



Public Health
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SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



Assessing changes in vaccination programmes of seasonal influenza: an evidence synthesis and modelling study

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Public health background

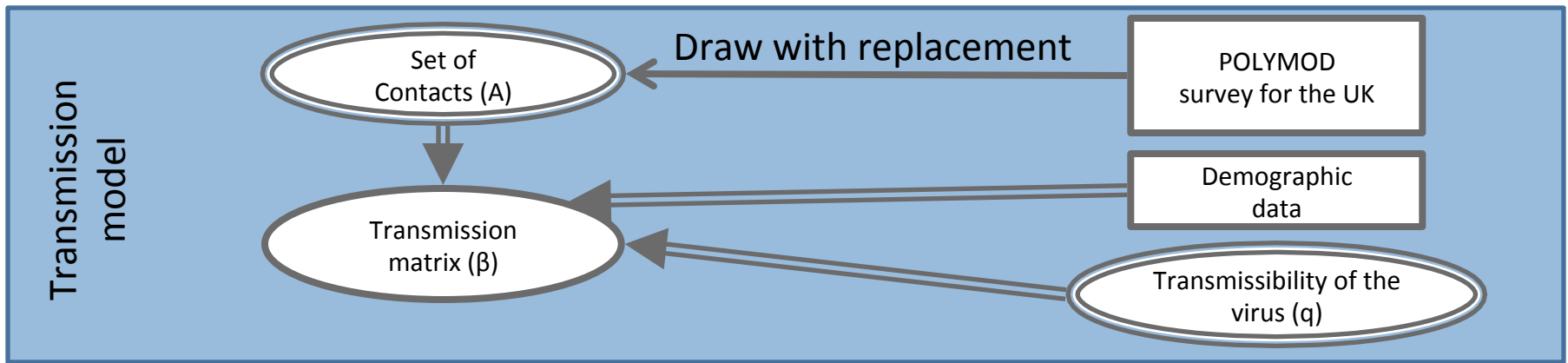
- Around 10 to 15,000 people are estimated to die of influenza every year in England and Wales (estimated during the 1999/2010 period)
- Difficult to quantify as many people die from secondary causes (pneumonia, heart attack...)
- Risk dependent on age and medical condition
- Population split in risk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

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

Data

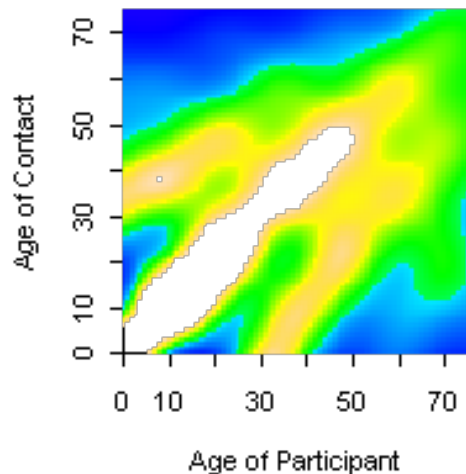
- Polymod data: contact survey, gives an idea of how age classes mix
- Demographic data: different age class and how they change, how many are in RG
- Coverage and match of the vaccine
- GP ILI data
- Virological surveillance in GPs
- Serology for one season



POLYMOD

Mossong et al.

GB



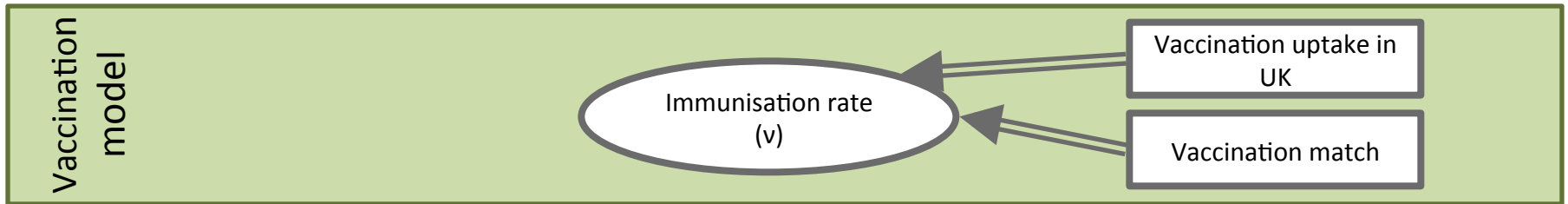
Survey: entries are number of contacts made by one participant during one day

