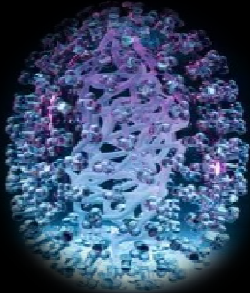


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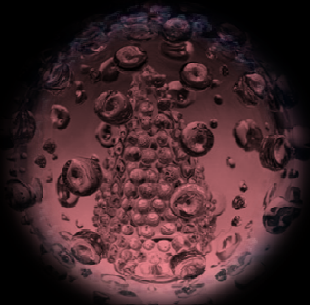
Dr Jake Dunning
MOSAIC Clinical Research Fellow
(Mechanisms of Severe Acute Influenza Consortium)

Imperial College
London Centre for Respiratory Infection

CRI

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**Pandemic (H1N1) 2009 Influenza
Meets HIV**

J Dunning, BHIVA 2010



Thank you!

Questions?

Since you're all here...

- **Overview of the 2009-2010 Flu Pandemic**
- **HIV and Pandemic H1N1 Influenza**
- **What next?**

Seasonal Influenza and HIV

Received Wisdom (note limited data)

- High rates flu-related admissions and mortality pre-HAART
- >50% decrease hospitalisation post-HAART
- Influenza hospitalisation rate remained above that of “healthy” population
- “Increased risk of complications, impairment of respiratory function with hypoxaemia, prolonged duration of illness and increased rates of hospitalization”

J Dunning, BHIVA 2010

Preventing Seasonal Influenza in HIV

BHIVA Immunisation Guidelines 2008

Influenza Vaccination

- Strongest recommendation if HIV + other risk factor – but advise for all
- Lower levels of antibodies produced overall
- Lowest Ab levels in those with CD4<200
- HAART + CD4 > 300
 - » Cellular and humoral responses similar to non-HIV
 - » Clinical efficacy 70-100%
- Protection against severe disease even in CD4<200

J Dunning, BHIVA 2010

Moving On: the World's Favourite Virus**Definitions****PANDEMIC INFLUENZA**

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

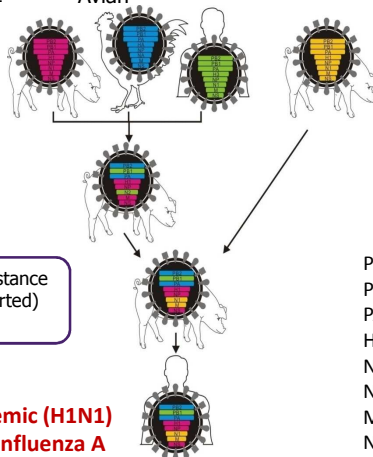
Tendency to cause severe disease?

- *Not a prerequisite*
- *Demonstrate characteristic "pandemic strain" illness*

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

J Dunning, BHIVA 2010

Pandemic (H1N1) 2009 Influenza A “Swine Flu”: OriginsClassical swine
derived from
1918 H1N1North
American
AvianHuman
H3N2Eurasian avian-like
swine

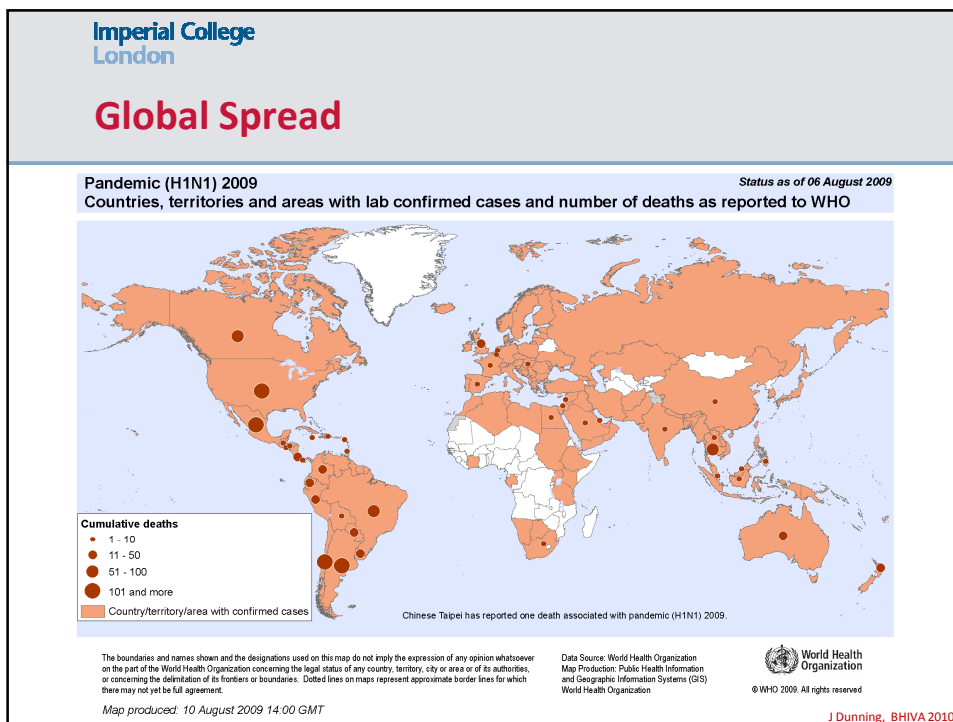
- Inherent adamantane [M] resistance (rare, sensitive mutant now reported)
- Inherent oseltamivir sensitivity

**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

J Dunning, BHIVA 2010

Dawood et al., NEJM, 2009; Garten et al., Science, 2009; Smith et al., Nature, 2009



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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*

