

Section 1: Presented by Shalene Nandlall and Sanela Bilic Vaccine Trials Group for the Telethon Institute for Child health Research

Background

Influenza viruses are grouped into three types, A, B, and C

These viruses are based on envelope based Matrix protein (M1) and a nucleocapsid protein (NP).

The surface of the virus defined by 2 different protein components, known as antigens. These spike-like features called haemagglutinin (H) and neuraminidase (N) components.

The genetic makeup of these viruses allows frequent minor genetic changes-antigenic drift

Pathogenicity

Only influenza A viruses can cause pandemics (genetic changes in H component)

Influenza A viruses have 16H subtypes and 9N subtypes.

Only 3 H types usually infect humans (H1-3)

Avian Influenza - "Bird Flu" is an infectious disease of birds caused by type A Influenza virus.

The H5 and N7 subtypes are known to cause highly pathogenic disease in poultry

The current outbreak is due to H5N1 strain and began in South East Asia in mid 2003

(<http://www.who.int/mediacentre/factsheets/avian>)

Migratory Birds and the spread of Avian Influenza

Wild waterfowl are considered a natural reservoir of all influenza A viruses. They are known to carry the H5 AND N7 subtypes.

Scientists are increasingly convinced that some migratory waterfowl are now carrying the H5N1 virus in its highly pathogenic form, introducing the virus to domestic poultry flock along their migratory routes.

(<http://www.who.int/mediacentre/factsheets/avian>)

Since 1959 only 24 outbreaks of highly pathogenic Avian flu has occurred in poultry worldwide. Majority having limited geographical spread, excluding the current H5N1 outbreak.

Bird migration is a recurring event and countries that lie along the flight pathways of birds migrating from central Asia may face persistent risk of introduction and re-introduction of the virus to poultry flocks.

(<http://www.who.int/mediacentre/factsheets/avian>)

The Implications For Human Health

The persistence of the H5N1 in poultry poses risks for human health by:

1. Direct infection when the disease crosses the species barrier to infect humans.
 - H5N1 has caused largest no of disease and death in humans
 - Rapid progression of the disease
2. The greater risk is, the virus will mutate into a form that is highly infectious for humans and spread from person to person and start a global outbreak .

(www.who.int/mediacentre/factsheets/avian)



**Cumulative Number of laboratory confirmed Cases(H5N1) reported to WHO
 Update as at 15 Feb 2008**

Since 2003 there have been a total of 361 cases reported with 227 fatalities.

Country	2003		2004		2005		2006		2007		2008		Total	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
Egypt	0	0	0	0	0	0	18	10	25	9	0	0	43	19
Indonesia	0	0	0	0	20	13	55	45	42	37	10	8	127	103
Pakistan	0	0	0	0	0	0	0	0	1	1	0	0	1	1
Thailand	0	0	17	12	5	2	3	3	0	0	0	0	25	17
Vietnam	3	3	29	20	61	19	0	0	8	5	2	2	103	49
Total	4	4	46	32	98	43	115	79	86	59	12	10	361	227

Production of antiviral drugs

- Antiviral drugs
 - reduce influenza symptoms
 - may shorten the time of sickness by 1 or 2 days
 (<http://www.cdc.gov/flu/protect/antiviral/>)
- Examples:
 - Tamiflu produced by Roche AG
 - Relenza produced by GlaxoSmithKline
 neuraminidase inhibitors
 (<http://www.medterms.com>)

Development of vaccine

- Egg culture
 - Virus grown in fertilized (embryonated) chicken eggs
 - Well established and cost effective production
 - Time lengthy and large amount of eggs required
 - 1 -2 eggs to produce one dose of annual flu vaccine
 - The entire process takes at least 6 months and uses about 100 million eggs in the U.S. alone
 (<http://usinfo.state.gov/gi/Archive/2005/Oct/20-598868.html>)
- Cell culture
 - Involves growing animal or human cells in the laboratory in a nutrient solution.
 - The virus is injected into cells, and cells and viruses multiply
 - Production not well established
 - Technology is under development
 (<http://usinfo.state.gov/gi/Archive/2005/Oct/20-598868.html>)

Studies around the world

- GlaxoSmithKline
 - clinical trial conducted in Belgium of 400 volunteers 18 to 60 years old
 - 4 doses of split antigen H5N1 vaccine containing adjuvant
(BBC News, March 2006)
(<http://www.gsk.com/infocus/influenza.htm>)
- Baxter Healthcare Corp.
 - Phase I/II study conducted in Europe
 - Whole virus, adjuvant free H5N1 vaccine
 - Highly immunogenic at low dose
 - Phase III study conducted last year
 - To evaluate the safety and efficacy of the candidate vaccine
(<http://www.medicalnewstoday.com/medicalnews.php?newsid=66573>)
 - Clinical trials of a bird flu vaccine to start in Indonesia
(<http://www.chicagobusiness.com>)
- Sanofi-Aventis
 - Clinical trials conducted in U.S (2005) for H5N1 strain
 - 451 healthy adults ages 18 to 64.
 - 2 doses of 90-µg H5N1 generated the highest immune response
 - The US Food and Drug Administration has announced the first approval in the US of a vaccine for humans against the avian flu (H5N1 strain)
(Pharmaceutical News, 2007)
 - Clinical trial conducted in France for a H5N1 strain
 - First clinical trial of H7N1 using cell based technology
(Sanofi Aventis, Press releases, September 2006)
- Novartis
 - Has provided H5N1 vaccines for stockpiling in the US and UK
 - Vaccine - Focetria®, a new human vaccine designed for use following declaration of an influenza pandemic
 - Focetria = influenza strain declared at the time of a pandemic + proprietary adjuvant MF59
 - Received European Union approval in all 27 member states as well as Iceland and Norway
(Novartis, MediaReleases, May 2007)
- CSL Ltd.
 - Clinical trial conducted in Australia
 - Based on H5N1 A/Vietnam/1194/2004 strain
 - Phase 1 study in 400 adults in November 05
 - Received either 7.5ug or 15ug with or without aluminium phosphate adjuvant as 2 dose schedule 21 days apart
 - All formulations well tolerated
 - Local reactions and systemic symptoms similar rates to standard influenza vaccine
 - Encouraging immunogenicity results



