenicity compared with 15 μg of Vaxigrip</td>
</tr>
</tbody>
</table>

FFU: Fluorescent focus unit; ID: Intradermal; IM: Intramuscular; IN: Intranasal.
Key Points

- Different types of inactivated vaccine (whole, split, subunit, virosomal)
- **Year round influenza vaccine timetable and limitations**
- Trivalent inactivated vaccine composition –
  Use of A high growth reassortants for influenza A and B
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Influenza vaccines are trivalent and contain the following vaccine strains:

- 1 Influenza A virus, subtype H1N1
- 1 Influenza A virus, subtype H3N2
- 1 Influenza B virus

The World Health Organization maintains a worldwide surveillance of influenza epidemiology and gives annual recommendations on the strain composition of the vaccine.
### WHO Influenza Virus Vaccine Recommendations for Northern (NH) and Southern Hemisphere (SH) 2006/2007 – 2012/2013

<table>
<thead>
<tr>
<th>Hemisphere</th>
<th>Season</th>
<th>A/H1N1</th>
<th>A/H3N3</th>
<th>B (Lineage)</th>
</tr>
</thead>
</table>
WHO Global Influenza Surveillance & Response System (GISRS)

- **VACCINE-RELATED ACTIVITIES ARE SUPPORTED**
- **FINANCIALLY & TECHNICALLY BY INDUSTRY**

**3 WHO COLLABORATING CENTERS**
- Isolate virus in eggs

**INDUSTRY; 1 UNIV LAB; 1 WHO LAB**
- Produce reassortant vaccine strains
- High growth/attenuated strains
- Produce vaccine 'seed' viruses

**INDUSTRY**
- Bulk manufacture 3 monovalent strains
- Standardize vaccine strains with reagents
- Formulate trivalent vaccine, fill in vials/syringes/sprayers and pack

**INDUSTRY**
- Release vaccine for local use

**INDUSTRY**
- Supply antigen for potency reagents
- Clinical swabs; virus isolation; preliminary analysis

**NATIONAL CENTERS**
- Detailed antigenic & genetic analysis
- Surveillance data
- Review data & recommend vaccine strains
- Review data & decide strains for licensing

**WHO**
- Recommendation

**LOCAL REGULATOR**
- Confirmation testing

**REGULATORY LABS**
- Produce potency testing reagents

**4 WHO LABS**
- Testing

**WHO Global Influenza Surveillance & Response System (GISRS)**

**Vaccine Production**
- Virus isolates
- Clinical samples
- Supply antigen for potency reagents
- Reagents
- Testing
- Vaccine for testing
- Approval
- Finished vaccine

**Surveillance Data**
- Clinical samples
- Virus isolates
- Detailed antigenic & genetic analysis
- Surveillance data
- Review data & recommend vaccine strains
- Recommendation

**WHO Global Influenza Surveillance System (GISRS)**

**Vaccine Production**
- 3 WHO COLLABORATING CENTERS
- INDUSTRY; 1 UNIV LAB; 1 WHO LAB
- INDUSTRY
- INDUSTRY
- INDUSTRY
- INDUSTRY
- INDUSTRY

**Regulatory Analysis**
- Clinical swabs
- Virus isolation
- Preliminary analysis
- Detailed antigenic & genetic analysis
- Surveillance data
- Review data & recommend vaccine strains
- Review data & decide strains for licensing

**Who**
- Recommendation

**Local Regulator**
- Confirmation testing

**Regulatory Labs**
- Produce potency testing reagents
- Testing
- Vaccine for testing
- Approval
- Finished vaccine
Schematic Illustration Of Major Activities During A Typical Influenza Vaccine Production Campaign

**Major Activities**

- Surveillance
- Strain Selection
- Reassortant Preparation
- Potency Reagent Preparation
- Vaccine Production
- Vaccine Release
- Vaccine Distribution
- Vaccine Administration

Source: James Matthews, Sanofi pasteur
(Adapted from Vaccines 4TH Edition S. Plotkin and W. Orenstein, p. 350)
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## Definitions

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Isolate (Swab)</td>
<td>original natural virus</td>
</tr>
</tbody>
</table>
| Wildtype virus (wt)                       | natural virus; isolated in  
- embryonated hens’ eggs or chicken embryo cells: accepted as vaccine seed strain  
- mammalian cell cultures:  
  not accepted as vaccine seed strain |
| High Growth Reassortant (HGR)            | Reassortant between a virus with high growth in embryonated hens’ eggs (i.e. PR 8) and the actual natural virus isolated emryonated hens’ eggs, carrying the surface glycoproteins  
  HA (hemagglutinin) and  
  NA (neuraminidase)  
  of the vaccine strain |

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Influenza Vaccine of Season 2012 / 2013
(WHO / EU Recommendations of February / March 2012)

- **Type A**
  - **Subtype H1N1**
    - A/California/7/2009-like
      - Used: HG NYMC X-179A, HG NYMC X-181, or A/California/7/2009-like
  - **Subtype H3N2**
    - A/Victoria/361/2011-like

- **Type B**
  - B/Hubei-Wujiagang/158/2009-like
    - Used: B/Hubei-Wujiagang/158/2009 or HG BX-39

HG High Growth Reassortant
Key Points

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Embryonated eggs are stored for 10 to 12 days, constantly turned to ensure the healthy development of the embryos. Courtesy: Solvay

Eggs being candled to evaluate their quality: left – healthy egg – unhealthy one to be removed. Courtesy: Solvay