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J Dunning, BHIVA 2010

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The Mexican Wave

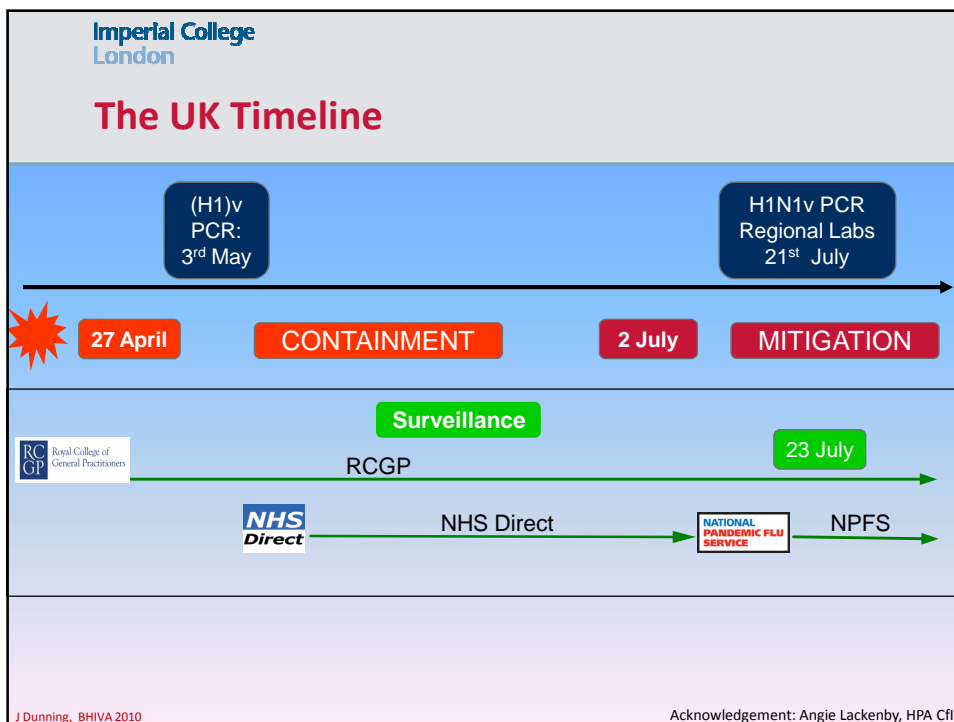
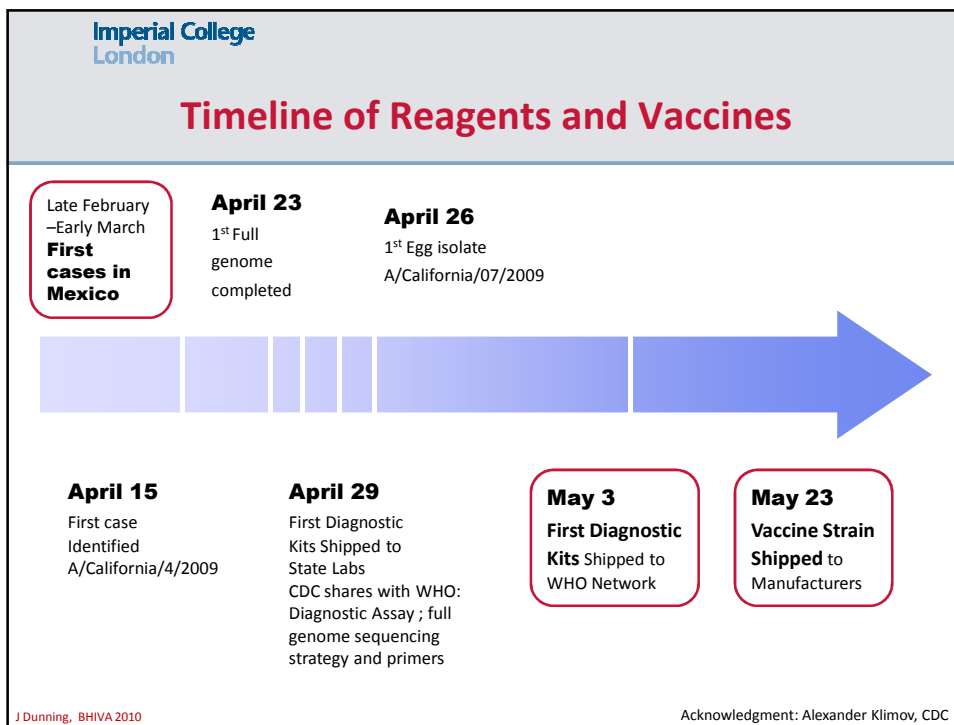
- April 24th 2009
- Cases of unusually severe respiratory illness, including healthcare workers
- Retrospective case & sample analysis:
 - February 24th

