Reconstruction of influenza transmission dynamics and optimal vaccination strategies

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Public health issue

• Around 10 to 15,000 people are estimated to die of influenza every year in England and Wales (estimated during the 1999/2010 period)
• Difficult to quantify as many people die from secondary causes (pneumonia, heart attack...)
• Risk dependent on age and medical condition
• Population split in risk (low and high) and age groups

Vaccination

• Vaccinated can prevent infection and reduce the burden of the disease
• Little side effect (GBS)
• Direct and indirect protection, who to vaccinate?

-> Question which was asked to us by the JCVI
Assessing seasonal flu options

• Seasonal flu vaccine
• Current strategy (since 2000) is to target high risk individuals & everyone over the age of 65
• Prior to 2000, strategy was to target those who were high risk only

• **Question: should we extend to low risk groups?**
  - <5 years
  - 50-64 years
  - 5-16 years
  - <5 & 50-64 years
  - <5 & 5-16 years
  - <5 & 5-16 & 50-64 years
  - <64 years

Increasing cost
Modelling and vaccination Scenarios
- Risk based
- Transmission based

Burden figures
- GP
- Hospital
- Death

Cost effectiveness Analysis
£/QALY
Reconstruction of epidemics

- Likelihood based approach
- The likelihood describes the probability of observing the data given the parameter
- For example for a binomial model

\[
P([1,1,1,0,1] \mid p=0.5) = 0.03125
\]
\[
P([1,1,1,0,1] \mid p=0.2) = 0.00128
\]
\[
P([1,1,1,0,1] \mid p=0.9) = 0.06561
\]
Here we are also interested in the uncertainty
Beyond the basic idea

• We are not interested in $P(\text{data}|\text{model})$ but in $P(\text{model}|\text{data})$
• Once we have selected the best models we can run counterfactuals
• We are interested also in integrated as many data sources as relevant/possible (evidence synthesis approach)
Bayes theorem

\[ P(A|B) = \frac{P(B|A) \cdot P(A)}{P(B)} \]

Interpretation: A can be seen as the model, and B the data. $P(A|B)$ is then the posterior, $P(B|A)$ the likelihood and $P(A)$, the prior.
Data (1)

- Polymod data: contact survey, gives an idea of how age classes mix


- Demographic data: different age class and how they change, how many are in RG

  ONS + HES

- Coverage and match of the vaccine

Data (2)

- **GP ILI data**

- **Virological surveillance in GPs**


- **Serology for one season**

Building a picture of what would have happened if....

• Epidemiology of flu has been disturbed by vaccination for many years

• Attempt to reconstruct epidemiology of flu
  – Detailed understanding of what happened (how many cases, including how many prevented by vaccination)
  – Estimate what would have happened if we had followed alternative policies
Survey: entries are number of contacts made by one participant during one day

Problem: As experience during the pandemic, these might not capture perfectly the dynamics of infections (potential bias)

Resampling with replacement allow to capture the variability of the mixing patterns

Baguelin, van Hoek et al.

Not doing the inference on the coefficients of the matrix but on a set of contacts. We can resample a small proportion of the contacts allowing the proposed matrix in the MC to be slightly perturbed.
A few relatively simple assumptions:

1. We assume that people get protected two weeks after vaccination
2. A proportion $\alpha$ is fully protected and a proportion $(1 - \alpha)$
3. $\alpha$ is dependent on age and season (vaccination match)
Transmission model

- Set of Contacts (A)
- Transmission matrix (β)
- POLYMOD survey for the UK
- Demographic data
- Transmissibility of the virus (q)

Vaccination model

- Immunisation rate (v)
- Vaccination uptake in UK
- Vaccination match
Number of Infections (Z)

Transmission matrix (β)

Immunisation rate (ν)

Susceptibility profile (σ)

Initial number of infections (I)

Epidemiological model
Equation of epidemic model

\[ \begin{align*}
\frac{dS^N_{ik}}{dt} &= -\lambda_i S^N_{ik} - \mu_i S^N_{ik} \\
\frac{dE^1N_{ik}}{dt} &= \lambda_i S^N_{ik} - \gamma_1 E^1N_{ik} - \mu_i E^1N_{ik} \\
\frac{dE^2N_{ik}}{dt} &= \gamma_1 (E^1N_{ik} - E^2N_{ik}) - \mu_i E^2N_{ik} \\
\frac{dI^1N_{ik}}{dt} &= \gamma_1 E^2N_{ik} - \gamma_2 I^1N_{ik} - \mu_i I^1N_{ik} \\
\frac{dI^2N_{ik}}{dt} &= \gamma_2 (I^1N_{ik} - I^2N_{ik}) - \mu_i I^2N_{ik} \\
\frac{dR^N_{ik}}{dt} &= \gamma_2 I^2N_{ik} - \mu_i R^N_{ik}
\end{align*} \]