Preparing for pandemic

- Governments around world are in the rush to stockpile vaccines and anti virals that treat or prevent bird flu.
 - Pandemic preparedness exercises within Western Australia (WAIPAC)
- WHO Meeting on Options for Increasing the Access of Developing Countries to H5N1 and other Potential Pandemic Vaccines (Geneva, 25 April 2007)
- Influenza Vaccine Supply International Task Force (IFPMA) established in 2002:
 - to collectively address communication, policy, regulatory, scientific & technical aspects of pandemic preparedness.
 - to strengthen public health and industry approaches to seasonal and pandemic influenza issues.

(WHO meeting, Geneva 25 April, 2007)

Protecting against seasonal influenza

- The world must increase the usage of seasonal vaccines (WHO Global Action Plan – Oct. 2006) (WHO meeting, IFPMA Influenza Vaccine Supply International Task Force, Geneva 25 April, 2007)
- The link between the vaccines against the seasonal influenza and those that protect against the pandemic strain:
 - Manufacturing processes are similar and take place in the same production facilities
 - Capability to produce pandemic vaccines is tied to the capacity to manufacture seasonal vaccine
 - Production of seasonal vaccine is driven by the current usage around the world (WHO meeting, IFPMA Influenza Vaccine Supply International Task Force, Geneva 25 April, 2007)
- USA recommends universal immunization for children under 5 years of age
- WA providing free flu vaccine for children between 6 months and 5 years this year
- Considering universal immunisation for adults
- The US Food and Drug Administration finalised guidelines that detail the steps vaccine manufacturers must take in order to use new technologies.

(Pharmaceutical News, 2007)
- The guidelines also aim to increase the number of companies making vaccines.

Possible population-wide interventions

- Restrictions of mass public gatherings
- Closure of all Schools
- Voluntary home isolation of cases
- Voluntary quarantine of contacts of known cases
- Antiviral treatment of cases and contact
- Screening of people entering Australian ports
- “Shoot to Kill” of transgressors. DON’T RUN!
- Vaccination



Travel restrictions:

delay in pandemic wave arrival

- Restrictions into Australia only (no international travel ban)
 - 90% effective ban 1 to 2 weeks
 - 99% effective ban 3 to 4 weeks
 - 99.9% effective ban 1 to 2 months

- International restrictions from all countries with epidemics
 - 90% effective ban 3 to 4 weeks
 - 99% effective ban 7 to 8 weeks
 - 99.9% effective ban 3 to 4 months

Summary

- Pandemic influenza is a major public health concern globally and the threat of pandemic flu is coming closer
- H5N1 vaccines are safe and produce functional neutralising antibody but high dose antigen content and adjuvants are required
- Novel adjuvants need to be used to reduce adjuvant content and allow whole populations to be vaccinated
 - GSK have a novel adjuvant that induces similar doses at 3.8ug dose (unpublished data)
 - Further studies are planned with CSL iscomatrix adjuvant
- Increase in the uptake of the seasonal flu vaccine will increase preparedness for the pandemic

SECTION 2: Update on Australian Influenza & vaccination resource websites By Filomena Mascaro, ICAWA Education Coordinator

Department of Health WA: www.public.health.wa.gov.au

- Infectious diseases – influenza fact sheet
- Immunisation – prevention of flu virus
- Pandemic influenza, Avian flu and other links including link to World Health Organisation (WHO)

National Australian flu website: www.fightflu.com.au

- Developed by National Institute of Clinical Studies (NICS) in collaboration with National Influenza Specialist Group (ISG) and National Health & Medical Research Council (NH&MRC)
- Developed to provide consumers, carers and health care workers with evidence based information about influenza vaccinations
- Supports Australian workplace vaccination programs providing tools and strategies
 - Flu virus and vaccination facts including common questions asked
 - Evidence reports supporting vaccination programs for health care workers
 - Health Care Professional pageTool kit: promotional material, posters, letter templates (reminder letters etc..) staff education powerpoint, barrier 'buster' information

Australian Immunisation Handbook 8th Edition: : www.immunise.health.gov.au/handbook.htm

Specific information on vaccine. Soon to be released 9th edition immunisation handbook