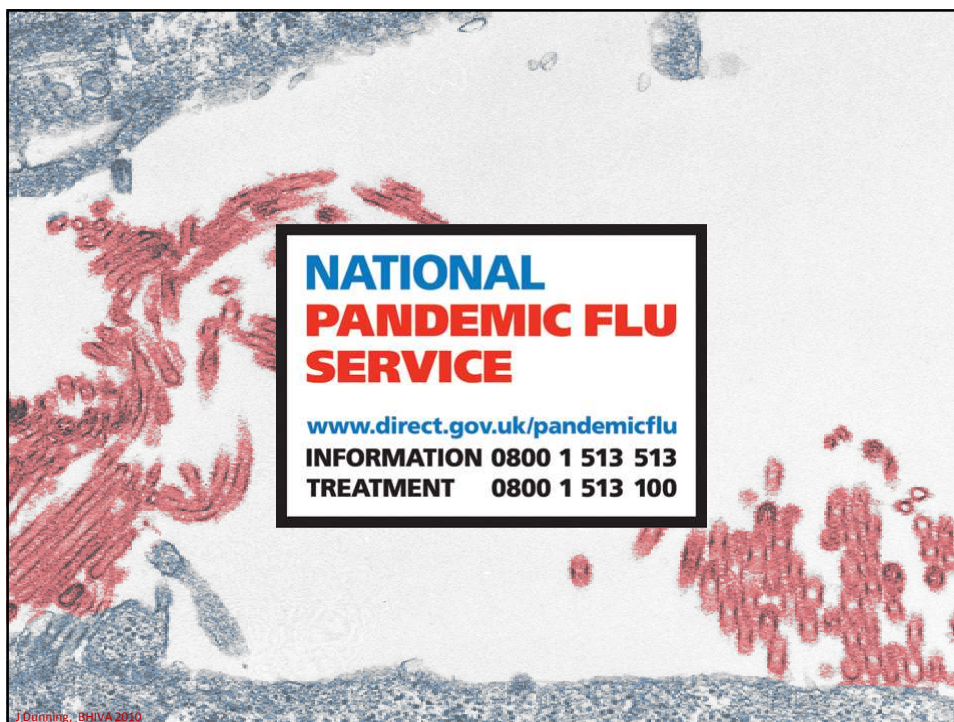


Edgar Hernandez, the Mexican boy who was widely regarded as the first person in the world diagnosed with swine flu. A year later, epidemiologists say the human form of the virus is unlikely to have originated in his village. Photograph: Pablo Spencer/AFP/Getty Images guardian.co.uk

How did this early data influence the global response?

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Imperial College London | Health Protection Agency | DH Department of Health

pH1N1 - UK Experience

Figure 1: Number of hospitalisations and RCGP ILI consultation rate. The number of hospitalisations peaks at approximately 220 in late July, while the RCGP ILI rate peaks at about 160 per 100,000 in late July.

Figure 2: Weekly number and proportion of specimens collected through GP sentinel virological schemes positive for influenza (England only).

Figure 2: Weekly number and proportion of specimens collected through GP sentinel virological schemes positive for influenza (England only). The number of positive specimens peaks at approximately 160 in week 44, and the proportion positive peaks at about 50% in week 44.

- >30,000 lab-confirmed cases
- 457 validated UK Deaths (75% England)
- 26 deaths <5 yrs
- 15 deaths in pregnancy
- >5,000 hospitalisations
- Peak (4/11/09): 848 inpatients; 172 critical
- 4/3/10: 50 inpatients, 13 critical

Estimated weekly all-cause death registrations in England & Wales, 09/10

Figure 3: Estimated weekly all-cause death registrations in England & Wales, 09/10. The observed number of deaths (red line) shows a significant spike in week 48, reaching approximately 13,000, which is well above the expected trend (blue line) and the 95% upper limit (green dashed line).

J Dunning, BHIVA 2010

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

J Dunning, BHIVA 2010 Hospital Episode Statistics, The NHS Information Centre for Health & Social care. Provisional monthly HES topic of interest: Influenza, April 2010

pH1N1 - UK Hospitalisations and Deaths

Death

94%
5%
<1%
<1%

Percentage of patients



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International Clinical Findings (Non-HIV Adults)

- **Mild-moderate disease in approx. 98% 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: ~ 2-15% 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

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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)

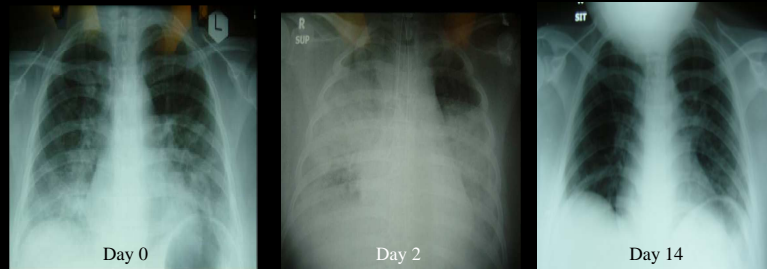


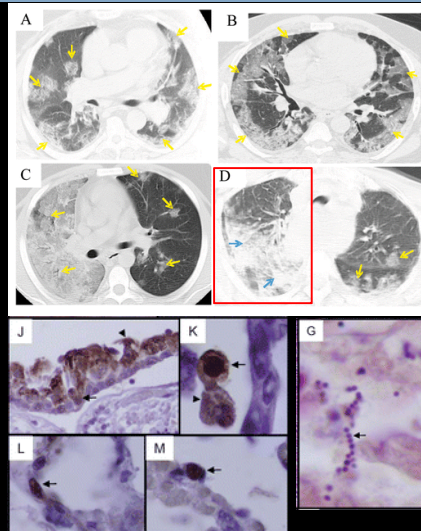
Image Acknowledgement: Dr Nelson Lee, Hong Kong University

J Dunning, BHIVA 2010

Agarwal PP et al. AJR 2009, Ajlan AM et al. AJR 2009

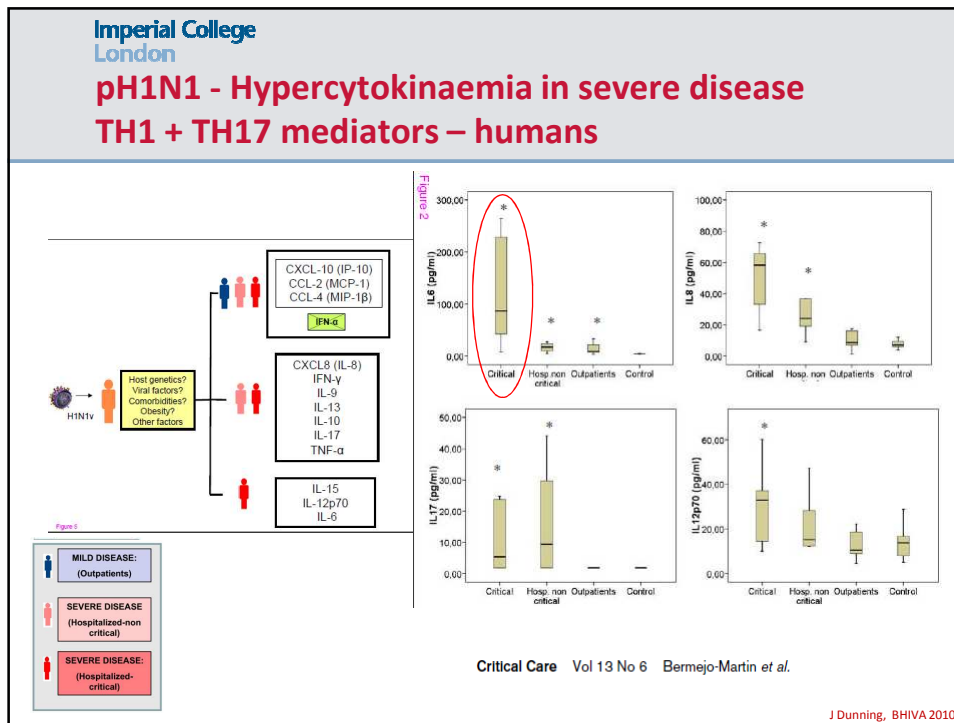
Latest New York PM series (n=34, all confirmed)

