

The Swine Flu Pandemic

What we know now

Dr Jake Dunning

Global Health BSc Course, Oct 2011

Personal Background

- Imperial (CXWMS) trained
- SpR ID & GIM
- Dangerous & emerging pathogens; zoonoses
- Pandemic influenza secondment – HPA Porton Down 2009
- National critical care guidelines for pandemic H1N1
- PhD: Mechanisms of Severe Acute Influenza Consortium, Oct 2009 -

- International Severe Acute Infectious Consortium (ISARIC)
- International Forum for Acute Care Trialists (InFACT)
- Health Connections International – TB & HIV care in Central Asia

- *No financial conflicts of interest!*

Interesting UK work: an imported Lassa fever case



Visiting clinics on Likomo, Lake Malawi

Today's Talk

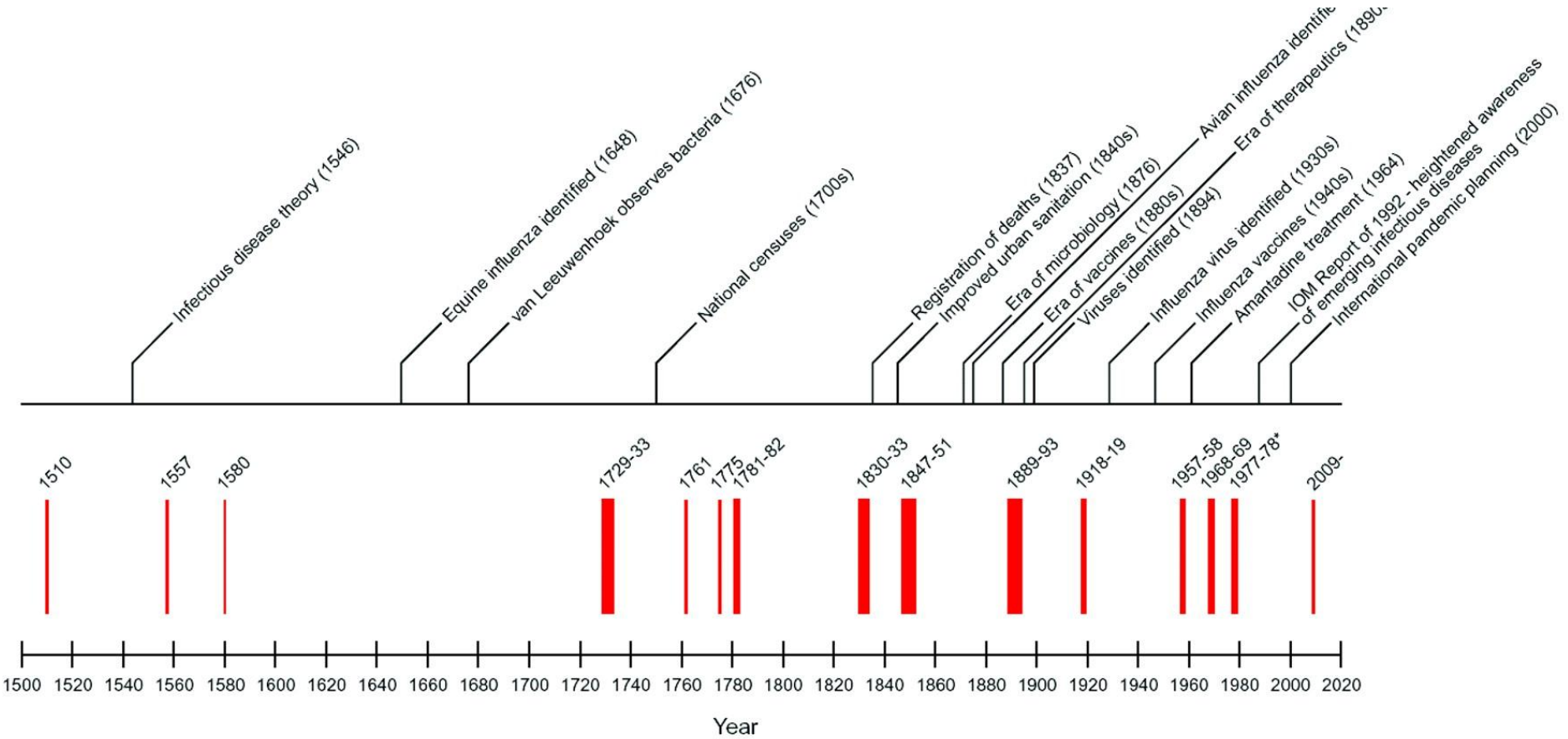
- Historical aspects of influenza pandemics
- Time course of the 2009-10 influenza pandemic
- Public health implications and management
- Clinical features of pH1N1/09
- Pathogenesis
- Treatment

Happy Birthday to you, Happy Birthday to (Pandemic) Flu...



- July 1510 - “Gasping Oppression” around the world
- Infectious theory 1546
- Microbes recognised 1676 (1876 human disease)
- *Haemophilus influenzae* 1892
- Influenza virus discovered 1930s

500 Years of Flu Pandemics



Morens D M et al. Clin Infect Dis. 2010;51:1442-1444

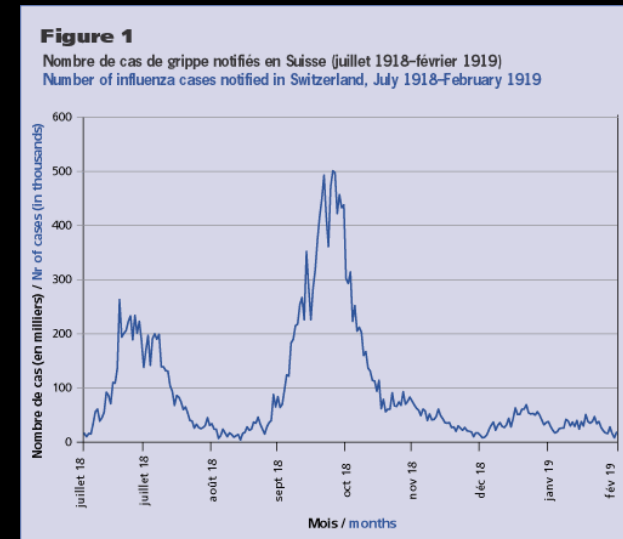
The “Great” Flu Pandemics

31 last 400 years

- **1918** **H1N1** **Avian** **50–100 million deaths**
- **1957** **H2N2** **Mixed** **1 million deaths**
- **1968** **H3N2** **Mixed** **1 million deaths**

1918 Spanish Flu: H1N1

- 1918-1919
- Europe, Asia, North America
- More deaths than WW1 itself
- 50 million + deaths
- 3 distinct waves
 - 1st: Contagious, generally not deadly (Spring)
 - 2nd: **Contagious, often deadly** (September)
 - 3rd: Less contagious?, generally not deadly

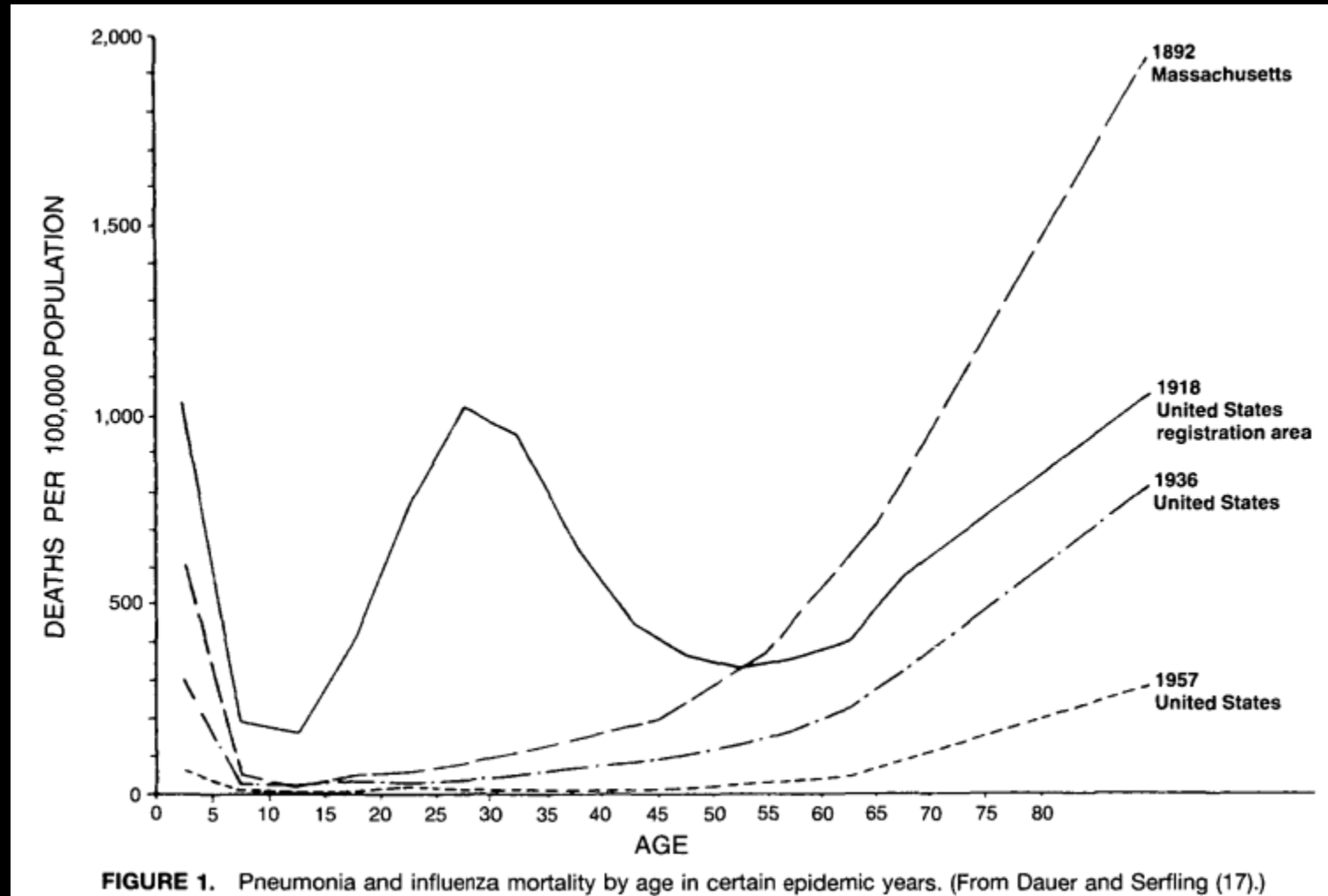


1918 Spanish Flu: H1N1

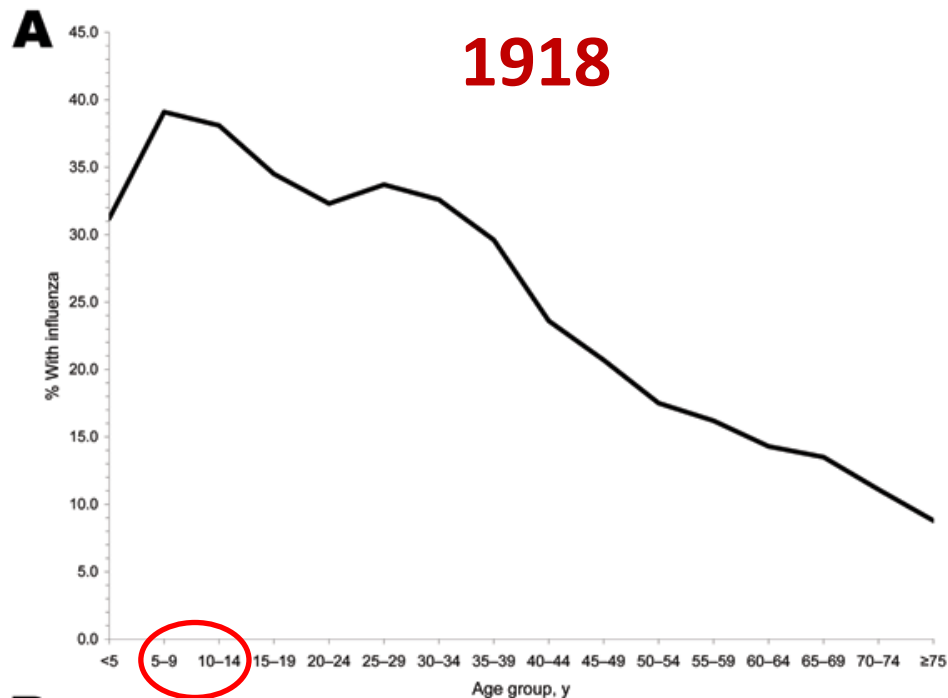
- Most deaths 15 – 35 years
- 99% deaths <65 years
- Many doubted it was flu
- Death in <72 hours
- Or typical flu
- 2% mortality in West
- 90% mortality Aborigines



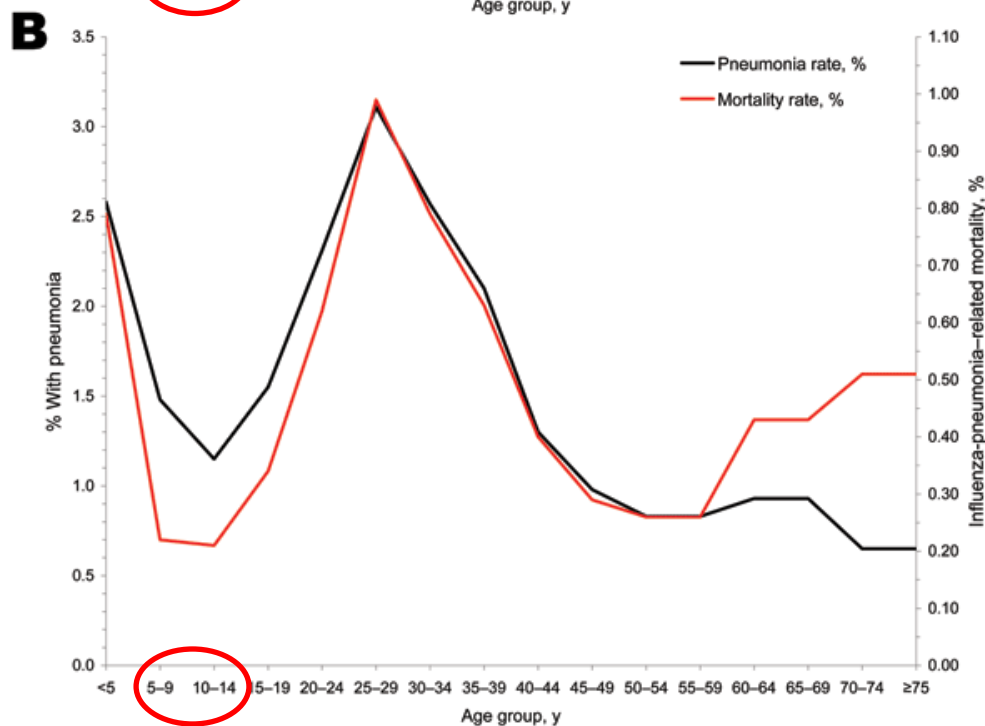
1918: The W Curve



Dauer CC, Serfling RE. Mortality from influenza, 1957-1958 and 1959-1960. *Am Rev Respir Dis* 1961;83(2 Suppl):15-26.



