

The health impact of influenza and how it might be reduced

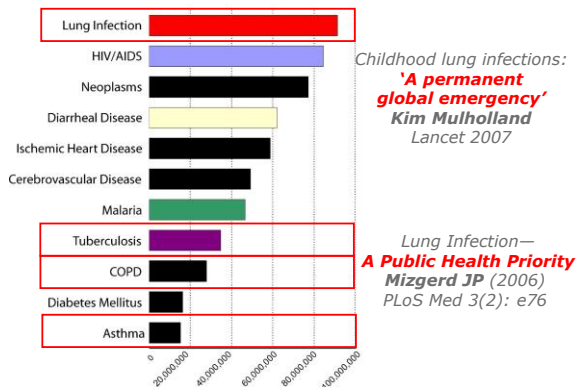
Peter Openshaw

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Global burden of disease (DALYs Lost worldwide/year)



HISTORICAL RESPIRAOTRY OUTBREAKS

- 1918 Spanish influenza
- 1976 Legionnaires' disease
- 1993 Hantavirus Pulmonary Syndrome
- 1994 Hendra virus infection
- 1997 H5N1 Influenza
- 1999 Nipah virus Encephalitis
- 2001 Human metapneumovirus
- 2002/3 H7N7 Influenza
- 2002/3 SARS

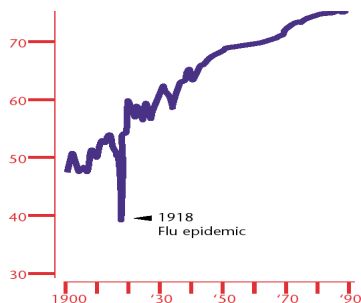
3

Major influenza A outbreaks

- 1918 H1N1 Spanish flu: ~50-100 million deaths
- 1957 H2N2 Asian flu: 70,000 deaths in USA
- 1968 H3N2 HK flu: 34,000 deaths in USA
- 1977 H1N1 Mainly young people born after 1957
- 1997-99 H5N2 Avian flu. Killed 6/18 infected humans in Hong Kong. Pandemic averted by slaughter of all chickens

4

Effect of Spanish flu on US longevity



The 1918 influenza pandemic reduced life expectancy in the US by approximately 10 years
The makings of a killer Peter Palese et al. Nature Medicine 8, 927 - 928 (2002)

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Influenza H5N1

- 1997: First infected man. Spread by wild birds along 'flyways'. Eradicated by poultry slaughter
- 2002: Antigenic drift- Lethal disease in wild water birds- high mortality
- 2003/4 Outbreak in chicken farms 5000 birds, 60% mortality in 5 days. Killed daughter, father and infected son 15 deaths in Vietnam, 8 in Thailand 100 million poultry slaughtered in HK

Resists M2 inhibitors. Sensitive to NA drugs

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SARS

November 2002: Severe atypical pneumonias appeared in Guangdong

21st Feb 03: Prof. Liew from Guangdong, booked into the Metropole

23rd Feb: Admitted to Kwong Wah hospital: warned staff.
(at least 70 hospital staff infected)

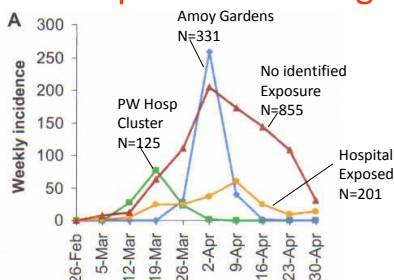
23rd Feb: Jonnie Chang flew to Hanoi

26th Feb: Admitted to hospital with fever
Examined by Carlo Urbani, who alerted WHO
(Dr Urbani and 3 other staff died; 63 were infected)

Canadian visitor to the Metropole returned to Toronto
(infected her son; both died)...