- 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%



J Dunning, BHIVA

Gill et al (Taubenberger), Arch Path & Lab Med, 134(2) Feb 2010



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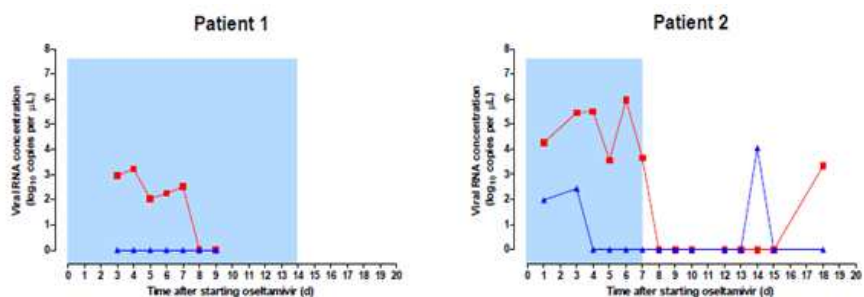
Diagnosis

- PCR
- **Not** rapid antigen tests
- Sample quality important
- False-negative nasal or nasopharyngeal swabs
- Lower respiratory tract sampling if mechanically ventilated

J Dunning, BHIVA 2010

Uyeki T, NEJM 2009; Rello Crit Care 2009; Fleury Eurosurveillance 2009; Blyth NEJM 2009

Corresponding viral RNA concentrations in the lower (TA--red) and upper (NPFS--blue) respiratory tract samples in 8 intubated patients, N Lee et al (Hong Kong University), XII International Respiratory Virus Symposium, Taipei, March 2010



J Dunning, BHIVA 2010

Acknowledgement: Dr Nelson Lee

Latest 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)

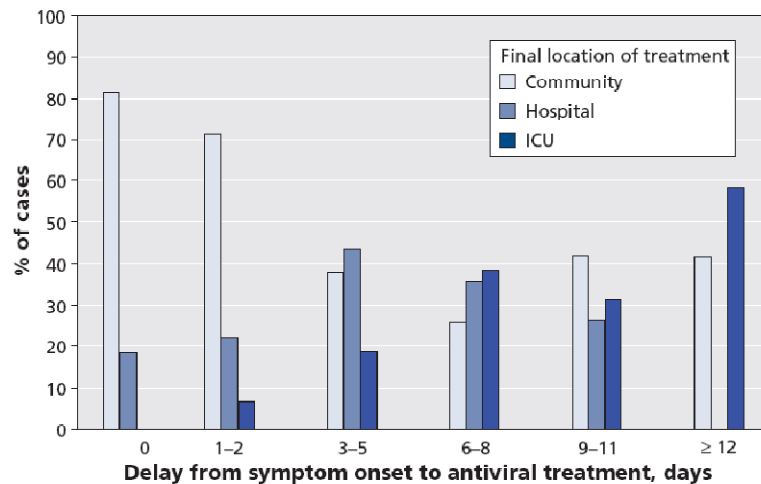
WHO Guidelines for Pharmacological Management of Pandemic Influenza A(H1N1) 2009 and other Influenza Viruses, Feb 2010

“Experimental” adjuvant steroids and immunomodulators not recommended!



J Dunning, BHIVA 2010

Avoid delays in commencing flu antivirals



J Dunning, BHIVA 2010

Ryan Zarychanski MD, Tammy L. Stuart PhD, Anand Kumar MD, Steve Doucette MSc, Lawrence Elliott MD MSc, Joel Kettner MD MSc, Frank Plummer MD

CMAJ 2010. DOI:10.1503/cmaj.091884

Are there any worrying changes in the virus?

- Rare vaccine low-responder isolates
- Uncommon D225G quasispecies
 - Found in "raw" clinical isolates
 - Reported in a few mild cases
 - Preferential binding in LRT (α -2,3 SA) rather than URT (α -2,6)
 - Association with clusters of severe and fatal cases (Norway; Hong Kong; Ukraine)
 - Detected in 7 (12.5%) of 57 patients with severe disease (4 of whom were previously healthy) – mainly ET aspirates¹
 - Detected in 0 of 60 patients with mild disease – NP aspirates
- Artificial PB1-F2 expression: minimal impact on virulence in animals²

Generally no signs of increasing virulence

J Dunning, BHIVA 2010

¹ Chen H, J Infect Dis. 2010 May 15;201(10):1517-21. ² Hai R, J Virol. 2010 May;84(9):4442-50.

Does the strain make a difference?