Incidence of influenza by age



Pneumonia and mortality by age

1918: Post Mortem / Clinical Data

- Primary viral pneumonia
- **Secondary bacterial pneumonia**
- All eight viral segments sequenced
 - Unfixed frozen lung
 - Fixed lung from PM's
 - r1918 highly pathogenic in animals/cells - cytokines
- *Not a reassortant virus – avian adapted*
- 1918 vs. avian viruses: 10 amino acid changes in viral polymerase
- **LIMITED HEALTHCARE, NO ANTIBIOTICS!**

Seasonal Influenza A & B

- **Different circulating strains**
 - Hemispheres (N v. S)
 - Year
 - Epidemics (drift)
- 3-5 million cases severe illness per year
- 300-500,000 deaths per year
 - Mainly >65 years, <2 years and/or comorbidities

H5N1 Highly Pathogenic Avian Influenza (Bird Flu)



HPAI H5N1: Key facts

- **1918 Pandemic: likely adapted *avian H1N1* virus**
- **Emergence of HPAI H5N1 in 2003**
- **>568 cases (ongoing e.g. Indonensia); 334 deaths**
- **Striking characteristics**
 1. **Young adults and children (previously well)**
 2. **High Mortality – 60%**
 - » **True case fatality rate? Denominator?**
 - » **1% seropositive in Cambodian village***
- **Endemic in birds in Asia: direct exposure**
- **Poor human-human transmission**
- **α -2,3 sialic acid galactose; other receptors?[†]**
- **LPAI H5N1 + Seasonal H3N2 PB2 polymerase → HP++ AI[‡]**

H5N1 Radiology – Hien TT, NEJM 2004, 350:1179-1188

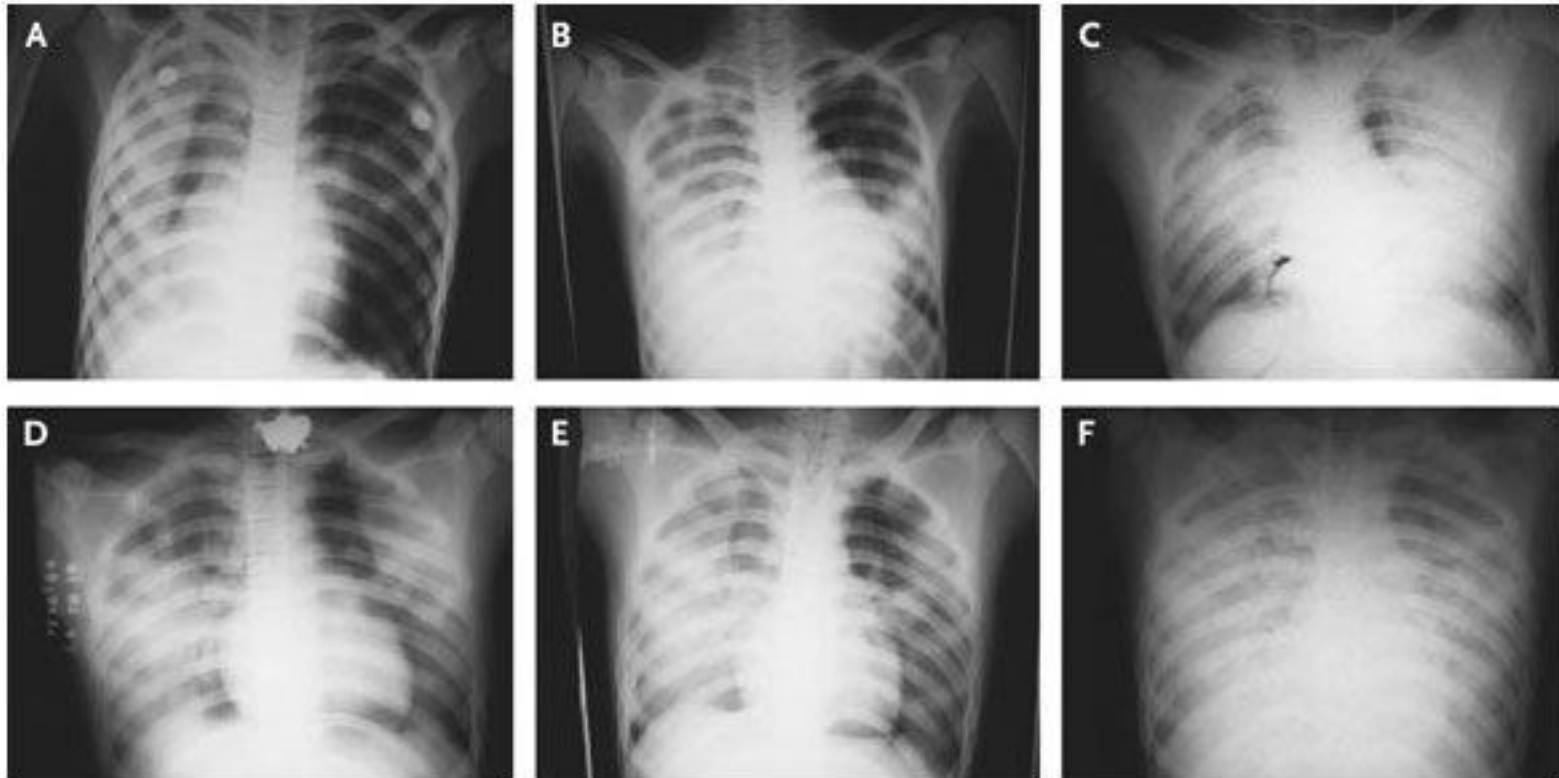


Figure 3. Chest Radiographs.

Radiographs from Patient 5 (Panel A), Patient 7 (Panel B), and Patient 9 (Panel C) show widespread consolidation, collapse, and interstitial shadowing. In Panels D, E, and F, three chest radiographs show the progression in Patient 8 on days 5, 7, and 10 of illness, respectively.

H5N1 – Clinical: Summary of published series

- **ILI, rapidly progressive dyspnoea**
- **Viral pneumonitis +/- ALI +/- MODS**
- **Bacterial infections RARE**
- **Extra-pulmonary & atypical presentations**
- **DAD + variable organisation**
- **Haemophagytosis described**
- **Viraemia recognised**

H5N1 – Dysregulated Immune Mediators

- **Effect of Infection**
 - Local acute lung injury
 - Apoptosis of alveolar epithelial cells: induces pro-inflammatory cytokines
- **Host inflammatory response**
 - *High levels of H5N1 associated with high levels of proinflammatory cytokines, chemokines, in turn associated with fatal outcomes*
 - Evidence of cytokine dysregulation
 - Increased plasma IL-10, IL-6, IFN- γ
 - *Early antiviral treatment needed to suppress viral replication, prevent cytokine dysregulation: “Get in there early (and hope the virus remains sensitive)!”*
- **Other factors**
 - Viremia, viral dissemination, haemophagocytosis
 - Prolonged viral shedding (up to 16 days)

H5N1 Antiviral Treatment

- **Effectiveness of Oseltamivir treatment of severely ill hospitalized patients with lower respiratory tract disease (*retrospective, uncontrolled*):**
 - Treatment associated with survival (Vietnam; WHO)
 - Earlier treatment associated with survival (Indonesia)
 - No *controlled* data available (similar to pH1N1)
 - WHO: consider higher dosing, longer duration of treatment for severely ill H5N1 patients (cf. pH1N1 critically ill advice)
 - Oseltamivir resistance documented with treatment
 - Can evolve rapidly
 - H5N1 virus strains have different antiviral susceptibilities (regional?)
 - Role for combination antiviral treatment (e.g. amantadine *if* sensitive)

Oseltamivir-resistant H5N1

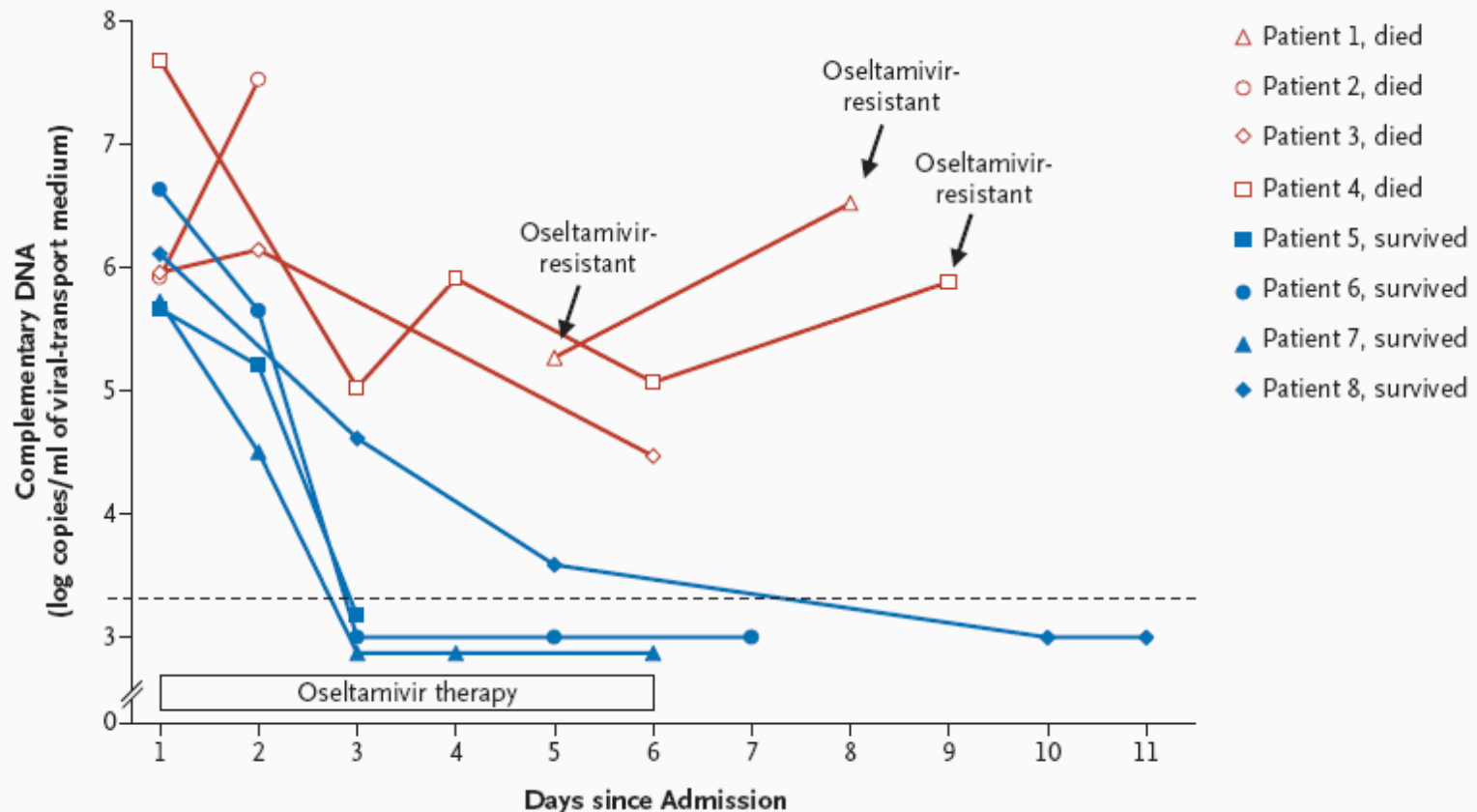


Figure 3. Influenza A (H5N1) Viral RNA Load in Throat Swabs from Eight Patients.

Blue lines represent patients who survived influenza A (H5N1) virus infection, and red lines represent patients who died. The dashed horizontal line denotes the limit of detection of the RT-PCR assay. The arrows indicate the specimens from which oseltamivir-resistant influenza A (H5N1) variants were isolated. No virus was isolated from any other specimen besides samples obtained at admission. *de Jong MD et al., NEJM 2005;353:2667-72*

H5N1 Control



Clade 2.3.2.1



Food and Agriculture
Organization of the
United Nations

for a world without hunger

Bird Flu rears its head again

Increased preparedness and surveillance urged against variant strain



Major resurgence H5N1 possible

29 August 2011, Rome - FAO today urged heightened readiness and surveillance against a possible major resurgence of the H5N1 Highly Pathogenic Avian Influenza amid signs that a mutant strain of the deadly Bird Flu virus is spreading in Asia and beyond, with unpredictable risks to human health.

The H5N1 virus has infected 565 people since it first appeared in 2003, killing 331 of them, according to WHO figures. The latest death occurred earlier this month in Cambodia, which has registered eight cases of human infection this year -- all of them fatal.

Evolution of H5N1 avian influenza virus does not increase risk to public health

30 August 2011 -- WHO closely monitors the evolution of influenza viruses and is aware of recent reports of an H5N1 virus (described as H5N1 clade 2.3.2.1) circulating in poultry in parts of Asia. Based on available information, this evolution of the H5N1 virus poses no increased risk to public health. It is not considered unusual because influenza viruses are constantly evolving, especially in areas where they circulate regularly in poultry.



World Health
Organization

Defining a Pandemic

World Health Organization (18 May 2009)

US Centers for Disease Control and Prevention® (1 March 2009)

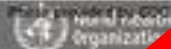


Requirements for a Pandemic

Global outbreak of disease

- New influenza A virus emerges in humans
- Minimal or no population immunity
- **Causes serious illness; high morbidity/mortality**
- Spreads easily from person to person

Pandemic Influenza – Rapid Containment



Requirements for an Influenza Pandemic

- A new influenza A subtype emerges that can infect humans
- AND
- Causes serious illness
- AND
- Spreads easily from human-to-human

Influenza Pandemic Viruses

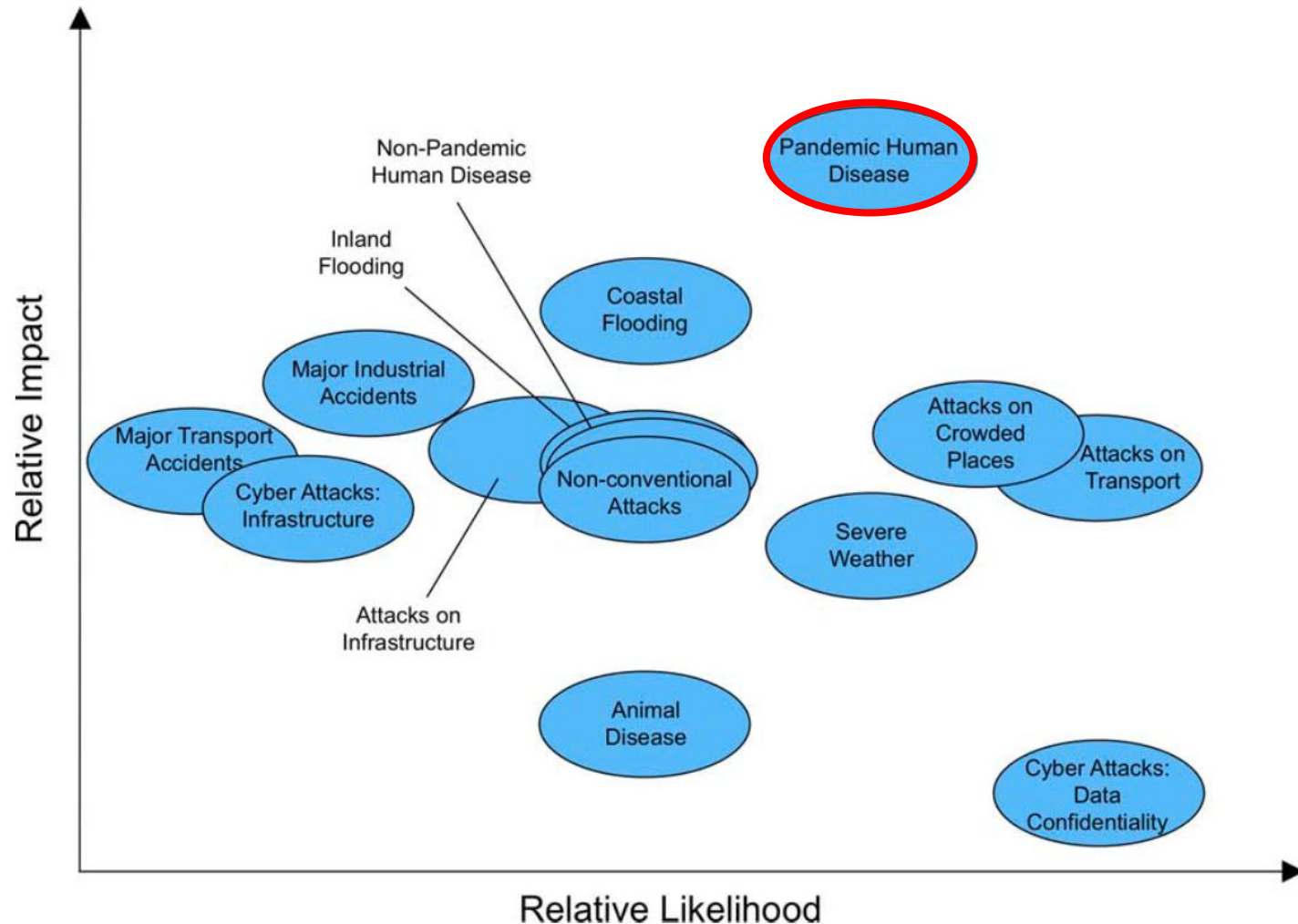
- A new influenza A subtype can infect humans
- AND
- Causes serious illness
- AND
- Spreads easily from human-to-human

The first two prerequisites have been met,
but not the last

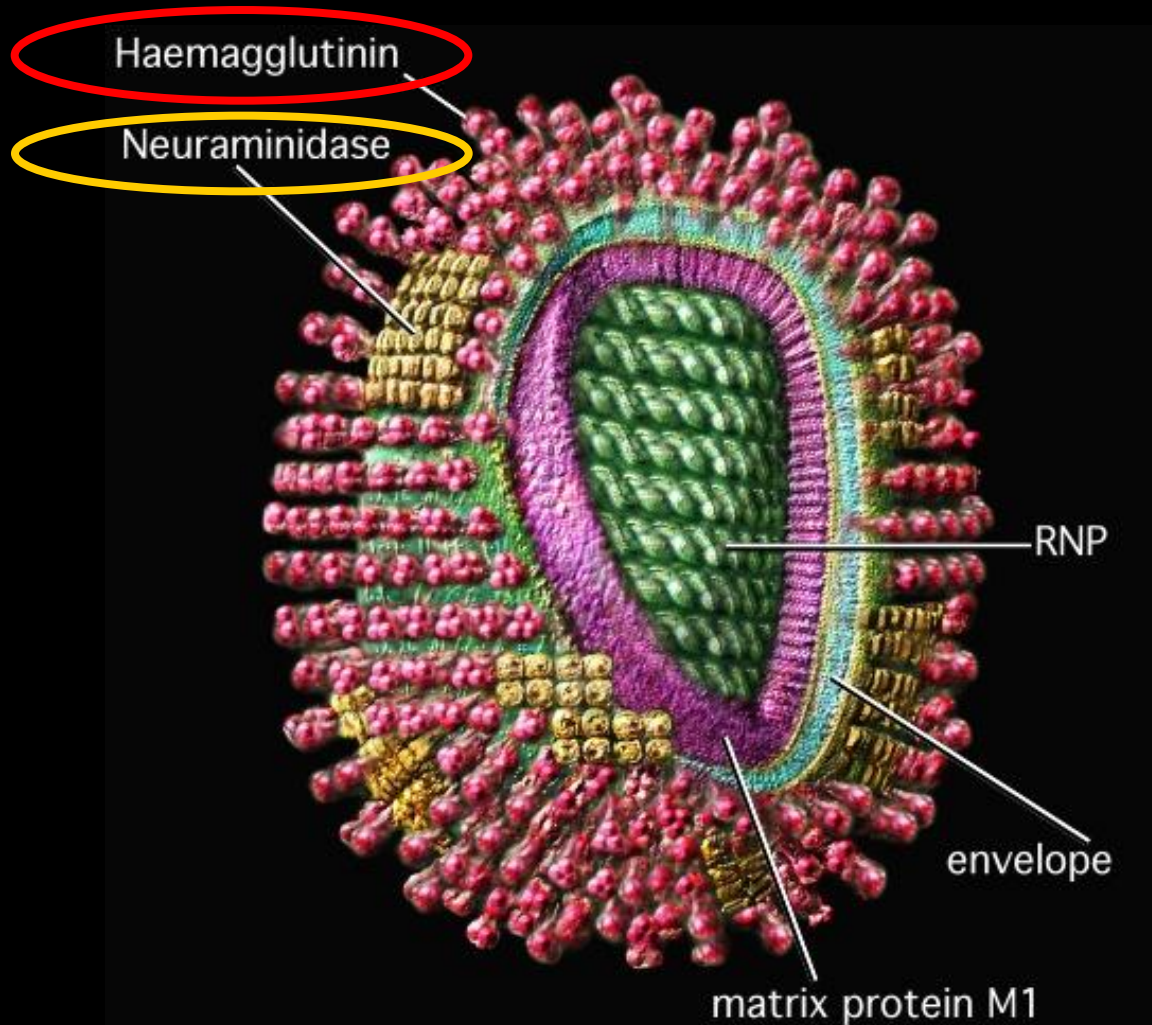
WHO Pandemic Phases

- **Phase 5** is characterized by human-to-human spread of the virus into at least two countries in one WHO region
- **Phase 6**, the pandemic phase, is characterized by community level outbreaks in at least one other country in a different WHO region in addition to the criteria defined in **Phase 5**. Designation of this phase will indicate that a global pandemic is under way.