7

SARS epidemic in Hong Kong



Riley, S et al www.sciencexpress.org/ 23 May 2003/10.1126/science.1086478

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SARS in Toronto

March 2003

- 33 new probable and 29 suspected cases
- More than 5,000 people quarantined
- 27 deaths
- Toronto declared safe May 14 2003

Unemployment rate rose from 7.3 to 7.52%
27,000 jobs lost. Cost estimated to be \$1.5 bn

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SARS in 2003

REPORTED PROBABLE CASES

	6 th May	28 th May
Worldwide cases	6727	8240
recovered	2826	4891
deaths	478	745
Europe		
cases	36	35
recovered	28	34
deaths	0	0

Source: WHO

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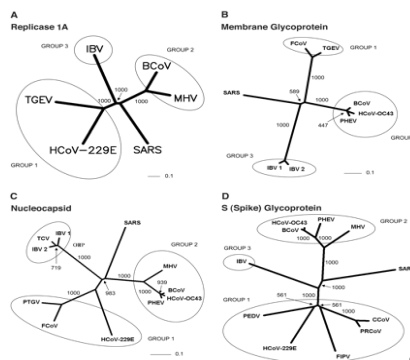
Coronaviruses

- Two known human coronaviruses (cause colds)
- Widespread in domestic animals (enteric, lung, liver etc)
- RNA genome 27-30 kb (largest RNA virus)
- Completely novel genetically
 - 11 open reading frames
 - S and E glycoproteins
 - matrix, replicase and nucleocapsid proteins
- Highly virulent in Vero cells



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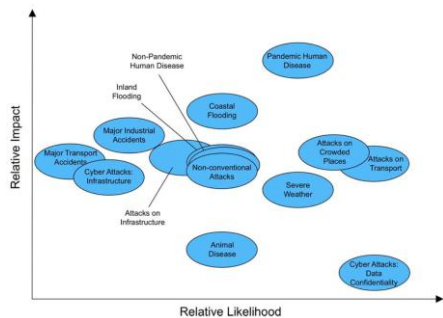
New unrelated coronavirus



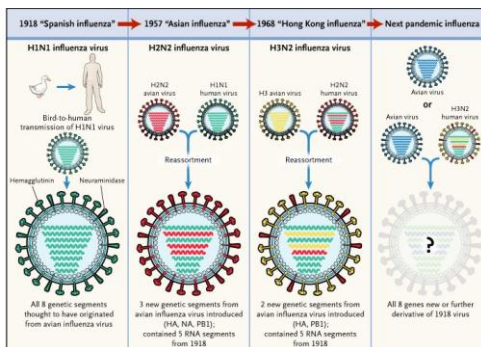
Marra MA et al Science 2003;300:1399-1404

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National Risk Register of Civil Emergencies
2010 Edition



Evolution of new flu strains

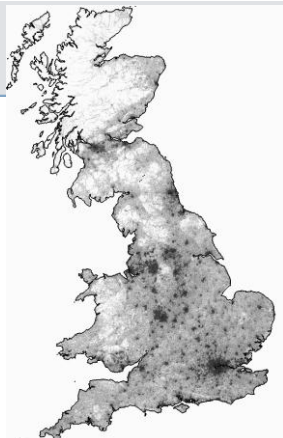


Belshe (2005) NEJM 353:2209-2211

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Neil M. Ferguson
Imperial College
London

Assume: R_0 1.8
Single source outbreak
One second per day



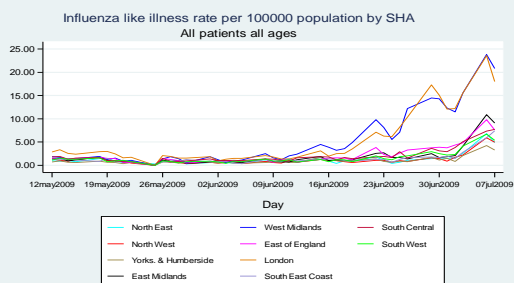
Imperial College
London

Phased UK pandemic plan

- Prepare:** *be ready*
- Vaccine/antiviral stockpiles
 - Advance purchase agreements
 - Modelling scenarios
- Contain:** *slow the spread, blunt the peak, buy time*
- Early diagnosis and treatment
 - Contact prophylaxis, self-isolation, school closures
- Treat:** *pragmatic, economical, targeted*
- Clinical diagnosis (suspend testing)
 - 'Treat all' policy (in England)
 - Focus on at-risk groups