Comparative H1N1 Pathotyping Results in Ferrets

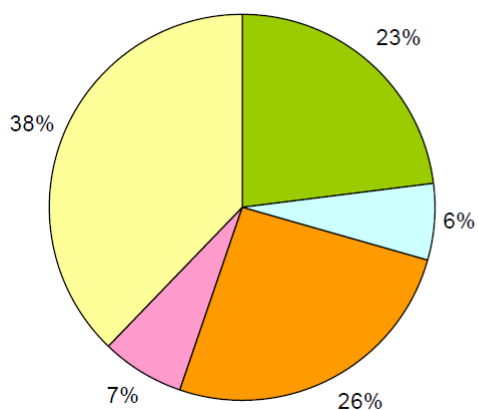
T Tumpey, XII International Symposium on Respiratory Viral Infections, Taipei, Mar 2010

Virus	Weight Loss (%)	Lung Titers (PFU/gm) (log)	Lethality
Brisbane/59/07 - Seasonal	4.9	ND	0/6
A/Texas/15/2009 (fatal)	9.1	6.0	0/6
A/California/4/2009 (mild)	10.3	5.8	0/6
A/Mexico/4482/2009 (severe)	17.5	4.1	3/6

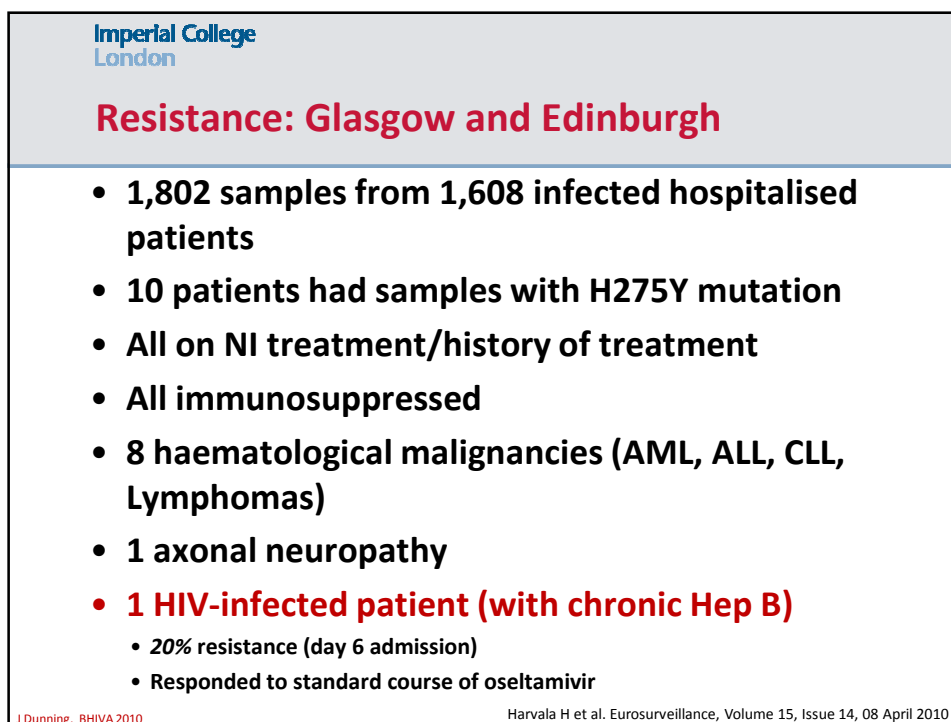
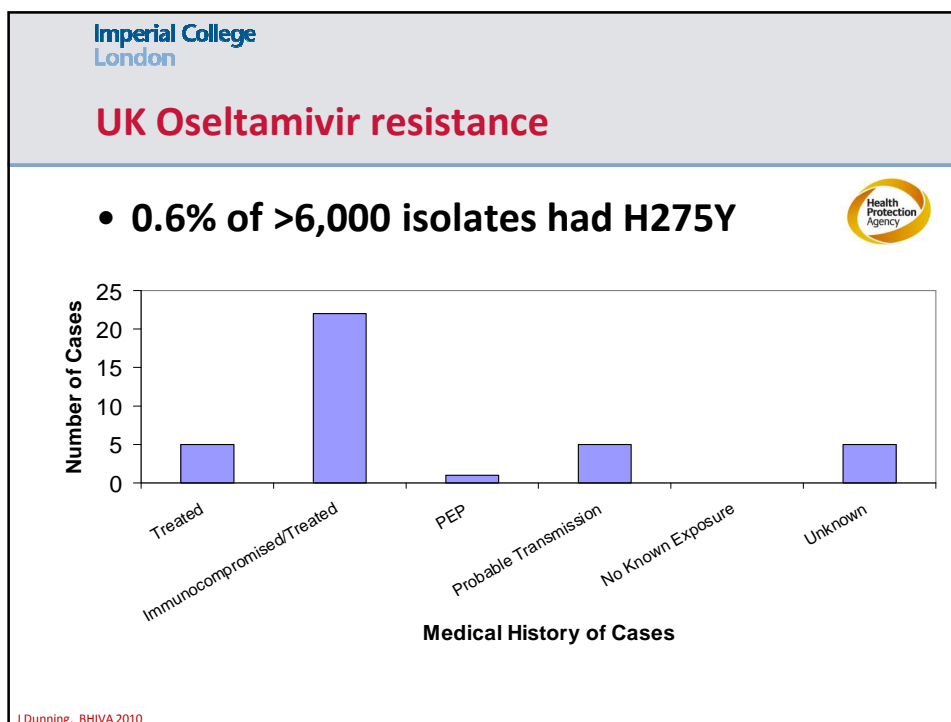
ND=not detected

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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)



So what about HIV- infected individuals?



Intra-pandemic planning for high risk groups

- *Define “Immunosuppression”*
- HIV: Concerns about greater risks of:
1. Influenza complications
 2. Vaccine failure/suboptimal response
 3. Long-term shedding
 4. Resistance
- Concerns about ARV treatment interruption
 - Significance of viral load and CD4?

Cautious, protective approach

Initial Advice for HIV-infected Patients

- High risk of complications so consider empirical oseltamivir/zanamivir
- pH1N1 Vaccination: two doses (adjuvanted)
- Mild ILI, no other explanation – manage in the community as flu - GP or NPFS

Influenza Antiviral Interactions

Charts updated May 2009. Full information available at www.hiv-druginteractions.org

	PROTEASE INHIBITORS								NNRTIs				NRTIs				OTHER						
	ATV	DRV	FPV	IDV	LPV	NFV	RTV	SGV	TPV	DLV	EFV	ETR	NVP	ABC	ddI	FTC	3TC	ddT	TDF	ZDV	MVC	RAL	
Neuraminidase Inhibitors																							
Oseltamivir	□	□	□	□	□	□	□	□	□	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Zanamivir	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
M2 Proton Channel Inhibitors																							
Amantadine	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆	◆
Rimantadine	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□	□

Key to symbols: □ Potential interaction – may require close monitoring, alteration of drug dosage or timing of administration.
 ◆ No clinically significant interaction expected.

