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The role of vaccination in responding to influenza pandemics

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Introduction

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Influenza

- Bird virus.
- Very diverse – many strains.
- All waterfowl infected at least once.
- Mostly with Low Pathogenicity Avian Influenza (LPAI).
- Rarely with High Pathogenicity (HPAI).
- Reports of 'Bird flu' typically HPAI.
- e.g. H7N7 in Netherlands 2003

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Cross-species transmission

- Mammals (people, pigs, horses) can also be infected with influenza.
- Infection difficult with bird viruses.
- Virus has to adapt (e.g. mutate) to transmit in mammals.
- If a transmissible virus emerges, can cause a pandemic - no immunity.

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Influenza A outbreaks & pandemics

Influenza A pandemics since 1800

Year	*Virus*	*Origin*
1830	?	Russia
1836	?	Russia (?)
1889	H2	Russia
1899	H3	?
1918	H1N1	Europe/USA
1957	H2N2	China
1968	H3N2	China
(1977	*H1N1*	*Reintroduction)*
2009	H1N1	Mexico

Other outbreaks of novel strains, since 1953 (WHO surveillance established)

Year	*Virus*	*Location*	*Source*	*Cases (Deaths)*
1976	Swine (H1N1)	USA	Pigs	>100 (1)
1996	H7N7	UK	Ducks	1 (0)
1997	H5N1	Hong Kong	Chickens or ducks	18 (6)
1999	H9N2	Hong Kong	Chickens or ducks	2 (0)

1976 outbreak resulted in mass vaccination across USA.

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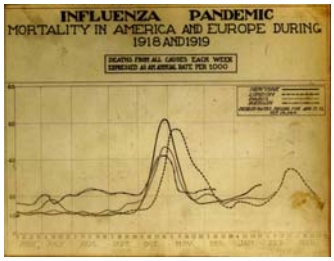
Pandemics

- 1918 ‘Spanish flu’ killed 40-100 million.
- Motivates ongoing preparedness efforts.
- Pandemics also seen in 1957, 1968 – killed ~2m, but 30-40% attack rate.
- After a pandemic, the virus stays in human populations (typically supplanting existing strains) – becomes a new ‘seasonal flu’ subtype.



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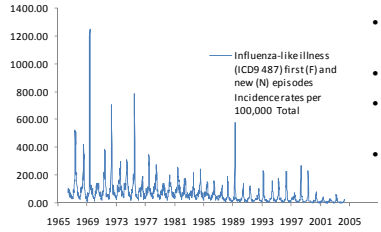
Seasonal influenza



- GP consultation rates for E&W (RCGP).
- Affected by healthcare seeking behaviour.
- Often not flu (e.g. RSV).
- Only measures disease, not infection.
- Real infection rate for influenza = ~ 7-18% p.a.

Similar pattern to measles/chickenpox…
… but each epidemic can involve different strain.

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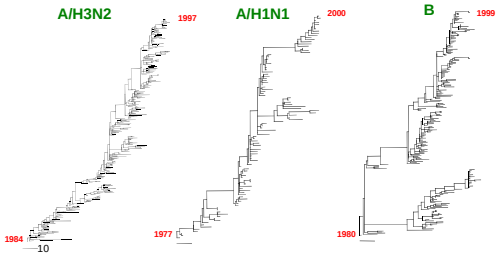
Influenza phylogenies

Derived from published sequence data (Bush et al.) for HA1 domain of HA.



Characteristic 'conifer'-like pattern (constant diversity through time)
- driven by strong *positive selection* for antigenic novelty.

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Influenza vaccines

- Most vaccines used today based on technology developed in the 1940s – inactivated subunit vaccine (mostly HA & NA), usually grown in eggs.
- These give high levels of strain-specific protection in healthy individuals.
- Live attenuated vaccines also available – more adverse events, but higher protection, esp. against drifted strains.
- Range of new manufacturing technologies under development (cell-grown, recombinant,…).
- Seasonal vaccines target 3 (sub)types:H3N2, H1N1, B.
- Seasonal vaccines need to be regularly updated to include new influenza strains.
- Pandemic vaccine target 1 strain – challenge is making it fast enough (takes 5-6 months currently).
- 'Universal' flu vaccine a long-term goal.

