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Epidemic inference: lessons learned from flu

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Health Protection Agency

SALUD
SECRETARÍA DE SALUD

CDC

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Goals of epidemic inference

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- 'Ecological determinants of observed pattern'
  - Want to distinguish/test different hypotheses.
  - 'macro' pattern more than 'micro' fit.
- Parameter estimation using detailed data
  - Often stretches data to inferential limits
- Real-time analysis
  - Want estimates of basic params (R, T_g, CFR).
  - Estimates need to be rapid and robust.
- Informing public health policy
  - Now-casting/Situational awareness.
  - Control policy decision making.
  - scenario analysis vs prediction.
  - How good is good enough?

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The example of influenza:

1. Preparedness modelling

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What did we expect?

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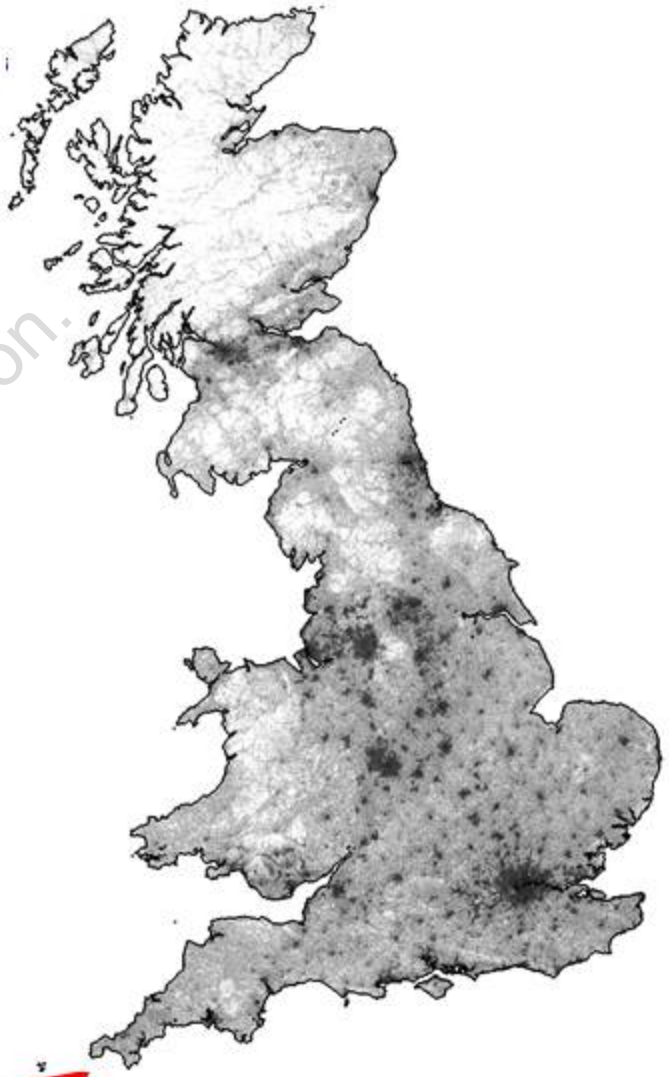
Past data and extrapolation ⇒

- 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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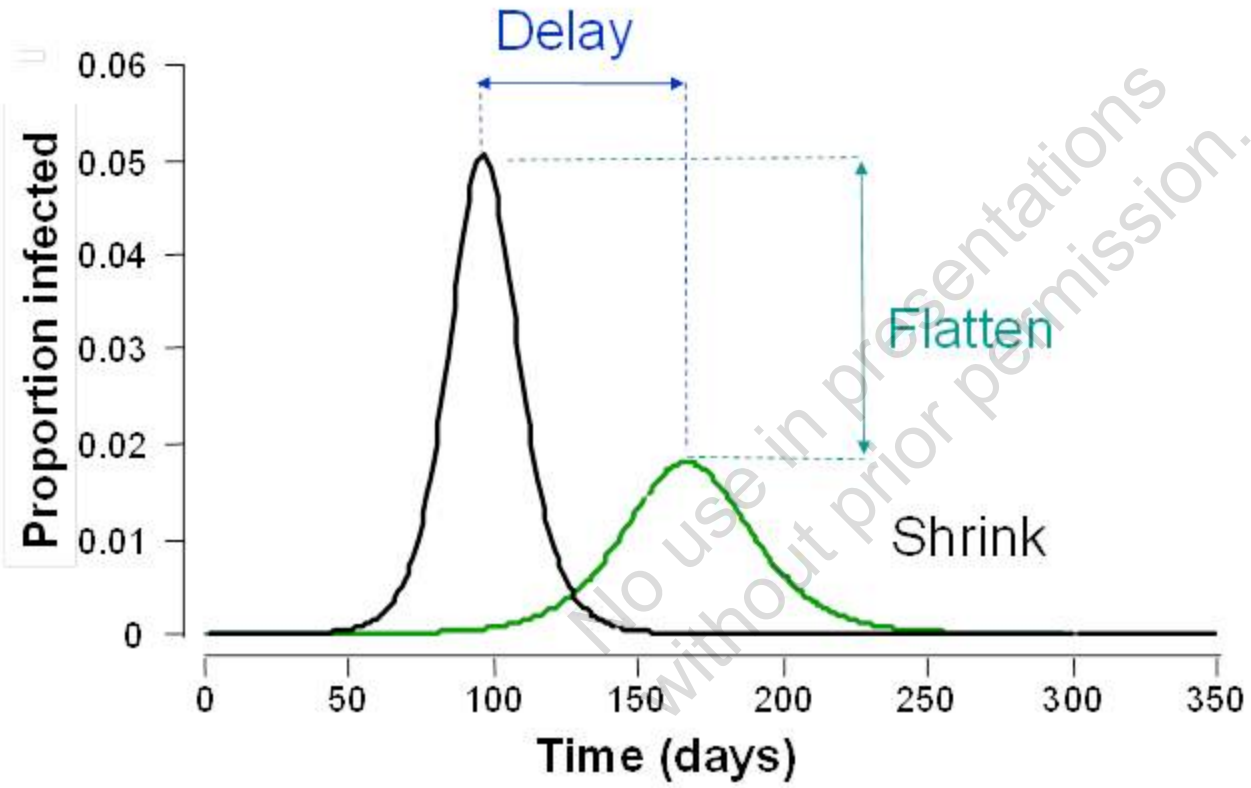
Modeling community mitigation

Aim: reduce impact, buy time:



- 2005-9 – epidemic of pandemic preparedness scenario modelling.
- Biggest distinction between good and bad was parameterisation:
  - R, T_g, natural history, treatment delays.

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2. Real-time analysis

- the 2009 H1N1 pandemic

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The start

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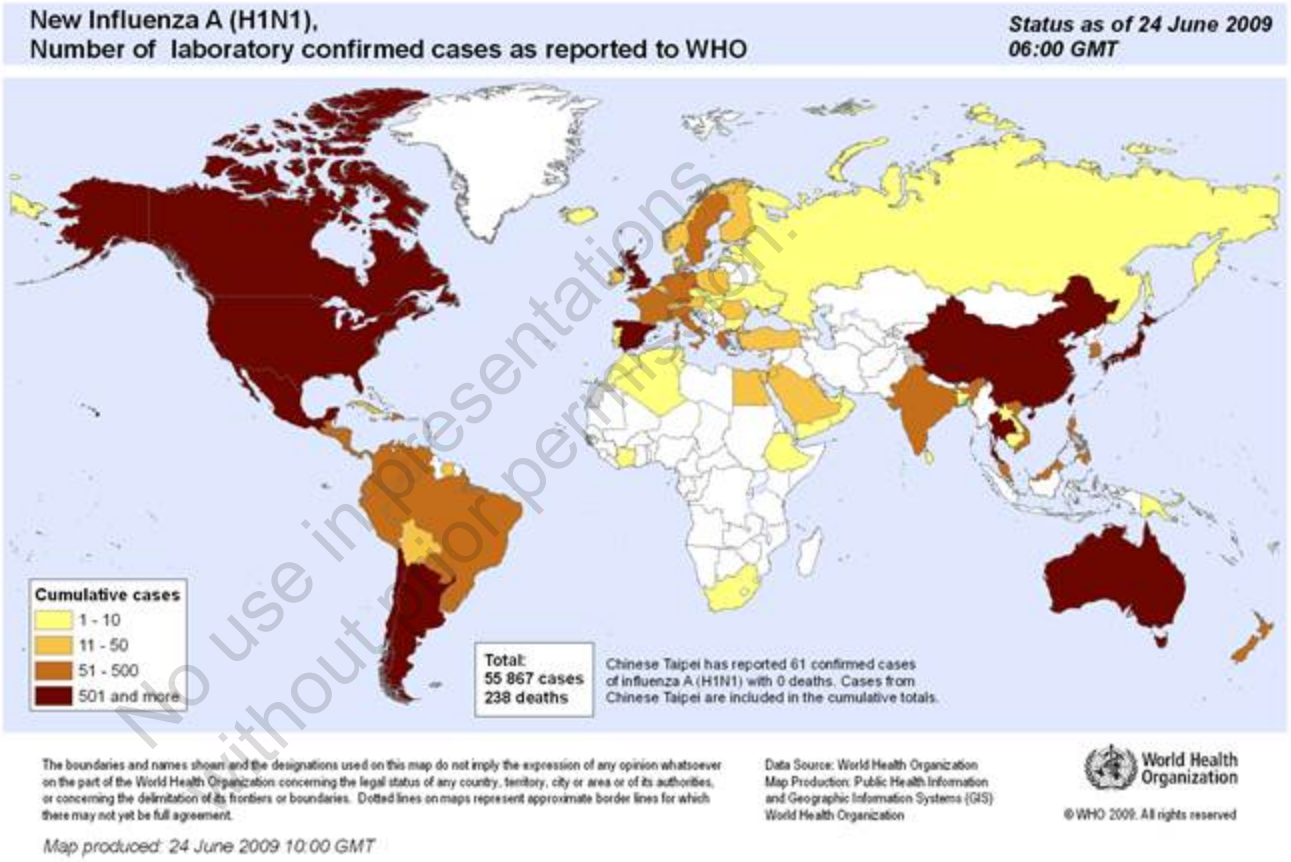
8 weeks in