Embryonated eggs at 10 to 12 days being inoculated by automated machinery. 1st larger needle (about 1 mm diameter) punches a hole in a shell and 2nd smaller needle injects a seed into the allantoic cavity of the egg followed by incubation for 2 to 3 days. It takes less than 10 seconds to inoculate a row of eggs. Courtesy: Solvay

Egg-based Influenza Vaccine Production
Projections for demand and supply seasonal influenza vaccines

<table>
<thead>
<tr>
<th>Year</th>
<th>Demand</th>
<th>(theoretical) Global Production Capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>449 million*</td>
<td>876 million**</td>
</tr>
<tr>
<td>2015</td>
<td>Depends on national policies and their implementation</td>
<td>1.764 billion**</td>
</tr>
</tbody>
</table>

1 – 2 eggs required for one dose = approx. 700 millions of eggs in 2009


**Technical studies under resolution WHA63.1 Dec 2010
No Hens – No Eggs – No Vaccine (?)
Influenza has been a significant public health problem worldwide, with three pandemics during the past century. Immunization is the most effective measure to control an influenza pandemic. Since rapid production of large amounts of influenza vaccine depends on the availability of fertile hens’ eggs to grow the viruses, there is an urgent need for the development of alternative cell culture systems, which would allow rapid scale-up of production in the event of a pandemic. This WHO meeting discussed the results of studies from several laboratories on the cultivation of influenza viruses in stable cell lines, and made recommendations for further work.
Ideal substrate to produce biologicals *

- Permanent / continuous cell line
  - MCB, WCB
  - quality controlled
- Serum-free and/or protein-free media

* WHO Technical report Series, No. 878, 1998;
CPMP/BWP/3088/99: Note for guidance on the quality, preclinical and clinical aspects of gene transfer medicinal products
# Cell Culture Technologies Used for Influenza Vaccine Production

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>Origin</th>
<th>Licensed Influenza Vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vero</td>
<td>Kidney of an African Green Monkey</td>
<td>Seasonal split and pandemic (-like) whole virus vaccines (H1N1pdm09; H5N1)</td>
</tr>
<tr>
<td>MDCK</td>
<td>Kidney of a female Cocker Spaniel</td>
<td>Seasonal and pandemic subunit vaccines (H1N1pdm09)</td>
</tr>
<tr>
<td>PER.C6</td>
<td>Human embryo retinoblast cells</td>
<td>None</td>
</tr>
<tr>
<td>EB 66</td>
<td>Duck embryonic stem cell</td>
<td>None</td>
</tr>
</tbody>
</table>

*Information shown as in public domain*
MDCK Cell-Based Influenza Vaccine Production

Electron micrograph of influenza virus particles

Cell Culture Production Plant
Courtesy: Novartis Vaccines and Diagnostics

Fermenter 4
Virus Production

Fermenter 3
Cell propagation
High Cell Density

Fermenter 2
Cell Propagation

Fermenter 1
Cell Propagation

cell line grown in suspension culture
at Novartis Behring GmbH & Co. KG.
Vero Cell-Based Influenza Vaccine Production

- Whole virus
- Split virus
- Subunit (surface antigen)
- Live attenuated

Large scale fermenters for virus production

Centrifuges for sucrose gradient purification
Key Points

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HA (Hemagglutinin) Molecule

- Receptor binding site
- Cleavage site
- Fusion peptide
Hemagglutination

... based on the interaction of the hemagglutinin of Influenzaviruses with receptors on the surface of Red Blood Cells (RBC)

The presence of many HA molecules on each virus particle resulted in a complete crosslinking of RBC's...
Determination of Hemagglutination (HA) Titer
Functional and Antigenic Sites of the HA (Hemagglutinin)
Hemagglutination / Hemagglutination-Inhibition
Determination of Hemagglutination Inhibition (HI) Titer
2.5 Antibody titration

All sera shall be assayed for anti-hemagglutinin antibody against the prototype strains by HI (Palmer et al., 1975) or SRH (Schild et al., 1975, Aymard et al., 1980) tests.

Positive and negative sera as well as reference preparations may be obtained from a reference laboratory.
The following serological assessments should be considered for each strain in adult subjects, aged between 18 and 60 (60+), and at least one of the assessments should meet the indicated requirements:

- number of seroconversions or significant increase in antihaemagglutinin antibody titre >40% (>30%),
- mean geometric increase >2.5 (>2.0);
- the proportion of subjects achieving an HI titre >40 or SRH titre >25 mm² should be >70% (>60%)
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## Comparison of Licensed Influenza Vaccines in Younger Adults

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of sero-protection (HI Titer &gt;40)</td>
<td>&gt; 70%</td>
<td>A/H1N1</td>
<td>97.8%</td>
<td>98%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A/H3N2</td>
<td>99.9%</td>
<td>97%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B</td>
<td>94.2%</td>
<td>87%</td>
</tr>
<tr>
<td>Rate of sero-conversion</td>
<td>&gt; 40%</td>
<td>A/H1N1</td>
<td>48.7%</td>
<td>63%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A/H3N2</td>
<td>71.5%</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B</td>
<td>69.7%</td>
<td>70%</td>
</tr>
</tbody>
</table>