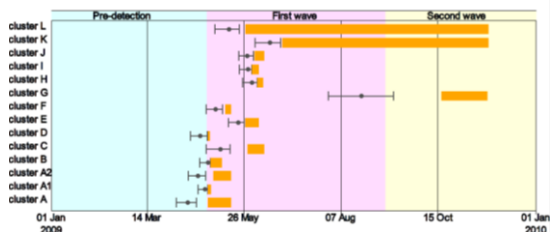
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London

QSurveillance® – daily consultation rate for influenza like illness in England by region (8th July 2009):



(Database version 1)
Copyright QRESURVEILLANCE 2009
Data source: QBSurveillance (daily data) - 8 Jul 2009

14 separate UK introductions documented...



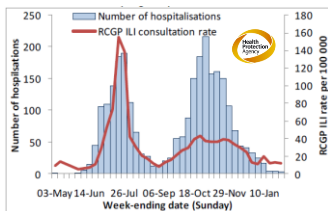
Many more introductions probable



Kindly provided by Paul Kellam and Maria Zambon

The UK's 2009-10 H1N1 Pandemic

- 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

Pandemic H1N1/09 influenza



"A mostly mild infection, that sometimes killed"
Sir Liam Donaldson

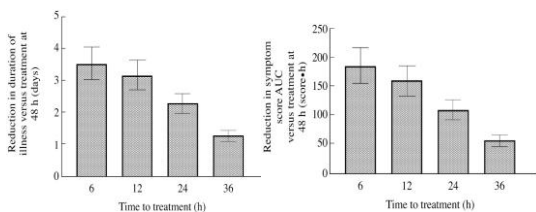
Antivirals in UK

- Government had a stockpile of 40 million courses of oseltamivir
- Some inhaled zanamivir stocks
- 'Zone' prophylaxis to household and school contacts of index cases
- Aim to blunt the peak number of cases
- Concerns about oseltamivir resistance

Treatment phase: after 2nd July 2009

- National Pandemic Flu Service (NPFs) was launched to authorise access to antivirals.
- Antivirals offered to anyone with a compatible clinical illness
- No routine testing
- Focus on 1st 48 hours of symptoms
- Issued about 10⁶ courses (?10% PCR+ flu)

Early administration of oral oseltamivir is important



Aoki, F. Y. et al. *J. Antimicrob. Chemother.*
2003 51:123-129; doi:10.1093/jac/dkg007

National Pandemic Flu Service (NPFs)

- England only
- Telephone/internet-based
- Presumptive algorithm
- "Voucher" access to antivirals
- 25% needed to see GP
- 2.7 million consultations
- 1.1 million courses of antivirals
- ? 1:10 had influenza



Imperial College
London

Hospitals crisis from 'mild' pH1N1

- 848 cases/week hospitalised (11/09)
- Flu bed-days rose 7-fold (Cf. to 2008)
- 20% needed critical care
- In 17-39 year age group:
37-fold increase in bed-days

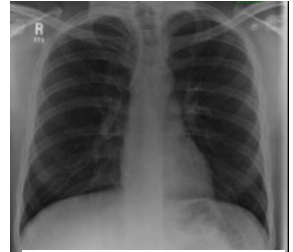
Hospital Episode Statistics (HES), The NHS Information Centre for health and social care. Provisional monthly HES topic of interest: Influenza.
<http://www.hesonline.nhs.uk/Ease/servelet/ContentServer?siteID=1937&categoryID=1243>

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Case 1

29 y, white-British man
 Well-controlled asthma
10 cigarettes/day
 School caretaker
 Wife, young daughter
Hx:
24h: Fever, cough, aches
2 h: Breathless at rest

No wheeze; O₂ sat 92%
 Raised pulse, breathing fast
pH1N1 RNA detected
 • Tamiflu 75 mg bd po 5/7
 • IV clarithromycin 500 mg bd



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Day 3: well; sent home

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London

Case 2

39 y, Pakistani Taxi driver (UK 12 years)
 10 cigarettes/day; Wife + 2 daughters
Hx:
5 d: 'Feverish flu', Dry cough, nausea/anorexia
24 h: Increasing SOB at rest; fast pulse/resps.
 O₂ sat 72% on air, 80% on 15L/min oxygen
 Tamiflu 75 mg bd po + antibiotics