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

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A wealth of data

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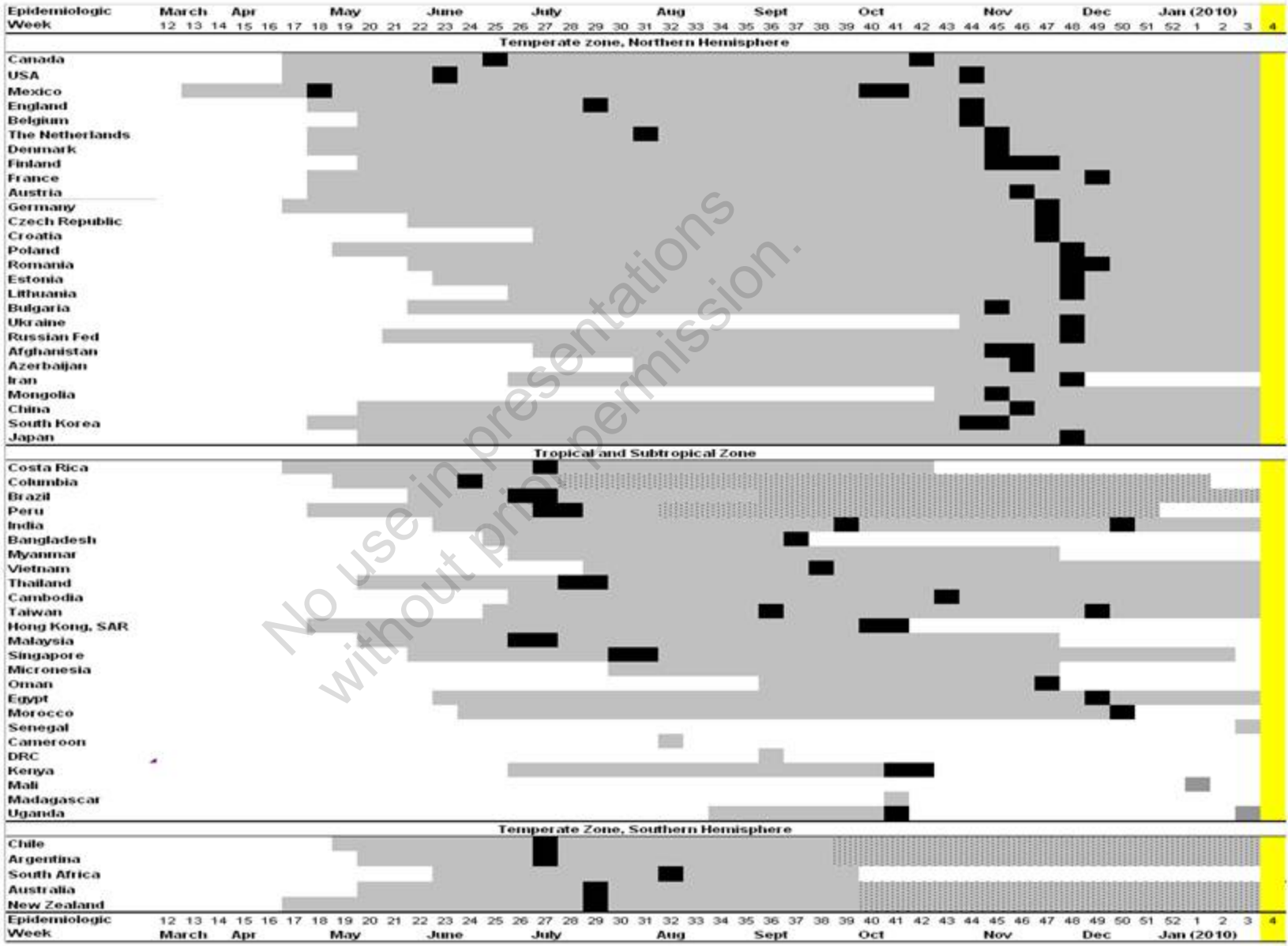
Time Course of the H1N1 Pandemic for select countries*



Peak(s) (N.B. Not all countries have detected a "peak" in activity)

Cases detected

Sporadic Cases Detected

Data sources vary by country and include: country provided epi curves of case onset, ILI consultation rates, Virus isolates by date, % positive specimens collected, media source (first case report for some countries)

*Table developed by: Maria Van Kerkove PhD, MRC Centre for Outbreak Analysis and Modeling, Imperial College London

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Analysis: transmission

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R for Mexico in April-May

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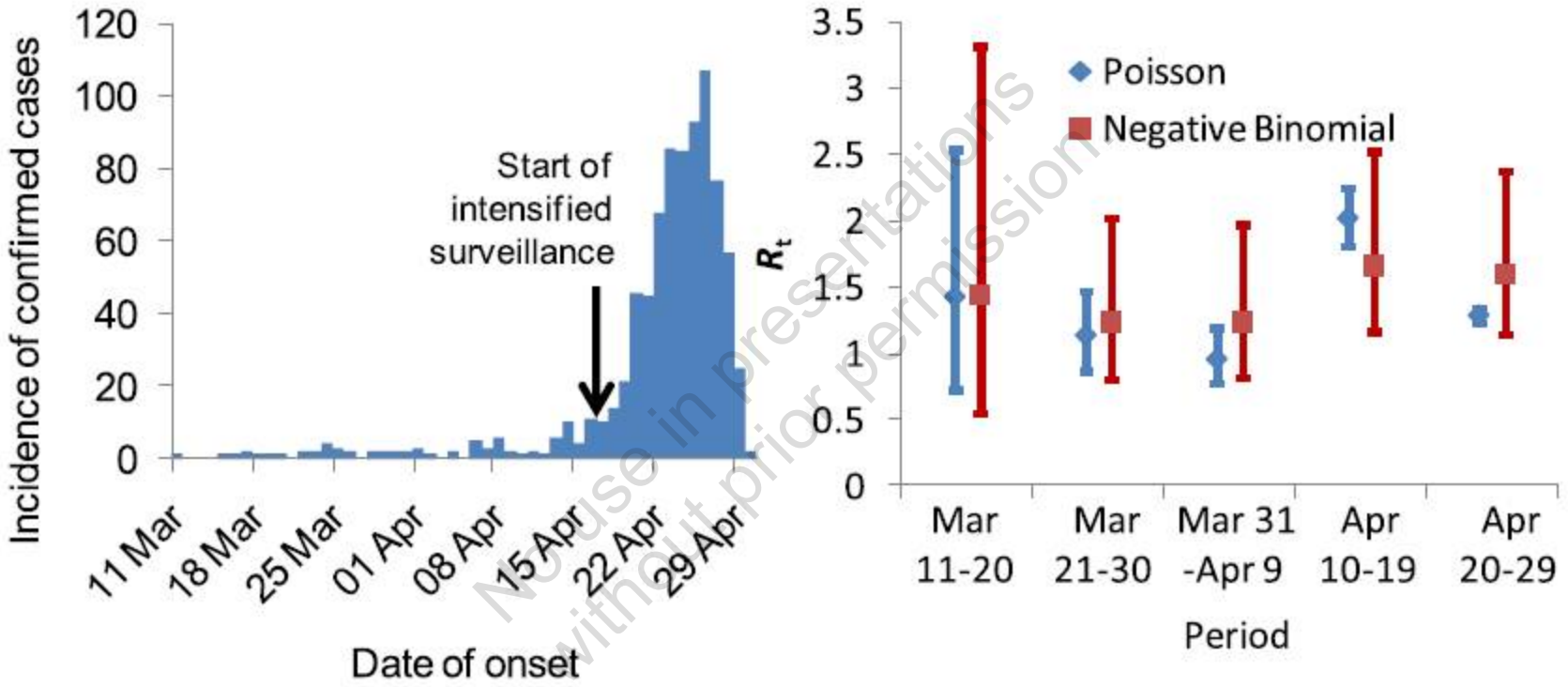

- *R*=1.5 (95% Cr.I.:1.2-1.9) from confirmed case epi curve.
- *R*=1.4 (95% Cr.I.:1.1-1.9) from spatial back-calculation.
- *R*=1.2 (95% Cr.I.:1.1-1.9) from sequence analysis.