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

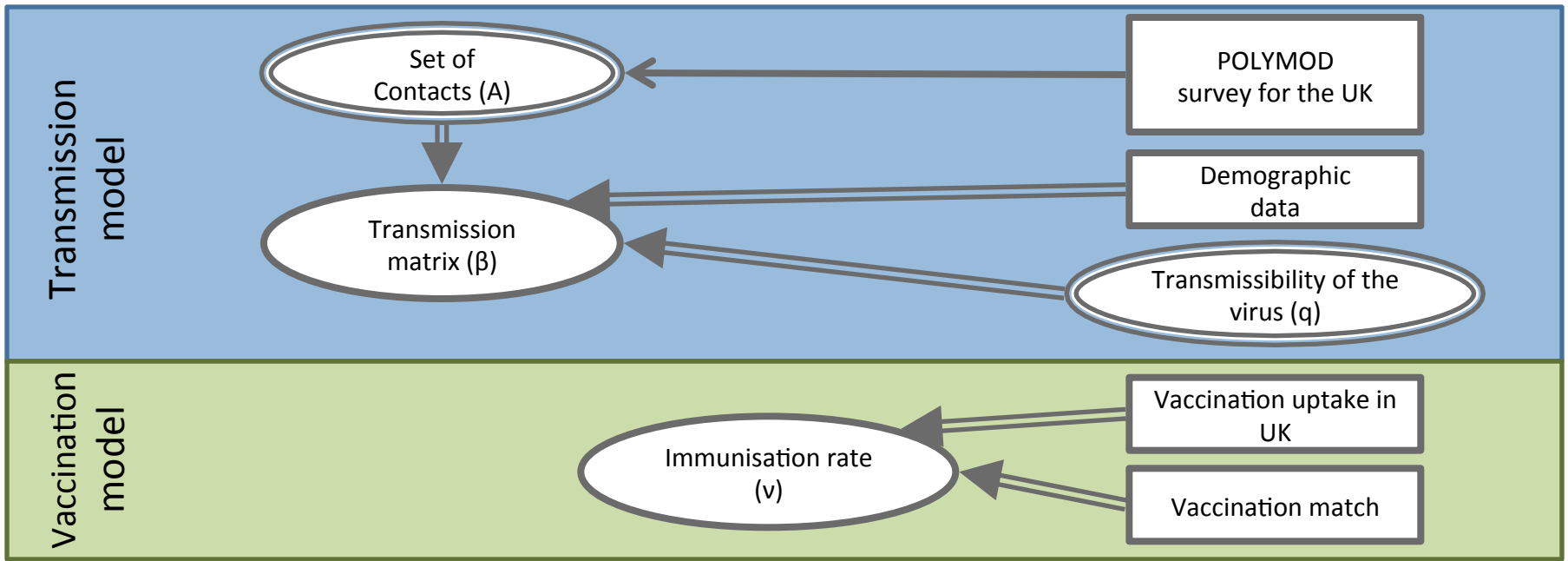
Baguelin, van Hoek et al.

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.

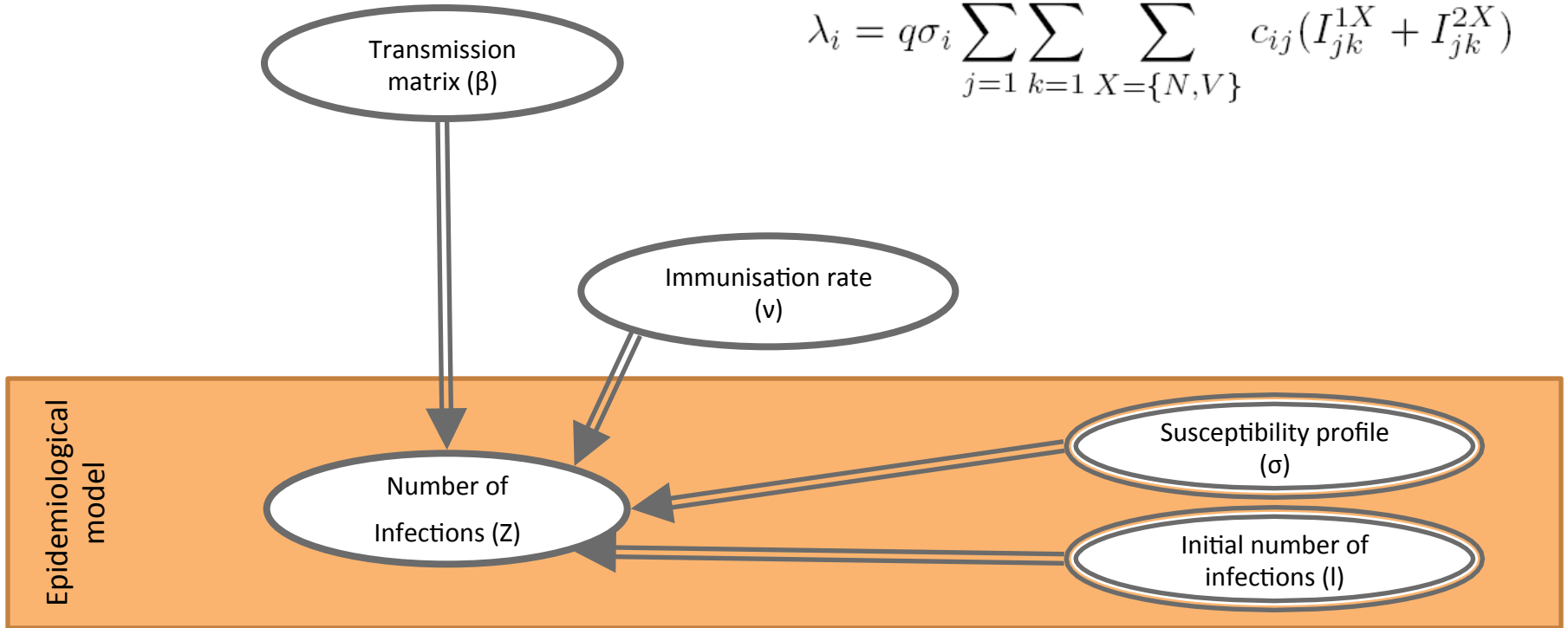


A few relatively simple assumption:

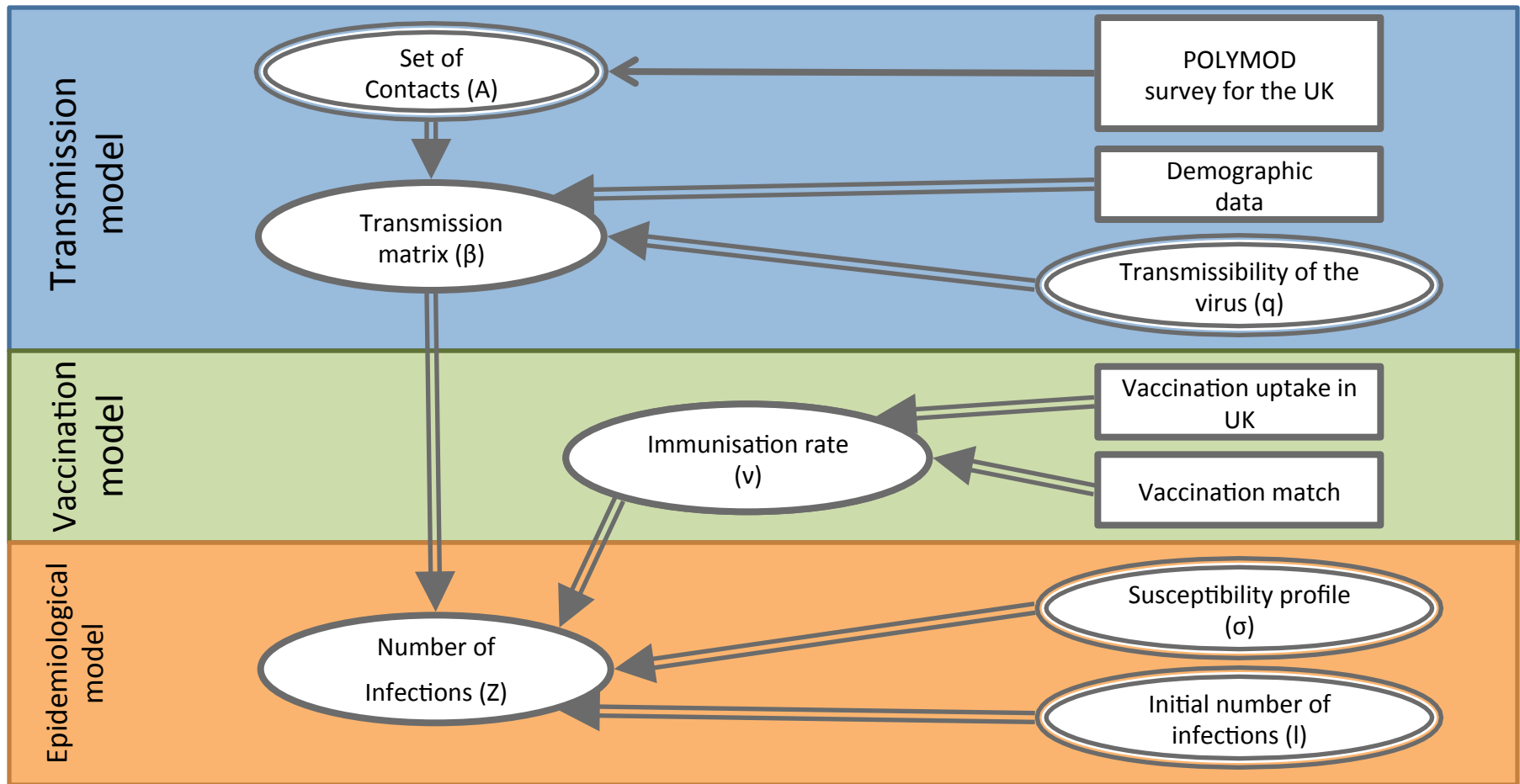
1. We assume that people get protected two weeks after vaccination
2. A proportion α is fully protected and a proportion $(1 - \alpha)$
3. α is dependent on age and season (vaccination match)



$$\lambda_i = q\sigma_i \sum_{j=1}^7 \sum_{k=1}^2 \sum_{X=\{N,V\}} c_{ij} (I_{jk}^{1X} + I_{jk}^{2X})$$



$$\left\{ \begin{array}{l} \frac{dS_{ik}^N}{dt} = -\lambda_i S_{ik}^N - \mu_{ik} S_{ik}^N \\ \frac{dE_{ik}^{1N}}{dt} = \lambda_i S_{ik}^N - \gamma_1 E_{ik}^{1N} - \mu_{ik} E_{ik}^{1N} \\ \frac{dE_{ik}^{2N}}{dt} = \gamma_1 (E_{ik}^{1N} - E_{ik}^{2N}) - \mu_{ik} E_{ik}^{2N} \\ \frac{dI_{ik}^{1N}}{dt} = \gamma_1 E_{ik}^{2N} - \gamma_2 I_{ik}^{1N} - \mu_{ik} I_{ik}^{1N} \\ \frac{dI_{ik}^{2N}}{dt} = \gamma_2 (I_{ik}^{1N} - I_{ik}^{2N}) - \mu_{ik} I_{ik}^{2N} \\ \frac{dR_{ik}^N}{dt} = \gamma_2 I_{ik}^{2N} - \mu_{ik} R_{ik}^N \end{array} \right. ; \left\{ \begin{array}{l} \frac{dS_{ik}^V}{dt} = -\lambda_i S_{ik}^V + (1 - \alpha_i) \mu_{ik} S_{ik}^N \\ \frac{dE_{ik}^{1V}}{dt} = \lambda_i S_{ik}^V - \gamma_1 E_{ik}^{1V} + \mu_{ik} E_{ik}^{1N} \\ \frac{dE_{ik}^{2V}}{dt} = \gamma_1 (E_{ik}^{1V} - E_{ik}^{2V}) + \mu_{ik} E_{ik}^{2N} \\ \frac{dI_{ik}^{1V}}{dt} = \gamma_1 E_{ik}^{2V} - \gamma_2 I_{ik}^{1V} + \mu_{ik} I_{ik}^{1N} \\ \frac{dI_{ik}^{2V}}{dt} = \gamma_2 (I_{ik}^{1V} - I_{ik}^{2V}) + \mu_{ik} I_{ik}^{2N} \\ \frac{dR_{ik}^V}{dt} = \gamma_2 I_{ik}^{2V} + \mu_{ik} (R_{ik}^N + \alpha_i S_{ik}^N) \end{array} \right.$$