Day 1
 Intubated and ventilated
 pH1N1 PCR* day 2 (NP swab/ET aspirate)
 Acute renal injury, ARDS

Day 19
 Discharged from ITU

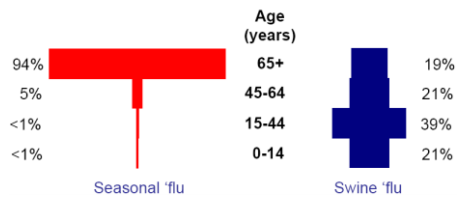
Day 23
 Allowed home



Imperial College Healthcare NHS Trust

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Different age of those dying of seasonal and H1N1/09 flu



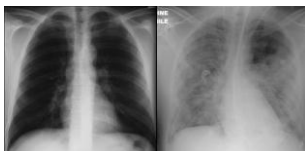
JID 2007; 54:530-538

CMO's enquiry
First 129 deaths (2009)

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Key unknowns about severe influenza

1. Why do some mild disease and others severe?
2. What determines outcome?



THE LANCET

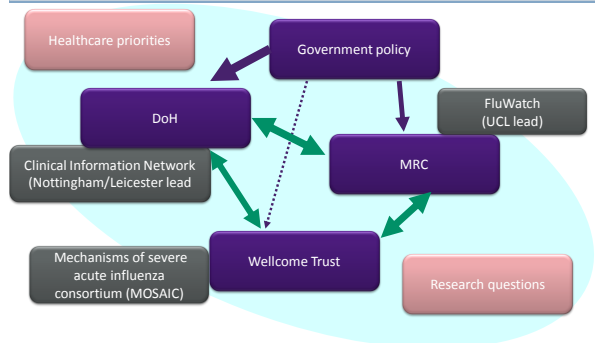
"Our major concern about the current response to H1N1 has been the dearth of any systematic, prospective, patient-oriented clinical research."

Doc Comment page 2485

June 2009

Imperial College
London

Pandemic H1N1/09 flu: National research plans (May 2009)



Two UK hospital studies of pH1N1

Flu-CIN

- DH funded, to aid health planners
- Aimed to collect clinical information fast
- No ethical permission needed (audit)
- Focus on providing real-time data

MOSAIC

- Wellcome/MRC funded
- Network of UK laboratories
- Comprehensive sampling of blood, mucus etc
- Focus on discovery of pathogenesis

*Dans ses écrits, un sage Italien
Dit que le mieux est l'ennemi du bien.*

In his writings, a wise Italian...
says that the best is the enemy of the good
Voltaire *La Béguéule*

Flu-CIN Clinical Data Collection

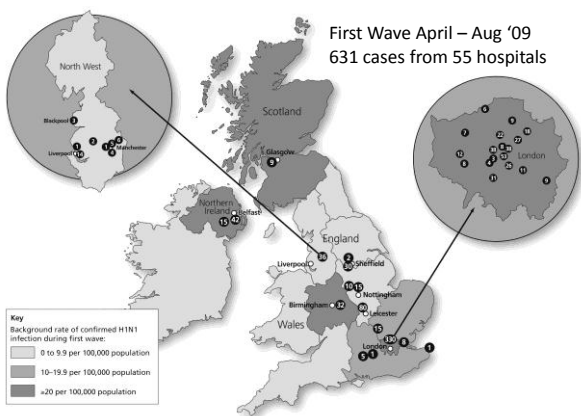
J Van-Tam
P J M Openshaw
A Hashim
E M Gadd
W S Lim
MG Semple
RC Read
BL Taylor
SJ Brett
J McMenamin
JE Enstone
C Armstrong
K G Nicholson

Completed retrospectively

40+ pages

With thanks to the Flu-CIN nurse teams

(especially Margaret Charlesworth & Ali Booth)



