

The Spectre of a Flu Pandemic – Is it Inevitable?

Dr. Lance Jennings, University of Otago, New Zealand
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Spectre of a Flu Pandemic: *is it inevitable?*

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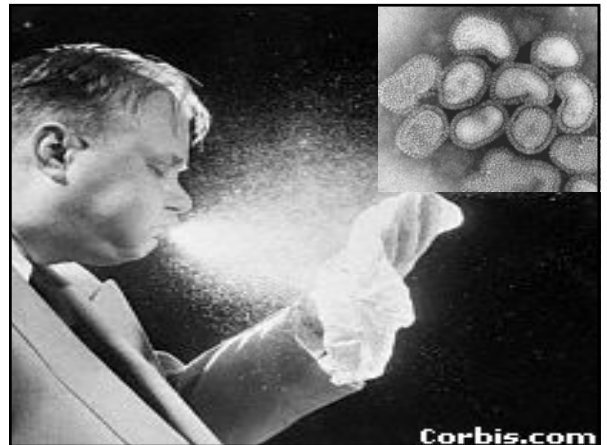
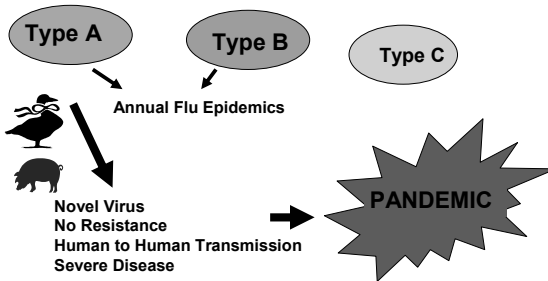
Outline

- The ecology of influenza
- Avian influenza
- Pandemic preparedness
 - Pharmaceutical interventions
 - Non-pharmaceutical interventions
 - Implementation

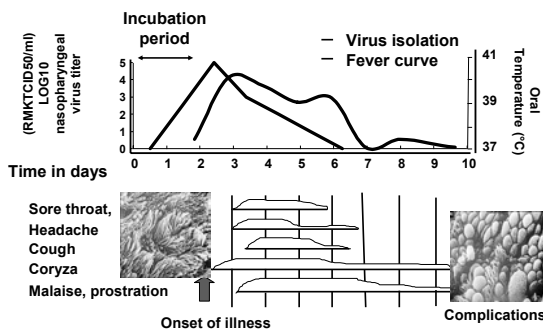


ABC of Human Influenza

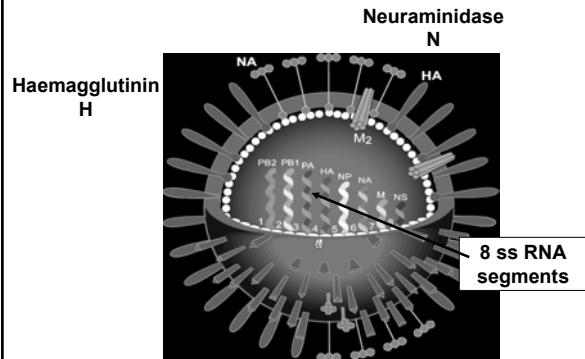
- Acute respiratory viral infection
- Caused by members of the *Orthomyxoviridae* family



Human Influenza



Influenza Virus



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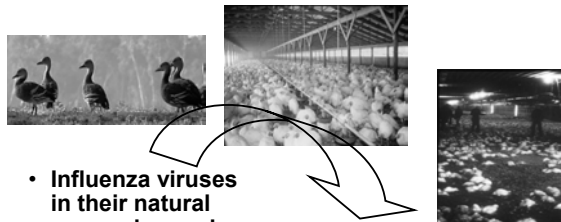
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Ecology of Influenza A Viruses

In wild aquatic birds, influenza viruses replicate predominately in the intestinal tract and are shed in the faeces. Transmission is faecal-oral, often through water