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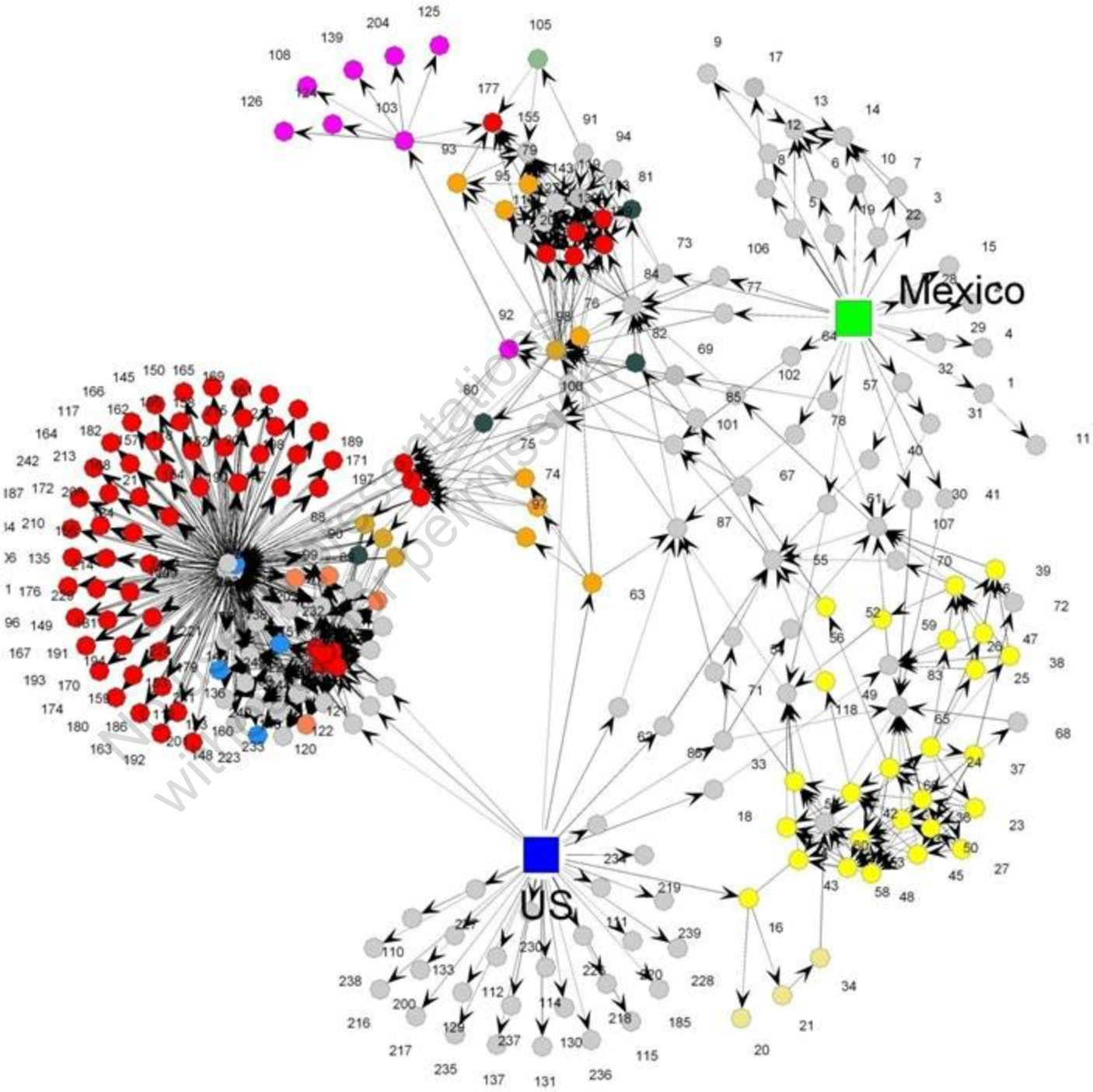
FF100 data

Early UK case data (with contacts) gave invaluable insight into transmission.

But in retrospect, only a minority of cases were being identified.

Data analysed in collaboration with HPA.



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England – real-time analysis May-June 2009

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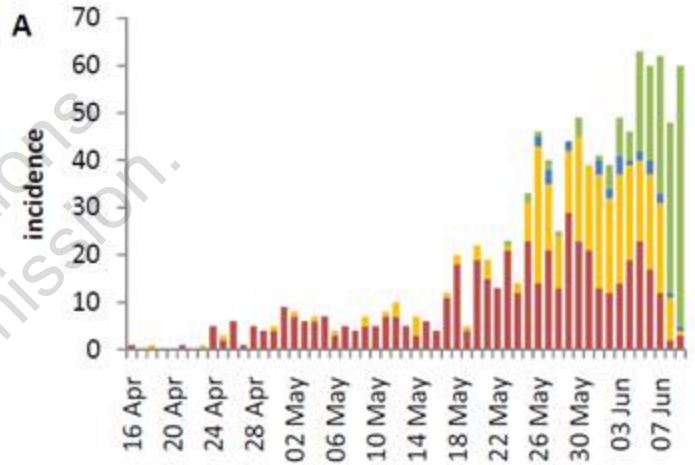
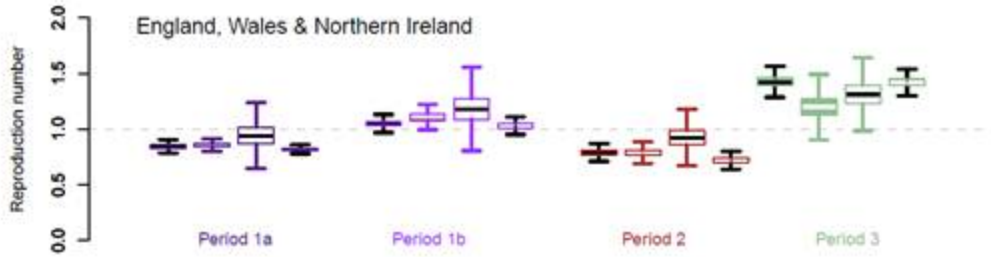
- Major decisions depended on when sustained transmission was detected in UK.
- Enormous effort put in by HPA and Imperial College teams in real time estimation of *R* from confirmed case data.
- A variety of methods developed.
- In retrospect, not a terrible useful activity:
  - ➢ Case tracing was missing an increasing proportion of cases.
  - ➢ Too many reputational issues!





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Generation time distribution

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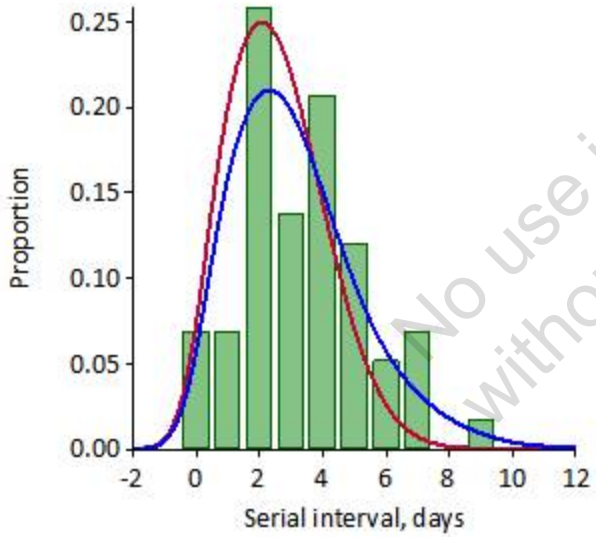
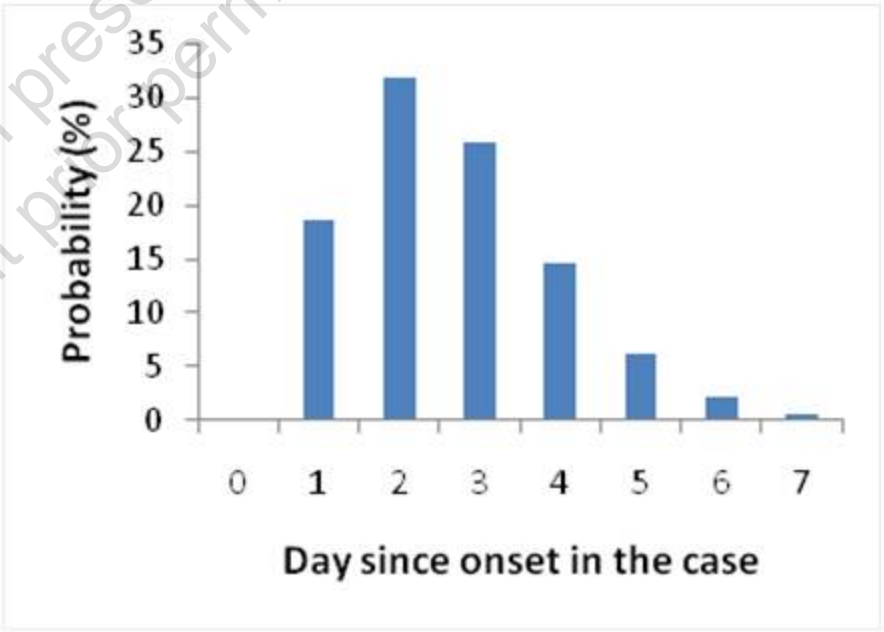
- US and UK data gave mean of 2.5-3 days
- Estimated mean incubation period of 1.5-2 days.





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Household transmission

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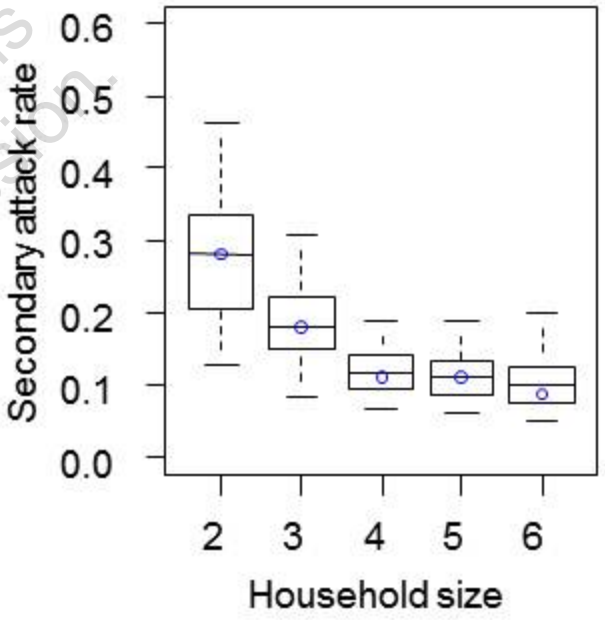
- US analysis (with CDC):
  - ➢12% mean household contact secondary attack rate for ARI, 8% SAR for ILI - low compared with previous pandemics.
- UK data (with HPA):
  - ➢8% household SAR for confirmed H1N1 infection, 11% for ILI (in the presence of AV use).