The Flu-CIN study



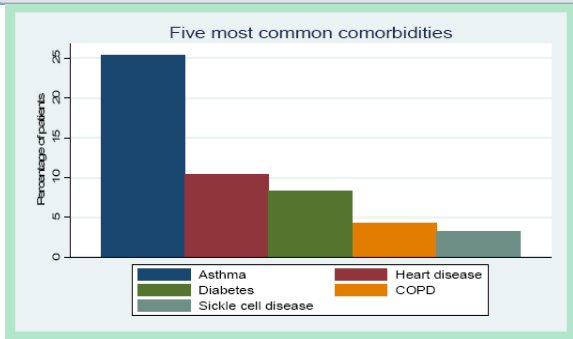
Risk factors for hospitalisation and poor outcome with pandemic A/H1N1 influenza: United Kingdom first wave (May–September 2009)

J S Nguyen-Van-Tam, P J M Openshaw, A Hashim, et al.

Thorax 2010 65: 645-651
doi: 10.1136/thx.2010.135210

- 60% from **non-white** ethnic backgrounds
- Even **mild asthma** increased the risk
- Greatest risk: **Pregnant women; <5 yrs**
- **13%** in ITU/HDU, of whom **31%** died
- 55% **no** underlying health problems

H1N1/09 Flu-CIN hospital study: risks for admission



Asthmatics in Flu-CIN

Myles, Van-Tam, Semple, Brett, Openshaw, Bannister, Read, Taylor, McMenamin, Enstone, Nicholson and Lim (submitted)

- **Greater respiratory compromise** at hospitalisation
- **Half as likely** to show **severe outcome** (11.2% vs. 19.8%, OR 0.51 (0.36, 0.72))
- Those on **inhaled steroids** were less likely to have severe outcome (7.4%) than those not (15.4%)
- 20.1% of those on inhaled steroids were 'non-asthmatic'
- Non-asthmatics showed **no benefit** from steroids

Conclusions: Vaccinate asthmatics and use steroid inhalers

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Hospital infections in Flu-CIN

1520 patients, 75 NHS hospitals:

30 cases of hospital acquired infection

- Most had serious underlying illnesses.
- Only 12 had antivirals within 48 hours
- 53% of patients needed ITU
- 8 (27%) of patients died

All staff and at risk patients should be vaccinated

Joanne E. Enstone, Puja R. Myles, Peter J.M. Openshaw, Elaine M. Gadd, Wei Shen Lim, Malcolm G. Semple, Robert C. Read, Bruce L. Taylor, James McMenamin, Colin Armstrong, Barbara Bannister, Karl G. Nicholson, and Jonathan S. Nguyen-Van-Tam

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 17, No. 4, April 2011



Flu-CIN



Barbara Bannister
Stephen J Brett
Joanne E Enstone
Wei-Shen Lim
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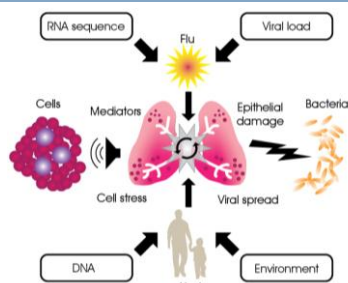
Imperial College Healthcare NHS Trust

Imperial College London
Centre for Respiratory Infection

CRI

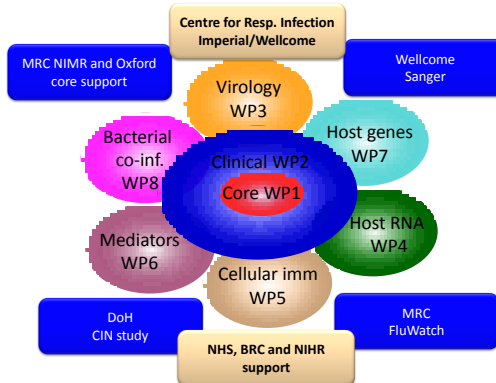
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What Causes Severe Disease?



Need to study host, pathogen and co-pathogen

MOSAIC



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MOSAIC Timelines



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Would there be a 2010/11 winter outbreak?

“after the second wave ... there has been sufficient infection of susceptibles ... that a third wave of infection in the 2010–11 influenza season is not to be expected...”

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

The pandemic in numbers...