\[ \frac{dS^V_{ik}}{dt} = -\lambda_i S^V_{ik} + (1 - \alpha_i) \mu_i S^N_{ik} \]

\[ \frac{dE^1V_{ik}}{dt} = \lambda_i S^V_{ik} - \gamma_1 E^1V_{ik} + \mu_i E^1N_{ik} \]

\[ \frac{dE^2V_{ik}}{dt} = \gamma_1 (E^1V_{ik} - E^2V_{ik}) + \mu_i E^2N_{ik} \]

\[ \frac{dI^1V_{ik}}{dt} = \gamma_1 E^2V_{ik} - \gamma_2 I^1V_{ik} + \mu_i I^1N_{ik} \]

\[ \frac{dI^2V_{ik}}{dt} = \gamma_2 (I^1V_{ik} - I^2V_{ik}) + \mu_i I^2N_{ik} \]

\[ \frac{dR^V_{ik}}{dt} = \gamma_2 I^2V_{ik} + \mu_i (R^N_{ik} + \alpha_i S^N_{ik}) \]

Force of infection

\[ \lambda_i = q \sigma_i \sum_{j=1}^{7} \sum_{k=1}^{2} \sum_{X=N,V} c_{ij} (I^{1X}_{jk} + I^{2X}_{jk}) \]
\[
\lambda_i = q \sigma_i \sum_{j=1}^{7} \sum_{k=1}^{2} \sum_{X=\{N, V\}} c_{ij} (I^{1X}_{jk} + I^{2X}_{jk})
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Transmission model
- Set of Contacts (A)
- Transmission matrix (β)

Vaccination model
- Immunisation rate (ν)

Epidemiological model
- Number of Infections (Z)
- Susceptibility profile (σ)
- Initial number of infections (l)

Observation?
Severity pyramid

- ILI
- Different possible pathogens

Knowledge fundamental for modelling

H3N2
Incidence of the seasonal epidemic

\[ Z_{ik}(n) = \int_{\gamma_1 \in \mathbb{R}} (\gamma_1 E_{jk}^2 + E_{jk}^2 N) dt \]

= the number of new (infection) cases appearing in one week from vaccinated and unvaccinated individuals
Surveillance (simplified)

Incidence of the seasonal epidemic is:

\[
Z_{ik}(n) = \int_\frac{7n}{7(n-1)} \gamma_1(E_{jk}^{2V} + E_{jk}^{2N})dt
\]

= the number of new (infection) cases appearing in one week from vaccinated and unvaccinated individuals

We rescale it to the monitored pop

\[
\theta_{ij} = \left| \frac{N_{mon}^{ij}}{N_{tot}^{ij}} \sum_{k=1}^{2} Z_{ik}(j) \right|
\]

GP + ILI

\[
m_{ij}^+ \sim \mathcal{B}(\theta_{ij}, \epsilon_i) + \mathcal{P}(\psi \epsilon_i N_{ij}^{mon})
\]

Virological surveillance and number of ascertainable cases in monitored population

Among the infected cases we only have access to the ones who are recorded to ILI and turn positive when tested (ascertainable cases $m^+$ among $m$ ILI)

Virological testing: $n_{ij}^+ \sim \mathcal{H}(n_{ij}, m_{ij}^+, m_{ij})$
Transmission matrix ($\beta$)

Set of Contacts (A)

POLYMOD survey for the UK

Demographic data

Transmissibility of the virus ($q$)

Transmission model

Immunisation rate ($\nu$)

Vaccination uptake in UK

Vaccination match

Vaccination model

Number of Infections ($Z$)

Susceptibility profile ($\sigma$)

Initial number of infections ($l$)

Epidemiological model
Number of influenza cases in GP ($m^*$) 

Number of infections ($Z$) 

Number of ILI cases ($m^*$) 

Number of virologically tested ($n$) 

Number of virologically positive ($n^+$) 

Outside infection ($\psi$) 

Ascertainment probability ($\epsilon$) 

\[
m_{ij}^+ \sim \mathcal{B}(z_{ij}^\theta, \epsilon_i) + \mathcal{P}(\psi \epsilon_i N_{ij}^{mon})
\]

\[
n_{ij}^+ \sim \mathcal{H}(n_{ij}, m_{ij}^+, m_{ij})
\]
Number of influenza cases in GP ($m^*$)