1) Source: SmPCs
## Comparison of Licensed Influenza Vaccines in Elderly Adults

<table>
<thead>
<tr>
<th>Endpoint (Day 21)</th>
<th>CHMP Criterium</th>
<th>Strain</th>
<th>2004 – 2005 Season</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Vaccine 5</td>
</tr>
<tr>
<td>Rate of sero-protection (HI Titer ≥40)</td>
<td>&gt; 60%</td>
<td>A/ H1N1</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A/ H3N2</td>
<td>98%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B</td>
<td>84%</td>
</tr>
<tr>
<td>Rate of sero-conversion</td>
<td>&gt; 30%</td>
<td>A/ H1N1</td>
<td>28%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A/ H3N2</td>
<td>48%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B</td>
<td>62%</td>
</tr>
</tbody>
</table>

1) Source: SmPCs
Vaccines for preventing influenza in healthy adults (Review)

In this meta-analysis of influenza vaccine efficacy trials performed in healthy adults from 1977 to 2009, inactivated vaccines were reported to be 73% efficacious (54% - 84%) when vaccine strains matched circulating virus strain.

Live, attenuated vaccines were reported to be 62% efficacious (45% - 73%)
Double Blind, Placebo Controlled Trial to Demonstrate Prevention of Influenza Infection

Population
- Healthy adults 18 to 49 years of age randomized 1:1 to receive either Preflucel or placebo
- N=7250
- USA: 36 study sites
- FSI: Dec 1, 2008; LSO: June 27, 2009

Primary Objective
- Demonstrate efficacy of Preflucel to prevent infection with an influenza virus that was antigenically matched to one of the three strains in the vaccine

Secondary Objective
- Compare the Safety of Preflucel with placebo
- Quantification of antibody response to each vaccine antigen by haemagglutination inhibition (HI) assay
- Establish a correlation between the Preflucel induced HI antibodies and protection against infection

This project has been funded in whole or in part with Federal Funds from the Office of Public Health Emergency Preparedness, Office of Research and Development Coordination, under Contract No HHSO100200600013C to DynPort Vaccine Company LLC CSC.
<table>
<thead>
<tr>
<th>Strain</th>
<th>Number (%) of subjects with Influenza Infection</th>
<th>Vaccine Efficacy (%)</th>
<th>95% CI^a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VCIV</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>A/H1N1</td>
<td>11 (0.3)</td>
<td>52 (1.4)</td>
<td>79.0</td>
</tr>
<tr>
<td>A/H3N2</td>
<td>2 (0.1)</td>
<td>4 (0.1)</td>
<td>50.0</td>
</tr>
<tr>
<td>All A strains</td>
<td>13 (0.4)</td>
<td>56 (1.5)</td>
<td>77.0</td>
</tr>
<tr>
<td>B</td>
<td>0 (0.0)</td>
<td>4 (0.1)</td>
<td>100.0</td>
</tr>
<tr>
<td>Total</td>
<td>13 (0.4)</td>
<td>60 (1.7)</td>
<td>78.5</td>
</tr>
</tbody>
</table>

Overall efficacy against all matching strains is 78.5 %

Efficacy of Baxter’s Vero Cell Vaccine over the Full Season 2008 / 2009

Protection over the whole influenza season against all circulating strains including drifted strains – Overall Efficacy of 71.5%
Amelioration of Disease Symptoms in Subjects with Culture Confirmed Influenza Infections

H.J. Ehrlich et al. A Cell Culture-Derived Influenza Vaccine Provides Consistent Protection Against Infection and Reduces the Duration and Severity of Disease in Infected Individuals. Clinical Infectious Diseases 2012, 54: 946-954
Correlate of Protection

The vaccine efficacy of a Vero cell-derived inactivated trivalent split vaccine efficacy correlates with an HI titer of ≥ 15; with no added benefit at HI titers > 30

Disease Symptoms

The vaccination significantly reduces the duration and severity of disease symptoms in those individuals in which infection is not prevented;

- significantly for myalgia (P = 0.003)
- headache (P = 0.025)
- fatigue (P = 0.013)

- but also for cough (P = 0.143)
- oropharyngeal pain (P = 0.083)
Double Blind, Placebo Controlled Trial to Demonstrate Prevention of Influenza Infection

Population

- Healthy adults 18 to 49 years of age randomized 1:1 to receive either Preflucele or placebo
- N=7250
- USA: 36 study sites
- FSI: Dec 1, 2008; LSO: June 27, 2009

Primary Objective

- Demonstrate efficacy of Preflucele to prevent infection with an influenza virus that was antigenically matched to one of the three strains in the vaccine

Secondary Objective

- Compare the Safety of Preflucele with placebo
- Quantification of antibody response to each vaccine antigen by haemagglutination inhibition (HI) assay
- Establish a correlation between the Preflucele induced HI antibodies and protection against infection
Immunogenicity Endpoint: Seroprotection Number (Rate) of Subjects with Seroprotective HI Titer

All CHMP criteria (seroprotection, seroconversion, GMT Increase) for all 3 vaccine strains met

Phase 3 Efficacy Study in Adults – Study Design

Double Blind, Placebo Controlled Trial to Demonstrate Prevention of Influenza Infection

Population

- Healthy adults 18 to 49 years of age randomized 1:1 to receive either Preflucel or placebo
- N=7250
- USA: 36 study sites
- FSI: Dec 1, 2008; LSO: June 27, 2009

Primary Objective

- Demonstrate efficacy of Preflucel to prevent infection with an influenza virus that was antigenically matched to one of the three strains in the vaccine

Secondary Objective

- Compare the Safety of Preflucel with placebo
- Quantification of antibody response to each vaccine antigen by haemagglutination inhibition (HI) assay
- Establish a correlation between the Preflucel induced HI antibodies and protection against infection

This project has been funded in whole or in part with Federal Funds from the Office of Public Health Emergency Preparedness, Office of Research and Development Coordination, under Contract No HHSO100200600013C to DynPort Vaccine Company LLC CSC.
The Youden Index shows that a cut-off level of 15 already separates infected from non-infected subjects. HI Titers ≥15 may represent appropriate cut-off levels for protection. No further benefit is predicted at HI titers ≥ 30.