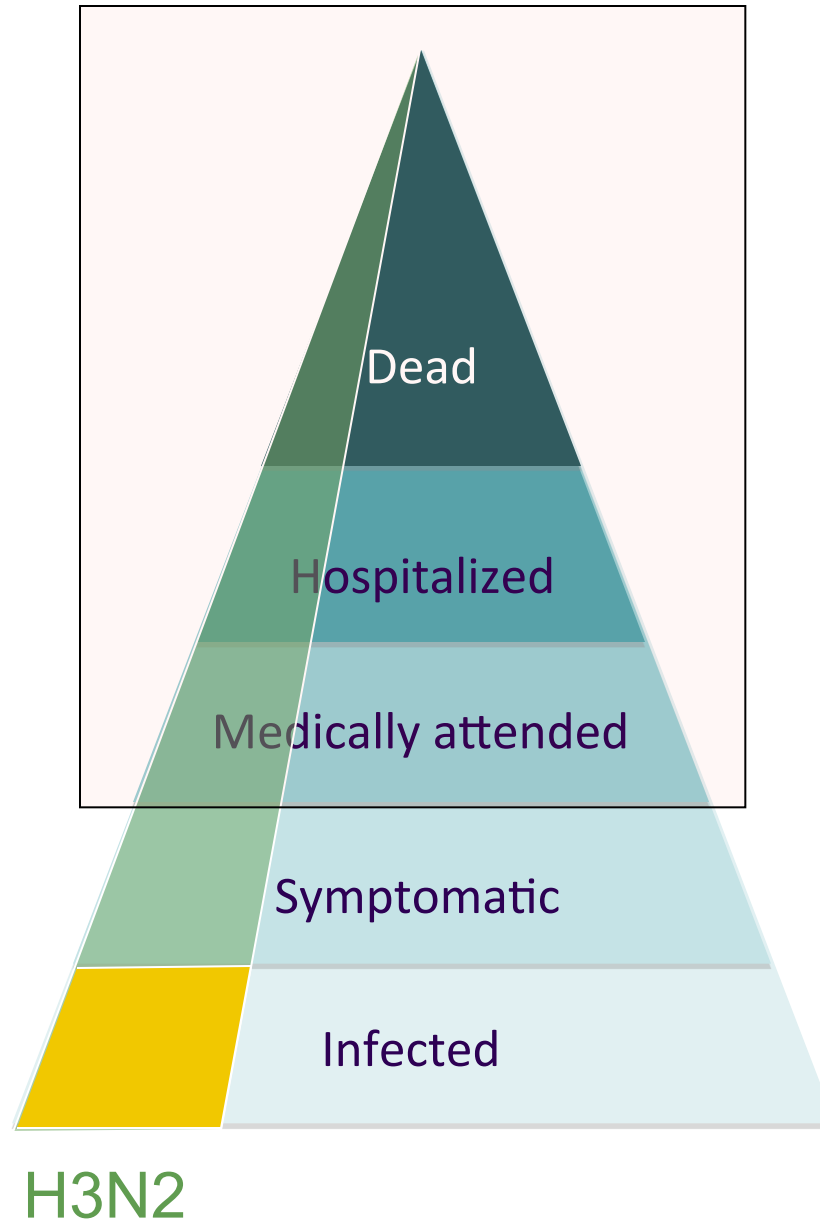


Observation?

