Modelling the influenza A/H1N1 (2009) pandemic in real time

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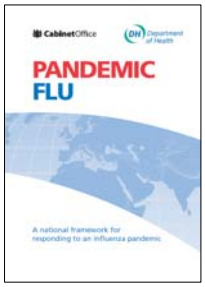
Pandemic influenza – UK planning & response

Modelling is embedded in planning & response: scenarios, data collection

SPI: Scientific Pandemic Influenza advisory committee

SPI-M: modelling sub-group

SAGE: Scientific Advisory Group for Emergencies. Links to ministers via Chief Scientific Advisor



Modelling in real time

What do we know, based on current data? (revised during epidemic)

Modelling synthesises data from multiple sources

What might happen, based on what we know – and don't know?

Quantification of uncertainty is a key strength of modelling

What would be the effects of different interventions?

e.g. school closures, travel restrictions
Vaccination: which should be the priority groups?

Modelling is not alchemy!

It cannot turn base metal (poor quality* or non-existent data) into gold (an accurate, precise prediction). [*NB. quality >> quantity]

Where data are lacking or imprecise, modelling can examine scenarios based on varying a parameter within its plausible range. This can determine the importance (or not) of measuring that parameter more accurately.

It might be possible to rule-out potential interventions even without quantifying them accurately – if the best case scenario is still unimpressive.

A model is **not** a substitute for data – it is a tool to analyse data.

Data sources & challenges

To model something mathematically it has to be **quantified**: models have parameters, which have numerical values – either:

(i) measured: usually hard – and requires a lot of high-quality data;

(ii) varied across plausible ranges – scenario analysis

Major data from syndromic surveillance:

GPs, NPFS (National Pandemic Flu Service – England only)
+ Swabbing schemes – specificity

Challenges (see Van Kerkhove et al. PLoS Med 2010)

What % of those infected seek care? (i.e. what is sensitivity of syndromic surveillance?)

- Temporal changes: trends in syndromic surveillance ≠ trends in infection spreading

Age-specific prior immunity – takes time to develop serological test

Seroincidence (i.e. how many infected?) – takes time to seroconvert

Severity (hospitalisations, deaths): ascertainment, reporting delays, denominator

UK pandemic surveillance

GPs: continued swabbing schemes throughout pandemic

National Pandemic Flu Service (NPFS): antiviral distribution system, provided surveillance (+swabbing)

Virological surveillance [<1% oseltamivir resistance detected]

Hospitalised cases:

New web-based reporting system

Flu-CIN cohort study of hospitalised cases

Mortality:

Real-time monitoring of all-cause mortality

Investigation of suspect pandemic-flu related deaths

www.FluSurvey.org: community, web-based surveillance

Other studies

First Few Hundred (FF100) project

Quality of life impact of illness (EQ5D) – informs vaccination policy cost-effectiveness analysis

Serology (immunity):
(i) pre-pandemic;
(ii) increase during ("seroincidence") – detect infections (> cases of illness)

Public opinion surveys (Ipsos-Mori)

Initial stages: active case-finding

Suspect cases swabbed to test for virus

Contact-tracing to find suspect cases

Case definition: sensitivity / specificity trade-off

Too narrow & cases are missed (lack of sensitivity)

Too broad & huge numbers of without the infection are tested (lack of specificity)

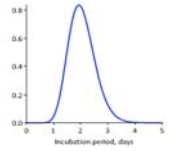
Lots of people with swine flu did not have fever >38ºC, so did not meet the case definition

If people are not ill, or don't seek care when ill, then they don't initiate case-finding & so cases are missed.

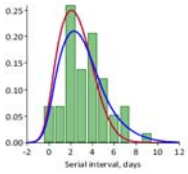
Reporting delays: time from onset of symptoms to entering the data-set:
Delays in seeking care / being found, lab testing, report entered into database
Problem is that delays are variable

First few hundred (FF100) analyses

Incubation period



Serial interval



'Containment' measures (treatment & prophylaxis) reduced *R(t)* by 16% (95% CI 12%-20%) – reducing delays would have increased effectiveness.