National Risk Register of Civil Emergencies 2010 Edition



The Flu Virus



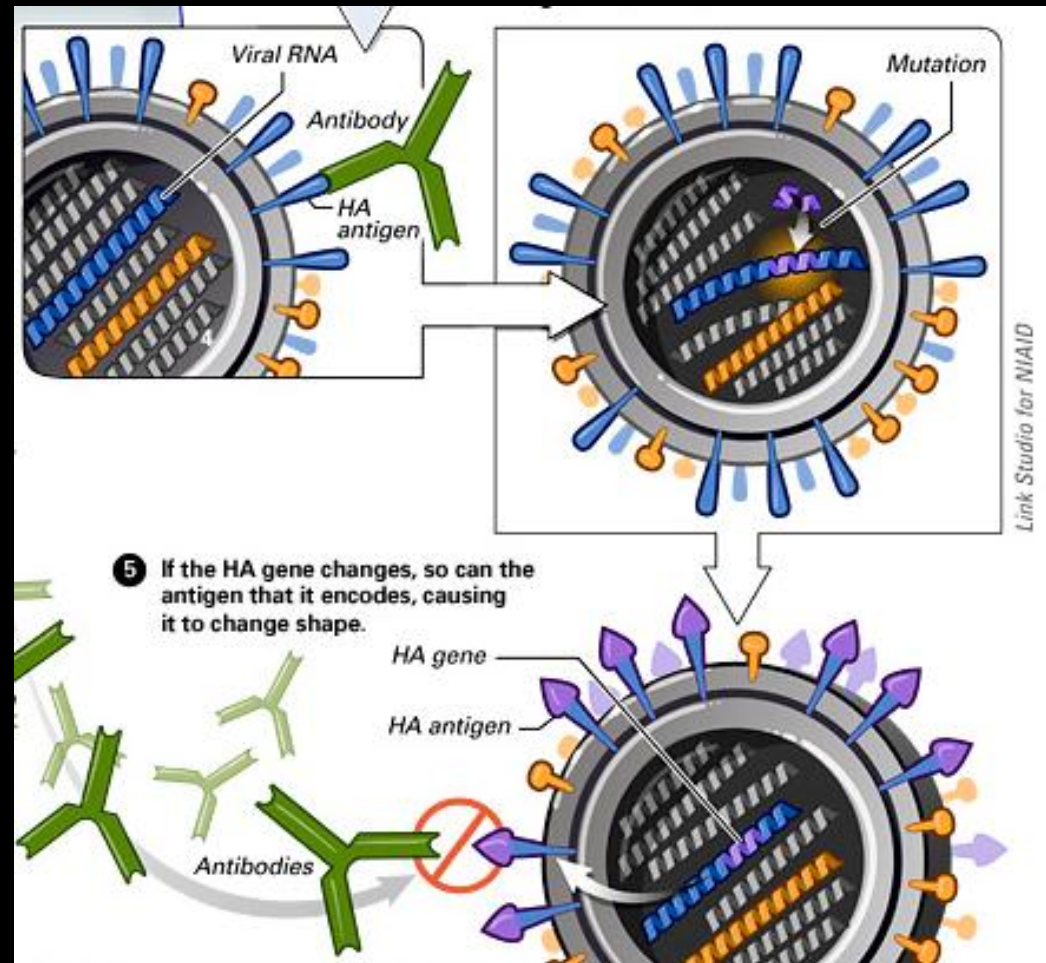
Spontaneous point mutation

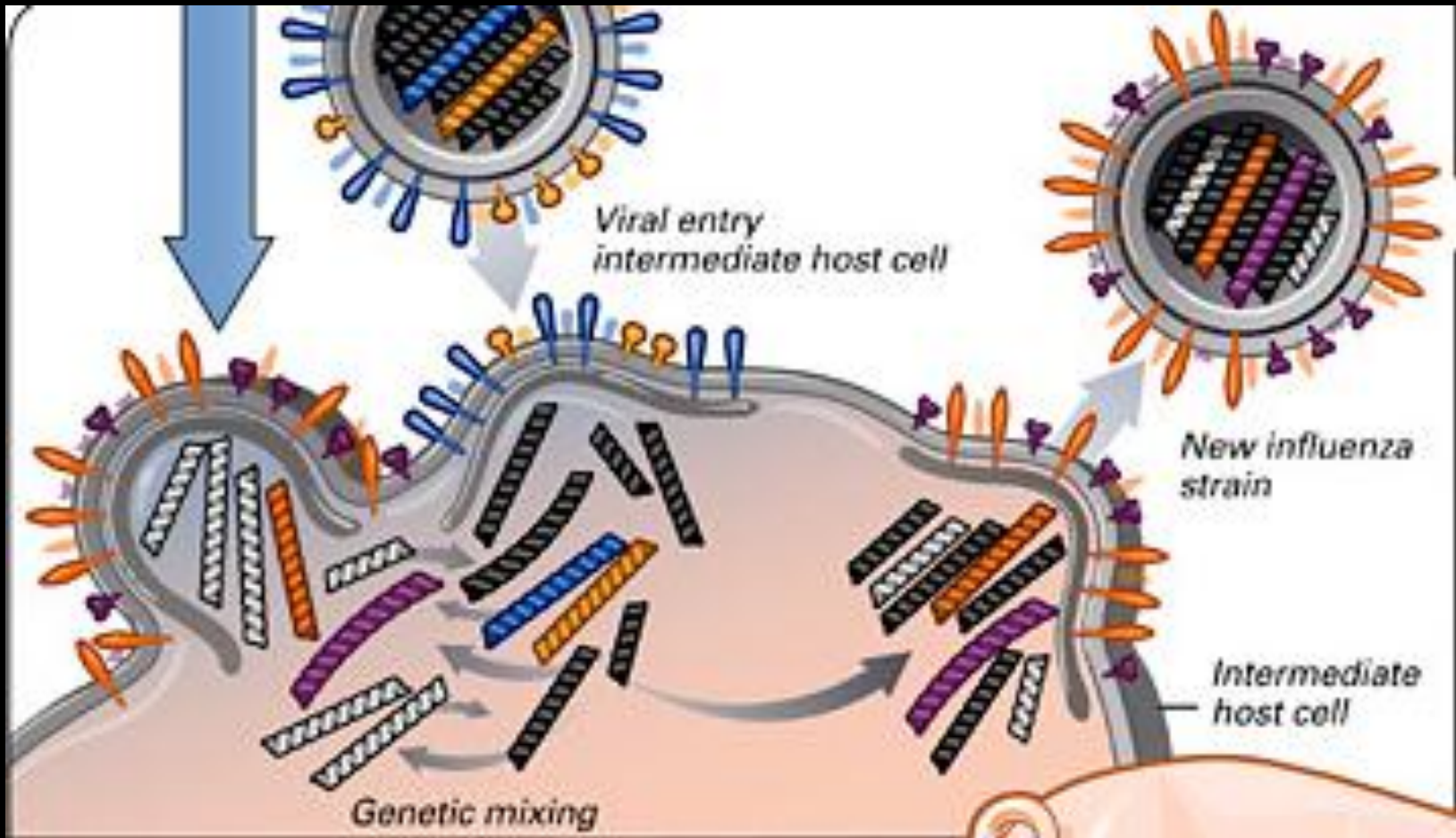


HA/NA conformational change



DRIFT





Hybrid virus with HA/NA of strains that combined

SHIFT

1918 "Spanish influenza"

1957 "Asian influenza"

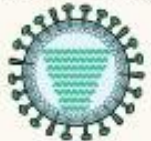
1968 "Hong Kong influenza"

Next pandemic influenza

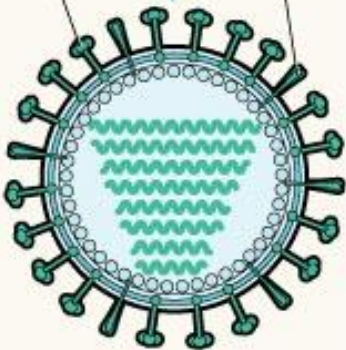
H1N1 influenza virus



Bird-to-human transmission of H1N1 virus

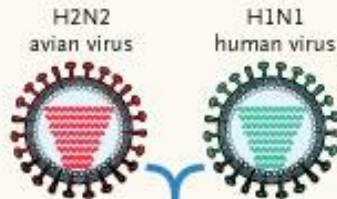


Hemagglutinin Neuraminidase

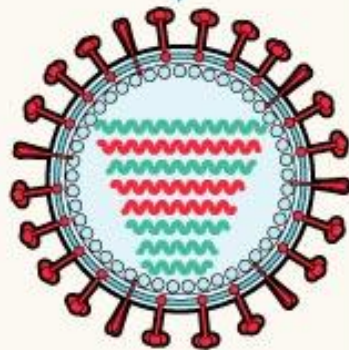


All 8 genetic segments thought to have originated from avian influenza virus

H2N2 influenza virus

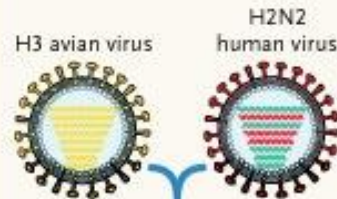


Reassortment

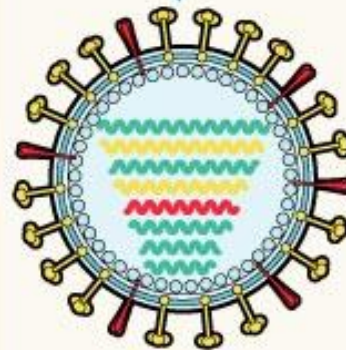


3 new genetic segments from avian influenza virus introduced (HA, NA, PB1); contained 5 RNA segments from 1918

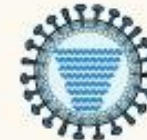
H3N2 influenza virus



Reassortment

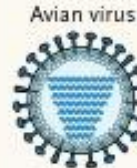


2 new genetic segments from avian influenza virus introduced (HA, PB1); contained 5 RNA segments from 1918



Avian virus

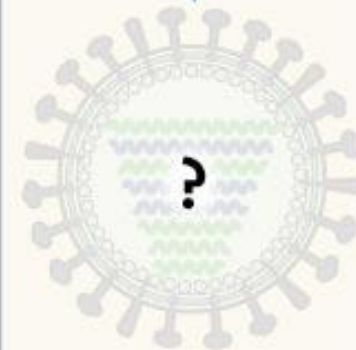
or



Avian virus



H3N2 human virus



All 8 genes new or further derivative of 1918 virus

Scan the horizon, no need to panic, make plans...





Taipingshan Plague 1894 (Hong Kong Museum of Medical Sciences)

We were too busy looking East!



The First Influenza Pandemic This Century





April 2009: Southern California

- **Mild influenza-like-illness in 2 children**
- **Non subtypable Flu-A (San Diego; Brawley)**
- **Wednesday April 15th → CDC**
- **RT-PCR suggests swine-origin triple reassortant influenza A**
- **Cases unrelated; no contact with pigs**
- **April 23rd: Mexican cases confirmed**
- **April 25th: Canadian case confirmed**

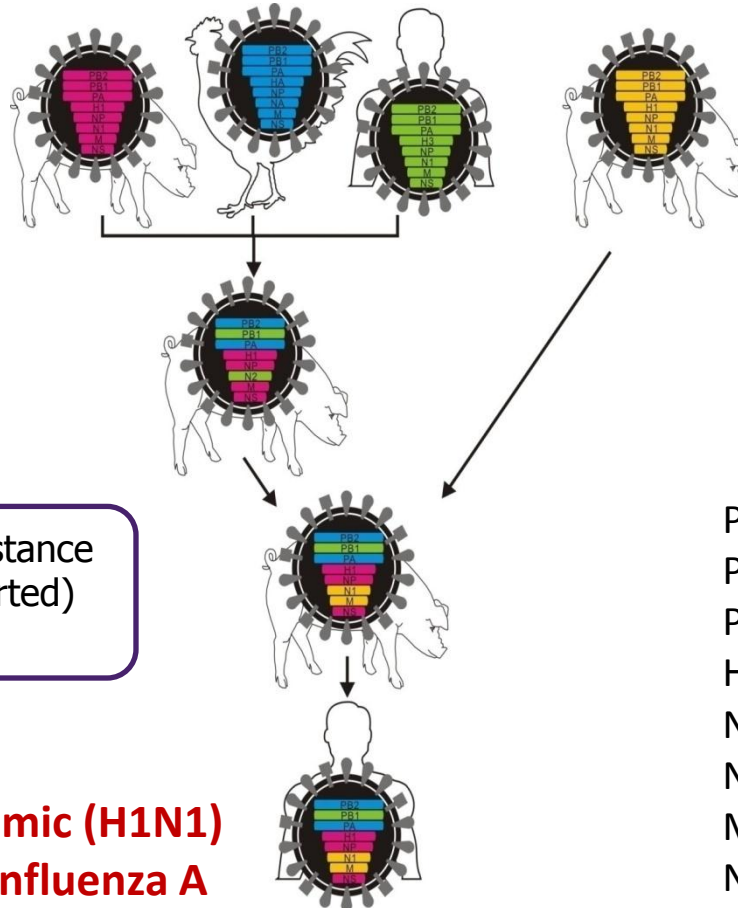
Pandemic (H1N1) 2009 Influenza A “Swine Flu”: Origins

Classical swine
derived from
1918 H1N1

North
American
Avian

Human
H3N2

Eurasian avian-like
swine



- Inherent adamantane [M] resistance (rare, sensitive mutant now reported)
- Inherent oseltamivir sensitivity

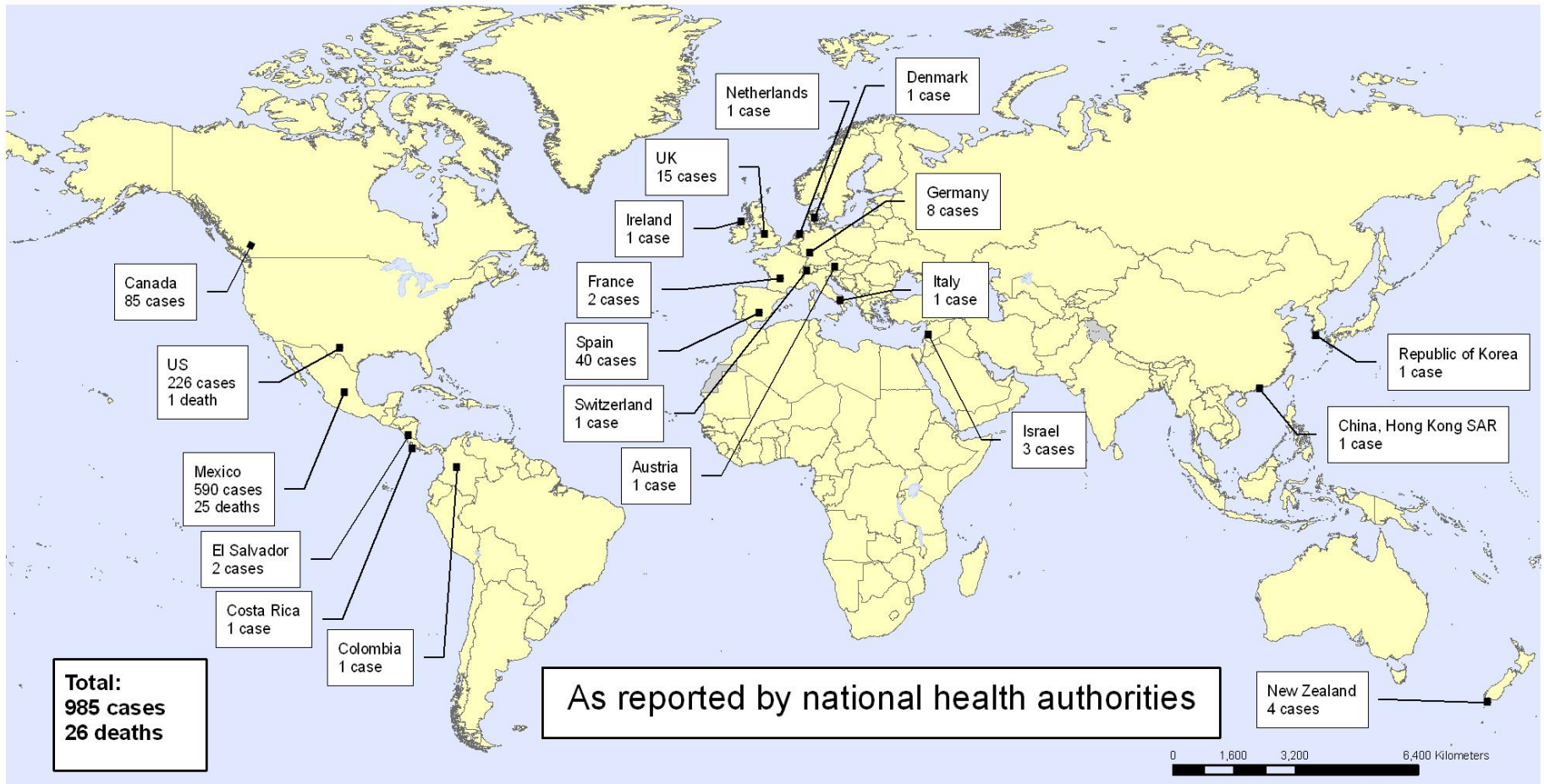
**Pandemic (H1N1)
2009 Influenza A**

PB2 - North American avian
PB1 - Human H3N2
PA - North American avian
H1 - Classical swine
NP - Classical swine
N1 - Eurasian avian-like swine
M - Eurasian avian-like swine
NS - Classical swine