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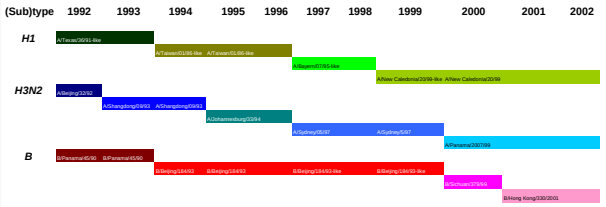
Impact of antigenic evolution on flu vaccine formulation



[MMWR reports on antigenic surveillance of influenza in US 1992-2003]

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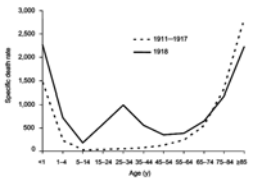
Seasonal flu: burden of disease

- Most mortality in the frail elderly or very young infants.
- But specific groups with risk factors (e.g. pregnant women) have higher risk of severe outcomes at other ages.
- Annual mortality and morbidity varies significantly, averages ~5000 excess deaths in UK, ~30000 in US.
- Burden estimates relatively poor, due to difficult of attribution.
- Vaccine has traditionally been targeted at those >50, and risk groups.
- But children now recommended to be vaccinated in the US and UK – partly for *indirect* benefits (reducing transmission).



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Before the 2009 pandemic

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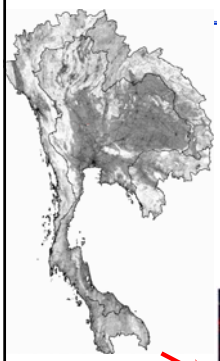
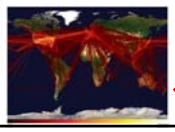
What did we expect?



- 2-4 months to peak at source, 1-3 months to spread to West.
- 1/3 of UK population would become ill, 0.5-1 million new sick people per day at peak.
- 1st wave over ~3 months after 1st UK case.



Thailand

GB

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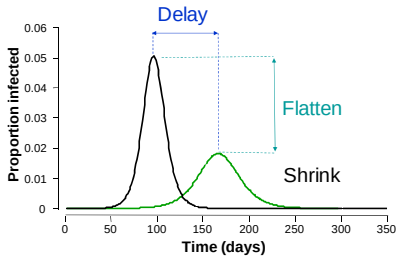
Goals of mitigation measures



- Buy time for seasonality to further reduce transmission, for vaccine production.
- Much modelling of different mitigation strategies (drugs, vaccines, NPIs).
- *Containment at source a special case – try to eliminate the new virus.*

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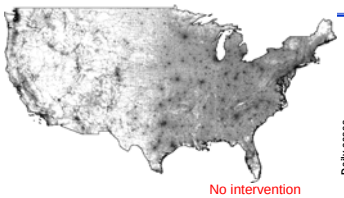
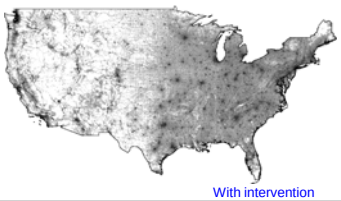
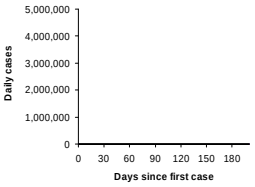
Modelling for pandemic planning



No intervention



With intervention



Intervention : next-day treatment of 90% of cases with anti-virals, reactive school closure, 50% household quarantine.

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Mitigation strategies: conclusions from modelling

Treatment

Needs to be fast (within 12-24h of symptoms) to be very clinically effective, but then can also reduce infectiousness (and thus attack rates by ~1/8).

Prophylaxis

Treating everyone in household rather than just first case, can reduce illness rates by >1/3, but need ~50% stockpile.

School closure

Main effect is to reduce peak height (by ~40%), not total numbers infected.

Vaccination

Better to stockpile in advance – despite strain selection being a gamble. 20% stockpile of 30% efficacy vaccine targeted at kids could reduce total illness rates by 1/3.

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Emergence of H1N1 (2009)

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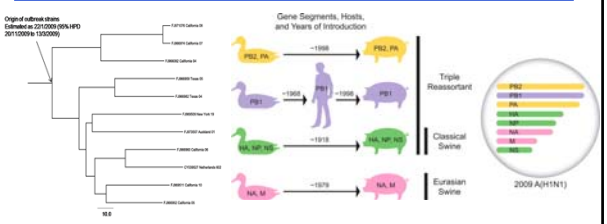
Origins



Fraser et al, Science 2009

Garten et al, Science 2009

- Genetic analysis dates origin to January 2009 (range Sept. 08-March 09).
- Location almost certainly Mexico.
- Quadruple reassortant virus.