Cauchemez et al, NEJM, 2009



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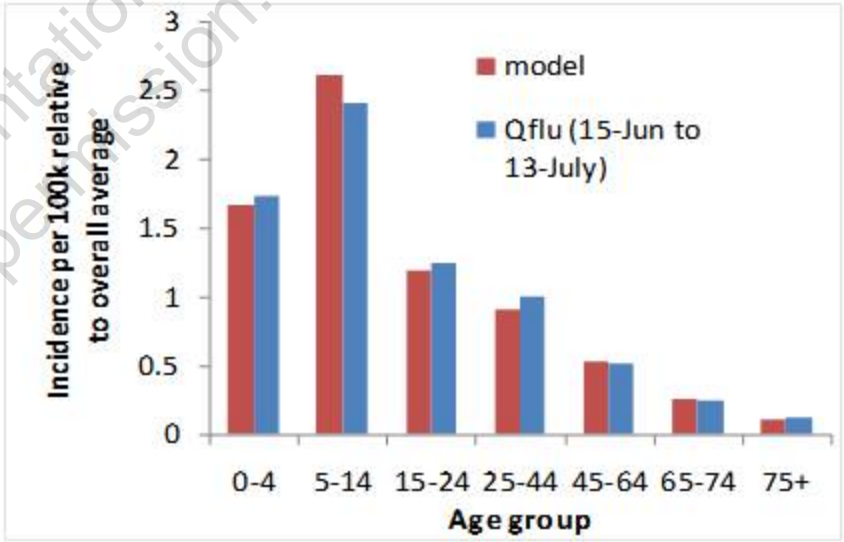
Age-specific patterns

- 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 indicated marked drop in susceptibility with age.
- But severity increased with age.



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England – predicting the autumn wave

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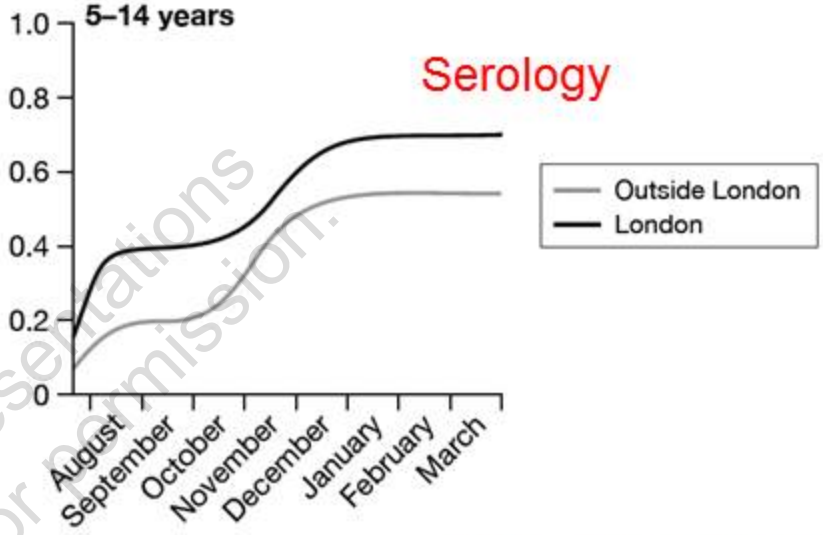
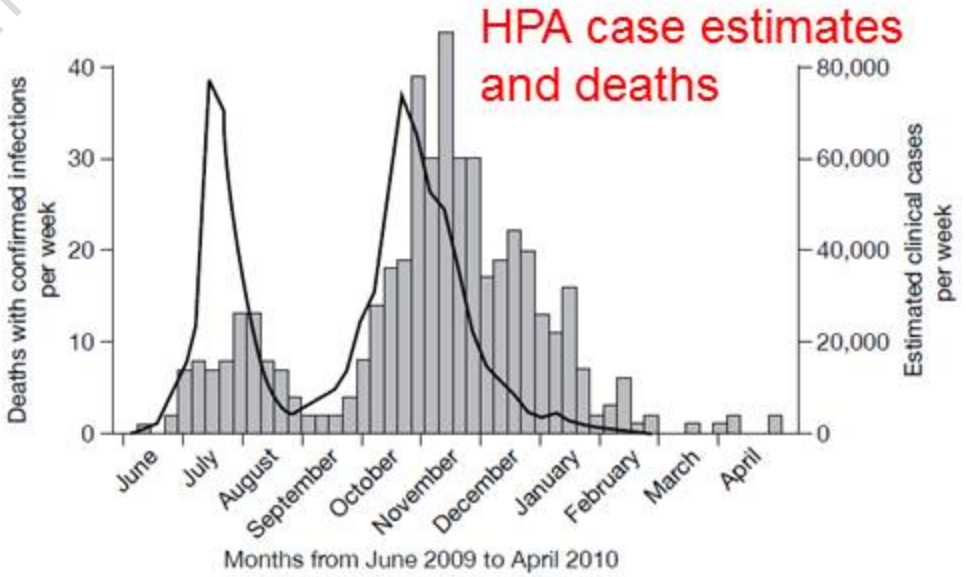
- Switched to using sentinel Influenza-like-illness (ILI) data.
- Exponential growth in June-July (R~1.4).
- Reversed once school holidays started.
- Models fitted first 'wave' well.
- But needed to know true number of infections to make predictions.
- Changes in healthcare seeking behaviour turned out to be key.
- Mortality/ICU data matched serology better.





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Epidemic inference using multiple surveillance data streams

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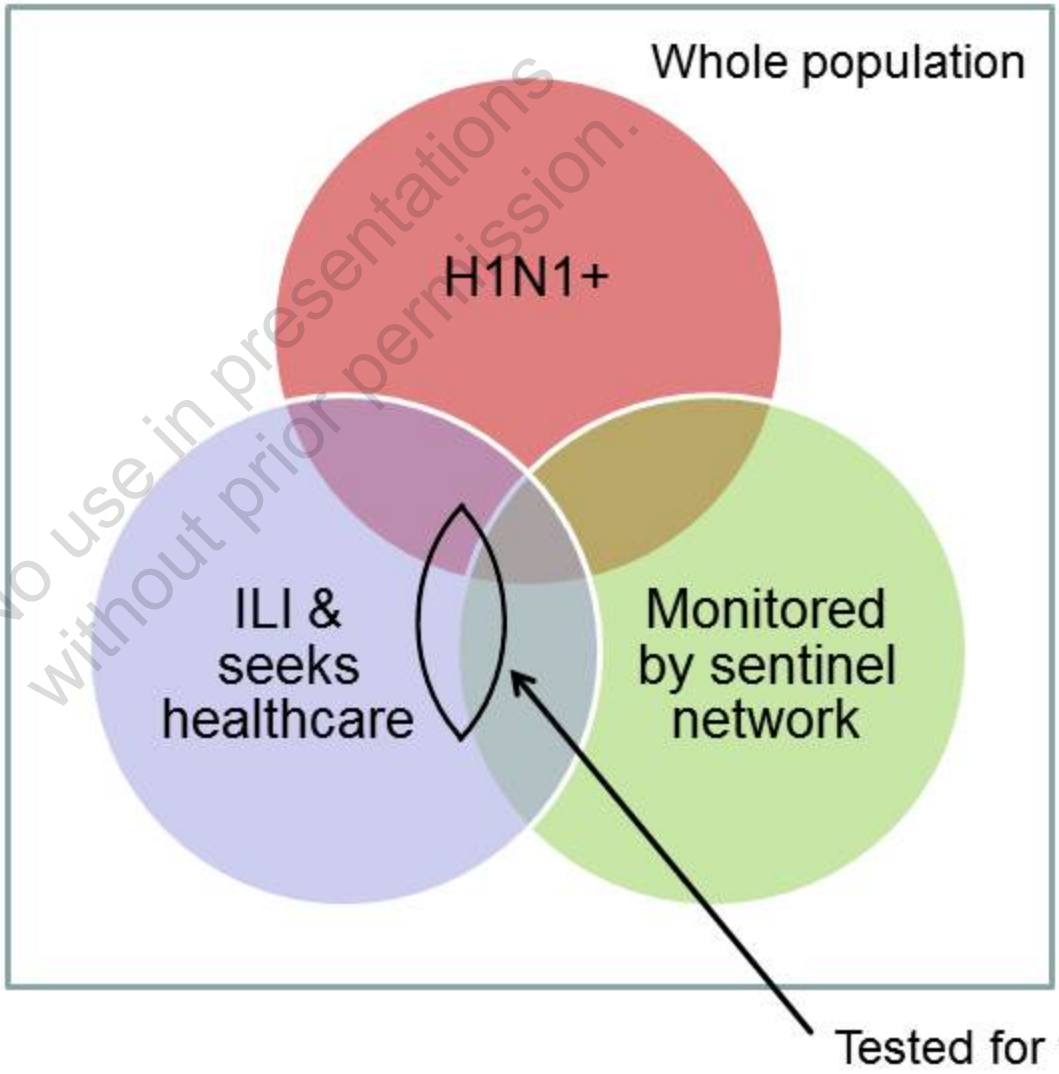
- Influenza-like-illness incidence at GPs (large sample, non-specific).
- Small sample of ILI cases swabbed and tested (sensitivity?).
- Serological data (small sample).
- Ad hoc methods used in 2009.
- Now being more systematic!