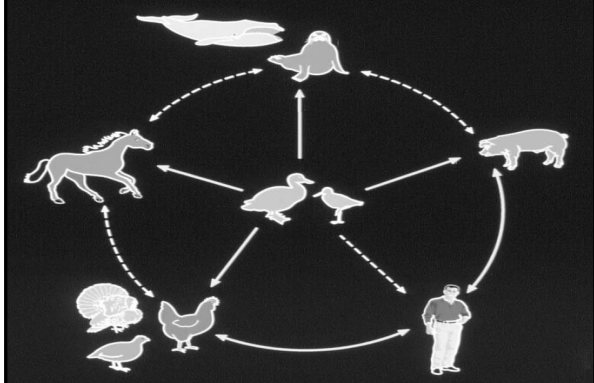


The Ecology of Influenza A Viruses



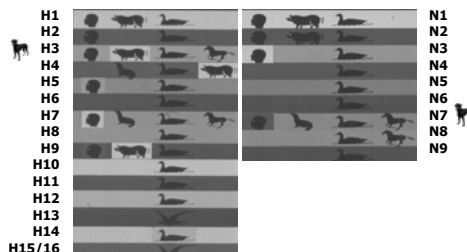
- Influenza viruses in their natural reservoirs are in evolutionary stasis
- Rapid evolution occurs after transfer to new hosts

The Ecology of Influenza A Viruses



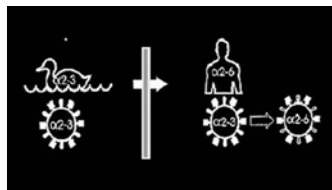
The Ecology of Influenza Viruses

- Subtypes based on surface glycoproteins Haemagglutinin (HA) Neuraminidase (NA)
- The natural reservoir for all HA and NA subtypes is water fowl
- Influenza A viruses infect multiple mammalian species



Cox N. 2005

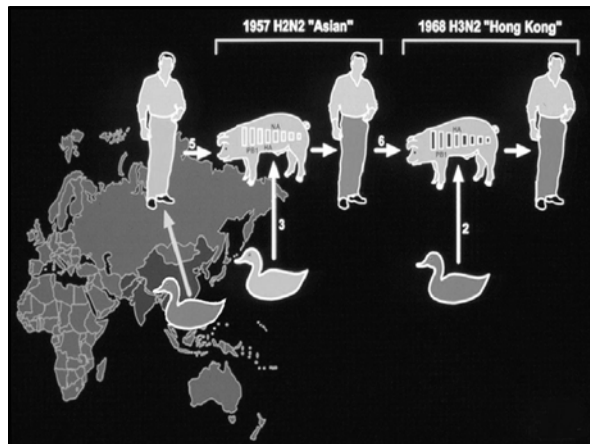
Factors Influencing the Interspecies Transmission of Influenza A Viruses



- Avian-human species barrier exists
- Factors multigenic

α 2-3 Receptors

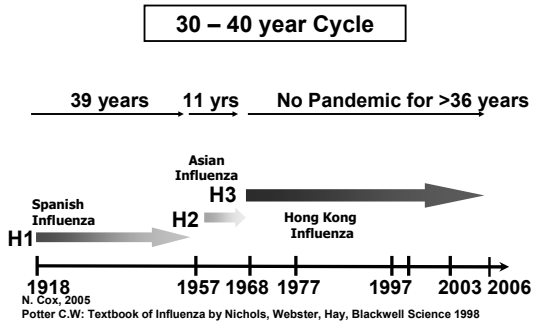
α 2-6 Receptors



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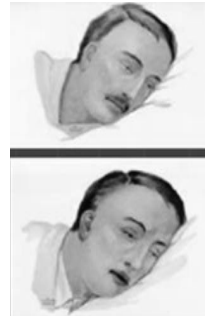
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Timeline of Emergence of Influenza Viruses in Humans

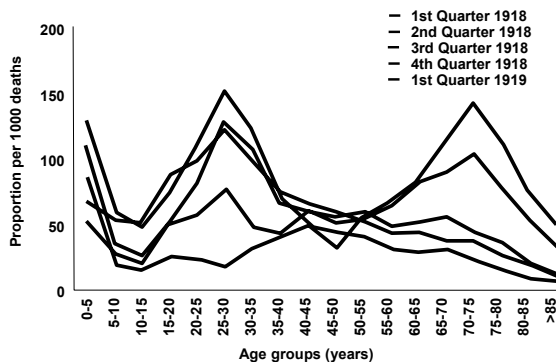


Spanish 'Flu Symptoms

- "they very rapidly develop the most vicious type of pneumonia that has ever been seen..."
- and a few hours later you can begin to see the cyanosis extending from their ears and spreading all over their face, until it is hard to distinguish the coloured men from the white.
- It is only a matter of a few hours until death"
Grist NR BMJ 1959