Household attack rates:

8/165 (4.5%) if received within 3 days of illness onset in household

24/186 (12.9%) if received later

Health Protection Scotland | Imperial College London

Ghani et al. (submitted)

After initial phase

Syndromic surveillance:

People going to GP with influenza-like illness (fast: data from previous day)

People with defined symptoms who used NPFS (fast: data from previous day)

Problems:

- Lots of other infections cause the symptoms (lack of specificity) – swabbing a sample of patients estimates the % with swine flu (slow, esp. for NPFS due to posting kits out & back)
- Some people infected with swine flu are not ill; others who are ill don't seek care (lack of sensitivity)

Hospitalisations

Lots people not tested for swine flu: do we consider suspect cases (lack of specificity) or only lab-confirmed cases (lack of sensitivity because lots of suspect cases not tested so can't become lab-confirmed)

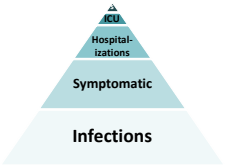
Deaths

Can be hard to distinguish dying OF flu vs dying WITH flu

Slow: long reporting delays

Challenges in assessing severity

- Very uncertain denominator (surveillance misses most mild infections) – initially only put upper bound on lethality (0.04%-0.4%).
- Now thought to be <1 death per 10,000 true infections.
- But ~3% of those seeking care in UK were hospitalised.
- Most hospitalised cases had other health conditions – e.g. asthma.
- Risk groups (~10% of people), had ~6 fold higher relative risk of death.
- But 1/3 of deaths not in risk groups.
- Deaths probably under-ascertained.



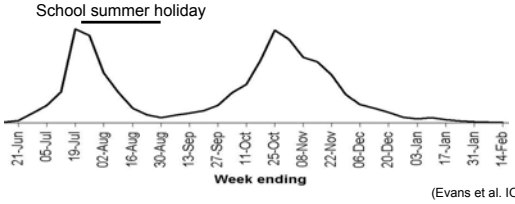
Garske et al. BMJ 2009

Estimation of numbers of cases in England

(England is 84% of the population of the UK)

GP consultations for ILI	×	% positive in GP swabbing scheme
+		
NPFS authorisations	×	% positive in NPFS swabbing scheme
=		
Numbers of people with pandemic flu who sought care		

Numbers of people with pandemic flu who did not seek care unknown



(Evans et al. IORV 2011)

Age-mixing patterns

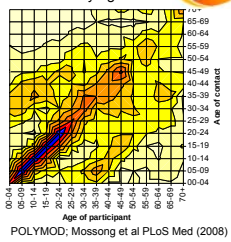
2009 swine flu epidemic dominated by transmission among children:
(i) high contact rates, esp. with other children, and
(ii) little immunity.

School holidays ↓↓ transmission – expected but hard to predict size of effect because little data on:

(i) effect of holidays on contact patterns; and

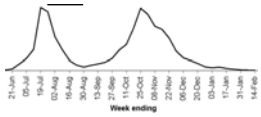
(ii) relationship between contact patterns and transmission – how to define & quantify the most important types of contact?

Contacts by age



POLYMOD; Mossong et al PLoS Med (2008)

Cases in England, 2009



The role of schoolchildren

Schoolchildren were the 'motor' of this epidemic, because:

High contact rate – likely to be exposed;

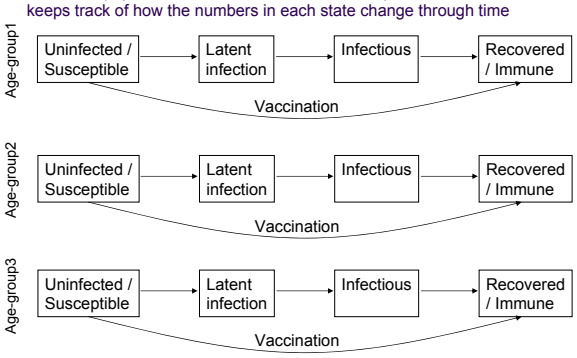
Low immunity – high risk of acquisition if exposed;

High contact rate – like to expose many others;

Contact predominantly with other schoolchildren – most of those exposed also at high risk of acquisition and then spreading it effectively.