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Key issues for data fusion

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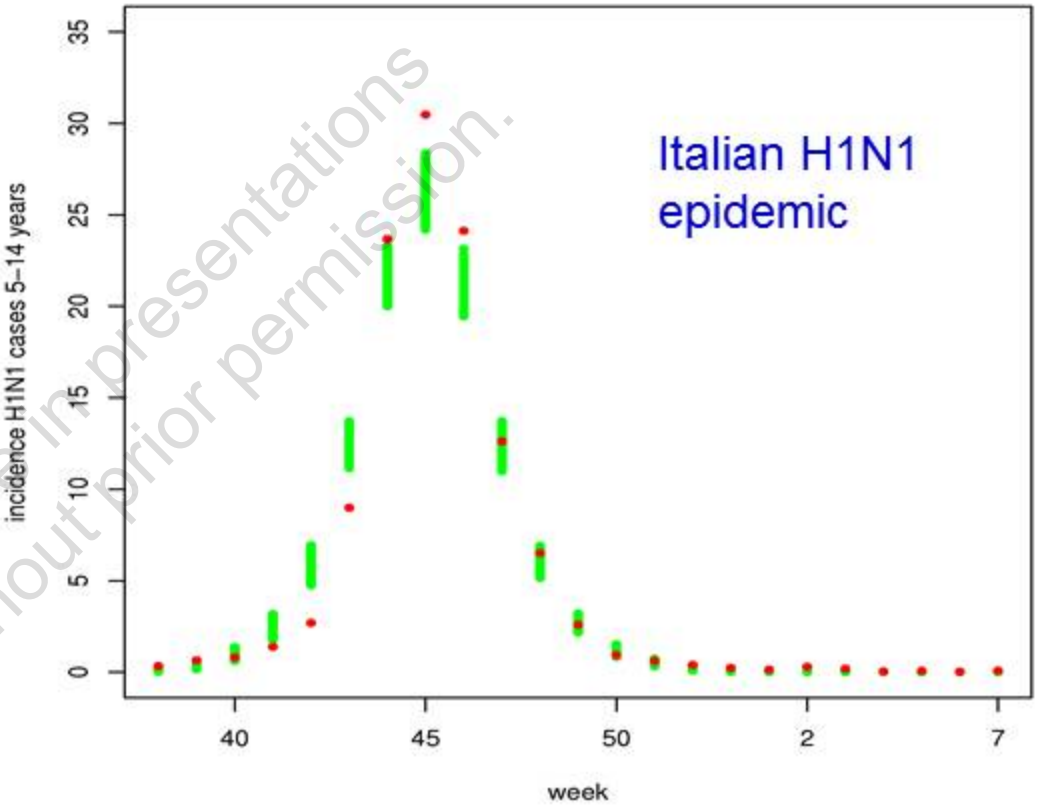
- Over-dispersion of ILI data (unmodelled variance).
- Efficient evaluation of the likelihood.
- Differences in sample sizes:
  - Serological and virological data more definitive.
  - But contribution to likelihood can be swamped by ILI – which is non-specific for flu.



Dorigatti et al, in prep.

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Severity

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Issues

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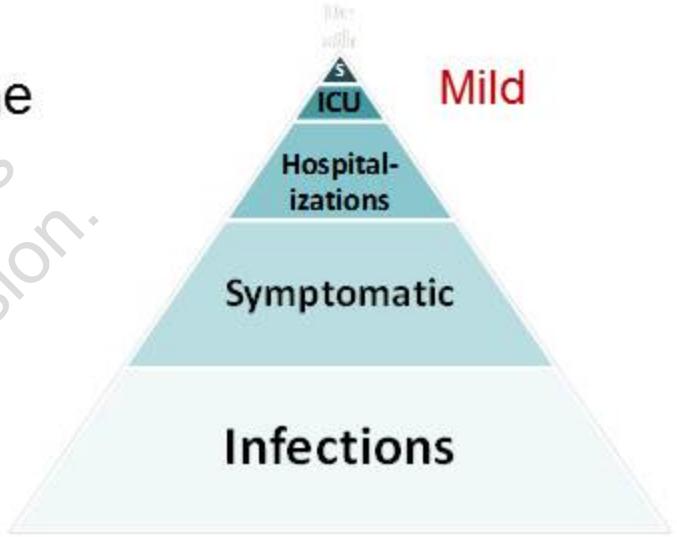
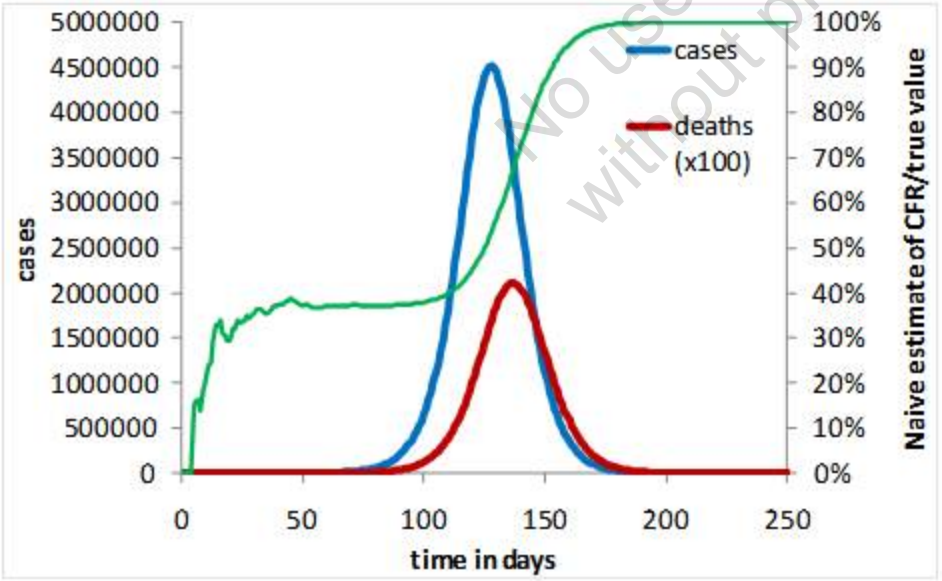
- Key challenge for real time estimation of severity: bottom of pyramid unobserved, in the absence of serology.
- Need innovative methods for estimating denominator in real time.
- Numerator also an issue – imperfect diagnosis, delays to severe outcomes.





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Early estimates

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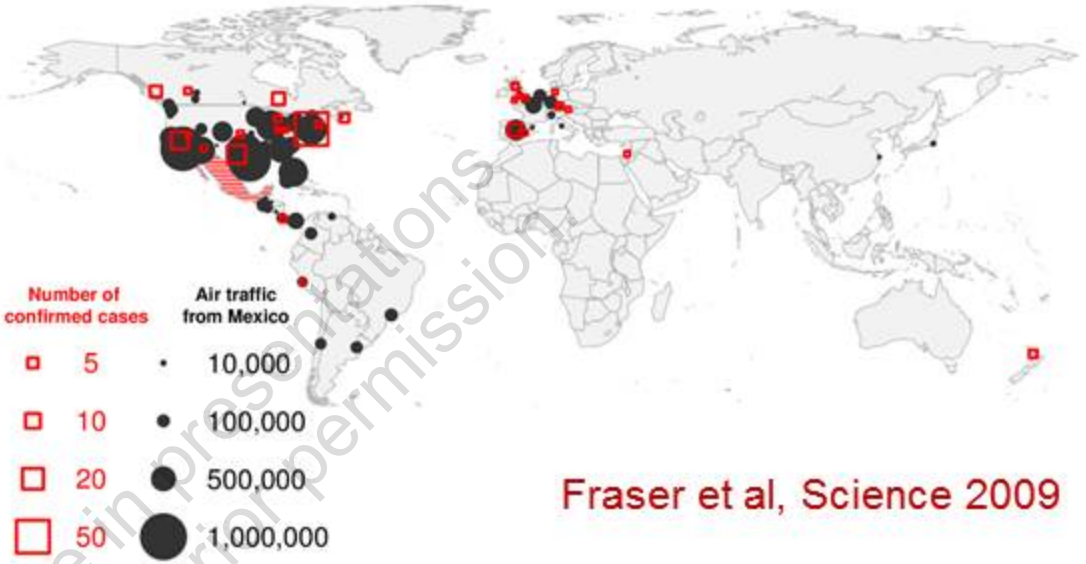
- Early back-calculation estimates from Mexico indicated mild-moderate severity – 0.04%-0.4%.
- Subject to over-estimation of numerator, assumptions of homogenous mixing.
- July CFR estimates for UK/EU of 0.1-0.2% -but using denom. of lab *confirmed* cases.
- *Not* the same as HPA H1N1 case estimates issued from June.
- Result: ***confusion***.



Fraser et al, Science 2009

Summary of data on cases (confirmed/probable), hospitalisations, deaths, crude and adjusted case fatality ratios (%), and crude hospitalisation ratios by country or region

	No of confirmed cases*	No of confirmed deaths*	Baseline for hospital admissions†	No of hospitalised cases	Crude case fatality ratio (95% CI)	Adjusted case fatality ratio‡ (95% CI)	Crude hospitalisation ratio (95% CI)
US[5-7]	37 246	211	4566	407	0.57 (0.49 to 0.65)	0.68 (0.59 to 0.78)	8.9 (8.1 to 9.8)
Mexico[8a]	11 699	121	NA	NA	1.03 (0.86 to 1.23)	1.23 (1.03 to 1.47)	
Canada[9]	9 717	39	9717	894	0.40 (0.29 to 0.55)	0.43 (0.30 to 0.58)	9.2 (8.6 to 9.8)
UK[10a]	9 718	14	9718	335	0.14 (0.08 to 0.24)	0.24 (0.13 to 0.41)	3.4 (3.1 to 3.8)
EU[11]	13 667	16	NA	NA	0.12 (0.07 to 0.19)	0.20 (0.11 to 0.32)	