Age Distribution of Deaths of Females in UK 1918-1919



1918 'Spanish' Influenza Pandemic - New Zealand

- New Zealand's greatest public health event
- Two waves July 1918 - mild Oct/Dec 1918 - severe
- Arrived SS Niagara, Auckland, 12th October 1918 (Prime Minister Massey)
- Deaths
 - Auckland 2000 "City of the dead" 12 Nov: 2 death trains per day
 - Canterbury 800
 - New Zealand 8,573 (DR 0.84% / 1.4% Maori)
 - Worldwide 20 - 50 million (2-3% Worlds population)



1918 'Spanish' Influenza Pandemic - New Zealand

BLACK NOVEMBER
The 1918 influenza pandemic in New Zealand

New Zealand's greatest public health event

July 1918 - mild Oct/Dec 1918 - severe

Arrived SS Niagara, Auckland, 12th October 1918 (Prime Minister Massey)

"City of the dead" 12 Nov: 2 death trains per day

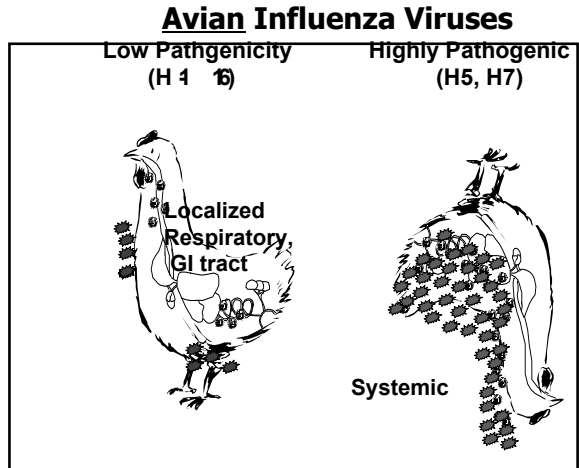
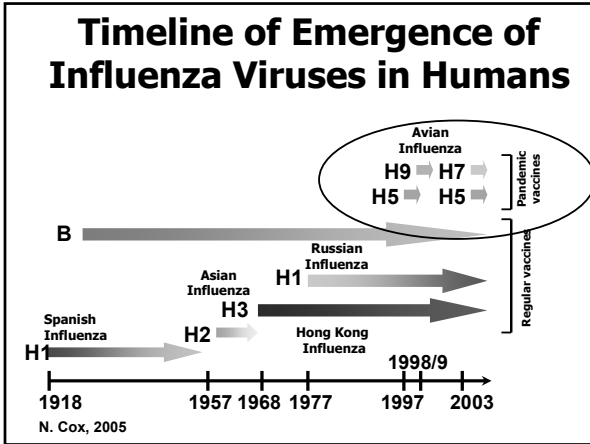
– New Zealand 8,573 (DR 0.84% / 1.4% Maori)
– Worldwide 20 - 50 million (2-3% Worlds population)

Victims of the Great Pandemic-Kansas 1918



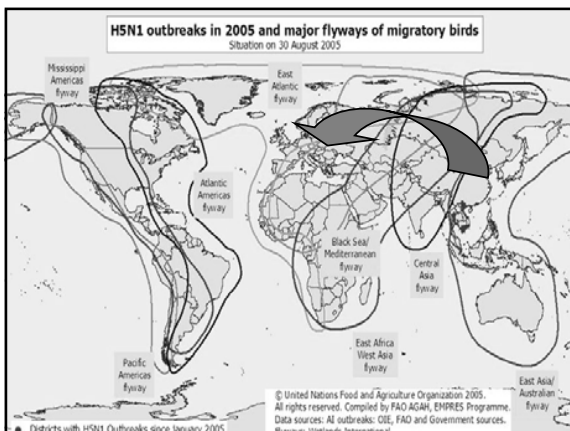
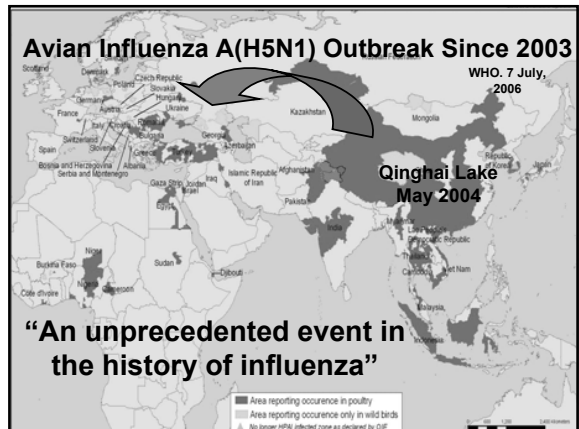
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Avian Influenza Viruses