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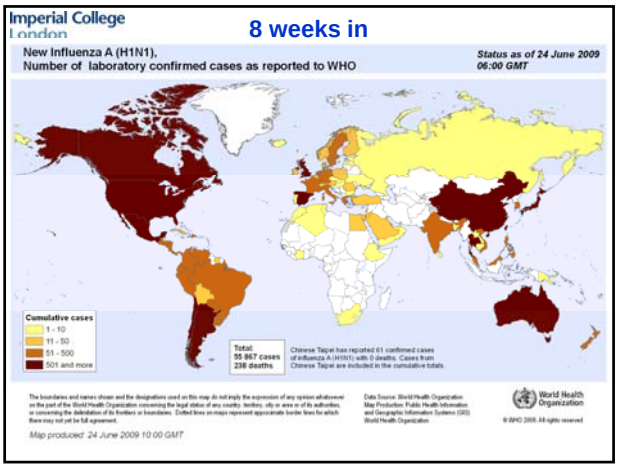
8 weeks in



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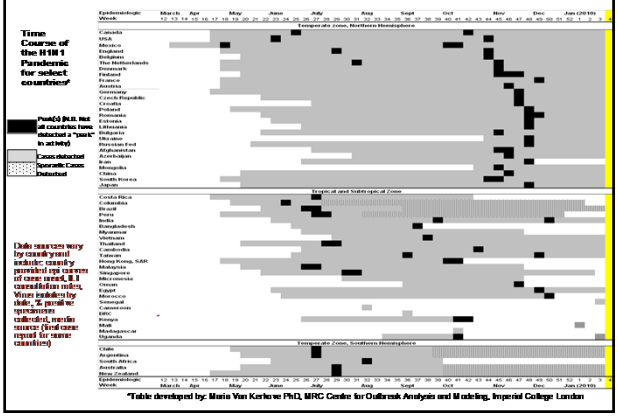
Time-course of pandemic



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Timeline in 2009

April 15th
Detection of the novel virus by CDC

End of April
First estimates of R, severity bounds
[analysis of the Mexican outbreak; online May 11th]

~ May 10th
Preliminary results of CDC community study in Chicago (AR)
[Delaware was even earlier]

May 15th
First analysis of household data from US case report forms (SAR, generation time)
[but could have started earlier]
& from UK first few hundred cases

June-July
Refinement of severity estimates for clinically attended cases, reliable estimate of final infection AR

End August
Per-capita mortality data
[from S hemi]

Vaccine available by October

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Analysis: transmission

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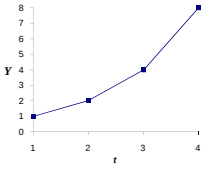
Epidemic dynamics

Epidemic as chain reaction:



Key: *how many* other people one person infects, on average.
= *the Reproduction Number* of an epidemic – ***R***.
= R_0 at the start of an epidemic, when no-one is immune.

Need R_0 >1 for a large outbreak.

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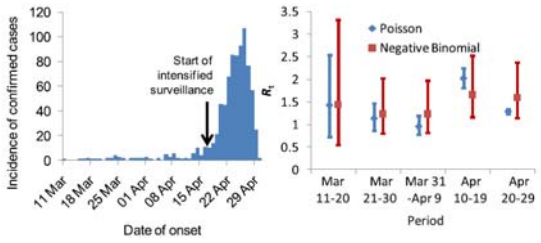
R for Mexico in April-May



- *R*=1.5 (95% Cr.I.:1.2-1.9) from confirmed case epi curve.
- *R*=1.4 (95% Cr.I.:1.1-1.9) from spatial back-calculation.
- *R*=1.2 (95% Cr.I.:1.1-1.9) from sequence analysis.

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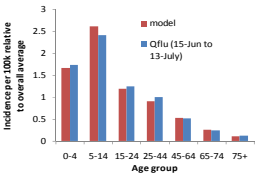
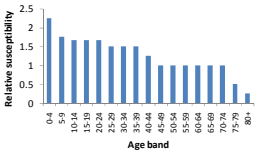
Age-specific patterns

- Household data - children >2 fold more susceptible than adults.
- Plus children mix more intensely than adults.
- Model-fitting to ILI and confirmed case age distributions indicates marked drop in susceptibility with age.
- But *severity* increased with age.





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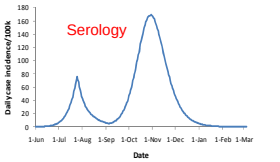
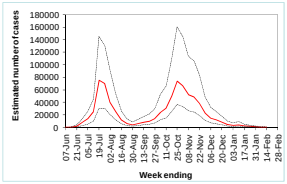
England – analysis and modelling

- Models fitted June-July increase well, and decline after schools closed.
- But needed to know true number of infections to make predictions.
- Serology data now indicates second wave substantially larger than first, but healthcare seeking behaviour changed over time.