Garske et al, BMJ July 2009

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The S hemisphere experience

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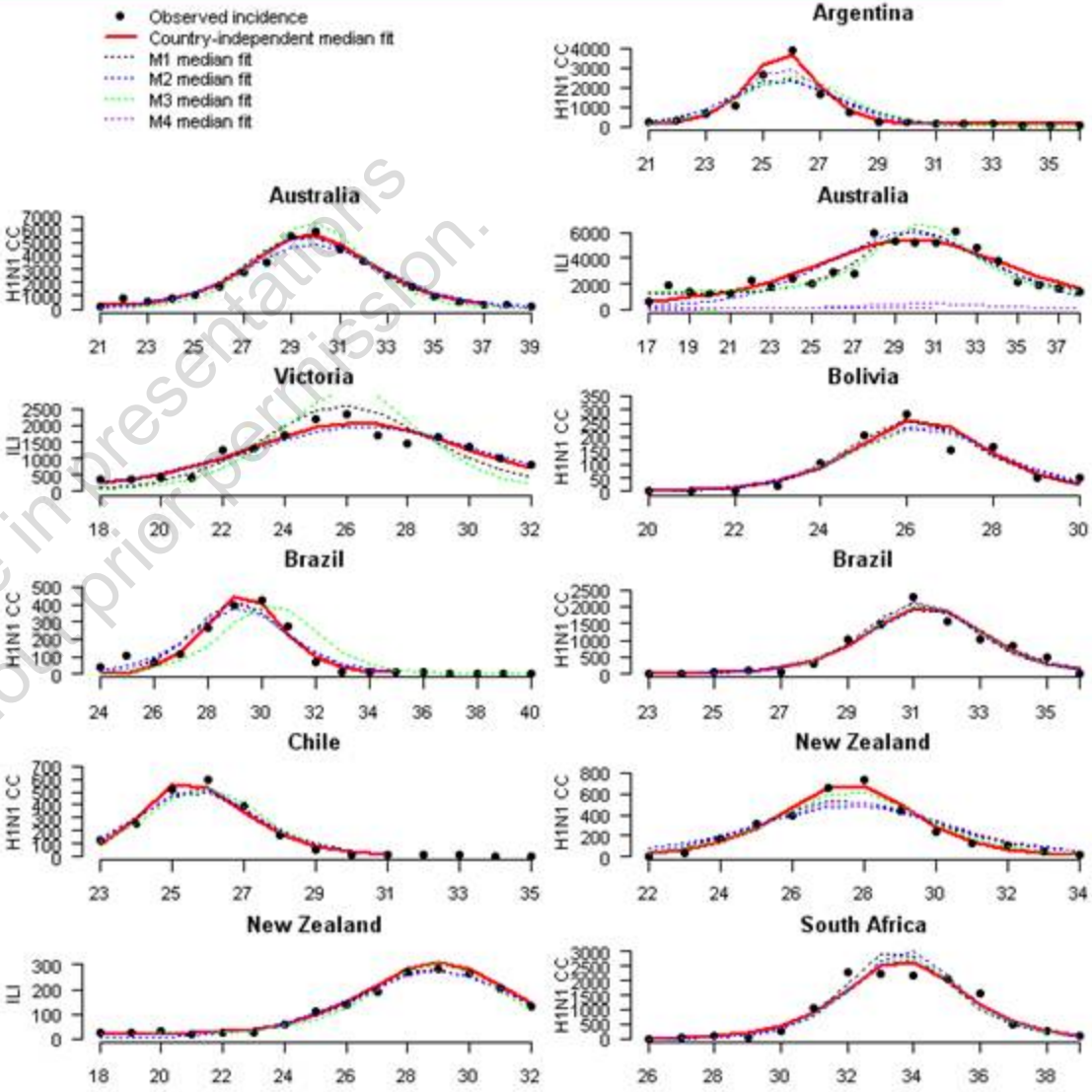
- Started analysis Aug 2009, *after* peak.
- R in range 1.25-1.55
- Infection attack rates in 20-40% range.
- Strong effect of demography.
- Very low case fatality (<0.01%).



Opatowski et al,

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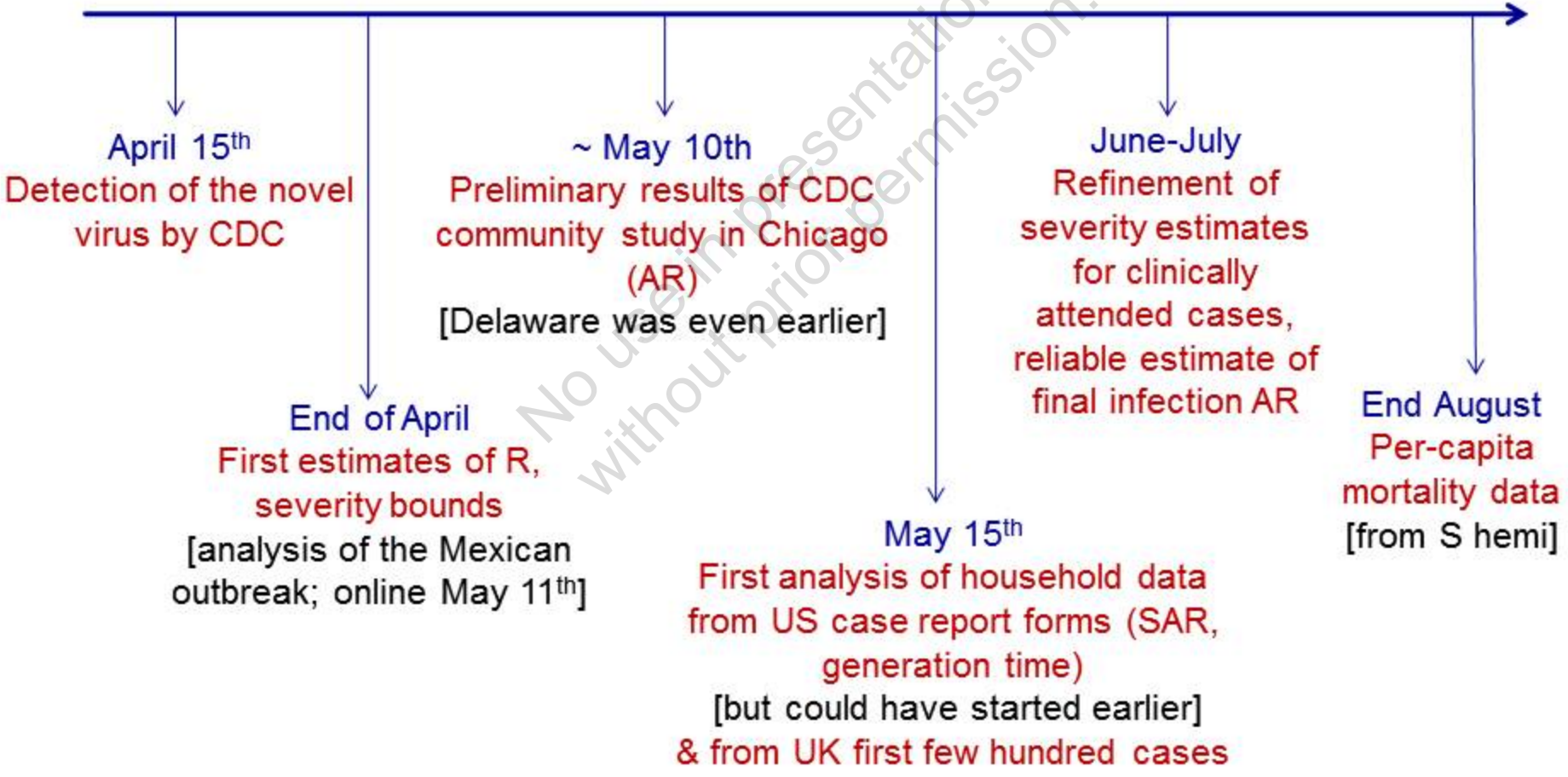
Timeline in 2009



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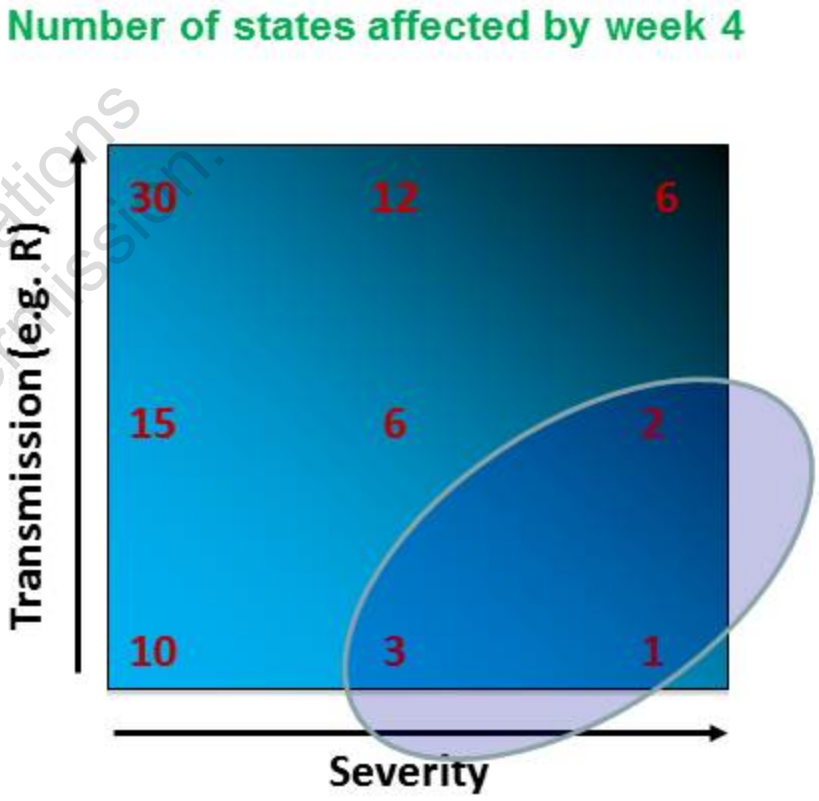
How can we do better?

- Had not thought about low severity pandemics pre-2009.
- Numerator problems understood (SARS), but denominator problem under-studied.
- Cautious in rapidly reducing severity estimates while uncertainty still high.
- Data needs: faster serology, plus community surveys of illness.
- But innovative analytical approaches possible (e.g. from spatial spread).