Virus	Tissue Tropism	Diseases in Chickens	Structure of HA	Responsible Proteases
LPAI	Respiratory & Alimentary Tracts 'Epithelial cells'	Subclinical Localized Infection		Specific Secretory Protease Trypsin Trypsin-Clara FXa Plasmin
HPAI	All tissues and organs	Fowl Plague Fatal Systemic Infection		Ubiquitous Protease present in Golgi Body Furin Plasmin



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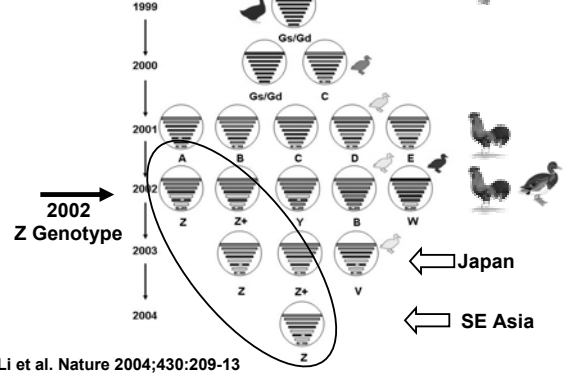
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Genesis of H5N1 influenza in Asia

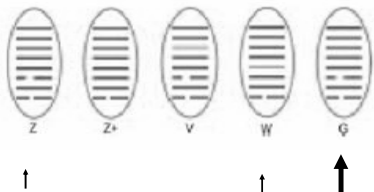
- 1996 A/Goose/Guangdong/1/96 H5N1
- 1997 emergence of H5N1 "bird flu"
 - A reassortant virus
 - Goose x Quail x Duck
 - H5N1 H9N2 H6N1
 - 18 people infected, 6 deaths
- 1997 -2002
 - Goose x multiple mating partners
 - H5N1 x
 - Antigenically conserved
 - Multiple genotypes
 - Pathogenic in chickens



Emergence of a Dominant H5N1 Genotype

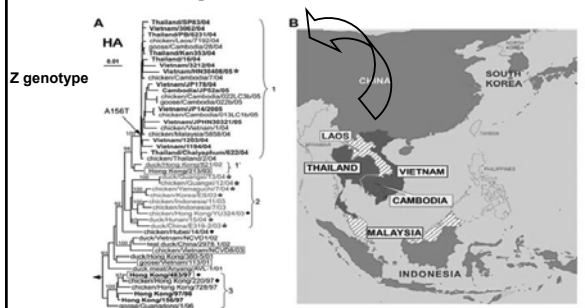


Genotypes of H5N1 influenza reassortants in Asia



Chen et al PNAS 2006;103:2845-50

Genetic analysis of H5N1 avian influenza



The WHO Global Influenza Program Surveillance Network Evolution of H5N1 avian influenza viruses in Asia. Emerg Infect Dis 2005 Oct
Chen et al. PNAS 2006;103:2845-50

Expanding Host Range of Influenza A (H5N1)



Tigers and leopards in Thailand 2004



Martens (Weasel Family) Germany March 06



Domestic cats in Thailand/Indonesia & Experimental transmission



Dogs in Thailand



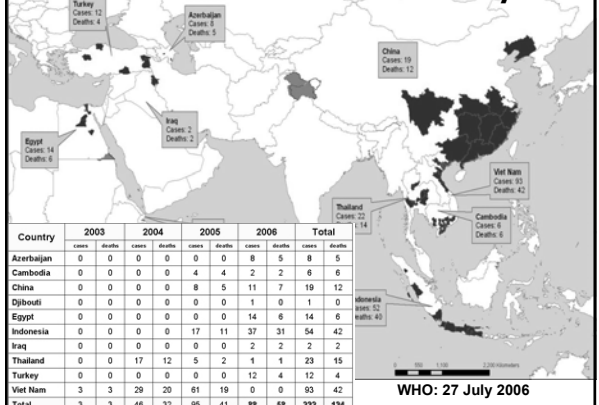
Infection of pigs in China, Viet Nam & Indonesia