(a) The Youden Index was calculated as sensitivity + specificity – 1.
Conclusions Seasonal Inactivated Influenza Vaccines

- Inactivated seasonal influenza vaccines have been and are routinely produced in embryonated hens’ eggs since more than 60 years.
- These vaccines have been shown to be safe and effective in all population groups; but with reduced effectiveness in risk groups.
- Novel alternative cell culture technologies have been developed or are under development for the production of inactivated influenza vaccines.
- The world’s demand for influenza vaccine supply suggest that cell culture vaccines cannot replace egg vaccines in the next years; both technologies will be used in parallel in future.
- Clinical studies have demonstrated that cell culture vaccines are at least as safe and effective as egg vaccines.
- The immune correlate of protection of an HI titer $\geq 40$ established for egg vaccines has been confirmed for a licensed Vero cell culture vaccine.
- Next-generations vaccines are under development for further improvement of vaccine efficiency, especially in risk groups.
Spread of H5N1 in Asia and Europe by Migratory Birds

**Affected Countries**, date of first appearance
WHO confirmed fatal cases in humans (since 2003: 358 of 607 infected = 59%)

- **Air routes of migratory birds from South East Asia**

**Status July 6, 2012**

- **China**
  - Jan. 2004
  - Cumulative Number of H5N1 cases: 28
- **Hong Kong**
  - 1997
  - Cumulative Number of H5N1 cases: 6
- **Vietnam**
  - Jan. 2004
  - Cumulative Number of H5N1 cases: 61
- **Cambodia**
  - Jan. 2004
  - Cumulative Number of H5N1 cases: 19
- **Thailand**
  - Nov. 2003
  - Cumulative Number of H5N1 cases: 17
- **Indonesia**
  - Jan. 2004
  - Cumulative Number of H5N1 cases: 158
- **Pakistan**
  - 2005
  - Cumulative Number of H5N1 cases: 5
- **Lao PDR**
  - 2005
  - Cumulative Number of H5N1 cases: 2
- **Nigeria**
  - 2005
  - Cumulative Number of H5N1 cases: 1

**Spread of H5N1 in Asia and Europe by Migratory Birds**

Modified Graphik @APA, Quelle: APA/Science/UNO World Food Programme

http://www.who.int/influenza/human_animal_interface/EN_GIP_20120706CumulativeNumberH5N1cases.pdf
Key Points

- Different types of inactivated vaccine (whole, split, subunit, virosomal)
- Year round influenza vaccine timetable and limitations
- Trivalent inactivated vaccine composition – Use of A high growth reassortants for influenza A and B
- Egg-based versus cell-based influenza vaccine production
- Serological criteria for influenza vaccine licensure
- Immunogenicity of seasonal influenza vaccines in different age groups
- **Immunogenicity of pre-pandemic vaccines in different age groups**
- Pre-pandemic non-adjuvanted inactivated vaccines (H5N1, H2N2, H9N2, H7 subtype) and immunogenicity challenges
- Inactivated vaccines against A(H1N1)pdm09 virus – Different global approaches
2.5 Antibody titration

All sera shall be assayed for anti-hemagglutinin antibody against the prototype strains by HI (Palmer et al., 1975) or SRH (Schild et al., 1975, Aymard et al., 1980) tests.

Positive and negative sera as well as reference preparations may be obtained from a reference laboratory.
## Published Data on Clinical Results with Egg-Derived Candidate Pandemic Strain Vaccines

<table>
<thead>
<tr>
<th>Candidate Vaccine</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H2N2 whole virus, wildtype, egg Al(OH)_3</strong> (Hehme et. al., 2004)</td>
<td>HI ≥ 40 in 98% of subjects with 2 x 3.8 µg in 82% of subjects with 2 x 1.9 µg</td>
</tr>
<tr>
<td><strong>H9N2 whole virus, wildtype, egg Al(OH)_3</strong> (Hehme et. al, 2002)</td>
<td>HI ≥ 40 in 82% of subjects with 2 x 7.5 µg in 71% of subjects with 2 x 1.9 µg</td>
</tr>
<tr>
<td><strong>H5N1 split, RG (VN 1203), egg Non-Adjuvanted</strong> (Treanor et. al., 2006)</td>
<td>HI ≥ 40 in 58% of subjects with 2 x 90 µg in 41% of subjects with 2 x 45 µg</td>
</tr>
<tr>
<td><strong>H5N1 split, RG (VN 1194), egg Al(OH)_3</strong> (Bresson et. al., 2006)</td>
<td>HI Seroconversion (≥ 32) in 67% of subjects with 2 x 30 µg</td>
</tr>
</tbody>
</table>

**HI** hemagglutination inhibition titer  
**RG** reverse genetics reassortant
Previous Experience with HI Assay

• HI (hemagglutination inhibition) assay measures antibodies against HA (hemagglutinin) which inhibit hemagglutination of red blood cells