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www.hiv-druginteractions.org

Chemoprophylaxis?

- Prompt treatment vs. Prophylaxis; “Risk assessment”
- Within 7 days of contact with ILI patient
- 10 day course (once daily dosing)
- Those who are likely to get secondary bacterial infection
- Those with a chronic disease that may become destabilised

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15th Oct 2009. Gateway Ref 12703

Conditions misdiagnosed as flu in the community

- Primary HIV infection (no rash in flu!)¹
- Bacterial gastrointestinal infections
- Syphilis
- Gonorrhoea

Have misdiagnosed/missed cases of *flu* received less attention?

pluralitas non est ponenda sine necessitate



Chelsea & Westminster 1st Wave Experience

- ~ 6000 HIV-infected patients under C&W
- Patients presenting with ILI (HPA criteria)
- May-August 2009
- 16 inpatients underwent testing for pH1N1 and commenced on empirical NI antivirals
- 2 uncomplicated confirmed pH1N1 cases
 - 1 pregnant; 1 Hodgkin's lymphoma
- Alternative diagnoses in 13:
 - CMV, Castleman's, Bacterial sinusitis, bacterial CAP; remainder were "presumed viral URTI/LRTI"
- No ADR/interaction issues
- One moderately severe case...

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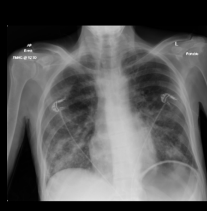
HIV pH1N1 Pneumonitis Case – Ward Managed



2008



Day 7 ILI (Admission)



Day 10 ILI



1 month (outpatient)

- 52 year old man, BMI 14, non-smoker, no flu contacts
- Hep C, pancreatic insufficiency
- Diagnosed 1991, CD4 296, VL<50 (TDF + FTC; r/DRV)
- 5 days OMV 75 mg bd in the community (NPFS) → DIB
- 10 days OMV 150 mg bd in hospital; empirical Moxifloxacin
- Remained pH1N1 PCR +ve at 15 days; no H275Y

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Pandemic influenza rapid appraisal

50 sites completed a survey, as follows:

Experience of pandemic influenza among HIV patients	Median	Range
Total cases including presumed/unconfirmed cases:	1	0-20
Virologically confirmed cases:	0	0-4
Requiring inpatient admission, including presumed/unconfirmed cases:	0	0-3

Advice to patients with symptoms:	Number (percent) of clinics
Contact HIV clinic by phone/email	36 (72)
Stay away from HIV clinic	15 (30)
Attend HIV clinic	1 (2)
Contact GP by phone/email	31 (62)
Stay away from GP	7 (14)
Attend GP	1 (2)

NB totals do not add as multiple answers possible.

- **38% departments experienced staff absence due to ILI**
- **54% centres unable to isolate suspected cases in outpatients**
- **1 ICU admission – new HIV and pH1N1 +/- PCP**
- **1 delivery at 33/40 (baby also had pH1N1)**

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Hospitalisations – International Series

Canada: 168 confirmed cases pH1N1

- 1.2% HIV-infected; no deaths

California: 1088 hospitalised or fatal cases

- 22 (2%) HIV-infected; 4 deaths
- Fatality 18% vs. 11% non-HIV; non-significant

J Dunning, BHIVA 2010

Kumar A et al. JAMA. 2009 Nov 4;302(17):1872-9; Louie J et al. JAMA. 2009;302(17):1896-1902



Mexico City HIV Cohort (INCMNSZ)


- April-June 2009
- 11/1017 HIV-infected patients had pH1N1
- 8 mild
- 2 moderate
- 1 fatal
 - Nosocomial acquisition
 - Concomitant PCP and CMV



More from Mexico City

- Instituto Nacional de Enfermedades Respiratorias (INER)
- Specialist centre, more underlying respiratory disease e.g. PCP & TB.
- 27 HIV-positive, H1N1-positive patients
- 14 hospitalised
- 6 deaths
- **“Opportunistic infections mask symptoms and [X-ray] signs of influenza, resulting in delayed treatment [of influenza]”**

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Barcelona

- April 26th – December 6th 2009
- 56 pH1N1 cases in HIV-infected patients
- 168 pH1N1 cases in non-HIV patients
- Smoking: 54% vs. 13%
- **No differences in outcomes**
- No impact on CD4/VL at 4-6 weeks
- Increased vigilance? More Tamiflu?

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Esteban Martinez, CROI 2010#802LB

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Barcelona - Symptoms


Results: Clinical symptoms at presentation

	HIV+ (n=56)	HIV- (n=168)	P value
Dysthermia (n, %)	56 (100)	159 (95)	0.1691
Cough (n, %)	48 (86)	145 (86)	0.9111
Arthromyalgias (n, %)	44 (79)	128 (76)	0.7148
Fatigue (n, %)	38 (68)	128 (76)	0.2176
Headache (n, %)	22 (39)	78 (46)	0.3518
Sore throat (n, %)	21 (38)	46 (27)	0.1521
GI symptoms (n, %)	21 (38)	31 (19)	0.0035
Rhinorrhea (n, %)	18 (32)	57 (34)	0.8063
Expectoration (n, %)	23 (41)	57 (34)	0.3330
Dyspnea (n, %)	10 (18)	36 (21)	0.5667

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Esteban Martinez, CROI 2010#802LB