H1N1: Distribution

New Influenza A (H1N1)
Number of laboratory confirmed cases and deaths

Status as of 4 May 2009
06:30 GMT



As reported by national health authorities

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Public Health Information
and Geographic Information Systems (GIS)
World Health Organization



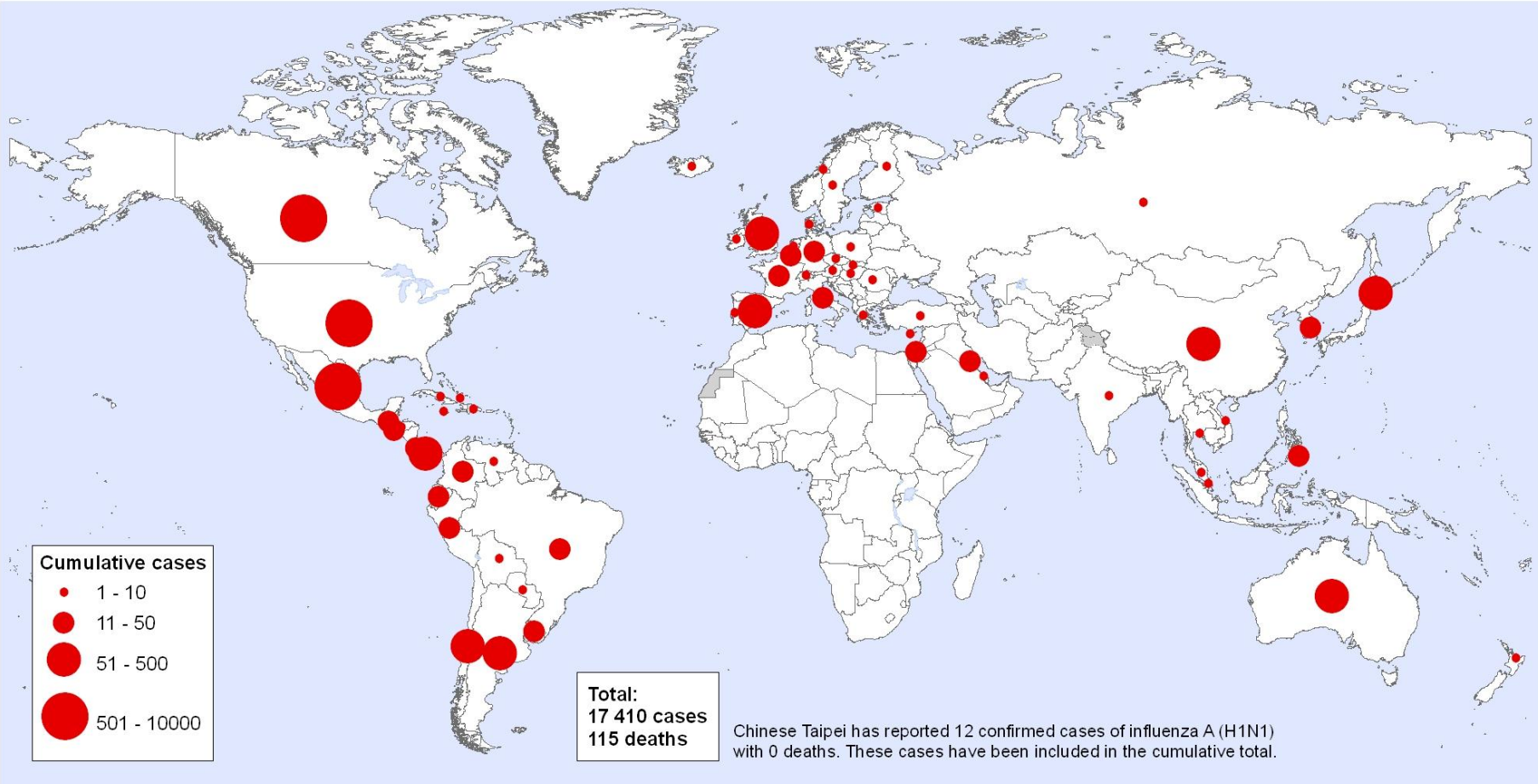
© WHO 2009. All rights reserved

Map produced: 4 May 2009 12:26 GMT

H1N1: Distribution

New Influenza A (H1N1),
Number of laboratory confirmed cases as reported to WHO

Status as of 01 June 2009
06:00 GMT



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
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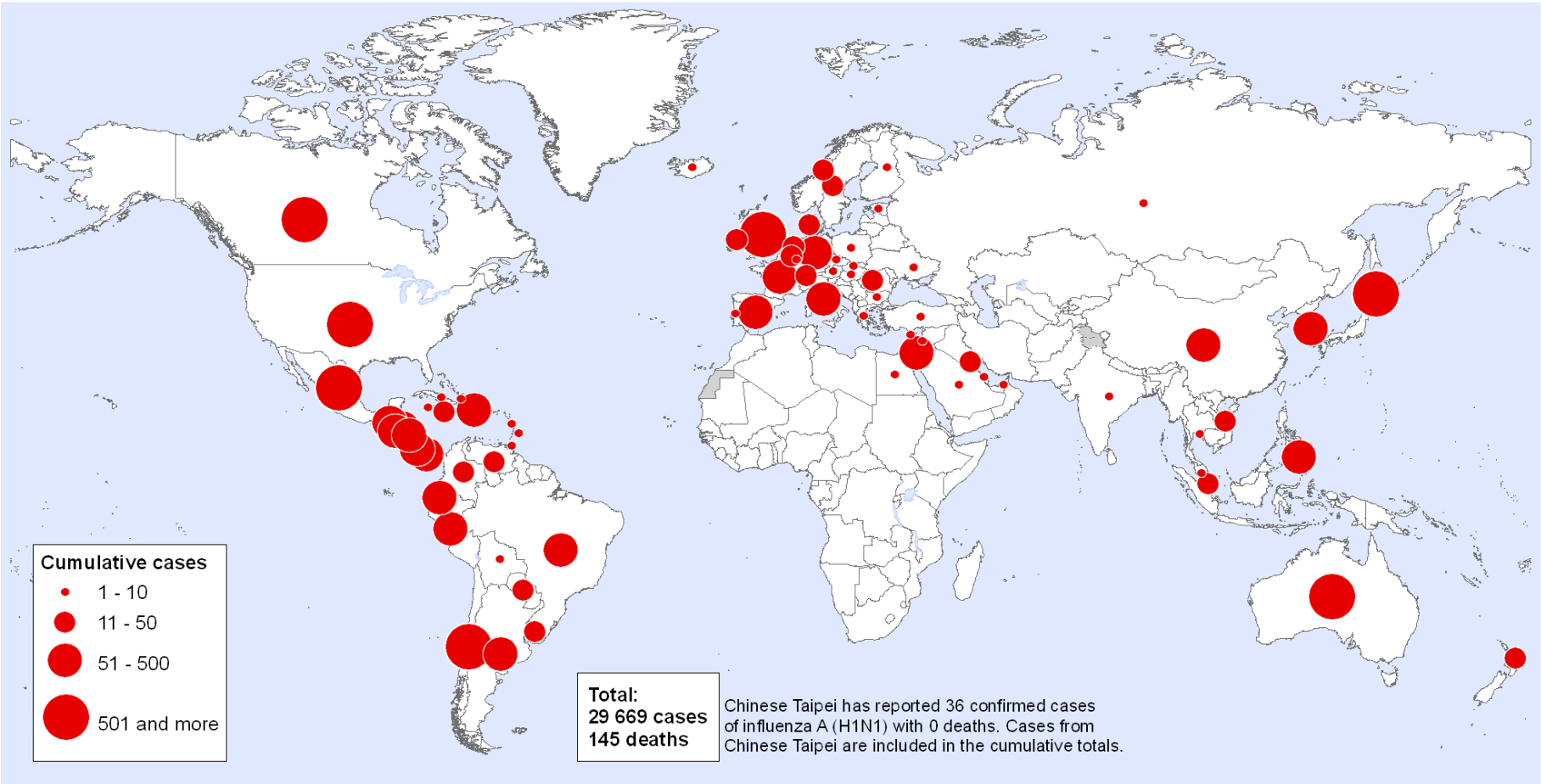
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Map produced: 01 June 2009 06:46 GMT

H1N1: Distribution

New Influenza A (H1N1),
Number of laboratory confirmed cases as reported to WHO

Status as of 12 June 2009
06:00 GMT



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Data Source: World Health Organization
Map Production: Public Health Information
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World Health Organization



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Map produced: 12 June 2009 07:00 GMT

Definition met?

PANDEMIC INFLUENZA

1. Widespread, sustained human-human transmission in multiple geographic regions across the globe ✓
2. A novel influenza strain demonstrating antigenic shift ✓

Tendency to cause severe disease?

- *Not a prerequisite*
- *Demonstrate characteristic “pandemic strain” illness*



The *Mexican Wave*

- April 24th 2009
- Cases of unusually severe respiratory illness, including healthcare workers
- Retrospective case & sample analysis:
 - February 24th



Edgar Hernandez, the Mexican boy who was widely regarded as the first person in the world diagnosed with swine flu. A year later, epidemiologists say the human form of the virus is unlikely to have originated in his village. Photograph: Pablo Spencer/AFP/Getty Images guardian.co.uk

How did this early data influence the global response?

Timeline of Reagents and Vaccines

Late February
–Early March
**First
cases in
Mexico**

April 23

1st Full
genome
completed

April 26

1st Egg isolate
A/California/07/2009

April 15

First case
Identified
A/California/4/2009

April 29

First Diagnostic
Kits Shipped to
State Labs
CDC shares with WHO:
Diagnostic Assay ; full
genome sequencing
strategy and primers

May 3

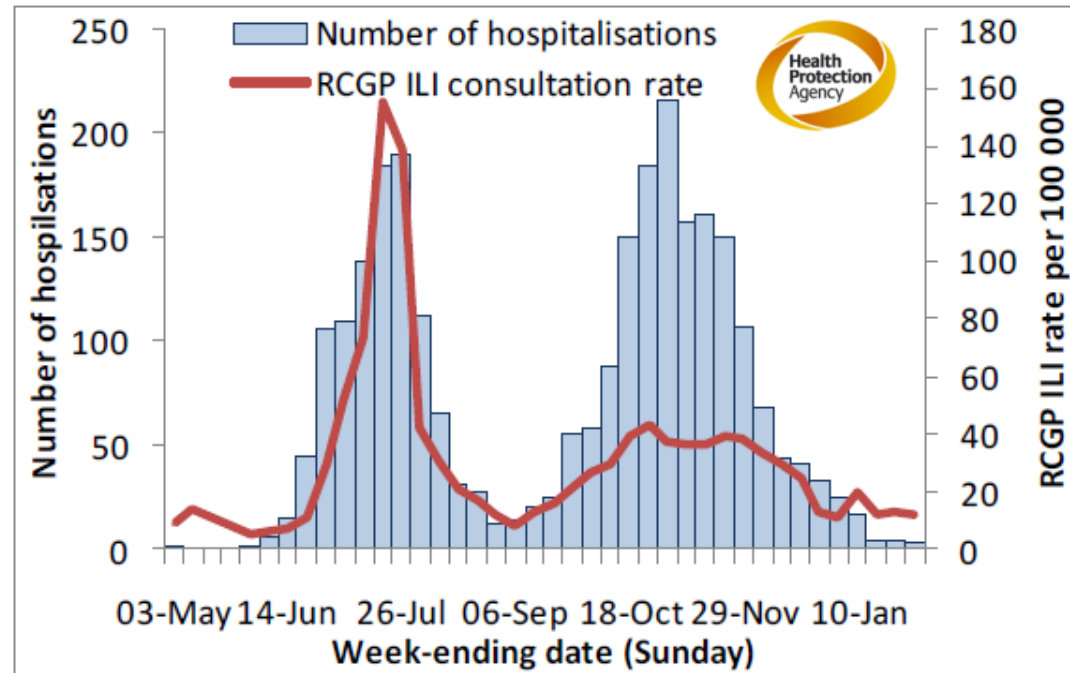
**First Diagnostic
Kits** Shipped to
WHO Network

May 23

**Vaccine Strain
Shipped** to
Manufacturers

Pandemic Experience in the UK

- **First UK case:** 27 April 2009
- **Pandemic declared:** 11 June 09
- **UK 1st wave:** Summer 09
- **UK 2nd wave:** Winter 2009/10
- **Pandemic over:** 10 August 2010



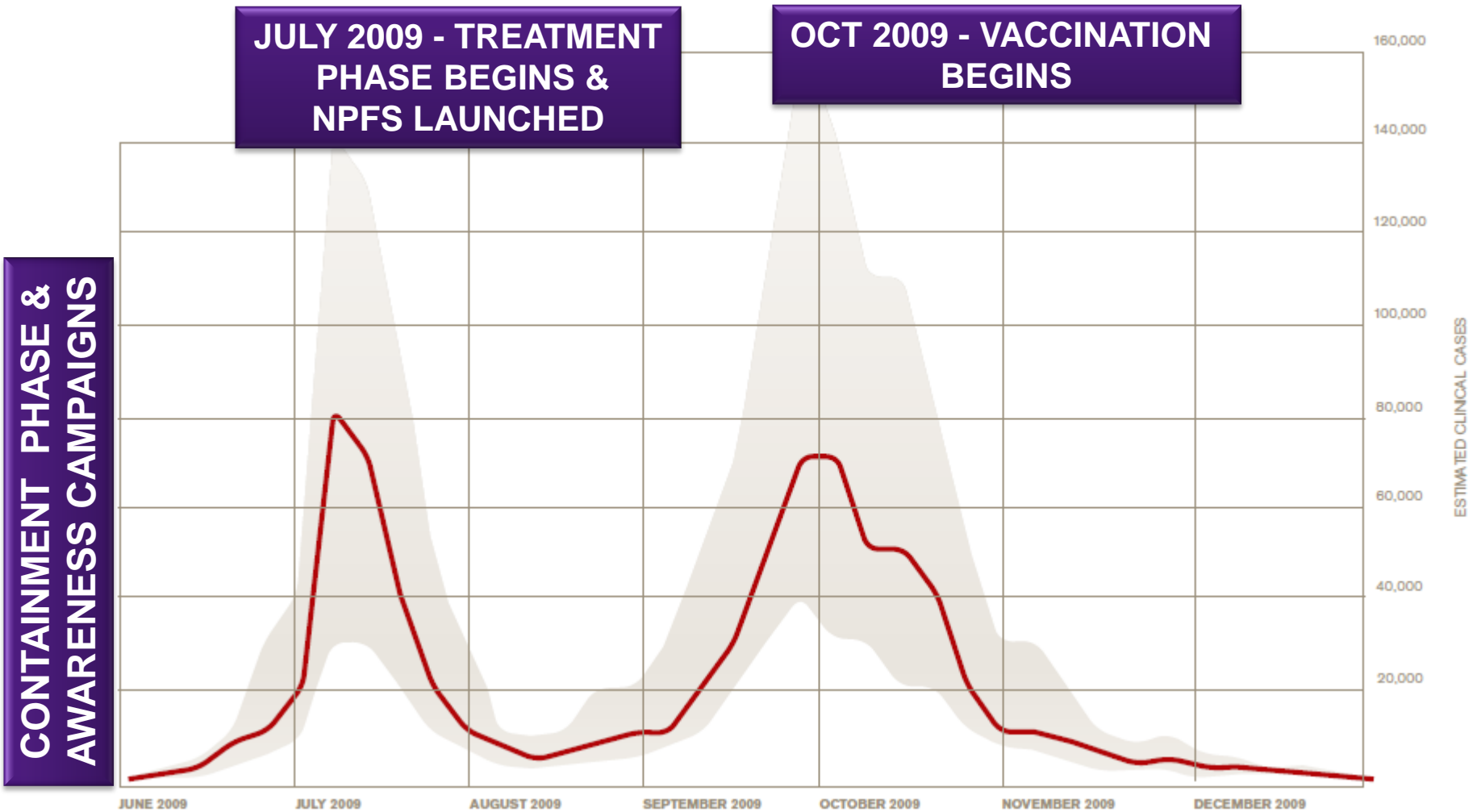
UK 1st and 2nd Waves

>30,000 confirmed cases

>5000 hospitalisations

457 confirmed deaths

UK Pandemic Response



Graph based on HPA data and published in the *2009 Influenza Pandemic* report

Specific Measures Taken During the Pandemic

Pandemic Preparedness

- Vaccine and antiviral stockpiles/advance purchase agreements
- Prepare for worst-case scenarios