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Severity

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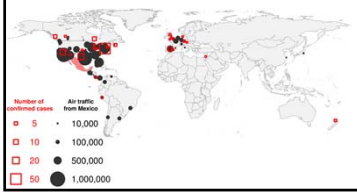
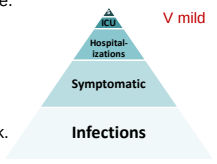
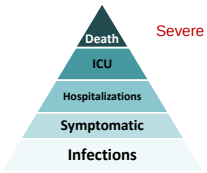
Assessing severity

- Critical for determining appropriate response.
- Case-finding misses most mild infections, giving uncertain denominator.
- Early estimates from Mexico : 0.04%-0.4%
- Real value: ~1 death per 10,000 infections.
- But clinical risk groups had much higher risk.
- But hospitalisations much higher.





V mild



Severe

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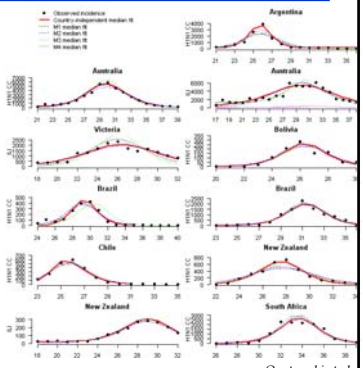
Learning from the S hemisphere

- Started analysis Aug 2009, *after* peak.
- R in range 1.25-1.55
- Infection attack rates in 20-40% range.
- Strong effect of demography.
- Very low case fatality (<0.01%).



Opatowski et al,

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Interventions

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School closure as a public health measure

- School closure does offer some potential benefits – esp. ~40% reduction of peak incidence; but at a very high costs.
- Impact on H1N1 pandemic even greater, due to role of children in transmission.
- Used early in the pandemic, and considered later (to buy time for vaccine) – but societal costs considered too high given severity.

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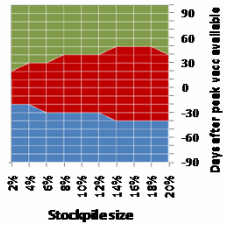
Vaccination strategies in 2009

- Vaccine the primary public health response.
- Vaccine orders placed in June 2009, before severity known.
- Could not *predict* impact of vaccination, due to uncertainty in timing of vaccination and pandemic.
- Key debates: target groups, prioritisation (children vs clinical risk groups).

e.g. H1N1 vaccination strategies



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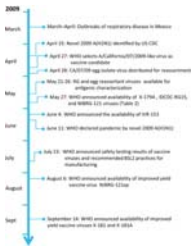
What happened with vaccination?

- Most vaccination occurred October-December – often after the peak of the N hemisphere autumn epidemic.
- US bought 291m doses, used 91m.
- EU largely used adjuvanted vaccine, but not US.
- Heterogeneity across EU in programmes – some targeted whole population (e.g. Sweden, Germany), others risk groups (UK, Netherlands, Italy), some children (e.g. UK, Netherlands).
- EU coverage varied – 7-30% overall.
- Coverage in targeted risk groups disappointing – UK: 25-30% in pregnant women, ~50% in other risk groups.
- Coverage probably reflected public perception of (low) risk.
- Health impact of vaccination still being assessed, but probably low.



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Lessons learned

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Data issues

- **Denominators -** not knowing infection rates made estimation of severity and prediction of peak difficult:
  - Serosurveillance
  - Web/telephone cohorts
- Non-systematic nature of confirmed case surveillance in early stages of pandemic.
- Impact of seasonal variation in transmissibility.

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Communication challenges

- Uncertainty around numbers often lost (e.g. CFR, case estimates).
- Communicating changing assessment of severity.
- Politics and policy inertia – decisions/updates lagged available data.
- Predictions vs scenarios – scenarios useful for assessing policy robustness, but are not predictions.
- Inconsistencies between modelling groups (quality control).

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Countering some emerging myths

- 'The fake pandemic' – changes in pandemic definitions were not last minute, but 3 years in the making.
- Not all pandemics need be 'severe' – responses need to be proportionate, taking account of uncertainty.
- Decisions about vaccine purchase had to be made before severity could reliably be estimated.
- Need to defend the precautionary principle when dealing with emerging infections – as learned from BSE/vCJD and SARS.


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WHO accused of losing public confidence over flu pandemic

Loss of credibility could endanger lives, says vice chair of Council of Europe's health committee

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Conclusions

- 2009 was the first pandemic for 40 years.
- Attack rate lower than previous pandemics – some population immunity.
- Despite being relatively mild, 2009 H1N1 pandemic caused substantial burden on healthcare systems.
- Vaccination is the primary pharmaceutical intervention (though antivirals also available).
- Fundamental challenge: making pandemic vaccine fast enough.
- Despite rapid production in 2009, most vaccination campaigns occurred after the peak of transmission.