• HI assay using chicken or turkey erythrocytes is the standard test for evaluating the immunogenicity of influenza vaccines against seasonal human influenza virus strains

• However, this standard HI assay is insensitive for the detection of human antibody responses to avian hemagglutinins, such as H5; even in the presence of high neutralizing antibodies or virus isolation (Beare et al., 1991 and Rowe et al., 1999)

• Use of horse erythrocytes can improve the performance of the HI assay, as shown in a clinical study with an H5N3 candidate vaccine (Stephenson et al., 2004)

• Therefore, the horse HI assay is now used for serological analysis in many H5N1 clinical studies
HI Assay Using Horse Erythrocytes

- Horse erythrocytes can improve the HI assay; but
- are highly sensitive to quality (only fresh erythrocytes can be used) and source of horse erythrocytes

Horse HI titers in human subjects

<table>
<thead>
<tr>
<th>Sample</th>
<th>Horse #1</th>
<th>Horse #2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient A S1</td>
<td>320</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Patient A S2</td>
<td>320</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Patient B S1</td>
<td>160</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Patient B S2</td>
<td>1280</td>
<td>640</td>
</tr>
</tbody>
</table>

Katz J: 'Modified hemagglutination-Inhibition assay using horse red blood cells (HHI).' Presented at the WHO workshop on standardization of microneutralization assay for influenza viruses. October 2, 2006; Copenhagen, Denmark
GUIDELINE ON INFLUENZA VACCINES PREPARED FROM VIRUSES WITH THE POTENTIAL TO CAUSE A PANDEMIC AND INTENDED FOR USE OUTSIDE OF THE CORE DOSSIER CONTEXT.

Immunological assessment and criteria

The comprehensive results from the HI, SRH and microneutralisation assays will form the basis for the assessment of immunogenicity. The choice of methodology and the standardisation of the assays should be addressed by the applicant. Applicants should predefine in the protocol which immunological parameter(s) will be used in the primary analysis of immunogenicity.
Serological Analysis of H5N1 Vietnam 1203 Phase I/II Clinical Study – Comparison of HI-, SRH- and MN-Assays

Serpottection against Vietnam 1203 – 7.5 µg non-adjuvantted

CHMP Criterion

Day 0  Day 21  Day 42

0  41  76
0  69  79
7  48  48
H5N1 & H9N2 Clinical Development Program

- EU Mock-up Licensure (A/Vietnam/1203/2004)
  - Phase I/II dose-escalation study (N = 270)
  - Phase II 12-17 month booster study with strain A/Indonesia/05/2005 – FU to Phase 1/2 Study (N = 77)
  - Phase III study in younger (18-59 years) and elderly (60+ years) adults with 6, 12-15 and 24 month booster (N = 550)
  - Supportive: Phase I/II A/Indonesia/05/2005 study (N = 110)

- EU Pre-Pandemic Licensure (A/Vietnam/1203/2004)
  - Phase III study in adults, elderly, risk groups (N = 3,560)
  - Phase I/II pediatric study (N = 670)
  - Supportive: Phase I/II Single Prime Boost study (N = 230)

- Japan H5N1 Vaccine Licensure (A/Indonesia/05/2005)
  - Phase II/III study in adults (N = 340)

- US Studies
  - NIAID Phase I/II study in adults, A/Vietnam/1203/2004 (N = 300)
  - Phase I/II study in adults, RG A/Indonesia/05/2005 (N = 420)
  - Phase I/II Study in adults, RG A/chicken/Hong Kong/G9/97 (N = 275)

N > 6700 Subjects
Phase III Study – Seroprotection
MN Titers against Vietnam 1203

The immunogenicity of a Vero cell-derived H5N1 whole virus wildtype vaccine is not affected by the age group as seen for seasonal influenza split vaccines; it is almost identical between the younger (18 - 59 years) and elderly (60+ years) adults.
Comparison of CD4 T Cell Responses among the Two Age Strata (Stratum A: 18 – 59 years of age; Stratum B: >60 years of age)

The homologous and cross clade H5N1 CD4⁺ T cell responses were not statistically significantly different for the two age population strata among the 6 month booster set of subjects evaluated.

EMA (European Medical Agency) Licensing Requirements for Vaccines against Influenza Viruses with Pandemic Potential – Mock Up License

- General License for the production of a pandemic vaccine in case of a pandemic (WHO Phase 6)
  - on basis of a vaccine against an influenza virus with pandemic potential i.e. H5N1

- Primary Endpoint: Immunogenicity

- License based on
  - Produktionsdaten mit Validierungen
  - a complete preclinical development program with multiple toxicity, immunogenicity and protection studies
  - a full clinical development program with Phase I/II/III studies in younger and elderly adults

**Goal**
Fast licensure of a pandemic vaccine with production and quality data and reduced non-clinical studies; but without clinical studies in case of a pandemic (WHO Phase 6); e.g. H1N1pdm09
EMA (European Medical Agency) Licensing Requirements for Vaccines against Influenza Viruses with Pandemic Potential – Pre-pandemic License

- License for a vaccine against an influenza virus with pandemic potential
- For use outside of a pandemic i.e. before WHO (World Health Organisation) declared a pandemic (Pandemic Alert Phase 6) e.g. at Pandemic Alert Phases 1 – 5
- Primary endpoint safety (1 severe AE (Adverse Event per 1,000 vaccinees) i.e. at least 3,000 vaccinees
- License with Mock Up Data and an extended Clinical program including
  - Risk groups e.g. chronically ill and immunocompromised
  - Children from 6 months to 17 years