Containment Phase

- Swabbing, presumptive treatment, case investigation, prophylaxis of contacts, self-isolation, school closures, selective port screening
- Slow initial spread and learn more about the virus

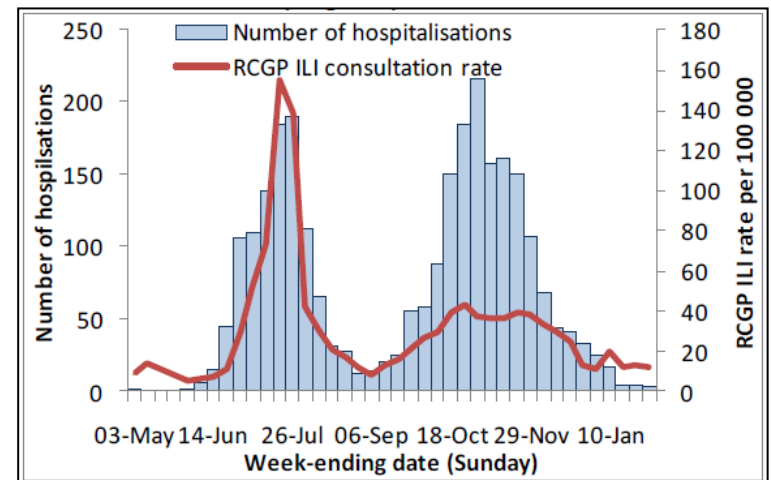
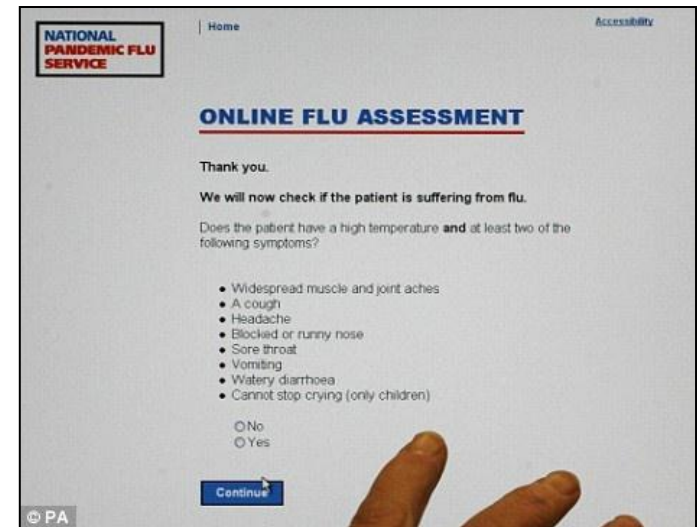
Treatment Phase

- NIs: Ability for 80% coverage based on 50% CAR
- Clinical, not lab-based diagnosis
- ‘Treat all’ policy in England; at-risk groups and clinical discretion elsewhere

Specific Measures Taken During the Pandemic

National Pandemic Flu Service (NPFS)

- England only
- Telephone and internet-based triage/presumptive diagnosis
- Special measure – not individualised care
- “Voucher” access to antivirals; 25% needed to see GP
- 2.7 million consultations; 1.1 million courses of antivirals
- ~ 1:10 NPFS patients thought to have had influenza



Specific Pandemic Response Measures

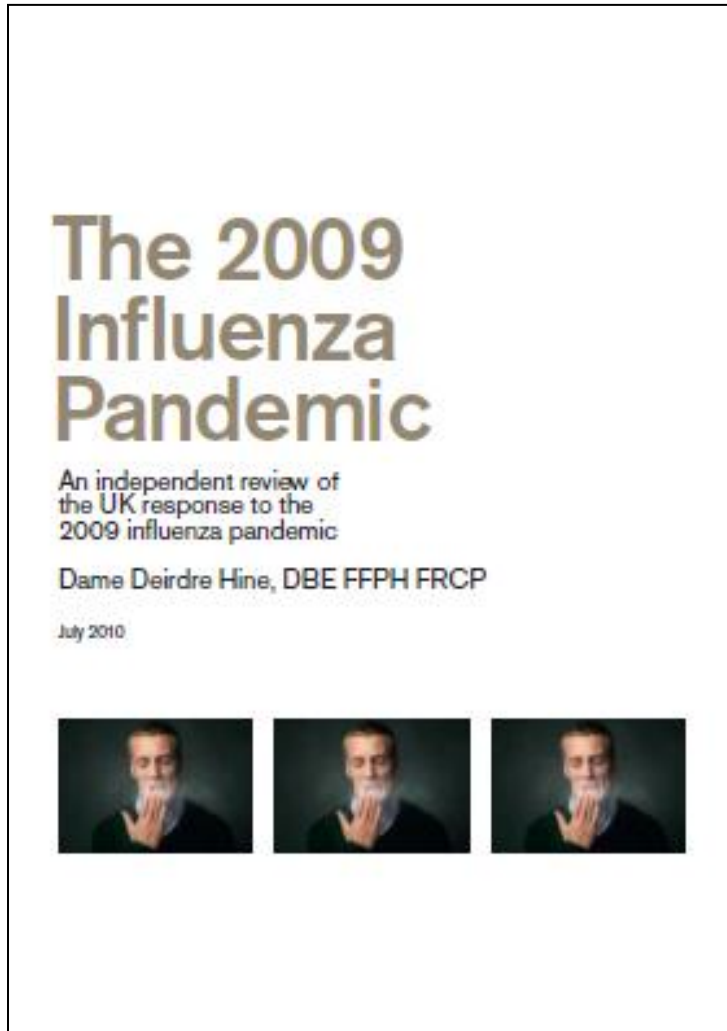
Vaccination

- Co-ordinated procurement and centralised distribution
- Widespread awareness campaigns
- Majority given by general practice surgeries – 6 Euro remuneration per dose
- Vaccination of healthy children under 5 years – Dec 2009

March 2010 – Pandemrix single dose uptake data, England

- Clinical risk groups, all ages: **37.1%** (30.5-42.6)
- Healthy children under 5 years: **20.4%** (13.4-27.5)
- Frontline healthcare workers: **39.9%** (35.5-43.9)

Pandemic Management in the UK



- Independent review of pandemic response
- Provide feed-back to the UK Government/Stakeholders

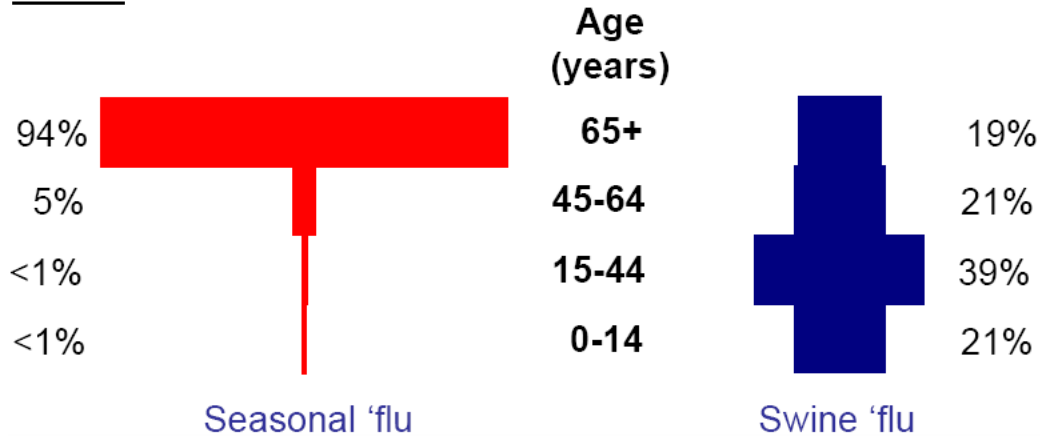
Summary of UK Pandemic Experience

- Mild illness in most of those infected with pH1N1
- Significant illness in an important minority
 - Pneumonitis, respiratory failure, ARDS
 - Younger adults and children
 - 50% hospitalisations and in-hospital deaths lacked significant risk factors¹
- Significant demands on healthcare services
- Risk-averse approach in the UK
- Difficulties in assessing and communicating risks
 - *“The boy who cried wolf”*
 - *“Damned if you do, damned if you don’t”*

¹, Nguyen-Van-Tam JS et al. Thorax. 2010 Jul;65(7):645-51.

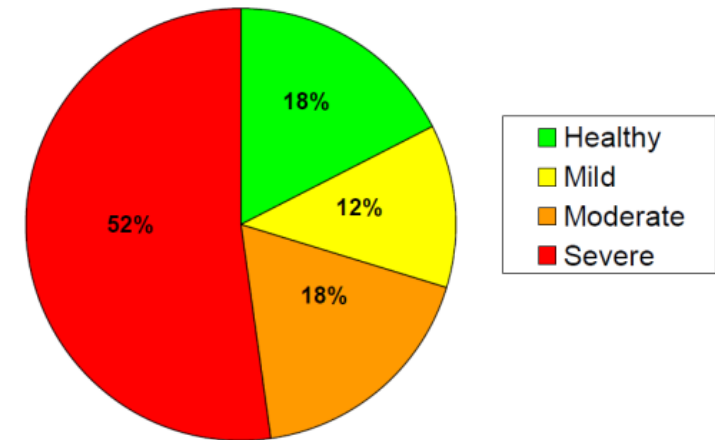
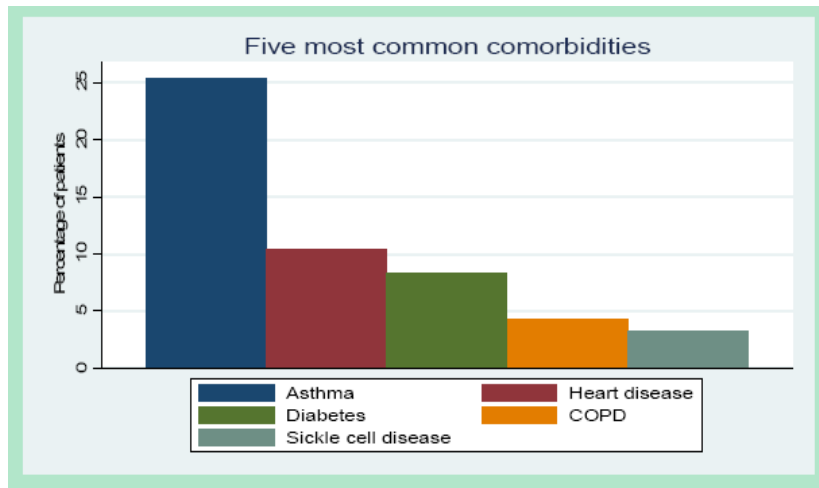
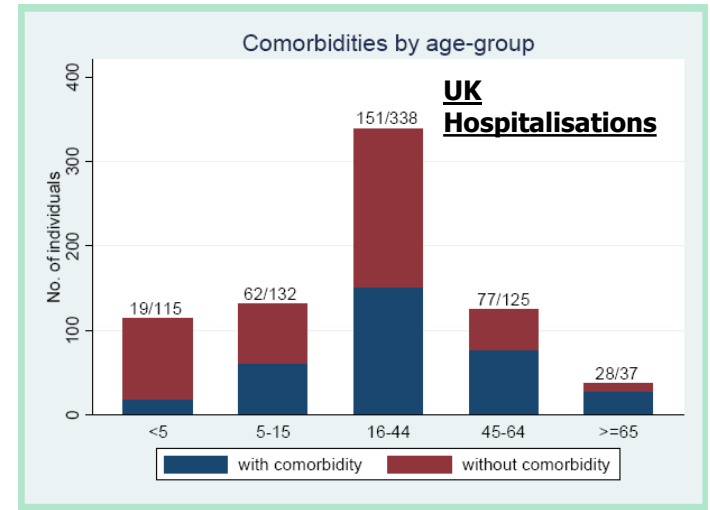
pH1N1 - UK Hospitalisations and Deaths

Deaths



Journal of Infection 2007; 54:530-538

CMO's enquiry First 129 deaths (2009)



pH1N1 - UK Hospitalisations and Deaths

Deaths

94%
5%
<1%
<1%

Percentage of patients

25
20
15
10
5
0



1
2
3
2

aths



It's Not Just About Deaths...

UK Hospital Bed Days due to Influenza

2008: 4,163

2009: 33,376

17-39 years old, October - December 2009

➤ **169 → 6,253 hospital bed days**

International Clinical Findings

Mild-moderate disease in approx. 98-99% infected

Clinical diagnosis difficult (*fever + two or more of...*)

- Variable, non-specific ILI symptoms
- Dyspnoea is not a feature of uncomplicated influenza
- Extra-pulmonary features, detectable virus (stool/urine) & non-respiratory presentations in small number
- Lymphopaenia common; modest ↑ CRP in many; ↑ CK in some

Primary viral pneumonitis

- 18% of hospital admissions; Mortality 6-29%

Low rates bacterial infection?

- Living: ~ 2-20% bacterial infection
- PM: 30%-50% (*S. pneumo* > *S. aureus*)

International Critical Care Series

- ~ 25% hospitalised require rapid (<24h) ICU admission
- 50-80% ALI/pneumonitis; Type I respiratory failure

Symptoms in 268 Hospitalised Adults

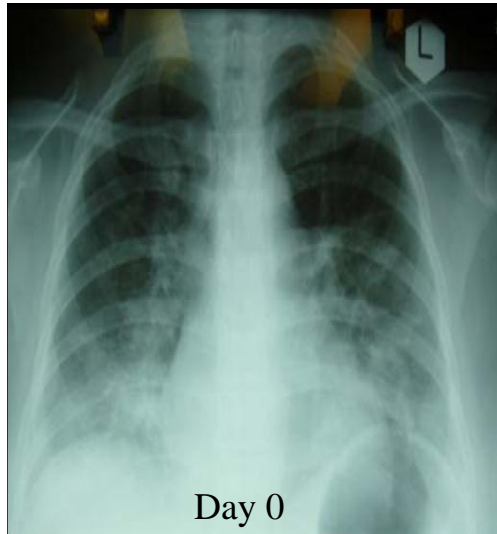
Symptom	Number (%)
Fever	249 (93%)
Cough	223 (83%)
Shortness of breath	145 (54%)
Fatigue / Weakness	108 (40%)
Chills	99 (37%)
Myalgia	96 (36%)
Rhinorrhoea	96 (36%)
Sore Throat	84 (31%)
Headache	83 (31%)
Vomiting	78 (29%)
Wheezing	64 (24%)
Diarrhoea	64 (24%)

pH1N1 Radiology

Airspace consolidation and ground-glass opacity

At presentation, 1, 2 and 3-4 zones were involved in 47%, 37% and 17% of cases respectively

Lower zones were more frequently involved than the upper zones
(63-70% vs 20-23% of cases)

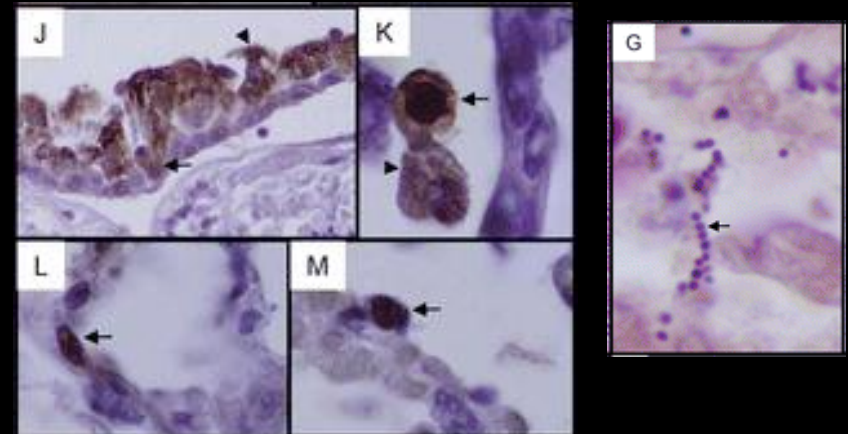
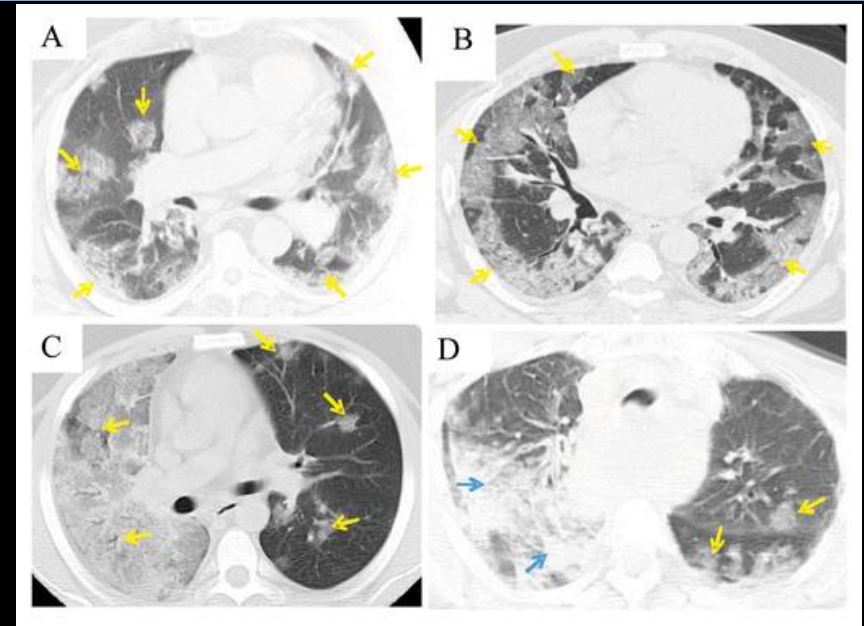