Underlying model structure

Divide the population into different states with respect to infection; the model keeps track of how the numbers in each state change through time

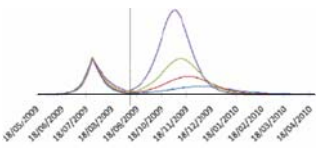


Care-seeking: a problem for syndromic surveillance

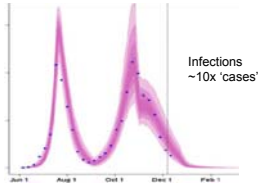
Syndromic surveillance (GPs, NPFS):
Numbers seeking care for flu-like illness
% of those with swine flu (swabbing)

Key unknowns:
% of swine flu infections symptomatic
% of those seeking care

Early Sept 2009: expect 2nd wave, probably similar size to 1st wave, but could be significantly bigger or smaller



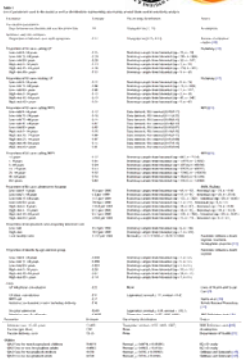
Later: observed growth rate in Sept reduced uncertainty by indicating numbers already infected



(Baguelin et al Vaccine 2010)

Synthesising multiple data sources

Vaccination against pandemic influenza A/H1N1v in England: A real-time economic evaluation



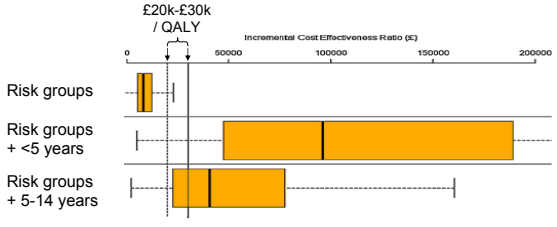
Contact patterns (by age) [Polymod]
Epidemic time-course [GP, NPFS, HPA swabbing]
% symptomatic [experimental infection studies]
% seeking care with GP, NPFS (by age) [FluSurvey]
Hospitalisations, incl. critical care (by age) [FluZone]
Deaths [Australia, NZ]
Costs: GP, NPFS, antivirals, hospitalisation, vaccination
Quality of life impacts: morbidity, mortality [HPA study]
Uncertainties included efficacy, uptake, delivery schedule

(Baguelin et al Vaccine 2010)

Incremental cost-effectiveness ratios

Vaccine available in October, England's epidemic advanced: most cost-effective to first vaccinate clinical risk-groups. (Direct, individual-level protection.)

If epidemic had been less advanced then vaccinating school children may have been cost-effective. (Indirect, population-level protection.)



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Conclusions

- The UK modified existing surveillance systems and rapidly implemented new ones to inform policy-making
- Very little oseltamivir resistance detected (<1%)
- Overall disease burden mild, but some GPs* and hospitals were under pressure [*highlighting that respiratory infection very common, even in summer]
- Further analysis of datasets required; analysis of serology from latter stage of epidemic in England under way
- Care-seeking behaviour needs to be better-understood and monitored to complement syndromic surveillance
- Need better surveillance, esp. of care-seeking behaviour & hospitalisations
- Oral fluid test to replace serology highly desirable – would enable simple population-based sampling

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Summary of infectious-disease modelling

Infectious disease epidemiology must take account of transmission dynamics – hence modelling is essential

Many interacting factors affect transmission in populations

- Modelling synthesises evidence & can quantify uncertainty
- Effective modelling requires integrated multidisciplinary teams

Expectations must be realistic:

- Modelling is not a substitute for empirical research, but can help identify research priorities – which parameters are most important?
- Multiple sources of uncertainty – mostly examine scenarios for planning, not make predictions
- Modelling is an area of intensive research activity: it is not a 'push-button' exercise