**Goal**

Vaccination of potential risk groups such as
- HCW’s (Health Care Workers)
- Persons in close contact with poultry (farmers, poultry industry personnel)
- Pandemic vaccine production personnel
- Travellers in risk areas
- To prime for the vaccination with the actual pandemic strain in a pandemic
Characteristics of Egg-Derived Pandemic (-like) Influenza Vaccines

- Monovalent, 3.75 – 90 µg HA per strain
- Mainly H5N1 and H1N1pdm09
- Produced in embryonated hens’ eggs
- Inactivated by Formalin or β-Propriolacton
- Whole virus, split, or subunit
- Not adjuvanted or adjuvanted (Al(OH)$_3$, MF-59, AS03)
- Use of attenuated RG (reverse genetics) reassortants with deleted polybasic cleavage site for H5N1, provided by WHO Collaborating / Reference Centers such as NIBSC or CDC
- Classical reassortants for H1N1pdm provided by WHO Collaborating / Reference Centers such as NYMC or Melbourne / CSL
Three vaccines are authorised as Prepandemic Vaccines for use “outside of a pandemic”

Prepandemic Vaccine (Novartis Vaccines and Diagnostics S.r.l.)
prepandemic influenza vaccine (H5N1) (surface antigen, inactivated, adjuvanted)
Egg, Reverse Genetics Reassortant of A/Vietnam/1194/2004, 7.5 µg, MF59

Prepandemrix (GSK Biologicals)
Prepandemic influenza vaccine (H5N1) (split virion, inactivated, adjuvanted)
Egg, Reverse Genetics Reassortant of A/Indonesia/05/2005, 3.75 µg, AS03

Vepacel (Baxter AG)
A/H5N1 pre-pandemic influenza vaccine (whole virion, Vero cell derived, inactivated)
Cell culture, wild type, A/Vietnam/1203/2004, 7.5 µg, no adjuvant
Key Points

- Different types of inactivated vaccine (whole, split, subunit, virosomal)
- Year round influenza vaccine timetable and limitations
- Trivalent inactivated vaccine composition – Use of A high growth reassortants for influenza A and B
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<tr>
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<td>HI ≥ 40 in 82% of subjects with 2 x 7.5 µg in 71% of subjects with 2 x 1.9 µg</td>
</tr>
<tr>
<td>H9N2 whole Virus, wildtype, egg Non-adjuvanted (Stephenson et al., 2003)</td>
<td>&lt; 32 years&lt;br&gt;HI ≥ 40 in 43% of subjects with 2 x 7.5 / 15 / 30 µg&lt;br&gt;&gt; 32 years&lt;br&gt;HI ≥ 40 in 66% of subjects with 2 x 7.5 / 15 / 30 µg</td>
</tr>
<tr>
<td>H9N2 subunit, wildtype, egg Non-adjuvanted (Stephenson et al., 2003)</td>
<td>&lt; 32 years&lt;br&gt;HI ≥ 40 in 14% of subjects with 2 x 7.5 / 15 / 30 µg&lt;br&gt;&gt; 32 years&lt;br&gt;HI ≥ 40 in 75% of subjects with 2 x 7.5 / 15 / 30 µg</td>
</tr>
</tbody>
</table>

HI: hemagglutination inhibition
H9N2 Cross-Reactive Antibody Titers in Different Age Groups and the Circulating Viruses of the Respective Years

Figure 2: Scatter plot of baseline H9N2 microneutralisation and haemagglutination-inhibition titres against year of birth. Arrows indicate period of circulation of human influenza virus subtype.

Clinical Study Outline of an PER.C6-Derived H7N1 Vaccine

- 60 healthy adults (21 males and 39 females, mean age 26.8 years old) vaccinated twice intramuscularly at three week intervals

- 4 groups (15 subjects/group) of participants received one of the following formulations:
  - Normal human dose (12µg HA)
  - Normal human dose plus adjuvant
  - Twice human dose (24µg HA)
  - Twice human dose plus adjuvant

- Serological antibody responses measured

- No serious adverse events and vaccine well tolerated in all 4 groups

Slide kindly provided by Rebecca Cox
Summary of Serological Response of H7N1 Vaccine produced in PER.C6 Cells

- Vaccine only weakly immunogenic
- 21 of 54 volunteers had detectable serum antibody response (≥ 1:8) after the second vaccination
- None of the vaccine formulations fulfilled conventional EU licensing criteria used to assess seasonal influenza vaccines
- Significantly higher number of responders in adjuvant groups

<table>
<thead>
<tr>
<th>Vaccine group</th>
<th>Adjuvant</th>
<th>No. of subjects</th>
<th>No. with detectable antibodies (% of responders)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>-</td>
<td>14</td>
<td>3 (21 %)</td>
</tr>
<tr>
<td>Normal</td>
<td>+ Al</td>
<td>14</td>
<td>7 (50 %)</td>
</tr>
<tr>
<td>Twice</td>
<td>-</td>
<td>13</td>
<td>3 (23 %)</td>
</tr>
<tr>
<td>Twice</td>
<td>+ Al</td>
<td>13</td>
<td>8 (62 %)</td>
</tr>
</tbody>
</table>