Extra-Corporeal Membrane Oxygenation (ECMO)



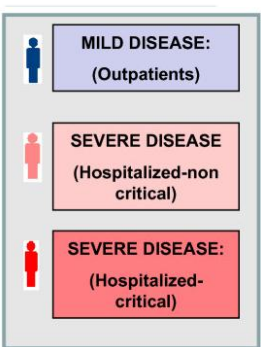
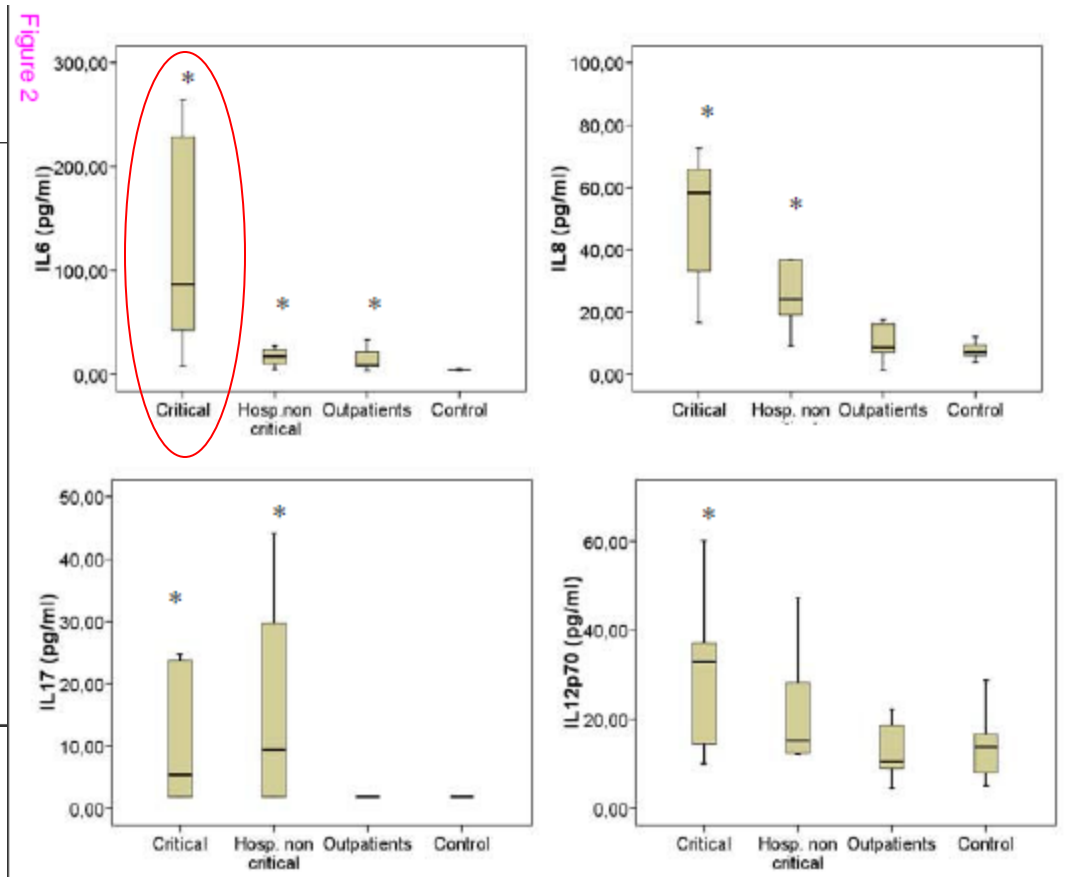
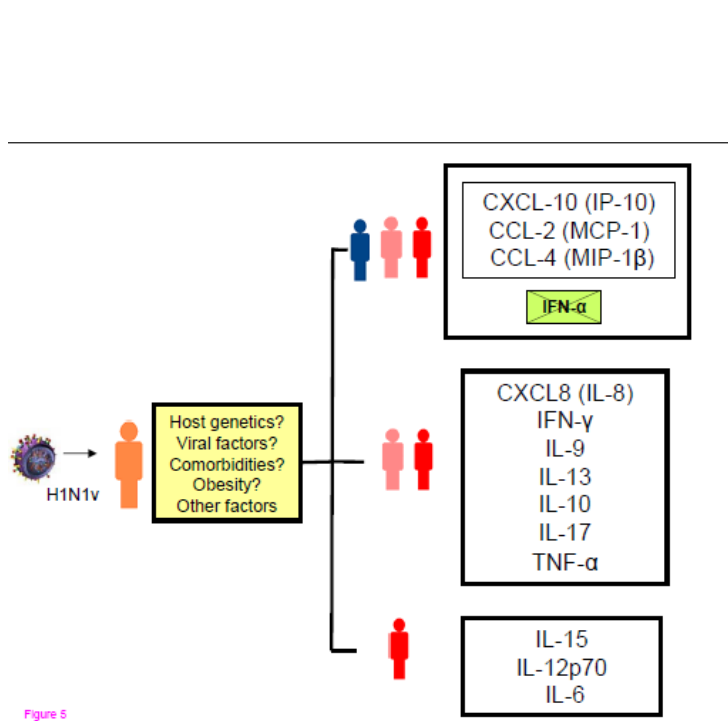
New York PM series (n=34, all confirmed)

- 62% were 25-49 years
- Tracheitis, bronchiolitis, DAD
- DAD – lymphocytes ++
- H1N1 antigen present
 - Mainly tracheobronchial tree
 - Also alveolar epithelial cells and alveolar macrophages
- Bacterial pneumonia 55%
 - Many cases DOA
 - *Pneumococcus* still most common
- PE in 9 patients
- “...impression of progression of fibrosis in a proportion; not related to mech. ventilation
- **Co-morbidity 90%**
- **Morbid obesity 70%**



pH1N1 - Hypercytokinaemia in severe disease

TH1 + TH17 mediators – humans



Diagnosis

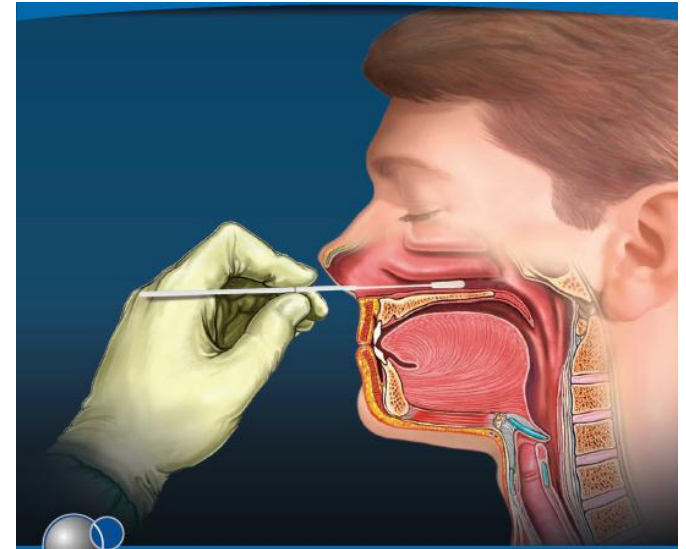
PCR

***Not* rapid antigen tests**

Sample quality important

**False-negative nasal or
nasopharyngeal swabs**

**→ Lower respiratory
tract sampling if
mechanically
ventilated**



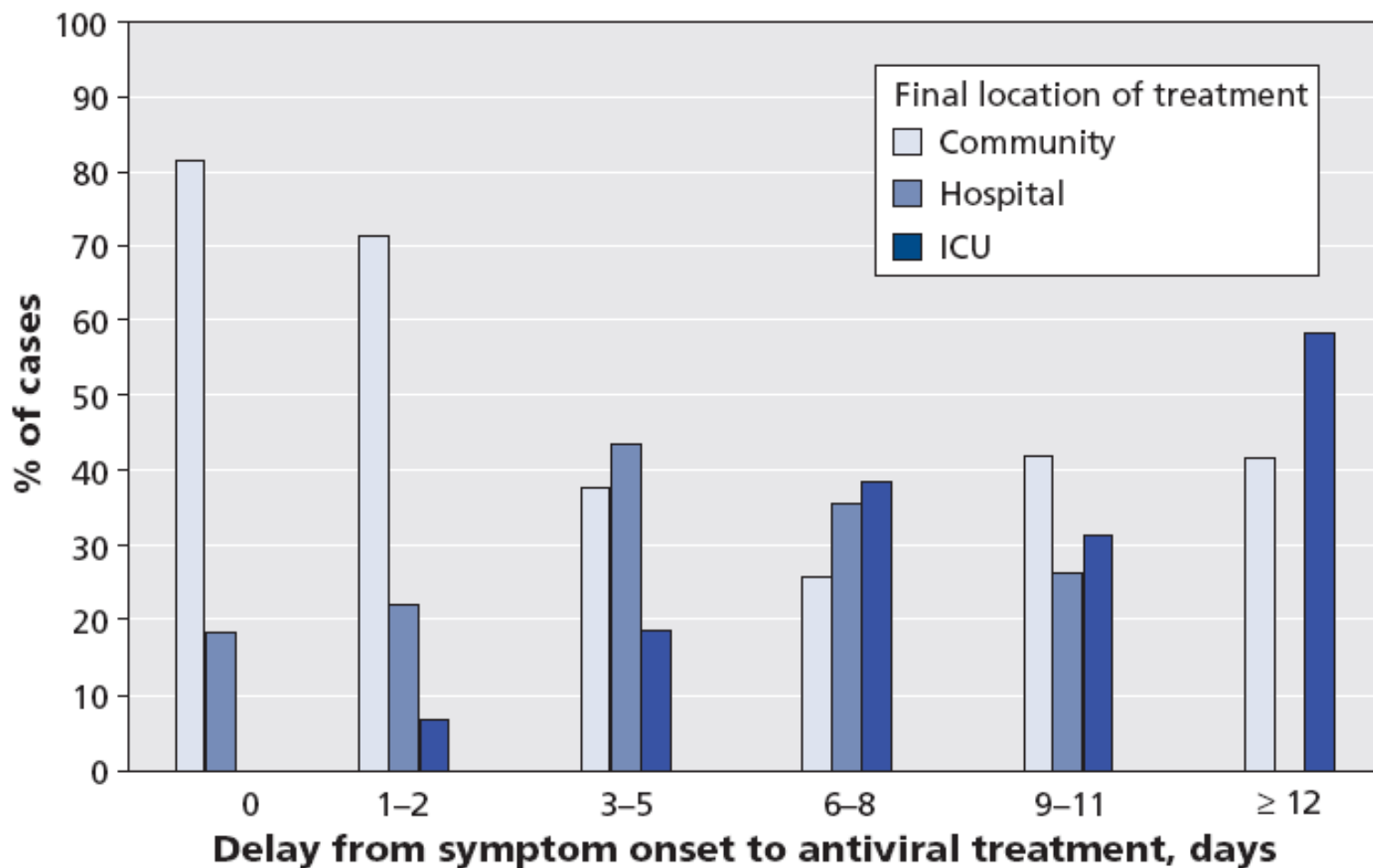
WHO Treatment Guidelines

Population	Pandemic influenza A (H1N1) 2009 and other seasonal influenza viruses	Influenza viruses known or suspected to be oseltamivir resistant
Uncomplicated clinical presentation		
Patients in higher risk groups	Treat with oseltamivir or zanamivir as soon as possible (05)	Treat with zanamivir as soon as possible (05)
Severe or progressive clinical presentation		
All patients (including children and adolescents)	Treat with oseltamivir as soon as possible (01) (zanamivir should be used if oseltamivir unavailable) (02)	Treat with zanamivir as soon as possible (03)
Patients with severe immunosuppression	Treat with oseltamivir as soon as possible. Consider higher doses and longer duration of treatment (03)	Treat with zanamivir as soon as possible (03)

WHO Guidelines for Pharmacological Management of Pandemic Influenza A(H1N1) 2009 and other Influenza Viruses, Feb 2010

“Experimental” adjuvant steroids and immunomodulators not recommended!

Avoid delays in commencing flu antivirals



The Post Pandemic Phase

WHO DG, August 10th 2010

“Pandemics are unpredictable and prone to deliver surprises. No two pandemics are ever alike. This pandemic has turned out to be much more fortunate than what we feared a little over a year ago.”

“Based on available evidence and experience from past pandemics, it is likely that the virus will continue to cause serious disease in younger age groups, at least in the immediate post-pandemic period.”

“...a small proportion of people infected during the pandemic, including young and healthy people, developed a severe form of primary viral pneumonia that is not typically seen during seasonal epidemics and is especially difficult and demanding to treat. It is not known whether this pattern will change during the post-pandemic period, further emphasizing the need for vigilance.”



Winter 2010/11

Britain's **new** concise quality newspaper

20p



The essential daily briefing
FROM THE INDEPENDENT

NEWS



Britain's **new** concise quality newspaper

Swine flu, 2010

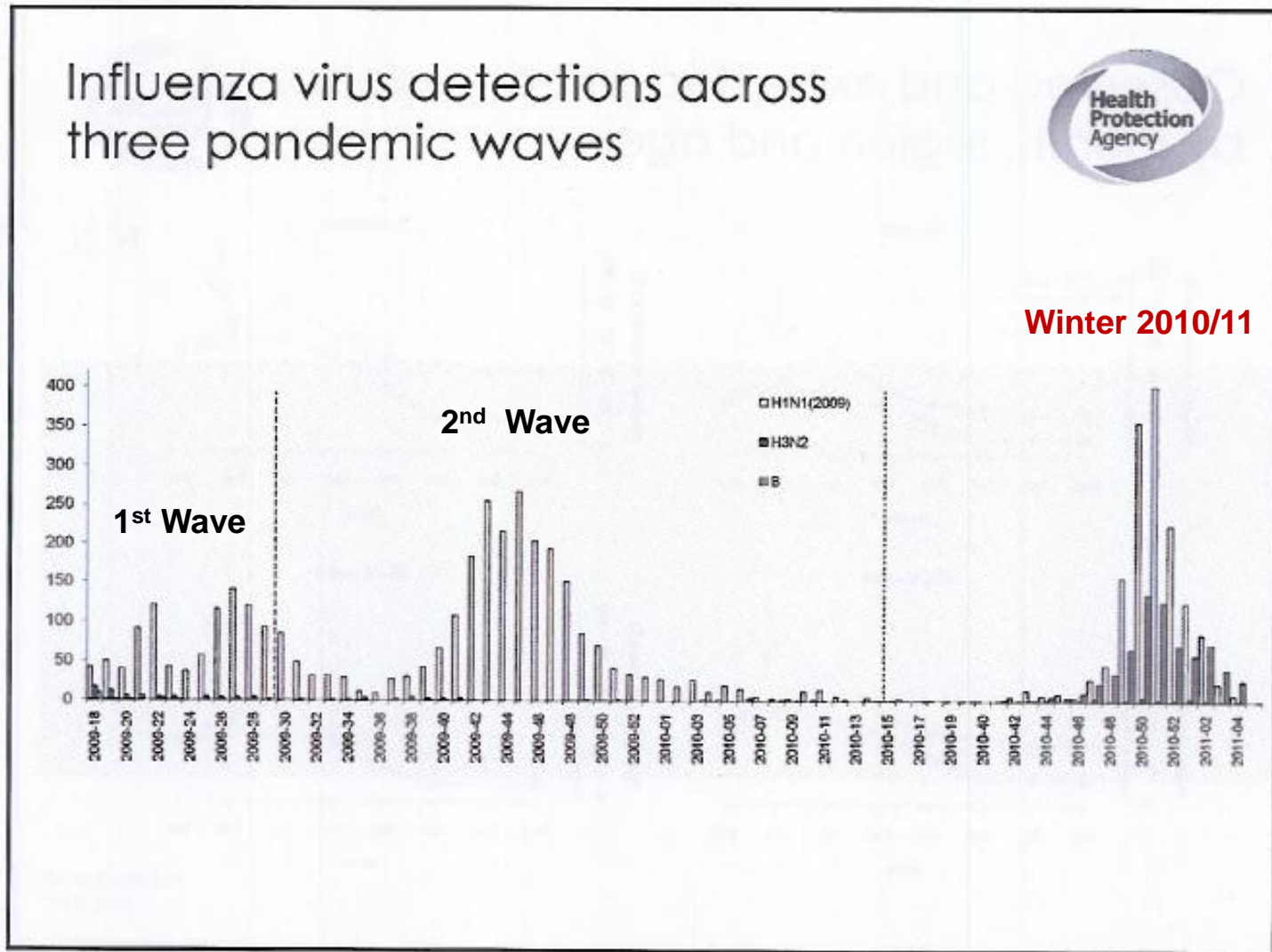
15 dead as outbreak takes hold
100 victims in intensive care
Experts warn pandemic worse than last year