- 132 million vaccine doses ordered (total £1bn)
- 13 million doses arrived by Feb 2010
- 17 million people offered vaccine
- 4.25 million vaccinated (140k pregnant women)
- £13.5m spent on the flu phone service
- ~1m courses of oseltamivir issued
- 411 people died

"Billions of pounds have been wasted on swine flu vaccines that will never be used" Victoria Fletcher, Daily Mail Feb 5th 2010



With thanks to Jake Dunning

Swine flu returns to UK, Winter 2010/11

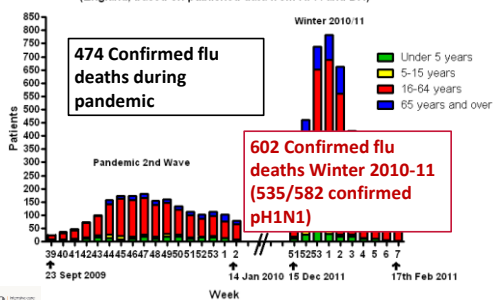
783 in intensive care by 1st week January

- 112 confirmed deaths by 2nd week January (49 of these had no risk factors)
- UK policy: only vaccinate those at high risk
- Normal under 5s not vaccinated
- Supplies of trivalent vaccine limited
- 2009 Pandemrix stocks again in use



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)

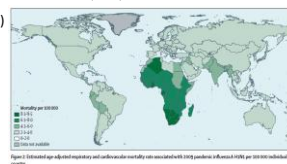


Estimated global mortality associated with the first 12 months of 2009 pandemic influenza A H1N1 virus circulation: a modelling study

18,500 laboratory-confirmed H1N1 deaths reported worldwide (April 2009- Aug 2010)

Respiratory and cardiovascular flu mortality rates calculated estimated by age, using known symptomatic attack and case fatality ratios (sCFR)

- Best global estimate:**
- 201k respiratory deaths (est. 105k–395k)
 - 83k cardiovascular deaths (46k–179k)
 - 80% of deaths in <65 years
 - 51% in southeast Asia and Africa

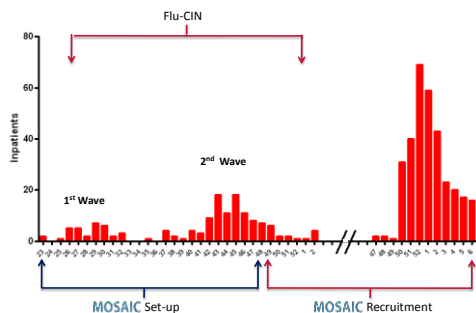


Total 284k deaths in 1st year
 70% of deaths were respiratory
 Flu mortality was 15x greater than known
 Many deaths were in Asia and Africa

However, UK 3rd wave was more lethal than the pandemic waves

Global toll likely to exceed half a million lives, even with a 'mild' outbreak

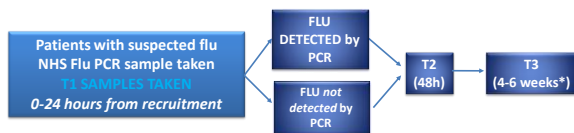
Imperial College London
Flu-CIN and MOSAIC timing



Imperial College London
MOSAIC
 Mechanisms Of Severe Acute Influenza Consortium

- Launched 1st December 2009
- Closed 11th February 2011
- 6 West London hospitals
- 5 Liverpool hospitals
- Total of 4800 beds
- Cases: **influenza-like illness**

Sample Collection (Adults)



Imperial College London
MOSAIC

257 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

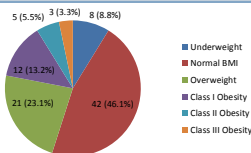
Virology and genomics Molecular bacteriology Mediators and cellular immunology Transcriptomics Host genomics