Slide kindly provided by Rebecca Cox
Key Points

- Different types of inactivated vaccine (whole, split, subunit, virosomal)
- Year round influenza vaccine timetable and limitations
- Trivalent inactivated vaccine composition – Use of A high growth reassortants for influenza A and B
- Egg-based versus cell-based influenza vaccine production
- Serological criteria for influenza vaccine licensure
- Immunogenicity of seasonal influenza vaccines in different age groups
- Immunogenicity of pre-pandemic vaccines in different age groups
- Pre-pandemic non-adjuvanted inactivated vaccines (H5N1, H2N2, H9N2, H7 subtype) and immunogenicity challenges
- Inactivated vaccines against A(H1N1)pdm09 virus – Different global approaches
Review of 2009 H1N1v Influenza Vaccine Manufacture

- Time pressure required enhanced collaboration and information sharing between WHO, WHO CC’s, ERL’s, and Industry for H1N1v vaccine production
  - 27 April 2009 - First WHO chaired general Telephone Conference (TC) followed by regular approximately weekly TCs
  - 18 June – WHO / CCs / ERLs /industry weekly technical TC calls initiated for discussion on specific vaccine production issues

- Factors affecting H1N1v SRID potency reagents supply and subsequent vaccine production:
  - Preparation, availability and evaluation of vaccine candidate strains
  - Biosafety actions/recommendations
  - Production of potency reagents
  - Clinical Studies

Adapted from IVS Presentation on “Workshop on lessons learned from potency testing of pandemic (H1N1) 2009 influenza vaccines and considerations for future potency tests”; 27-29 July 2010
Comparison Production Times of Egg and Cell Culture Technologies

- Secure egg supply
- Create reassortants
- Safety test viral reassortants
- Inoculation of eggs and viral growth
- Separation, filtration and purification
- Testing and packaging

Secure viral strain
- Inoculation of cells and viral growth
- Separation, filtration and purification
- Testing and packaging

H1N1 Pandemic Influenza – Course of Events

- **March**
  - 4: BX receives wild-type virus from US CDC

- **April**
  - 24: First reports on swine flu

- **May**
  - 11: WHO phase 6
  - 27: WHO phase 4
  - 29: WHO phase 5

- **June**
  - 3: First infect of 6,000 l fermenter

- **July**
  - 24: First batch released internally

- **August**
  - 12: First shipments to APA customers

- **Sep**
  - 13: FSD Adults/elderly

- **Oct**
  - 7: FSD children

- **Nov**
  - 6: EU license CELVAPAN
H1N1pdm09 Immunogenicity and Safety Study in Adults

- **Design**
  - Phase 1/2, prospective, randomized, open label, multicenter

- **Objectives**
  - Obtain immunogenicity and safety data at two different dose levels of a H1N1 pandemic influenza vaccine in healthy adults

- **Subjects**
  - 18 – 59 yrs (Stratum A) and 60+ yrs (Stratum B)
  - 400 subjects total
  - 4 study arms, n = 100 each

- **Vaccination**
  - 2 vaccinations 21 days apart
  - 2 dose levels: 7.5 µg, 3.75 µg
  - Strain A/H1N1/California/07/2009
HI Assay Results after 1\textsuperscript{st} and 2\textsuperscript{nd} Vaccination in Adults and Elderly

\textbf{Adults and Elderly 18 – 59 years and ≥ 60 years}

\% Seroprotection

\begin{table}
\centering
\begin{tabular}{ll}
\textbf{3.75µg (n=103)} & \textbf{7.5µg (n=99)} \\
34 & 36 \\
85 & 87 \\
93 & 91 \\
\end{tabular}
\end{table}

\textbf{18-59 years}

\begin{table}
\centering
\begin{tabular}{ll}
\textbf{3.75µg (n=100)} & \textbf{7.5µg (n=101)} \\
49 & 45 \\
70 & 75 \\
75 & 89 \\
\end{tabular}
\end{table}

\textbf{≥ 60 years}

\textbf{CHMP Criterion}
H1N1pdm09 Pediatric Immunogenicity and Safety Study

- **Design**
  - Phase 1/2, prospective, open-label, randomized, multicenter

- **Objectives**
  - Dose-finding immunogenicity and safety investigation
  - To assess primary immune response, antibody persistence and booster response

- **Subjects**
  - 400 subjects total, 8 study arms (50 subjects each)
  - 4 age strata: 9 - 17 years, 3 – 8 years, 12 – 35 months, 6 – 11 months

- **Vaccination**
  - 2 vaccinations 21 days apart, booster at either day 180 or 360
  - 2 dose levels: 3.75 µg, 7.5 µg of HA strain A/H1N1/California/07/2009
HI Responses after 1\textsuperscript{st} and 2\textsuperscript{nd} Vaccination in All Pediatric Age Cohorts

\% Seroprotection

<table>
<thead>
<tr>
<th>Age Cohort</th>
<th>Baseline</th>
<th>Post 1st Dose</th>
<th>Post 2nd Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-35 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.75(\mu)g (n=50)</td>
<td>4</td>
<td>22</td>
<td>82</td>
</tr>
<tr>
<td>7.5(\mu)g (n=52)</td>
<td>4</td>
<td>35</td>
<td>89</td>
</tr>
<tr>
<td>3-8 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.75(\mu)g (n=49)</td>
<td>17</td>
<td>8</td>
<td>73</td>
</tr>
<tr>
<td>7.5(\mu)g (n=51)</td>
<td>8</td>
<td>100</td>
<td>68</td>
</tr>
<tr>
<td>9-17 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.75(\mu)g (n=49)</td>
<td>22</td>
<td>88</td>
<td>94</td>
</tr>
<tr>
<td>7.5(\mu)g (n=51)</td>
<td>12</td>
<td>88</td>
<td>88</td>
</tr>
</tbody>
</table>