P4

stay healthy

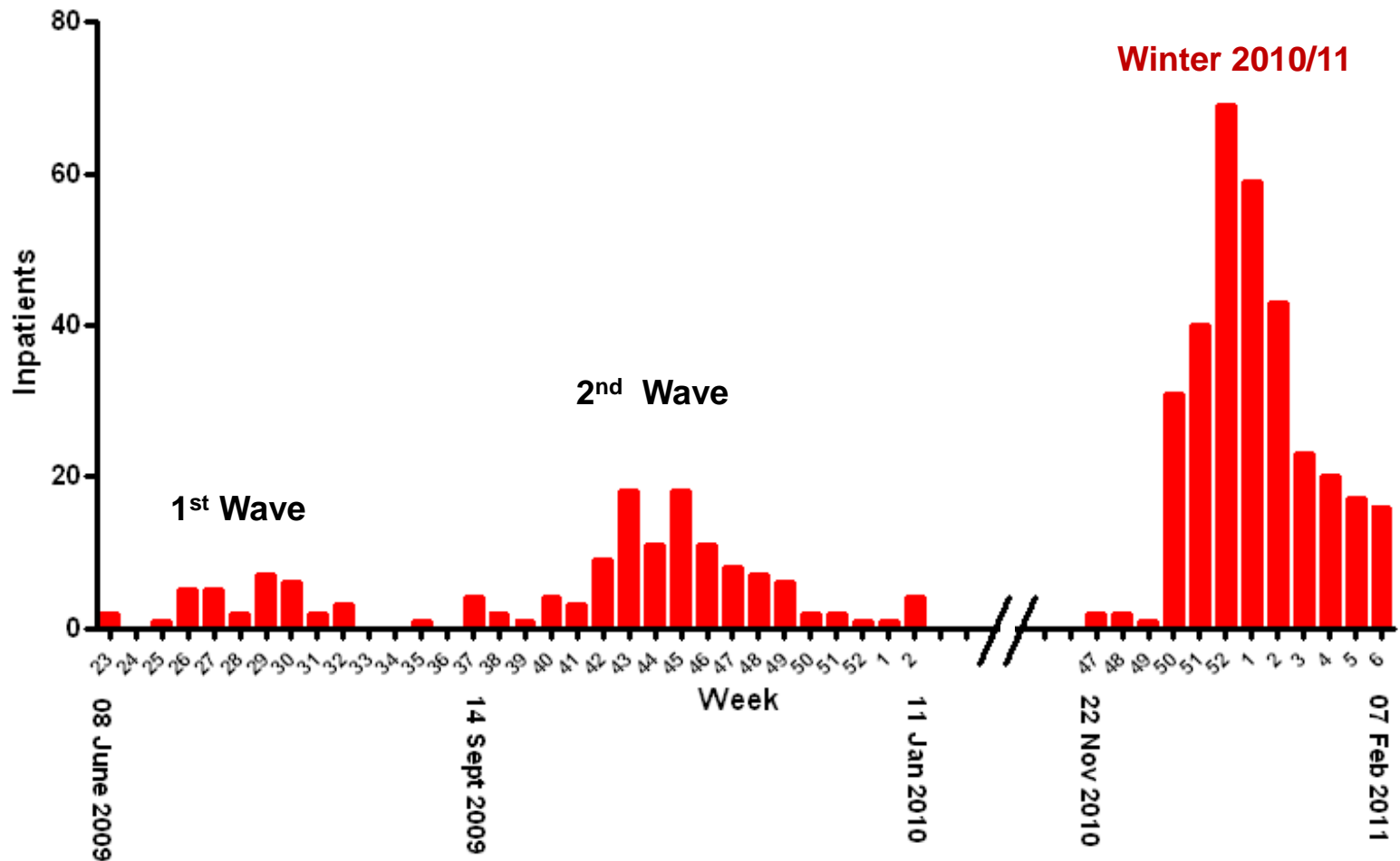
see the movie!

UK Pandemic “Waves”



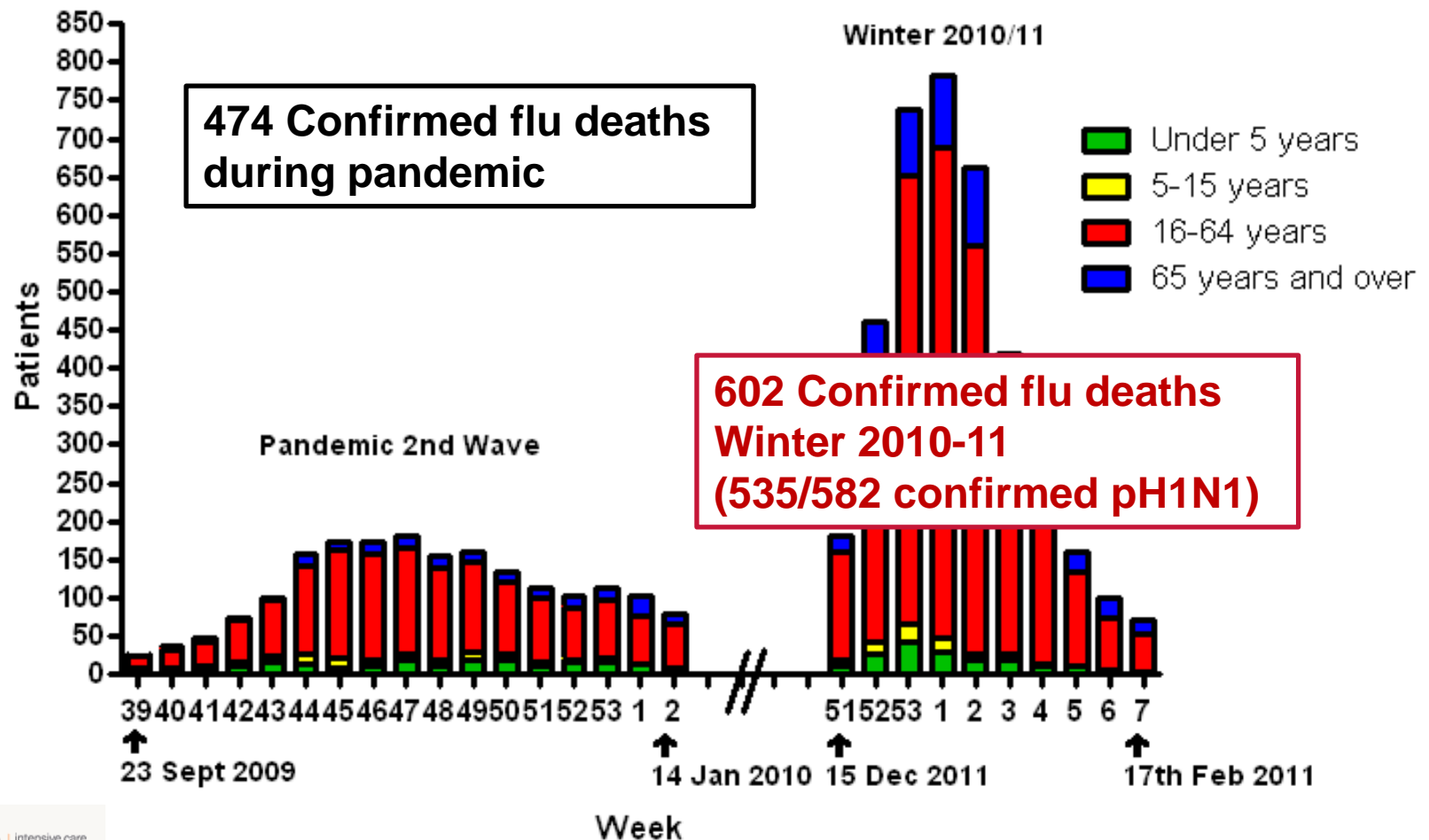
West London: Influenza Hospitalisations

Inpatients with confirmed influenza by week



Critically Ill Cases – 2nd and 3rd Waves

Number of patients with suspected or confirmed influenza in critical care beds by week
(England, based on published data from HPA and DH)



Winter 2010-11

15p OFF TOMORROW'S DAILY EXPRESS
SAVE £1.20 A WEEK ON YOUR DAILY & SUNDAY EXPRESS

DAILY EXPRESS

THE MOST SENSITIVE NEWS
NEWS AND SPORT

WIN A CITROËN PICASSO
WORTH £17,545
SEE PAGE 21



New Year honour for Poirot...but still no 'Sir Bruce'
SEE PAGE 24



FLU CRISIS AS DEATH TOLL SOARS

- 700 patients fight for life
- Huge pressure on nurses

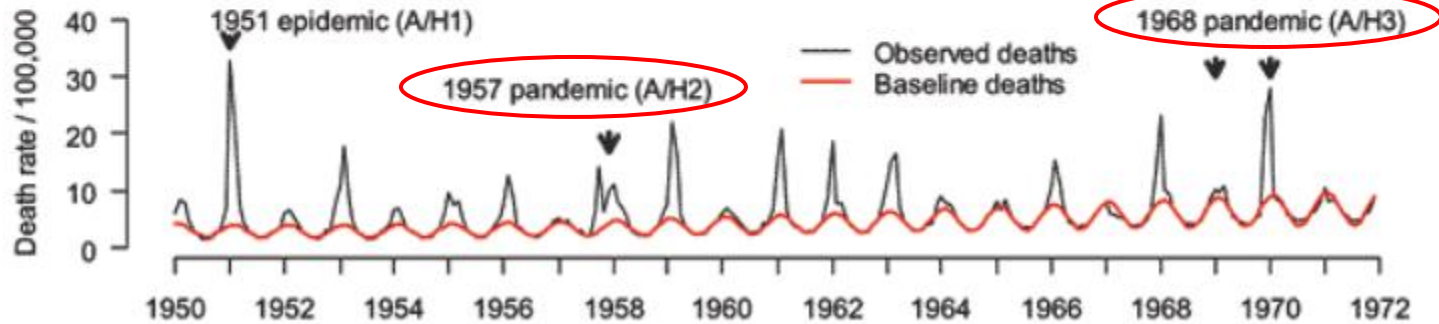
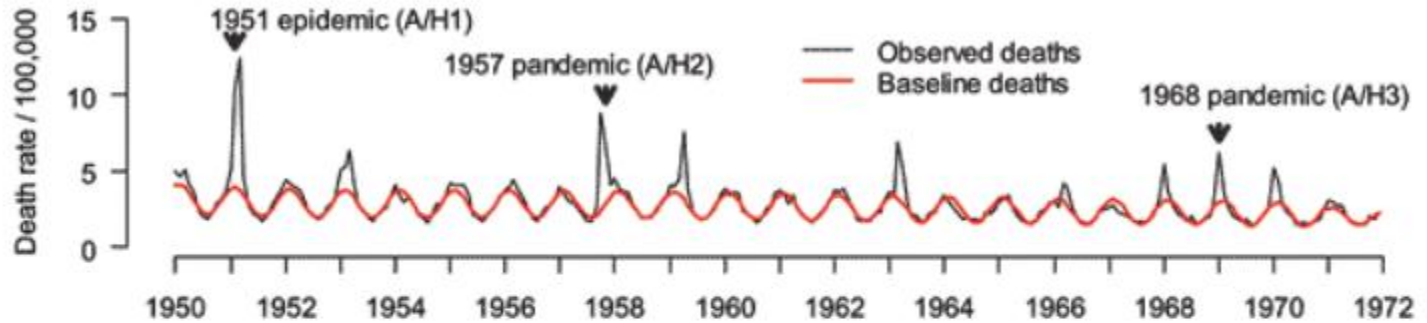
Strangled Joanna: Landford quizzed



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Lessons from History

Pneumonia & Influenza Mortality, 1950-1972



Why Was the UK 3rd Wave Worse?

- Changes in Virus?
- Bacteria?
- Host?
- Behaviour/Management?
- Weather?!

A Combination of Factors?



No significant changes in pH1N1 HA sequence

Eurosurveillance, Volume 16, Issue 1, 06 January 2011

Rapid communications

VIROLOGICAL ANALYSIS OF FATAL INFLUENZA CASES IN THE UNITED KINGDOM DURING THE EARLY WAVE OF INFLUENZA IN WINTER 2010/11

J Ellis (joanna.ellis@hpa.org.uk)¹, M Galiano¹, R Pebody¹, A Lackenby¹, CI Thompson¹, A Bermingham¹, E McLean¹, H Zhao¹, S Bolotin¹, O Dar¹, J M Watson¹, M Zambon¹

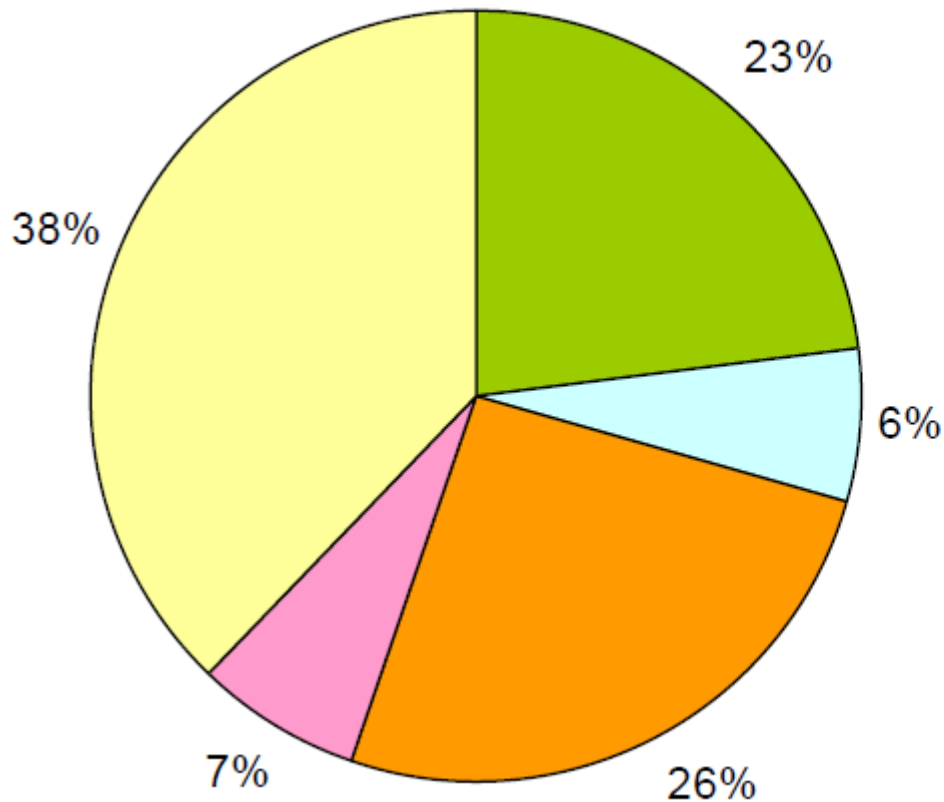
1. Health Protection Agency, Centre for Infections, London, United Kingdom

- Samples from community, hospitalised & fatal cases
- Antigenically homogeneous
- Similar to A/California/7/2009
- Minor genetic drift
- No unique mutations associated with severe or fatal cases of pH1N1
- Further comprehensive analysis required (e.g. MOSAIC WGS)

pH1N1 Antiviral Resistance Remained Low

- Pyrosequencing for H275Y by HPA network, winter 2010/11 season
- 56/1781 (3%) viruses had H275Y

Global pH1N1 Oseltamivir Resistance



- Association with treatment
- Associated with post-exposure prophylaxis
- Severe immunosuppression
- No known association with treatment or likely person-to-person transmission
- Preliminary report (full data not yet available)



Bacterial Co-infection Concerns

From the Chief Medical Officer (Interim)
Professor Dame Sally C Davies



Gateway Reference Number: 15416

Richmond House
79 Whitehall
London

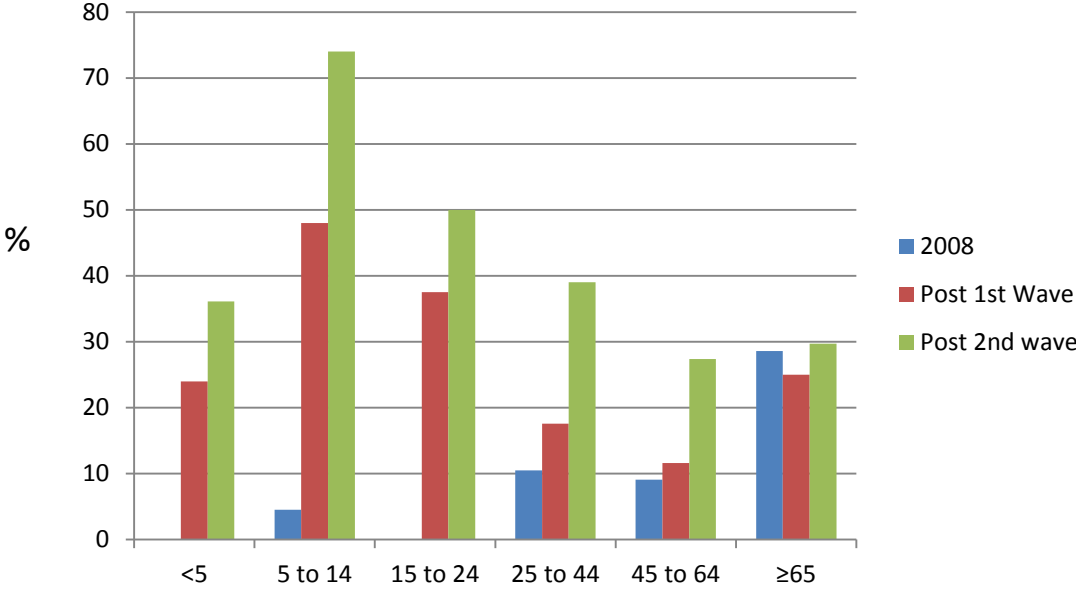
Dear Colleagues,

Re: Influenza, meningococcal infection and other bacterial co-infection including pneumococcal and invasive Group A streptococcal Infection (IGAS)

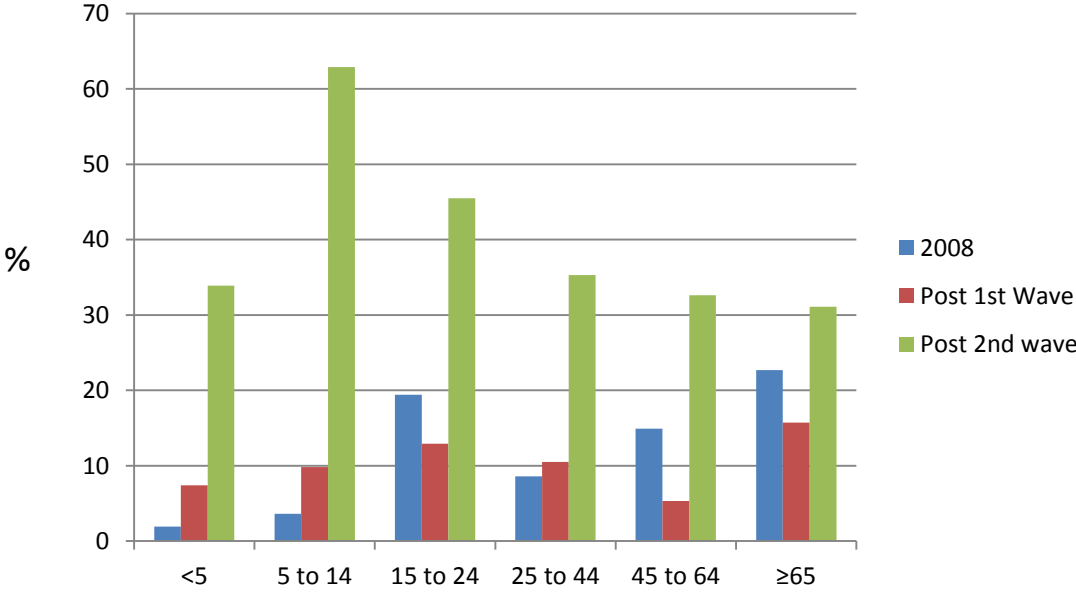
I write to alert you to an increase in a number of significant bacterial infections such as those caused by *Neisseria meningitidis* (meningococcal disease) and others that may occur as co-infections with flu. Organisms such as *Streptococcus pyogenes* (Group A *Streptococcus*), *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Haemophilus influenzae*, which can cause co-infection with flu, may affect people who typically are not considered to be at risk of severe illness from flu, such as those not currently in a risk group for seasonal influenza vaccination. Some of these

Proportion of serum samples with titre >1:32 in the baseline, post 1st wave and post 2nd wave

London



Other Regions



Data source: Health Technol Assess. 2010 Dec;14(55):115-92. **Assessment of baseline age-specific antibody prevalence and incidence of infection to novel influenza A/H1N1 2009.** Hardelid P, Andrews NJ, Hoschler K, Stanford E, Baguelin M, Waight PA, Zambon M, Miller E. <http://www.hta.ac.uk/execsumm/summ1455-03.shtml>

Did Seroprevalence Influence Winter 2010/11 experience?