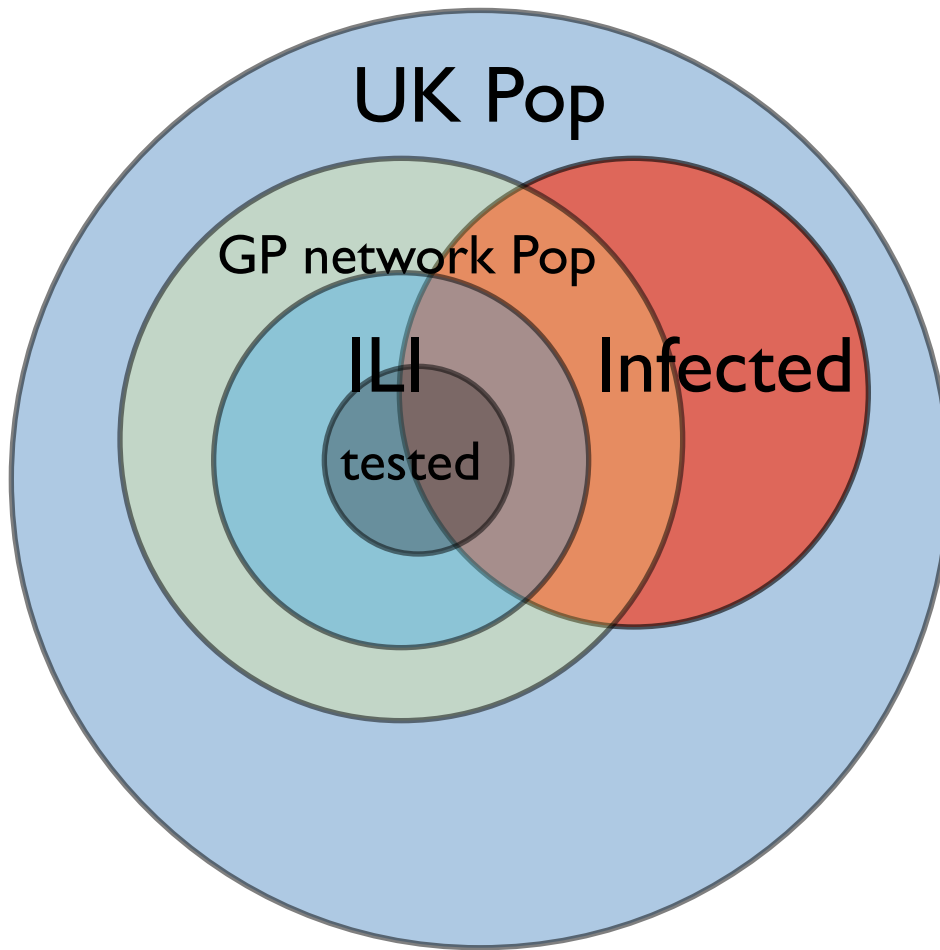
Severity pyramid ► ILI ► different possible pathogens

Only the top is
observed by
surveillance

Knowledge
fundamental
for modelling



Surveillance (simplified)

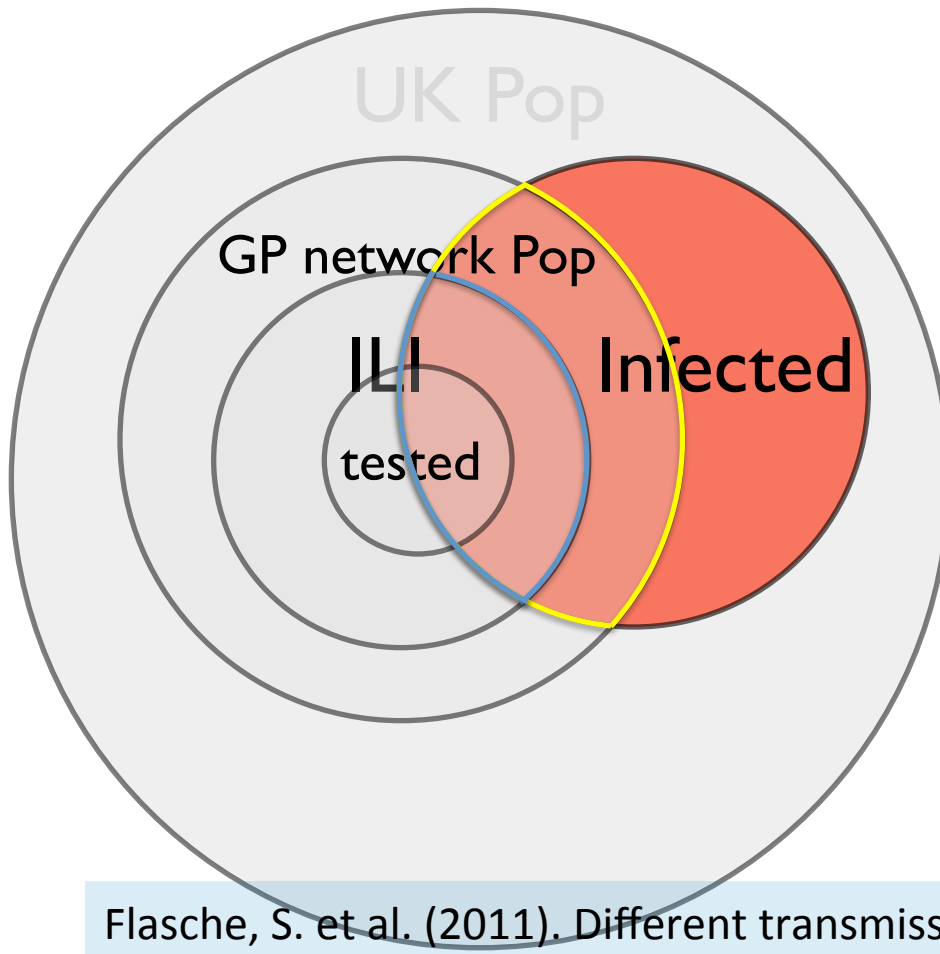


Incidence of the seasonal epidemic

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

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

Surveillance (simplified)



Incidence of the seasonal epidemic is:

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

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We rescale it to the monitored pop