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Barcelona - Bacteriology


Results: Concomitant bacteria detected

	HIV+ (n=56)	HIV- (n=168)	P value
• Concomitant bacteria * (n, %)	4 (7)	13 (8)	0.8842
– <i>S. pneumoniae</i>	3	9	
– <i>S. aureus</i>	0	4	
– <i>Capnocytophaga spp</i>	1	0	

* Detected from blood cultures and/or urine antigens and/or valid respiratory samples

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SOUTH AFRICA – National Deaths (April-October 2009)

- 91 pH1N1 deaths overall (HIV and non-HIV)
- 34 were tested for HIV; 18 HIV positive
- 25/45 women childbearing age
- 10 HIV +ve pregnant (8 were T3); 3 live neonates
- Median CD4 = 58 (n=6); 4/18 HAART
- Features similar to non-HIV
- 2 patients had *S. Pneumoniae*
- Active TB in 7 of 72 cases

J Dunning, BHIVA 2010 Archer B N et al. Eurosurveillance 2009;14(42) 19369

**pH1N1 vaccine response in HIV infected patients:
CROI 2010****ANRS HIFLUVAC Trial (Launay #804LB)**

- 306 HIV-infected patients (237 on HAART), median CD4 536
- Adjuvanted Single Dose: 95% seroprotection
- Unadjuvanted Single Dose: 77%

Frankfurt (Bickel #805LB)

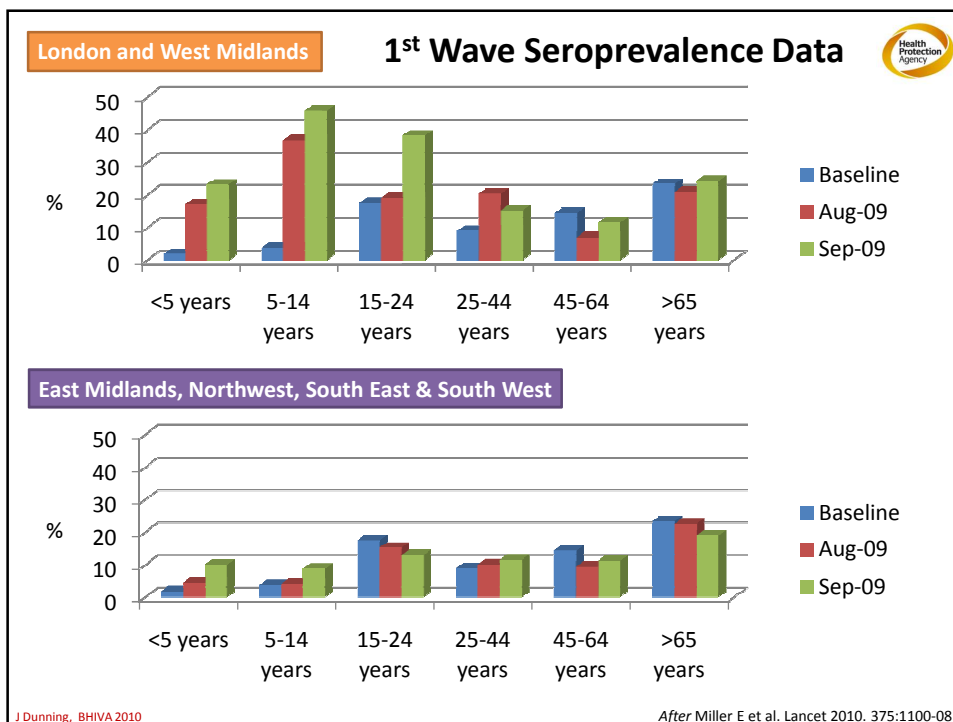
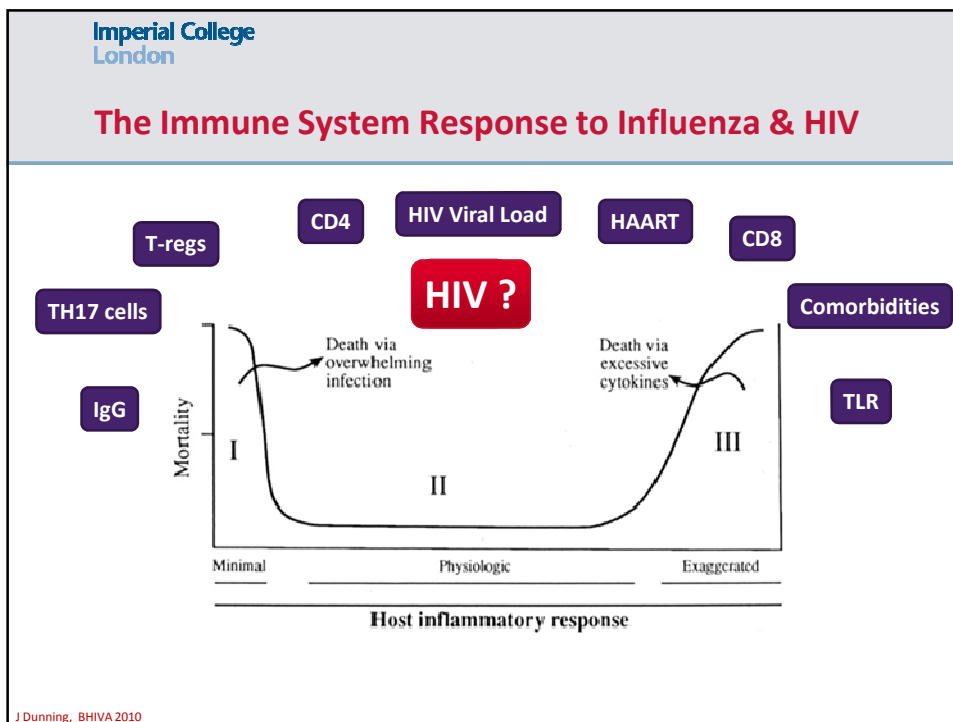
- 160 HIV-infected patients
- Single dose, split virion, adjuvanted
- 69% seroconversion
- Responders CD4 532 vs. 475