No Experimental transmission



HUMANS

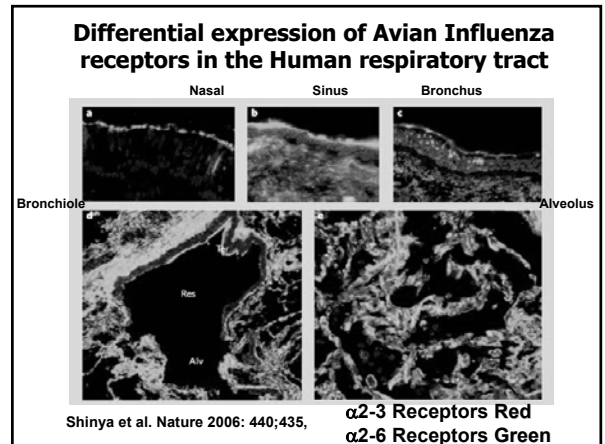
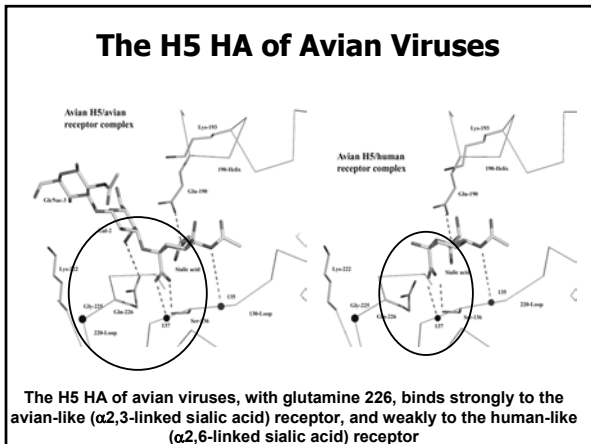
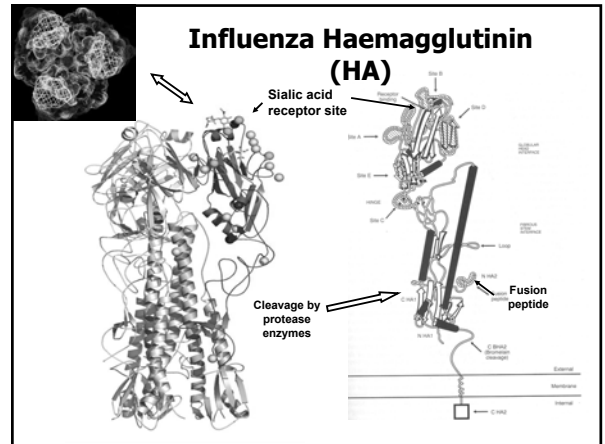
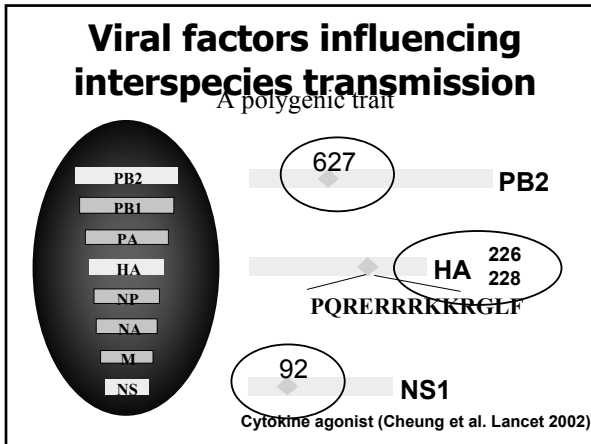
Confirmed Human cases 2003-20 July 2006



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Avian Influenza A/H5N1: Transmission

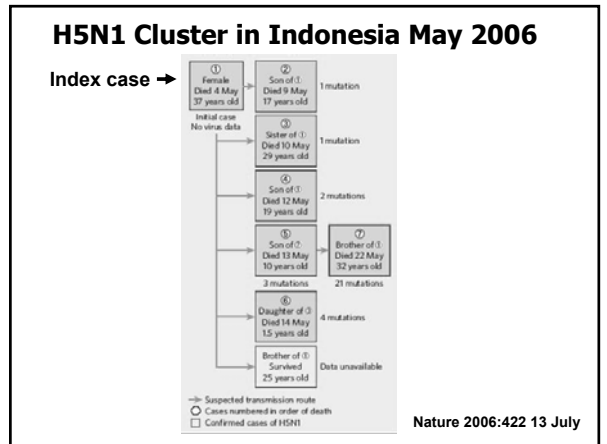
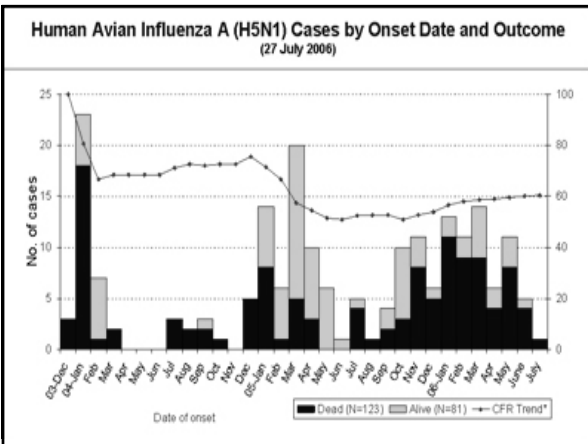
- Bird to human**
 - Implicated in ~80% of patients
 - Handling, plucking/preparing
 - Ingestion of undercooked poultry (duck blood)
- Environment to human**
 - ? Exposure to contaminated water (swimming)
 - ? Aerosols of bird droppings
- Human to human**
 - Inefficient; no sustained chains of transmission
 - Family clusters in Thailand, Vietnam, Turkey and Indonesia
 - Rare infections in cullers and exposed HCWs