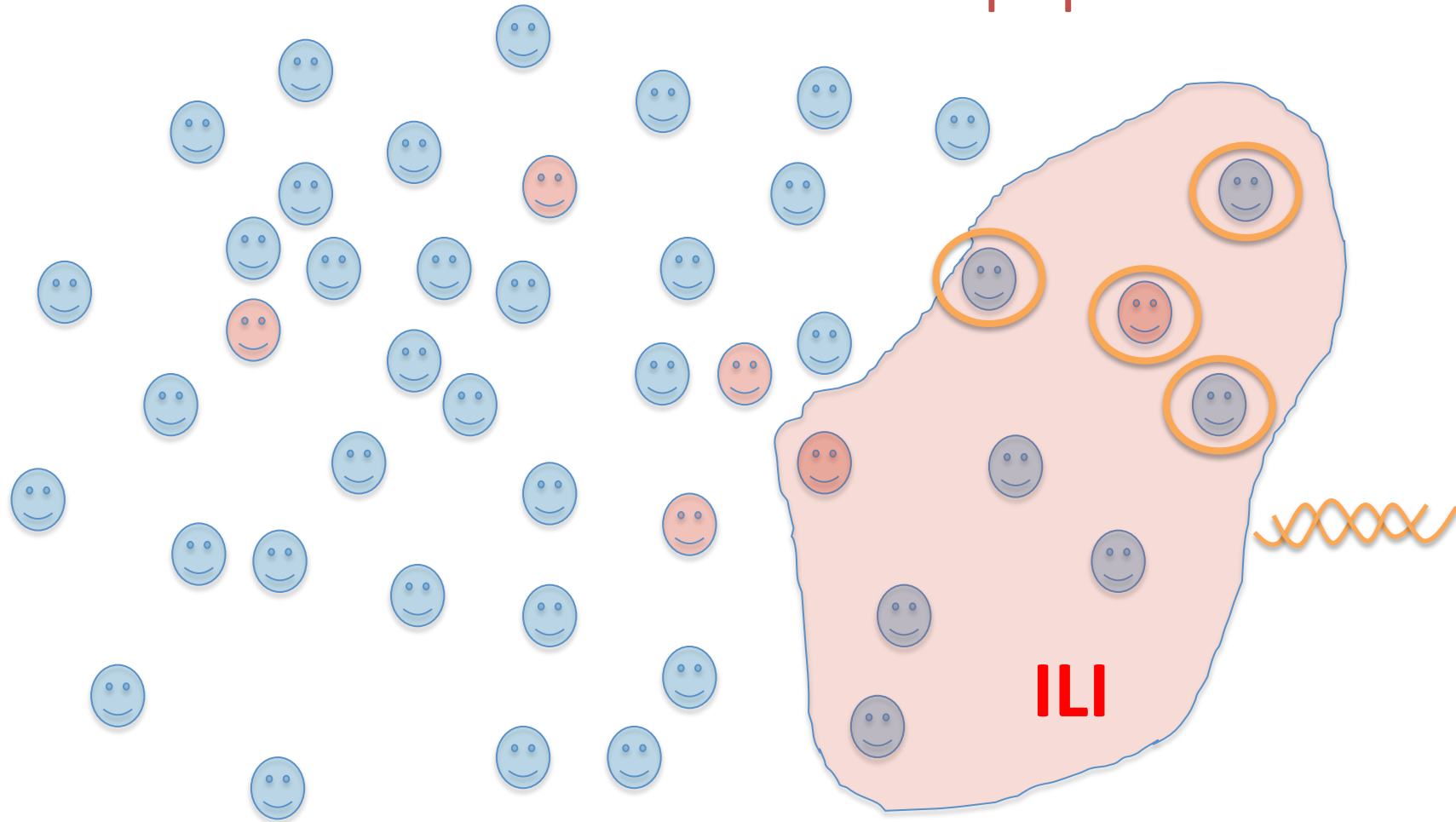
$$z_{ij}^{\theta} = \left\| \frac{N_{ij}^{mon}}{N_{ij}^{tot}} \sum_{k=1}^2 Z_{ik}(j) \right\|$$

GP + ILI

$$m_{ij}^{+} \sim \mathcal{B}(z_{ij}^{\theta}, \epsilon_i) + \underbrace{\mathcal{P}(\psi \epsilon_i N_{ij}^{mon})}_{\text{GP + ILI}}$$