- “The current low levels of susceptibility to the H1N1 2009 virus in the population of England after the second wave, imply that **there has been sufficient infection of susceptibles in the population such that a third wave of infection in the 2010–11 influenza season is not to be expected**, although sporadic cases of H1N1 are likely to continue to occur, some of which may arise in particular risk groups and be associated with severe illness.”

Pre-Hospital Measures

- **3rd Wave, 106 Influenza +ve Adults**
- 18% influenza-vaccinated
- <3% community antivirals
- 22% community antibiotics

Antiviral Use – *Seasonal* Influenza Guidelines



*National Institute for
Health and Clinical Excellence*

- **Oseltamivir or zanamivir should be used only if all of the following apply:**
 1. National surveillance schemes indicate that influenza virus A or B is circulating
 2. The patient is in an at-risk group e.g. asthmatic
 3. the person presents with an influenza-like illness and can start treatment within 48 hours of the onset of symptoms

The Meta Effect...

BMJ helping doctors make better decisions

BMJ 2009;339:b5106 doi: 10.1136/bmj.b5106 (Published 8 December 2009)

Cite this as: BMJ 2009;339:b5106

Research

**Neuraminidase inhibitors for preventing
and treating influenza in healthy adults:
systematic review and meta-analysis**



OPEN ACCESS

SEASONAL

“...we have to generalise from the trials, and this seems reasonable given that the pandemic influenza A/H1N1 virus will likely be acted on in the same biological manner as previously circulating influenza viruses, such as seasonal A/H1N1.”

4 Daily Express Friday December 21 2010

U-turn as flu toll puts NHS under strain

FROM PAGE ONE

Christmas holidays and the flu outbreak. He said: "To help ease pressures on the NHS, I want to remind people what we can all do to prevent the spread of flu.


"The first line of defence is to be vaccinated. I urge everyone in an at-risk group to contact their GP and book an appointment.

"The second line of defence is to practise good hygiene - to cover our nose and mouth when we sneeze, put tissues in the bin and wash our hands regularly. That's why we're re-launching the Catch it, Bin it, Kill it campaign from this Saturday.

"The third line of defence is a well-prepared NHS with the ability to treat those who do need help. Thanks to robust early planning, the NHS is coping well with the pressures of seasonal flu this year."

Figures released by the Health Protection Agency yesterday show that 738 patients are in critical care, up from 460 the week before.

Peak





Daily Mail

FREE INSIDE BUMPER NEW YEAR PUZZLE PULLOUT

£250,000 TO BE WON!
Thousands of cash prizes in our new scratchcard game

PLUS THE BIGGEST AND BEST TV LISTINGS GUIDE IN ANY PAPER

Pregnant women and elderly turned away from surgeries and told to get jab at Tesco

NOW GPs RUN OUT OF FLU VACCINE

Sparkling start to 2011

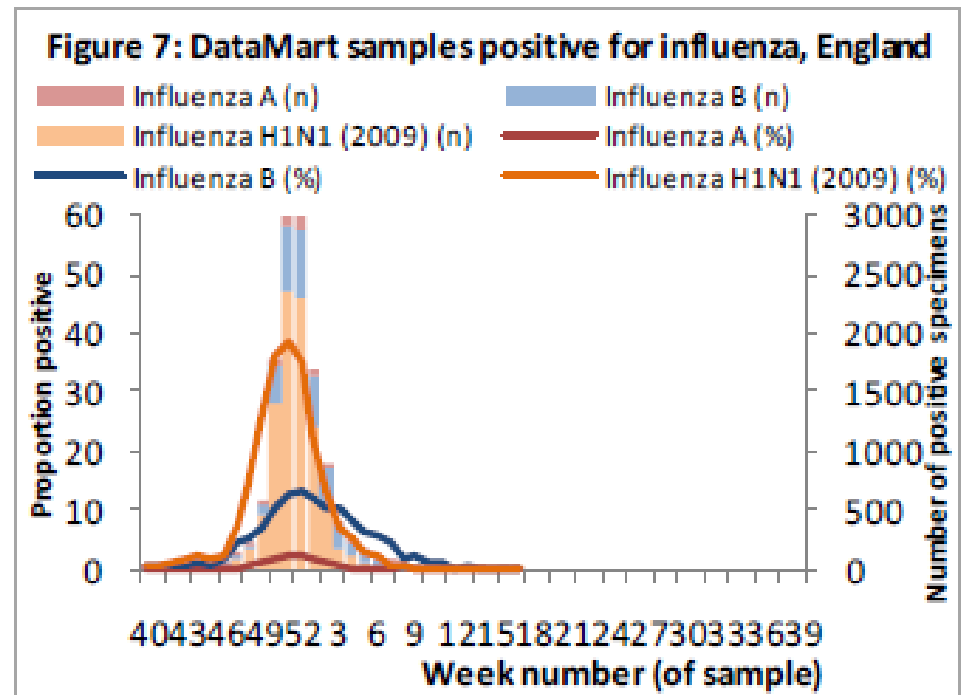
Trivalent Vaccine Uptake

	1 st Nov 2010	16 th Dec 2010	16 th Jan 2011	27 th Feb
>65 years	48%	67%	72%	73%
<65 years + risk factor	26%	42%	48%	50%
Frontline HCWs	?	?	26%	34%

Source: HPA Weekly National Influenza Reports.

<http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/SeasonalInfluenza/>

Winter 2010/11: A Short but Intense Flu Season



UK Experience - Conclusions

- The UK had its “3rd Wave”
- More severe than the 1st & 2nd waves – why?
- Dominated by pH1N1 (and Influenza B)
- Pandemic strain behaviour persisted in the post-pandemic period
- Cause of increased severity is unclear and probably multifactorial
- Pandemic viruses are unpredictable
- **UK experience should encourage global vigilance**

The Future?

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WEATHER: SUNSHINE AND SHOWERS

MONDAY SEPTEMBER 24, 2011 45p



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READER**

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AND GET YOURS TODAY AT www.dailypress.co.uk London

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KILLER FLU TO GRIP BRITAIN

New outbreak will be worst for years

EXCLUSIVE By Lucy Atkins

BRITAIN is facing one of its worst winter flu outbreaks in years, according to the country's leading expert on the virus.

Professor John Oxford said a big leap in cases in Australia in recent months points to what is likely to happen here.

Many Britons have little immunity after two years of relatively limited outbreaks.

Despite this, the Department of Health last week announced there would be no high-profile flu awareness campaign this winter.

Public health leaders have condemned the inaction as "irresponsible" and "naïve".

Professor Oxford, a Virologist at Barts and The London School of Medicine and

Dentistry, is a world-renowned expert on flu. He warned that the disease posed a threat to everyone, not just high-risk groups.

He said: "I go to Australia every summer to monitor what's going on and it was pretty bad - hospitals were filling up."

"No one is sure why our patterns of flu tend to follow what happens in the southern hemisphere during the summer but it does."

"Unfortunately in Australia there has been a sharp outbreak with higher than normal numbers of flu strains A and B."

"The chances are the same will happen here."

"We won't know until a bit later into the year when the levels start to peak - which

TURN TO PAGE 5



This pair had it licked on the beach at Great Yarmouth yesterday

KEEP COOL AND CARRY ON

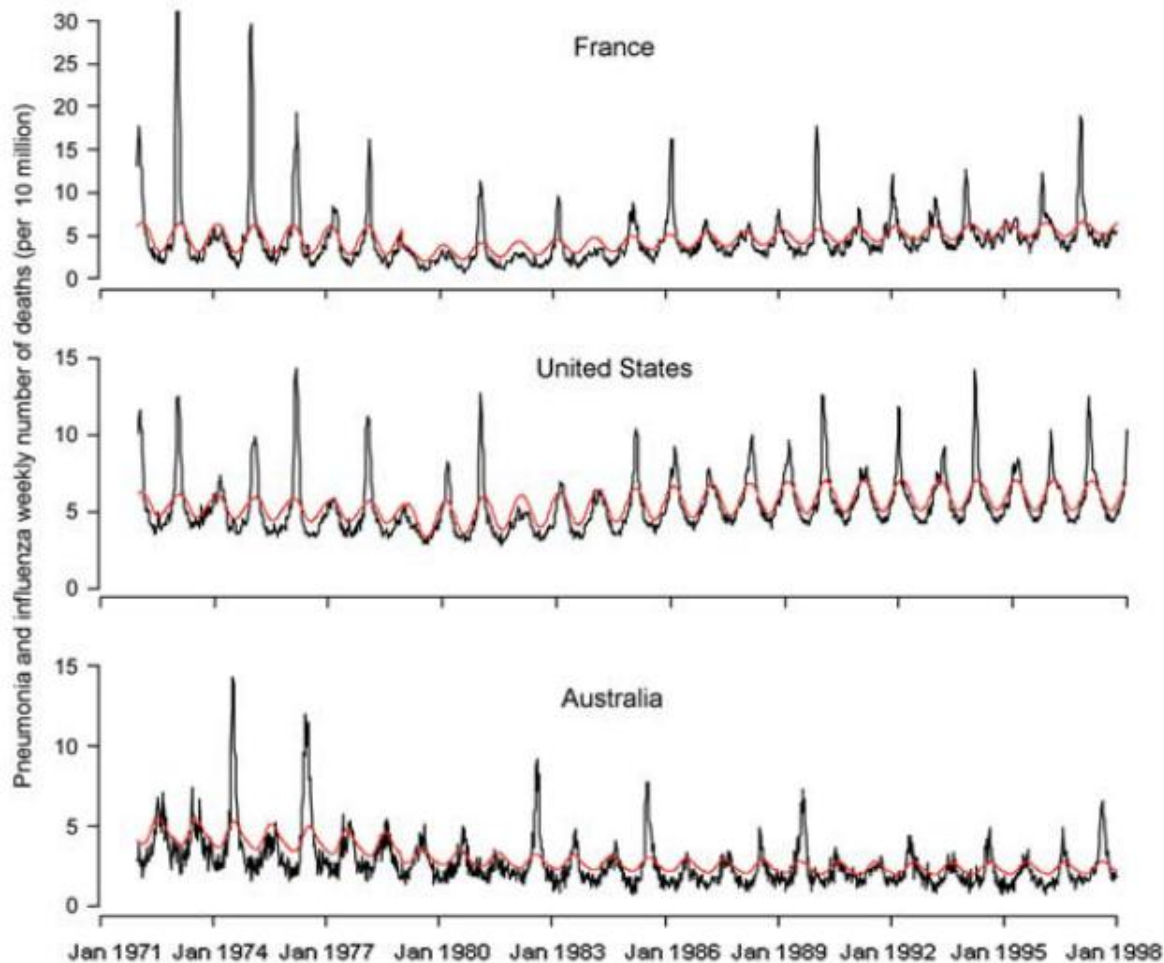
Now experts say
Indian summer
could last three
more weeks

SEE PAGE 8

PLUS! GET OK! MAGAZINE FOR JUST 99p

PAGE 21
GET OK!
YOURSELF

Europe Doesn't Follow Australia (Influenza activity)



Investigational Anti-Influenza Agents

- **NA inhibitors (NAIs)**
 - Peramivir, zanamivir (IV)
 - A-315675 (oral)
- **Long-acting NAIs (LANIs)**
 - Laninamivir (topical)
 - ZNV dimers (topical)
- **Conjugated sialidase**
 - DAS181 (topical)
- **Protease inhibitors**
- **HA inhibitors**
 - Cyanovirin-N
 - Arbidol (oral)
- **Polymerase inhibitors**
 - Ribavirin (oral, IV, inhaled)
 - Favipiravir/T-705 (oral)
 - Viramidine (oral)
 - siRNA (IV, inhaled)
- **NP inhibitors (nucleozin)**
- **Interferons**
 - IFN inducers
 - RIG-I activator (5'PPP-RNA)
- **Antibodies (anti-HA, NA, M2)**
- **Cationic airway lining modulators (iCALM)**

Proposed Immunomodulators

- Multiple suggested interventions e.g.
 - Anti-TNF (TH1 hypercytokinaemia; murine receptor knock-out studies)
 - CC10 (Clara cell protein)
 - Statins, fibrates, glitazones (PPAR)
 - » Recent epidemiological data *less* supportive of statins protecting against seasonal flu complications*
 - Zanamivir + mesalazine + celecoxib
 - ACE 2 supplementation
 - TLR modulators; protective poly-ICLC (phase I)?
 - Pooled/convalescent anti-sera

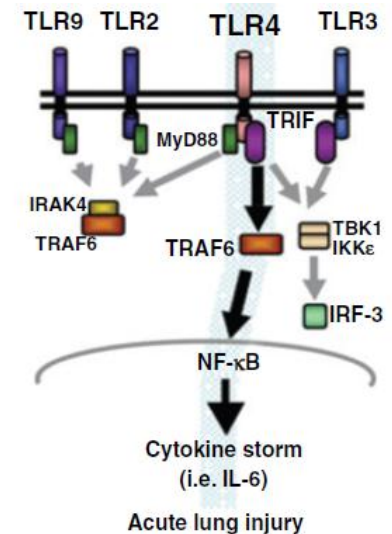


Figure 2. Schematic diagram of the signaling cascade that leads from Toll-like receptor 4 (TLR4) through TIR-domain-containing adaptor-inducing IFN- β (TRIF), tumor necrosis factor-receptor associated factor (TRAF6), and NF-kappaB to the up-regulation of pro-inflammatory cytokines and resultant acute lung injury [from figure 2(J) in Ref. (42)].

First Improve Our Understanding of Pathogenesis

- An assessment of all the factors that might determine severity in one intensively studied group of patients*

257 hospitalised patients with influenza-like illness
169 (65%) with PCR-confirmed influenza

45 page
booklet
(Flu-CIN)

Extensive clinical
information

Samples from
multiple timepoints

Respiratory, blood
and other samples

8000
sample
biobank

Virology and
genomics

Molecular
bacteriology

Mediators and
cellular immunology

Transcriptomics

Host
genomics

+ community (mild) controls, matched healthy controls, ILI controls

Pandemic Influenza - Global Health, Global Research



Estimating the global impact of pH1N1: Dawood FS et al.



◉ 1125. Preliminary Estimates of Global 2009 H1N1 Influenza Mortality

• **Session:** Poster Abstract Session: Influenza and H1N1 Diagnosis, Epidemiology, and Viral Outcome

Saturday, October 22, 2011

Room: Poster Hall B1

- ~ 249,000 deaths globally during the 2009-10 pandemic
- ~ 60% deaths occurred in Africa and SE Asia
- ~ 90% deaths occurred in those <65y
- ~ 10 million years of life lost

Recommended Reading

*The members of the Writing Committee of the World Health Organization (WHO) Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza, who are listed in the Appendix, assume responsibility for the content of the article. Address reprint requests to Dr. Frederick G. Hayden at P.O. Box 800473, University of Virginia Health System, Charlottesville, VA 22908, or at fgh@virginia.edu.

N Engl J Med 2010;362:1708-19.
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The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

MEDICAL PROGRESS

Clinical Aspects of Pandemic 2009 Influenza A (H1N1) Virus Infection

Writing Committee of the WHO Consultation on Clinical Aspects
of Pandemic (H1N1) 2009 Influenza*