Ungchusack et al. NEJM 2005; 352:333
Liem et al. Emerg Infect Dis 2005; 11:210,
Nature 2006:442 13 July



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Pre-requisites for a Human Pandemic

1. Emergence of an antigenically novel strain to which the population has no immunity
2. Transmission to humans in whom the strain can cause severe disease
3. Efficient human to human spread

AVIAN → HUMAN
 AVIAN ⇌ HUMAN ⇌ HUMAN ⇌ HUMAN

Pandemic Planning

“having a framework to respond to a pandemic threat, to lessen the impact on a countries health system, society and its economy ..”

Components:

- **Pharmaceutical Interventions:**
 - Antivirals, Vaccines, Antibiotics, etc
- **Non-pharmaceutical Interventions**
 - Public health measures

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Influenza Pandemic Preparedness in New Zealand

National Health Emergency Plan : Infectious Diseases

2004
Updated in line with WHO Revised Plan 2005;
Now Version 15 2006

First Published 1999
Revised 2002

NZ Influenza Pandemic Action Plan 2005

Current WHO Alert Phase 3: Human infection; rare spread to contacts

WHO PERIOD	WHO PHASE	NZ SCENARIO	NZ STRATEGY	WHO ALERT CODE*	
Interpandemic Period	Phase 1	Scenario 1	Planning	NA	
	Phase 2	Scenario 2			
	Pandemic Alert Period	Phase 3			Scenario 1
					Scenario 2
Pandemic Period	Phase 4	Scenario 1	Border Management	YELLOW (Standby)	
		Scenario 2			
	Phase 5	Scenario 1	Cluster Control	RED (Activation)	
	Phase 6	Scenario 2			
	Post Pandemic Period	Post Pandemic Period	Scenario 1	Pandemic Management	GREEN (Stand down)
		Scenario 2	Recovery		

NZ Influenza Pandemic Plan outline

Plan for it (Current phase)
– Engage with all relevant agencies

Keep it out
– Border management

Stamp it out
– Cluster control operations

Manage it
– Public health measures,
– Public gatherings, antivirals

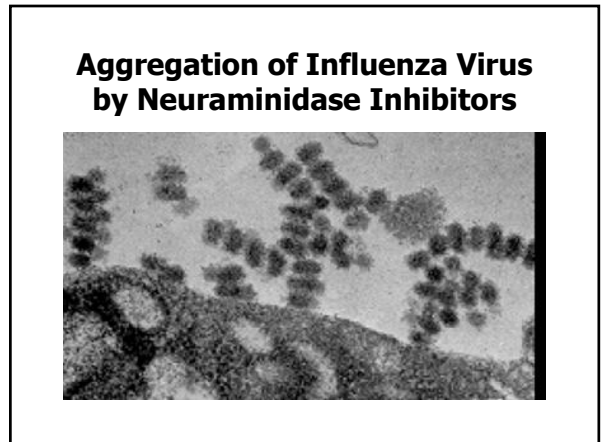
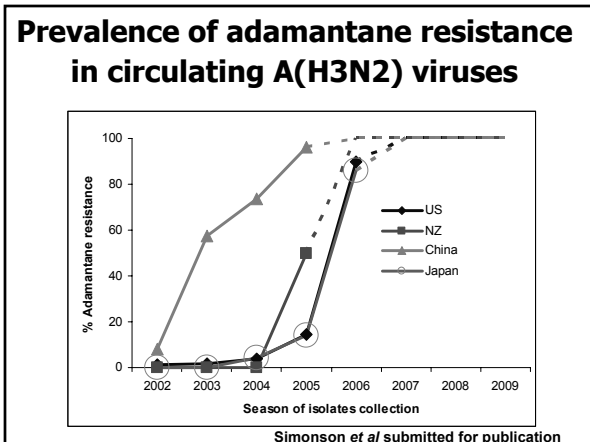
Recover from it
– Return to normal service delivery