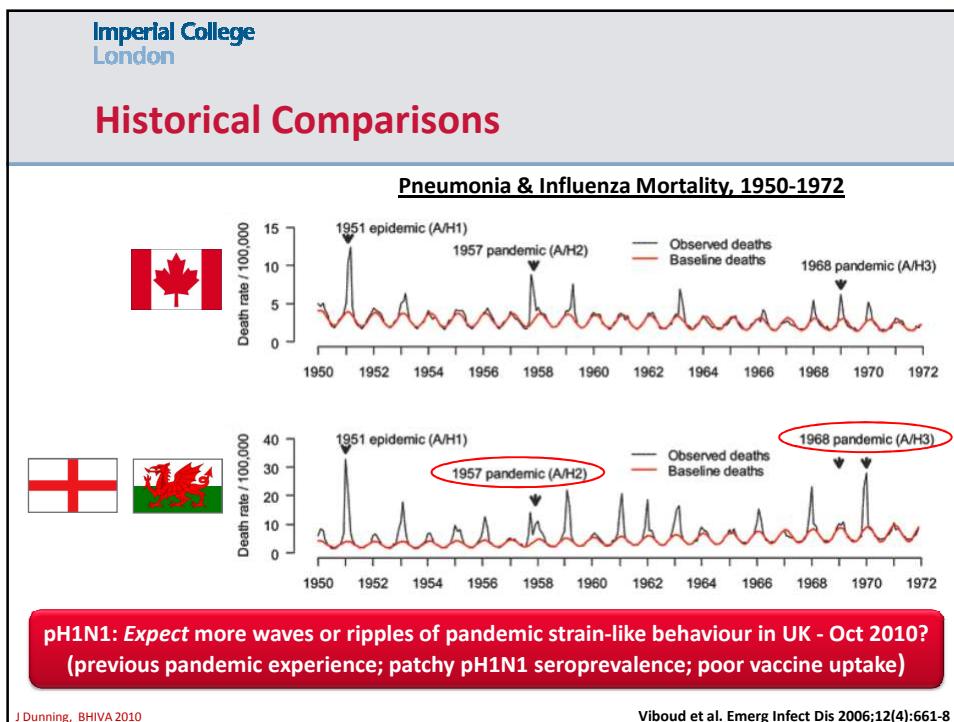
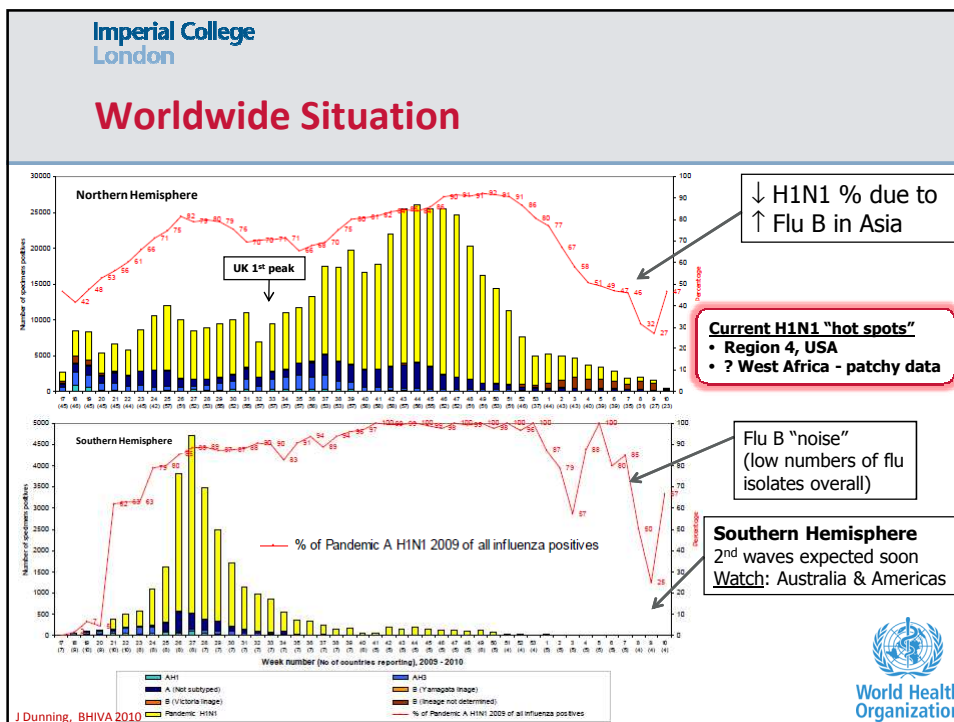
Pennsylvania (Tebas #806LB)

- 120 HIV-infected patients, median CD4 502; all on ARV
- Single dose, unadjuvanted vaccine
- 69% achieved protective antibody level
- (61% if exclude those with prior H1N1 exposure)
- Responders CD4 394 vs. 501; VL<50 31 months vs. 19 months

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So Nothing to Worry About Then?





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Animal-Human Interactions Will Continue: Surveillance, Surveillance, Surveillance



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Unprecedented Levels of International Co-operation



Influenza Pandemics Will Continue to Occur

- **“It is quite probable that influenza will continue to be prevalent...all over the world for some years to come...May we hope that etiological and epidemiological work...will furnish us with more competent methods for prevention and delimitation before the world is visited by another pandemic”**

Hans Zinsser, 1922

J.Dunning, BHIVA 2010

Acknowledgements

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- **Prof Peter Openshaw, Imperial College CRI**
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- **Dr Gail Thomson & Nick Gent, HPA CEPR**
- **Dr Tim Uyeki, Influenza Division, CDC**
- **Prof Fred Hayden, The Wellcome Trust & University of Virginia**
- **Dr Angie Lackenby, HPA CfI**
- **Dr Heli Harvala, Specialist Virology, Edinburgh Royal Infirmary**
- **Hilary Curtis, BHIVA Audit & Standards Subcommittee**

J.Dunning, BHIVA 2010