Number of ILI cases ($m$)

Number of virologically tested ($n$)

Number of virologically positive ($n^*$)

Ascertainment probability ($\epsilon$)

Outside infection ($\psi$)

Number of infections ($Z$)

Immunisation rate ($\nu$)

Susceptibility profile ($\sigma$)

Initial number of infections ($l$)

Transmissibility of the virus ($q$)

Transmission model

Vaccination model

Epidemiological model

Observation model

Set of Contacts ($A$)

Transmission matrix ($\beta$)

Immunisation rate ($\nu$)

Susceptibility profile ($\sigma$)

Initial number of infections ($l$)

Vaccination uptake in UK

Vaccination match

Demographic data

POLYMOD survey for the UK

Transmission model

Vaccination model

Epidemiological model

Observation model
Priors

• For one season (2003/04 H3N2), we have serology, so we can derived priors for $\varepsilon$.
• We can also derive priors for $\sigma$ for this particular season
• Which can be turn into (slightly inflated) prior for $q$ (transmissibility) for the other strains/seasons
Implementation

- Adaptive McMC (Roberts & Rosenthal)


- 10M iterations
- 42 season-strain
- 1000 samples for each season-strain
- 35 vaccine scenarii tested (many more for DH)
- converted in deaths (full CEA for DH)
Results
Algorithm recover from simulated epidemics both:
- Epidemiological parameters
- The structures of contacts.
Results from the inference
Results:

extending vaccination

In the graph, the results show the impact of extending vaccination on incidence and mortality over time. The x-axis represents the number of doses in million per year, while the y-axis represents the average yearly count (1995 - 2008) for incidence and mortality.

- **Incidence (in million)**: The graph shows a decrease in incidence as the number of doses increases, with different lines representing various targeted populations and coverage levels.

- **Mortality (in thousand)**: Similar trends are observed for mortality, with a decrease as the number of doses increases.

**Reference**
- Black square: 65+ at 29.3% (as pre-2000)
- Star: historical
- Solid circle: 65+ at 70% (as post-2000)
- Triangle: all HR at 75%

**Targeted populations**
- S1: 0.5-4 y (LR)
- S2: 5-16 y (LR)
- S3: 50-64 y (LR)
- S4: S1+S2
- S5: S1+S3
- S6: S1+S2+S3

**Coverage**
- Black dot: 30%
- Gray circle: 50%
- Black square: 70%
Costs & QALYs

- Costs of vaccination from DH
- NHS reference costs for treatment
- Non-fatal QALYs lost from literature
- Fatal cases assumed to lose average risk and age-specific life-expectancy adjusted for average age-specific QoL (from RCGP)

Incremental cost-effectiveness analysis

1. Rank scenarios by increasing cost
   - 2-4 years
   - 50-64 years
   - 5-16 years
   - 2-4 & 50-64 years
   - 2-4 & 5-16 years
   - 2-4 & 5-16 & 50-64 years
   - 2-64 years

2. Remove the ‘dominated’ ones (more money, less QALYs saved)

3. Compute incremental CEAC (cost-effectiveness acceptability curve)

4. Stop until not CE anymore
20,000£/QALY threshold

Death associated QALD incremental on current

ILI associated QALD incremental on current
Cost-effectiveness of vaccinating children

- Cost-effective to vaccinate school children for their own benefit (i.e. ignoring benefits to other groups)
  - ICER=8155 £/QALY
  - Mean Net Benefit £107m  [90%CI: -£34m £390m]
  - Burden exclusively in term of saved influenza episodes and hospitalisations
Cost effectiveness of (low risk) paediatric and high risk components

• With baseline of no vaccination:
  – 2-16 year old low risk children ICER of 1679 £/QALY (NB: 610 M£ [145; 1975])
  – risk groups ICER is 6231 £/QALY (NB: 242 M£ [28; 780]).

• Extensions of one to the other are also highly cost effective
Cost-effectiveness of the elderly component

- With paediatric programme, incremental ICER of 16,482 £/QALY, NB: 5 M£ [-14; 39]
- Provide much smaller benefits and uncertain cost effectiveness (32% of simulations are not under a threshold of 25,000 £/QALY).
Conclusions

• Of all the components of the UK immunisation programme against influenza, the paediatric component is the most cost effective, followed by risk groups

• The elderly component appears to be just cost effective in most scenarios under current definition, nevertheless it is not cost effective in many scenarios
What are the primary results?

Pebody et al. (2015) Eurosurveillance
Further work

- We are developing a R package to allow dissemination of the model
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