Surveillance

Antiviral Agents for Influenza

Class/Agent	Brand Name	Route
M2 Inhibitors		
Amantadine	Symmetrel	PO
Rimantadine	Flumadine	PO
Neuraminidase		
Zanamivir (GG167)	Relenza	Inhaled
Oseltamivir (GS4104)	Tamiflu	PO
Permivir (RWJ270201)#		PO

Investigational



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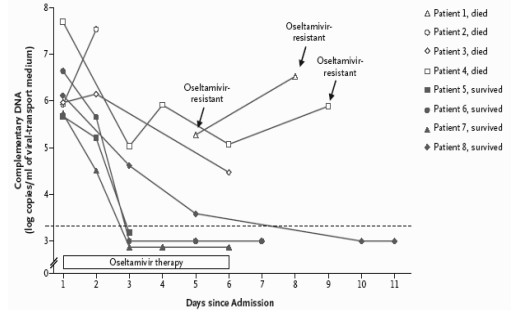
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Oseltamivir Therapy in H5N1, Thailand and Vietnam, 2004-5

Oseltamivir treatment	No. patients	No. (%) survivors
Yes	25	6 (24%)
No	12	3 (25%)

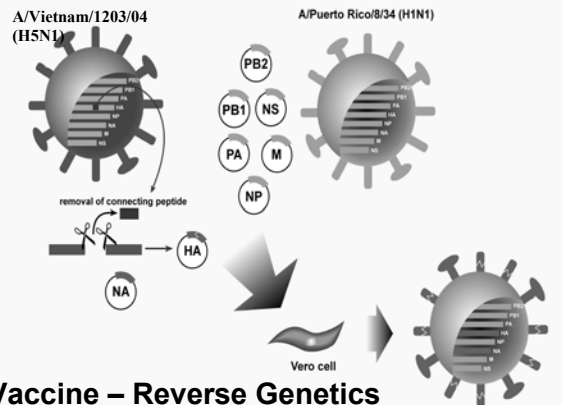
Writing Committee. NEJM 353:1374, 2005

Pharyngeal Viral Loads during Oseltamivir Treatment of H5N1



Pandemic Influenza Vaccines: will be different from seasonal vaccines

- Unlikely to be available for first 6-9 months
- NZ contract with CSL Ltd,
 - 8 million doses pandemic vaccine
 - H5N1 vaccine ??



Immunogenicity of Candidate H5N1 Vaccines in Healthy Adults

Vaccine type (N)	Route	HA dose (µg)	% HI titer ≥ 1:40
Sub-virion, egg-grown (N=451) (Treanor, 2006)	IM	7.5	10
		15	22
		45	42
Sub-virion, egg-grown (N=400) (Nolan, 2006)	IM	7.5	14
		7.5 + alum	34
		15	30
		15 + alum	41

Immunogenicity of Candidate H5N1 Vaccines in Healthy Adults (18-60 years)

Vaccine type (N)	Route	HA dose (µg)	% HI titer ≥ 1:40
Sub-virion, egg-grown; Novel Adjuvant; 2 doses (N=400 18-60yrs)	IM	3.8	>80%
		7.5	>70%
		15	>70%
		30	>70%

(GSK, Media Release 26th July 2006)

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Major Issue is current Global Influenza Vaccine Production Capacity

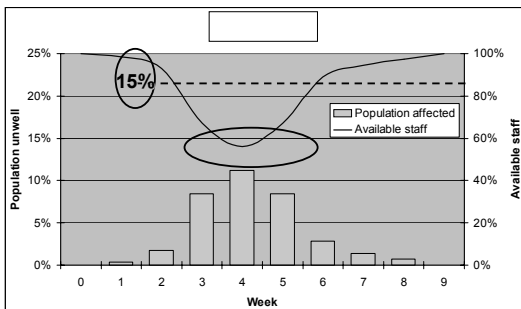
- 65-70% Vaccine manufactured in Europe; ~50% exported



Non-pharmaceutical Interventions (Public health measures)

- Effectiveness of measures may depend on the characteristics of the outbreak
- Given the limited availability of vaccines and antivirals, non pharmaceutical public health interventions are of prime consideration but, as yet, of un quantified value