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

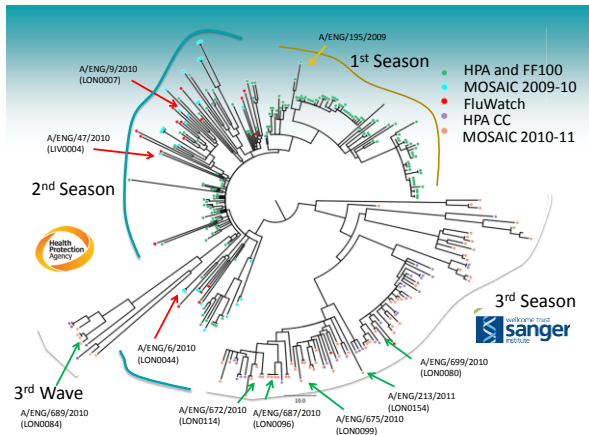
Probably the world's most comprehensive study of the causes of severe pandemic influenza

Imperial College London
Interim analysis: 128 Adults (96% pH1N1)

- Mean age: 41y (17-74y)
- 48% Female, 71% White
- 22% Obese (BMI ≥30)



- 20% No co-morbidities
- 24% Asthmatic
- 23% Immunosuppressed (13% HIV)
- 37% of women aged 15-44y were pregnant



Mediator samples – both seasons combined

	T1	T2	T3	Adult HC	TOTAL
Serum	229	108	70	36	443
Plasma (paeds)	27	15	5	36	83
NPA	183	79	50	35	347
SAM	237	110	77	36	460
TOTAL	676	312	202	143	1333
BAL				15	
GRAND TOTAL				1348	

MOSAIC

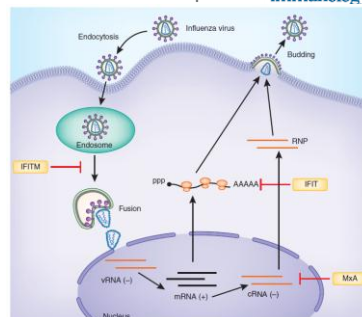
Intrinsic antiviral immunity

Nan Yan^{1,2} & Zhijian J. Chen^{1,3}

- IFITM1, 2 and 3 block viral entry into cytosol.
- M3 Induced by infection with flu; RNAi /deletion favours virus replication; Overexpression inhibits viral replication
- Avian cells lack M3 homologue
- Inhibit the replication of flaviviruses (dengue, West Nile); DNA viruses (CMV, HSV) induce IFITM

The interferon-induced transmembrane proteins

nature immunology



Feeley, E. M. et al. IFITM3 inhibits influenza A virus infection by preventing cytosolic entry. *PLoS Pathog.* 7, e1002337 (2011).

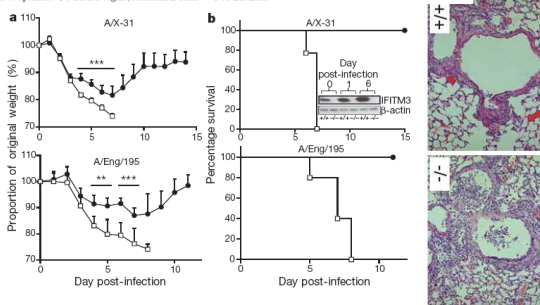
Figure 3 Intrinsic antiviral factors against influenza virus. The life cycle of influenza virus life cycle and known intrinsic antiviral factors that act against influenza virus. RNP, RNA-protein; ppp, triphosphate; AAAAA, poly(A) tail; vRNA (-), negative-strand viral RNA; mRNA (+), positive-strand mRNA; cRNA (-), positive-strand complementary RNA.

Published online 16 February 2012; doi:10.1038/ni.1229

IFITM3 restricts the morbidity and mortality associated with influenza

Nature nature10921.3d

Aaron R. Everitt¹, Simon Clare¹, Thomas Pertel², Simu P. John², Rachael S. Wash¹, Sarah E. Smith¹, Christopher R. Chin², Eric M. Feeley³, Jennifer S. Sims³, David J. Adams¹, Helen M. Wise¹, Leanne Kane¹, David Goulding¹, Paul Digard³, Veronika Anttila¹, J. Kenneth Baille⁴, Tim S. Walsh⁵, David A. Hume⁶, Aaron Palacios¹, Yali Xue¹, Vincenza Cokomon⁴, Chris Tyler-Smith¹, Jake Dunning⁷, Stephen B. Gordon⁷, The GenSIS Investigators⁸, The MOSAIC Investigators⁸, Rosalind L. Smyth¹, Peter J. Openshaw⁹, Gordon Dougan¹, Abraham L. Brack¹⁰ & Paul Kellam¹¹