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3. Understanding ecological determinants

- seasonality

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The problem

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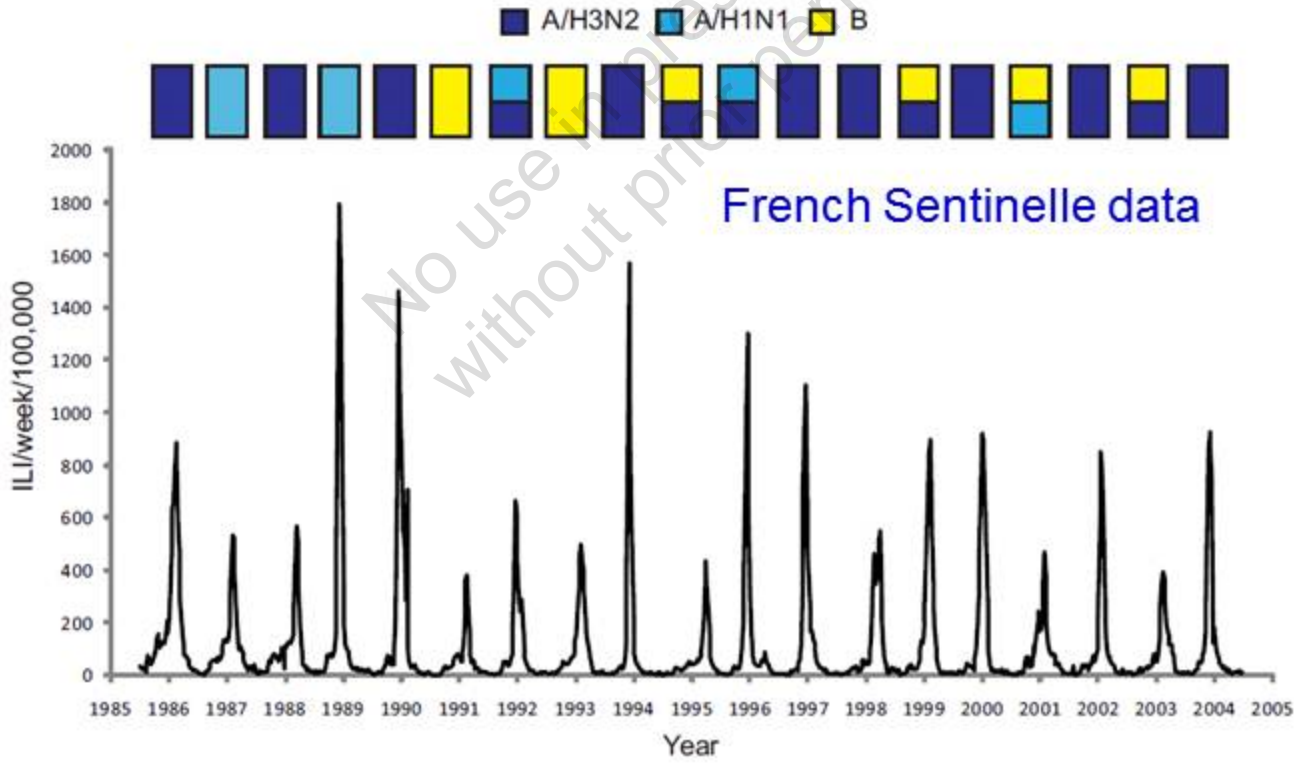
- Flu incidence is highly seasonal in temperate areas.
- What is the magnitude of seasonal forcing?
- Critical to predicting rate of spread over the summer and autumn.
- Not testing mechanistic hypotheses (humidity, vitamin D, mixing).



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Dynamically constraining seasonality

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- Flu evolution unpredictable and ILI data has many frailties…
- … more interested in key features than precise fitting.

- SIRS model with sinusoidal forcing and imported infections.
- Identify which parameter regimes give:
  - Annual epidemics with mean infection rate of 15±5%.
  - 90% of infections occurring within 11±2 weeks each year.
- Use KL distance to compare model & empirical distribution.

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Results

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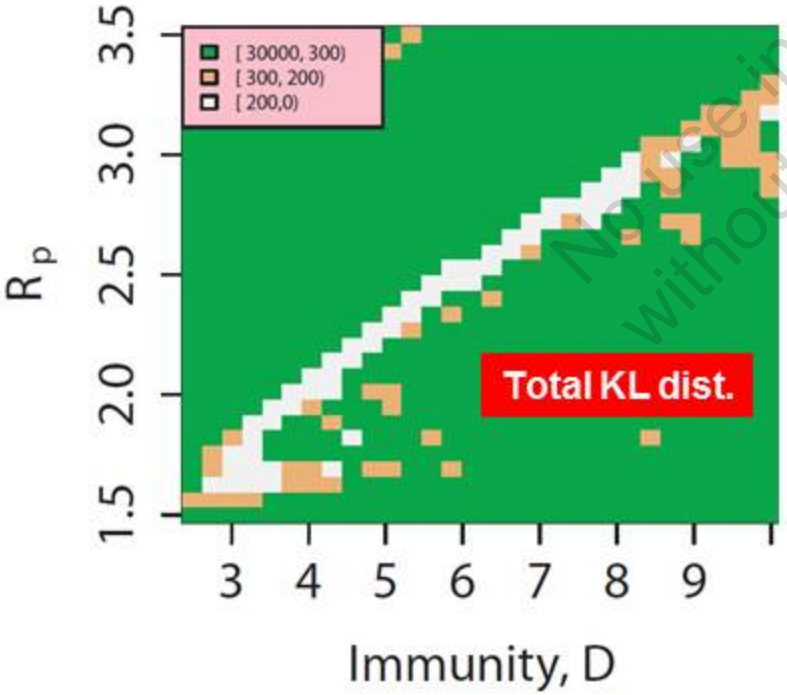
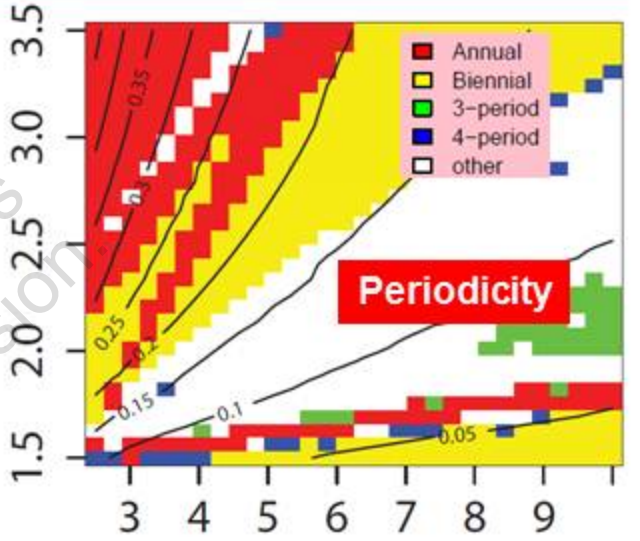
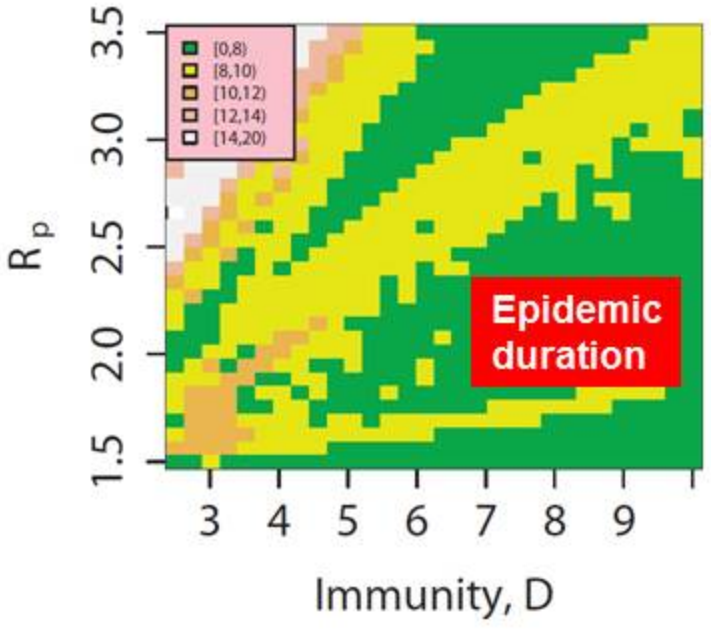
- Fairly narrow window of parameter space reproduces key characteristics.
- $1.5 < R_0 < 2.5$ at seasonal peak, probably <2.
- 2 strains and age structure needed.