Worst Case 1918 Scenario: 40% attack rate over 8 weeks



1° & 2° Healthcare Sector Patient Management

Separated Streamed Services:

Green stream
Red stream

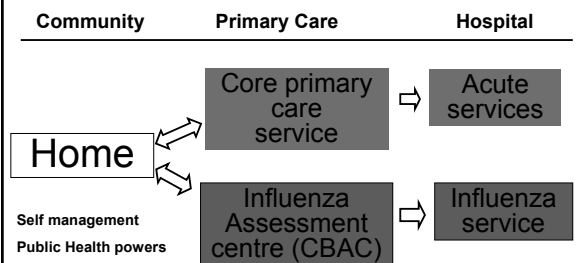


Principles "Patient focused"

- Most people with Influenza will be OK with no health service input
- Many will need reassurance
- Some will need antivirals
- Some will need antibiotics
- Some may need fluids (IV or SC)
- Small % will need hospital/intensive Rx
- Others will need treatment related to underlying conditions
– e.g. COPD, diabetes, asthma, heart failure



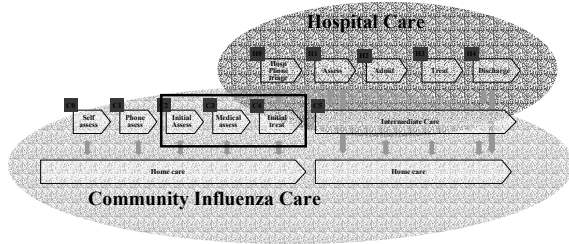
1° & 2° Healthcare: Separated streamed services



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Red Stream Influenza care pathway



Community Support

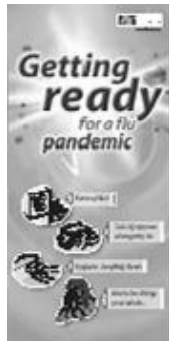
CDHB Draft 2006

Self care at home






- Message
 - Most people will be OK, if you are worried or if the following occur then call phone 0800 - support
 - Continue to self assess – web supported
- What to look out for
 - Trouble breathing
 - Fast breathing
 - Chest pain (other than with cough)
 - Confusion or drowsiness
 - Fever persists longer than 4 days –
 - Flu symptoms go away and then come back
- Outcomes
 - Continue self care at home
 - Call support line
 - Attend CBAC (exception)

- Surge capacity exists in the community
- Communication with the community is a priority



Simple Advice for People at Home

- **Stay home:** If sick keep away from other people -- avoid visitors and visiting others "Social Distancing" 
- **Wash and dry your hands:** before handling food, after coughing, sneezing, using the bathroom, wiping or nose-blowing (your's or your child's), and when looking after sick people. 
- **Keep coughs and sneezes covered:** Tissues are best. Put the tissue in a rubbish bin. 
- **Give plenty to drink:** to people who have a fever and/or diarrhoea.
- **Emergency survival kit:** Include paracetamol (for fever)

www.moh.govt.nz/pandemicinfluenza



Understand how respiratory viruses are transmitted / concept of "social distancing"

CORBIS.COM



Understand concept of "respiratory hygiene".

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**The end of the Spectra:
H5N1 the “rule” breaker**

- Direct transmission from birds to humans
- High lethality / diversity of pathogenicity for waterfowl
- Transmission of influenza virus genes from domestic poultry to migratory waterfowl
- Transmission of viruses mainly via the respiratory route
- Increased thermal stability
- Transmission to felids
- *Is highly pathogenic H5N1 now endemic in waterfowl?*

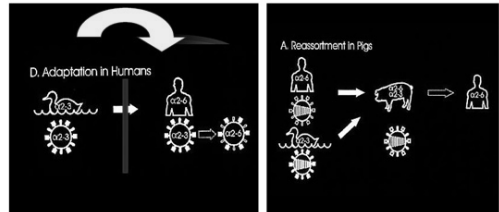
 **Continued rapid evolution**

**How could the next human
pandemic virus arise?**

It happened with SARS CoV

It happened in 1918 with “Spanish Flu”

**DO NOT IGNORE
HISTORY**



**A “narrow window of opportunity”
exists providing a unique opportunity
to intervene.**



We Must Prepare Now

South Pacific Teleclass Series 2006

August 27

The Spectre of a Flu Pandemic – Is it Inevitable

... with Dr. Lance Jennings, University of Otago

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September 20

SARS in Singapore – What Can We Learn?

... with Dr. Chris Wynn, Christchurch Hospital

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