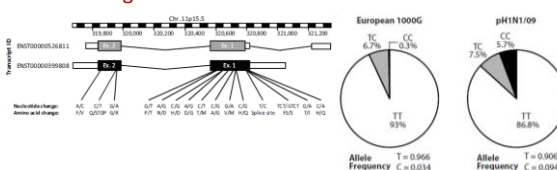


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IFITM3 genes in MOSAIC cases of severe influenza



- Screened 53 hospitalized cases of severe influenza
- Sequenced 1.8kb of IFITM3 locus, including exons, intron and untranslated
- IFITM3 splice variant with 21 aa N terminal deletion identified
- Differ significantly from matched Europeans (WTCCC1: p<0.00007; Fisher's exact test)
- Genotypes differ from Hardy Weinberg equilibrium (p=0.003)

Summary

<p>IFITM3:</p> <ul style="list-style-type: none"> • Is upregulated in response to interferon • Restricts viral exit from endocytosed vesicles
<p>Mouse studies:</p> <ul style="list-style-type: none"> • Mice with IFITM3 deletion show enhanced flu • Increased wt loss, delayed viral clearance
<p>Human studies:</p> <ul style="list-style-type: none"> • Defect in 1 :400 people, 1:20 in hosp flu cases • Defect common in SE Asian population and avians
<p>Gene tests might predict risk/target therapies but more complete genetic analysis awaited</p>

What have we learnt from MOSAIC?

Problems with studying outbreaks:

1. Almost impossible from a standing start
2. UK has great advantages internationally
3. We need to improve if we want to do this again

The integrated host/pathogen approach:

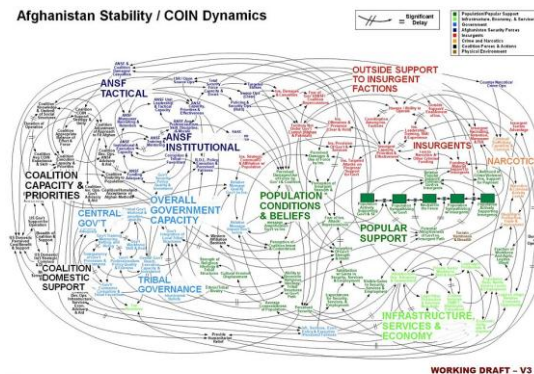
1. It works, but needs great collaborators
2. Exciting interim results, but it takes time
3. Very likely to impact on clinical management

Known knowns, known unknowns...**What we know:**

1. There will be more flu outbreaks
2. Some strains are more lethal than others
3. Mild in 2009, but big impact
4. We need to plan and be ready

What we don't know:

1. When, where from and how bad it will be
2. What the host response contributes to disease
3. Which new treatments to try

Afghanistan Stability / COIN Dynamics

"When we understand that slide, we'll have won the war." General McChrystal, Kabul 2009

MOSAIC INVESTIGATORS

Imperial College London: Deborah Ashby, Paul Aylin, Wendy Barclay, Stephen Brett, William Cookson, Alison Holmes, Tracy Hussell, Trevor Hansel, Onn Min Kon, Michael Levin, Miriam Moffatt, Simon Nadel, Peter Openshaw

Liverpool: Paul McNamara, Calum Semple, Peter Simmonds, Rosalind Smyth, Stephen Gordon

Nottingham: Jonathan Van Tam

Oxford: Ling-Pei Ho, Andrew McMichael

Edinburgh: Kenneth Baillie, David Hume, Tony Nash

Glasgow: William Carman, Walt Adamson

HPA: Maria Zambon

NIMR: Anne O'Garra

UCL/Sanger: Paul Kellam, Andrew Hayward

The patients and their relatives

Jake Dunning

MOSAIC support

Mary Cross
Lindsey Anne Cumming
Matthew Minns
Tom Ford

Mark Walport
John Saville
Sally Davies
Gordon Duff