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Magnitude of seasonality

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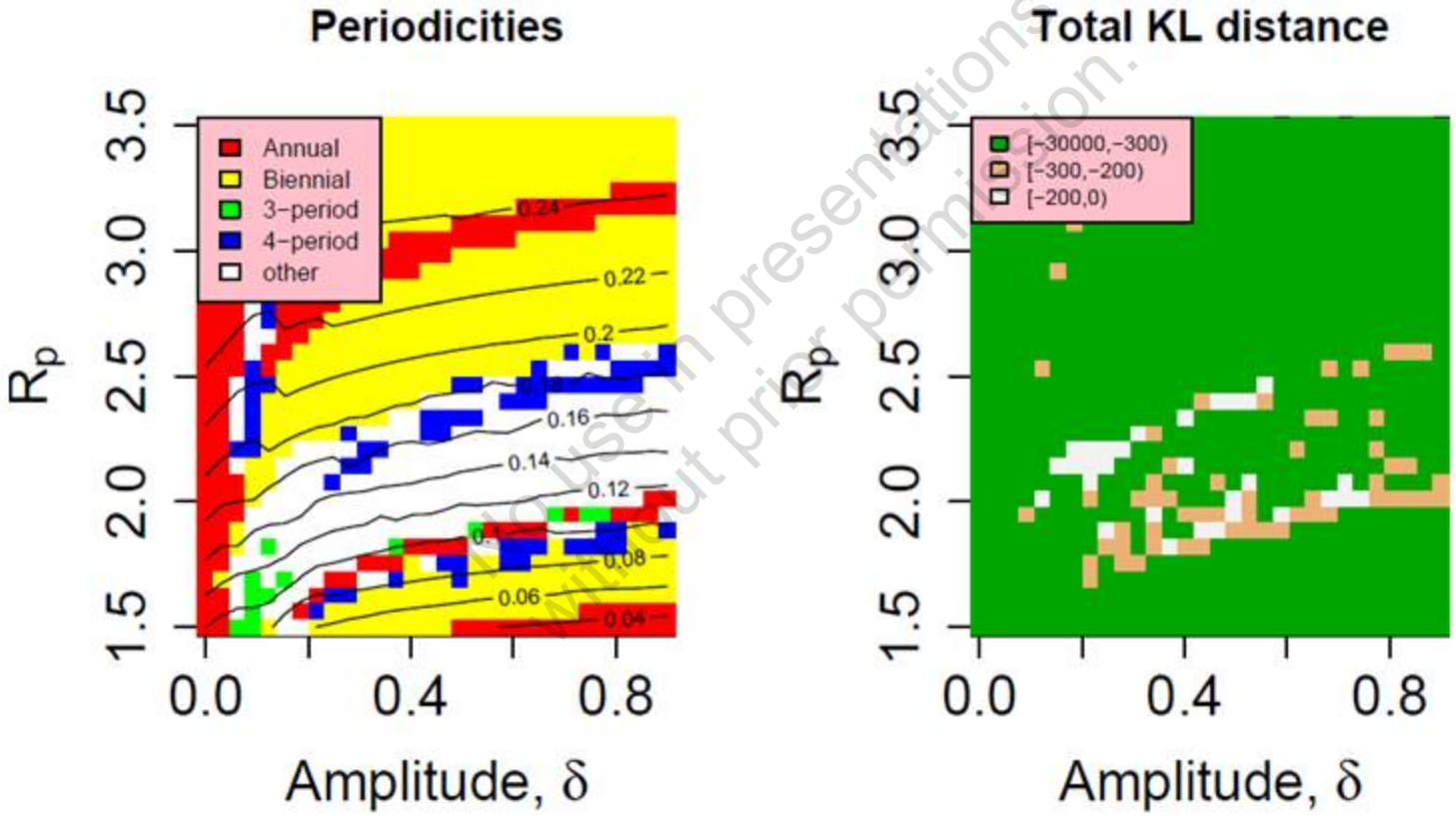
- Not well estimated – 10-75% possible, though perhaps 15-30% more likely.



2009 pandemic should allow more refined estimates…

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A few more general thoughts

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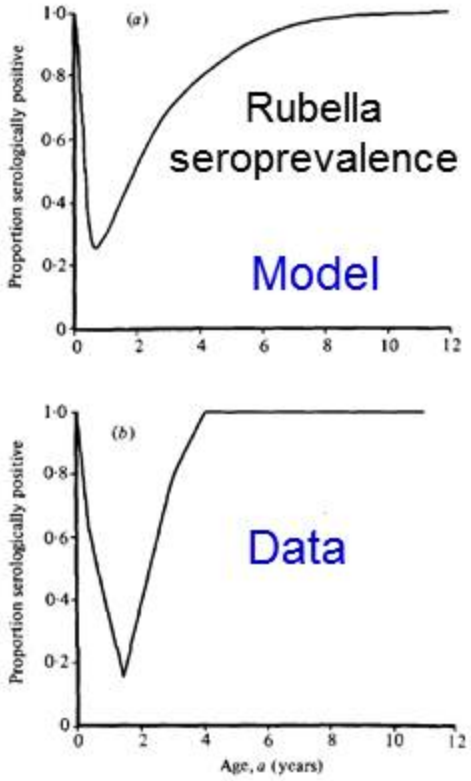
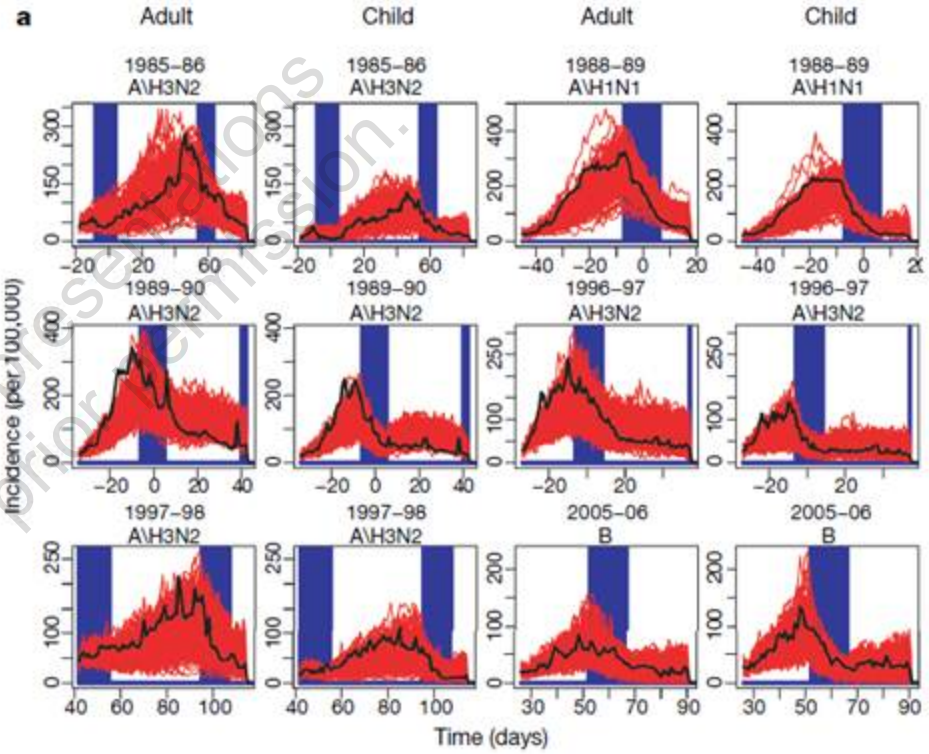
25 years of progress?

Anderson and May, J Hyg Camb, 1983



Qualitative matching/least squares

Cauchemez et al, Nature, 2008



Sequential MCMC with stochastic models

Dynamical insight vs model fitting?

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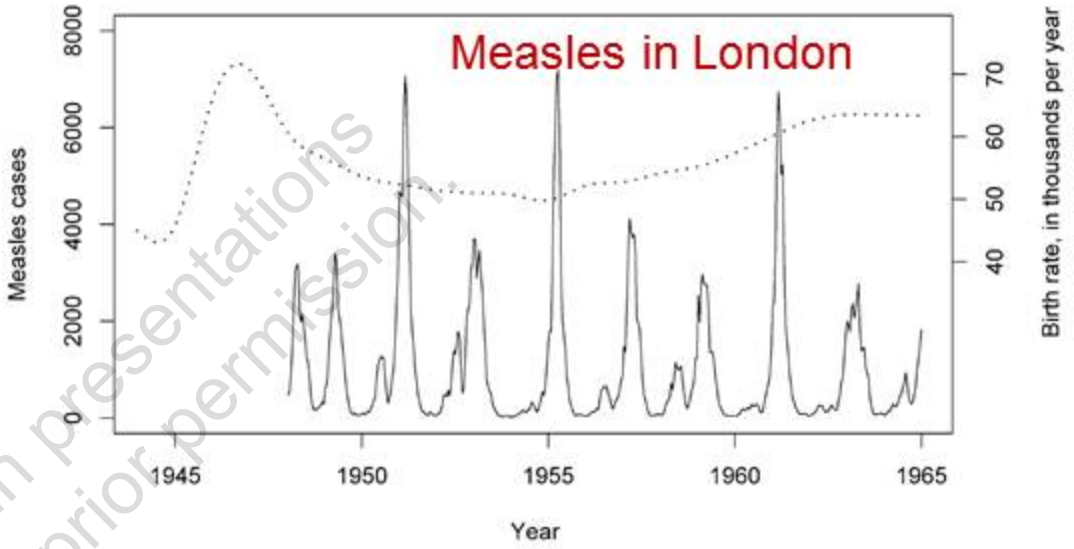
Goodness of fit

- Need to think broadly about goodness of fit – residuals, not just likelihood.
- What *aspects* of a dataset are we trying to fit?
- Overdispersion (environmental stochasticity) – all-pervasive in surveillance data - Poisson or Binomial likelihoods rarely appropriate.
- Small sample sizes and non-linear models (with bifurcations) challenge normality assumptions underpinning most model comparison statistics.
- Need to *understand* dynamical impact of model features.



Breto et al determined **environmental stochasticity** critical for reliable estimation from measles timeseries.

Cauchemez & Ferguson, Interface, 5:885-897, 2008

Breto et al, Ann. Appl. Stat. 3: 319-348, 2009

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Reliable inference

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- Less about methods, than who does it.
- Interdisciplinary teams give real-world challenge.
- Critical, informed evaluation of data frailties essential.
- Allow for over-dispersion (esp. if confidence bounds are tight!).
- Understand the limitations of standard tests.
- Think about goodness of fit.
- Cite original sources for assumed parameter values.
- Think (and consult) before publishing results meant to inform policy.

Country	R_0 estimate (95%CI)
Australia	1.2-1.5
Australia (Victoria)	1.6 (1.5-1.8)
Brazil	1.3-1.4
Chile	1.2-1.4
Japan	2.0-2.6*
Mexico	1.4-1.6
New Zealand	2.0 (1.8-2.1)
New Zealand	1.3 (1.2-1.4)
Peru	1.2-1.6
Thailand	1.8-2.1
United Kingdom	1.3-1.6
United States	1.8 (1.5-2.2)

H1N1 pandemic R_0 estimates collated for WHO by Maria van Kerkhove, Oct 2009.

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Thanks to:

Imperial College: Rebecca Baggaley, Francois Balloux, Simon Cauchemez, Christl Donnelly, Ilaria Dorigatti, Christophe Fraser, Azra Ghani, Nick Grassly, Jamie Griffin, Wes Hinsley, Bill Hanage, Déirdre Hollingsworth, Helen Jenkins, Maria Van Kerkhove, Emily Lyons, Lulla Opatowski, James Truscott, Eric de Silva

and collaborators at:

HPA, WHO, CDC, Mexican Ministry of Health,

Universities of Trento, Oxford and Edinburgh