CHMP Criterion: 6-35 months

- 3.75\(\mu\)g (n=50): 4% baseline, 22% post 1st dose, 82% post 2nd dose
- 7.5\(\mu\)g (n=52): 4% baseline, 35% post 1st dose, 89% post 2nd dose

3-8 years:
- 3.75\(\mu\)g (n=49): 17% baseline, 8% post 1st dose, 73% post 2nd dose
- 7.5\(\mu\)g (n=51): 8% baseline, 100% post 1st dose, 68% post 2nd dose

9-17 years:
- 3.75\(\mu\)g (n=49): 22% baseline, 88% post 1st dose, 94% post 2nd dose
- 7.5\(\mu\)g (n=51): 12% baseline, 88% post 1st dose, 88% post 2nd dose
CELVAPAN H1N1 is safe and well-tolerated in all age groups, with a tolerability profile very similar to that seen for trivalent seasonal influenza vaccines.

The vaccine is highly immunogenic, with a high percentage of subjects in all age groups demonstrating seroprotective levels of antibody after one or two immunizations.

There is an age dependent response with substantially higher responses being seen in the younger age groups.

In general, responses to CELVAPAN H1N1 are very similar to those seen after seasonal flu vaccination and very different to those seen in response to H5N1 vaccination.
Why was this virus less harmful than classical pandemic viruses?

The H1N1pdm09 virus was, in contrast to the earlier pandemic viruses which also originated from animals, not fully unknown to the human immune system i.e. many persons were at least partially protected and primed.
EMA (European Medical Agency) Licensed Influenza A (H1N1)pdm09 Vaccines

Three vaccines were originally authorised as **Mock-Up Vaccines** and converted to pandemic-influenza vaccines once the A/H1N1 flu strain had been identified:

**Celvapan (Baxter AG)**
Influenza vaccine (H1N1)v (whole virion, Vero cell derived, inactivated)
Cell culture, wild type, A/California/7/2009, 7.5 µg, no adjuvant

**Focetria (Novartis Vaccines and Diagnostics S.r.l.)**
Influenza vaccine (H1N1)v (surface antigen, inactivated, adjuvanted)
Egg, High Growth Reassortant NYMC X-181, 7.5 µg, MF59

**Pandemrix (GSK Biologicals)**
Influenza vaccine (H1N1)v (split virion, inactivated, adjuvanted)
Egg, High Growth Reassortant NYMC X-179A, 3.75 µg, AS03

Two vaccines were authorised using the **Emergency Procedure**

**Arepanrix (GlaxoSmithKline Biologicals s.a.)**
License withdrawn
Pandemic influenza vaccine (H1N1)v (split virion, inactivated, adjuvanted); 3.75µg, AS03

**Humenza (Sanofi Pasteur SA)**
License withdrawn
Pandemic influenza vaccine (H1N1) (split virion, inactivated, adjuvanted); 3.8µg, AF03
US Licensed Influenza A (H1N1)pdm09 Vaccines

Proper Name: Influenza A (H1N1) 2009 Monovalent Vaccine
Tradenames: None

CSL Limited
Indication: Active immunization of persons ages 6 months and older against influenza disease caused by pandemic (H1N1) 2009 virus

ID Biomedical Corporation of Quebec
Indication: Active immunization of persons ages 18 years of age older against influenza disease caused by pandemic (H1N1) 2009 virus

Novartis Vaccines and Diagnostics Limited
Indication: Active immunization of persons 4 years of age and older against influenza disease caused by pandemic (H1N1) 2009 virus

Sanofi Pasteur, Inc.
Indication: Active immunization of persons 6 months of age and older against influenza disease caused by pandemic (H1N1) 2009 virus

http://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm181950.htm
Several additional products have received a national authorisation in one or more European countries. As of 10 December 2009 these are known to include the following:

**Hungary:** Fluval P; Omninvest, Hungary

**France:** Panenza; Sanofi Pasteur (Belgium, Germany, Italy, Luxembourg, Spain will follow the authorisation in France (acting as the ‘Reference Member State’)

**Germany:** PanVaxH1N1, CSL, Australia

**Romania:** CANTGRIP, Cantacuzino, Romania

**Switzerland; Germany:** Celtura (MDCK), Novartis, Germany

Conclusion – H1N1 2009 Pandemic Response

- 3 billion doses estimated capacity for H1N1
- 500 million doses produced based on actual demand
- Adjuvant, whole virion & cell culture, and egg-based (inactivated and live attenuated) technologies played a role against H1N1
- Donations (166m H1N1 doses pledged against 200m dose WHO target)
- Tiered-pricing approaches for developing countries
- Timing: Pandemic Alert Level 6 declared by WHO June 11, first vaccines licensed 1st Week of September (~8 weeks)
- Usage: e.g. Australia ~ 72% of population had HEARD of the vaccine, but only ~ 15% were vaccinated
IFPMA IVS members have heavily invested to ensure that expanded production facilities meet global demand.

In the event of a pandemic, entire populations would require vaccination.

Industry continues to invest heavily to develop solutions to efficiently increase pandemic vaccine supply:

- Antigen-sparing strategies;
- Manufacturing facilities modified for pandemic production (to meet biosafety requirements);
- More facilities based on various production platforms;
- Development of different types of influenza vaccine.