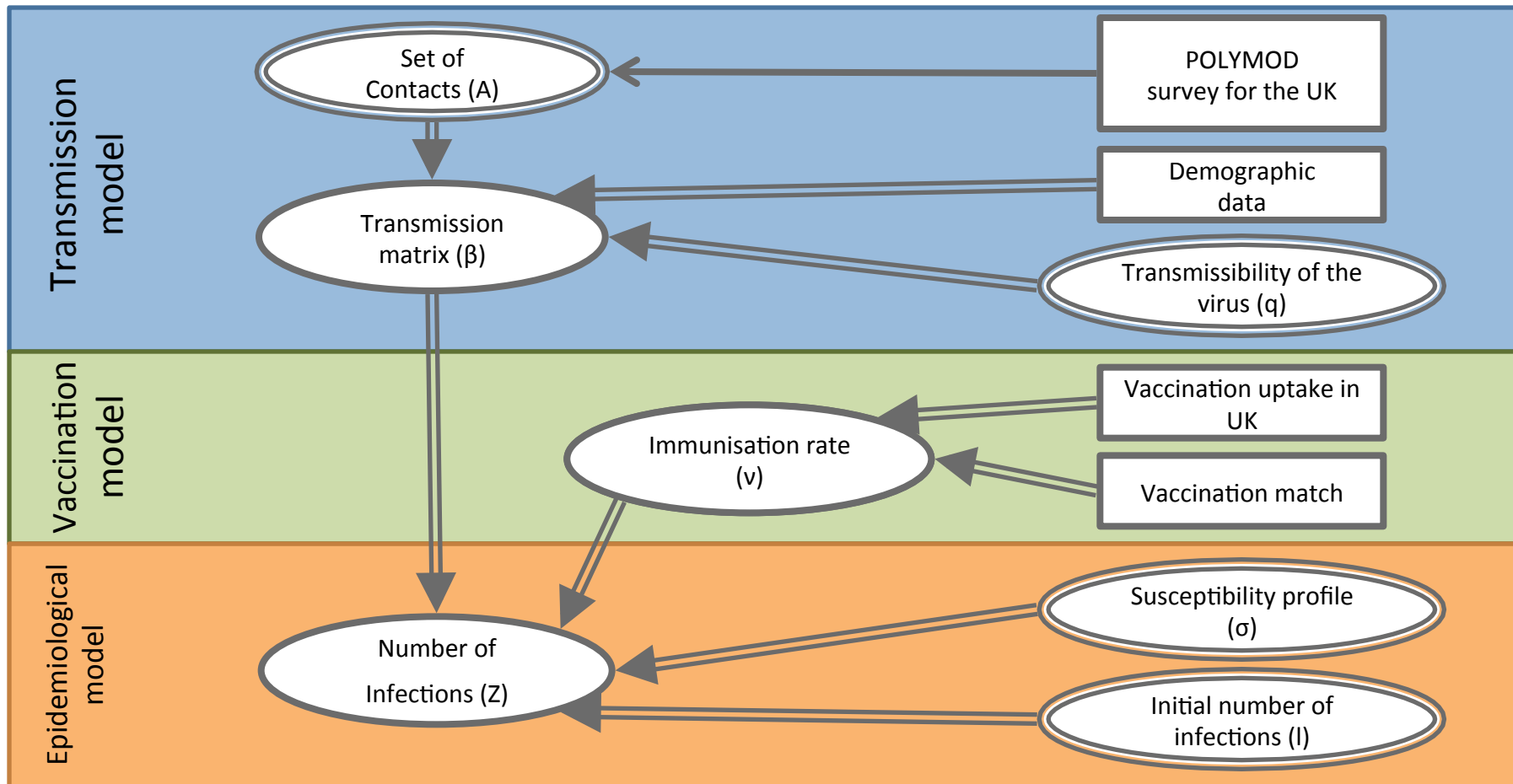
Flasche, S. et al. (2011). Different transmission patterns in the early stages of the influenza A(H1N1)v pandemic: A comparative analysis of 12 European countries. *Epidemics*, 3(2), 125–33.

Virological surveillance and number of ascertainable cases in monitored population



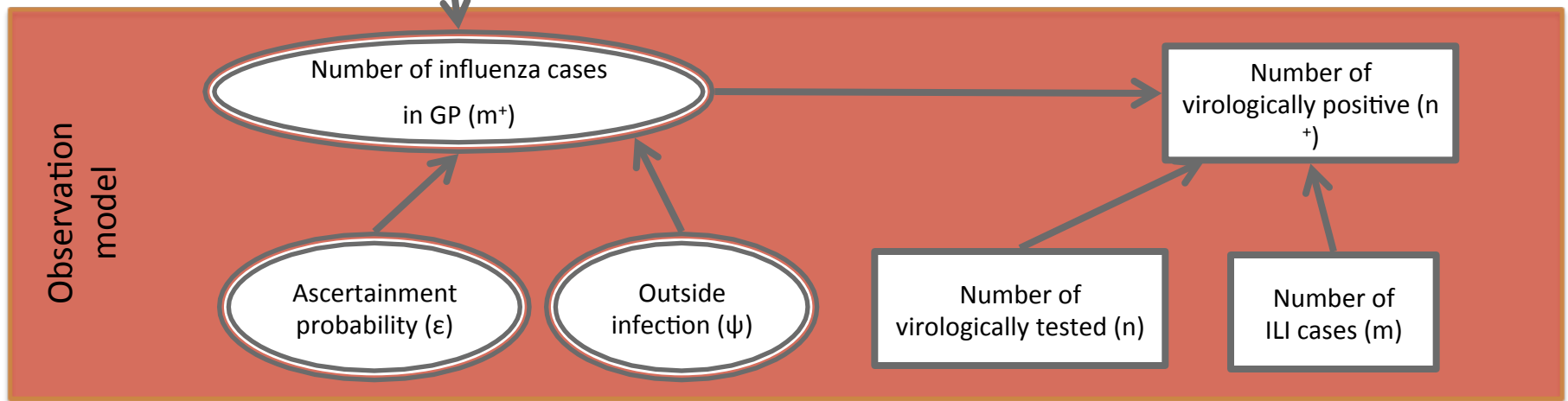
Virological testing:

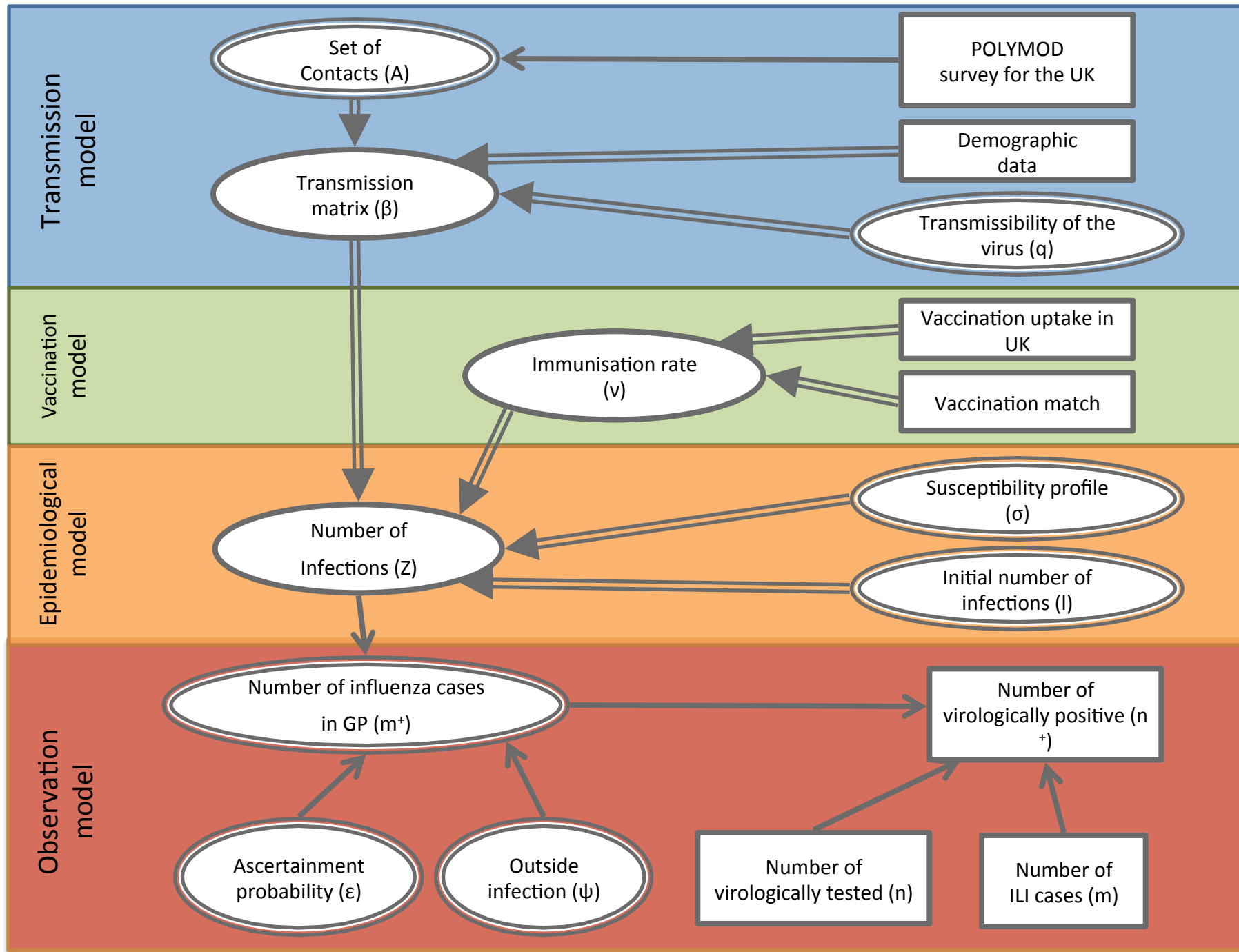
$$n_{ij}^+ \sim \mathcal{H}(n_{ij}, m_{ij}^+, m_{ij})$$



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

$$n_{ij}^+ \sim \mathcal{H}(n_{ij}, m_{ij}^+, m_{ij})$$





Derivation of the likelihood

Hierarchical model, two “likelihoods” depending of what we do with m^+ :

$$\mathcal{L}_1(\mathcal{D}|m^+, \epsilon, \theta, \psi) = \prod_{i=1}^5 \prod_{j=1}^{52} \underbrace{\frac{\binom{m_{ij}^+}{n_{ij}^+} \binom{m_{ij}^+ - m_{ij}^+}{n_{ij} - n_{ij}^+}}{\binom{m_{ij}}{n_{ij}}}}_{\text{Hypergeometric}} \sum_{h=h_{ij}^{min}}^{m_{ij}^+} \underbrace{\left[\binom{z_{ij}^\theta}{m_{ij}^+ - h} \epsilon_i^{m_{ij}^+} (1 - \epsilon_i)^{z_{ij}^\theta - m_{ij}^+ + h} \frac{(\psi N_{ij}^{mon})^h}{h!} e^{-\psi N_{ij}^{mon} \epsilon_i} \right]}_{\text{Poisson + Binomial}}$$

$$h_{ij}^{min} = \max(m_{ij}^+ - z_{ij}^\theta, 0)$$

m^+ summed out

$$\mathcal{L}_2(\mathcal{D}|\epsilon, \theta, \psi) = \prod_{i=1}^5 \prod_{j=1}^{52} \sum_{k=n_{ij}^+}^{k_{ij}^{max}} \left[\frac{\binom{k}{n_{ij}^+} \binom{m_{ij} - k}{n_{ij} - n_{ij}^+}}{\binom{m_{ij}}{n_{ij}}} \sum_{h=h_{ij}^{min}}^k \left[\binom{z_{ij}^\theta}{k - h} \epsilon_i^k (1 - \epsilon_i)^{z_{ij}^\theta - k + h} \frac{(\psi N_{ij}^{mon})^h}{h!} e^{-\psi N_{ij}^{mon} \epsilon_i} \right] \right]$$

$$k_{ij}^{max} = \min(z_{ij}^\theta, m_{ij} - n_{ij} + n_{ij}^+)$$

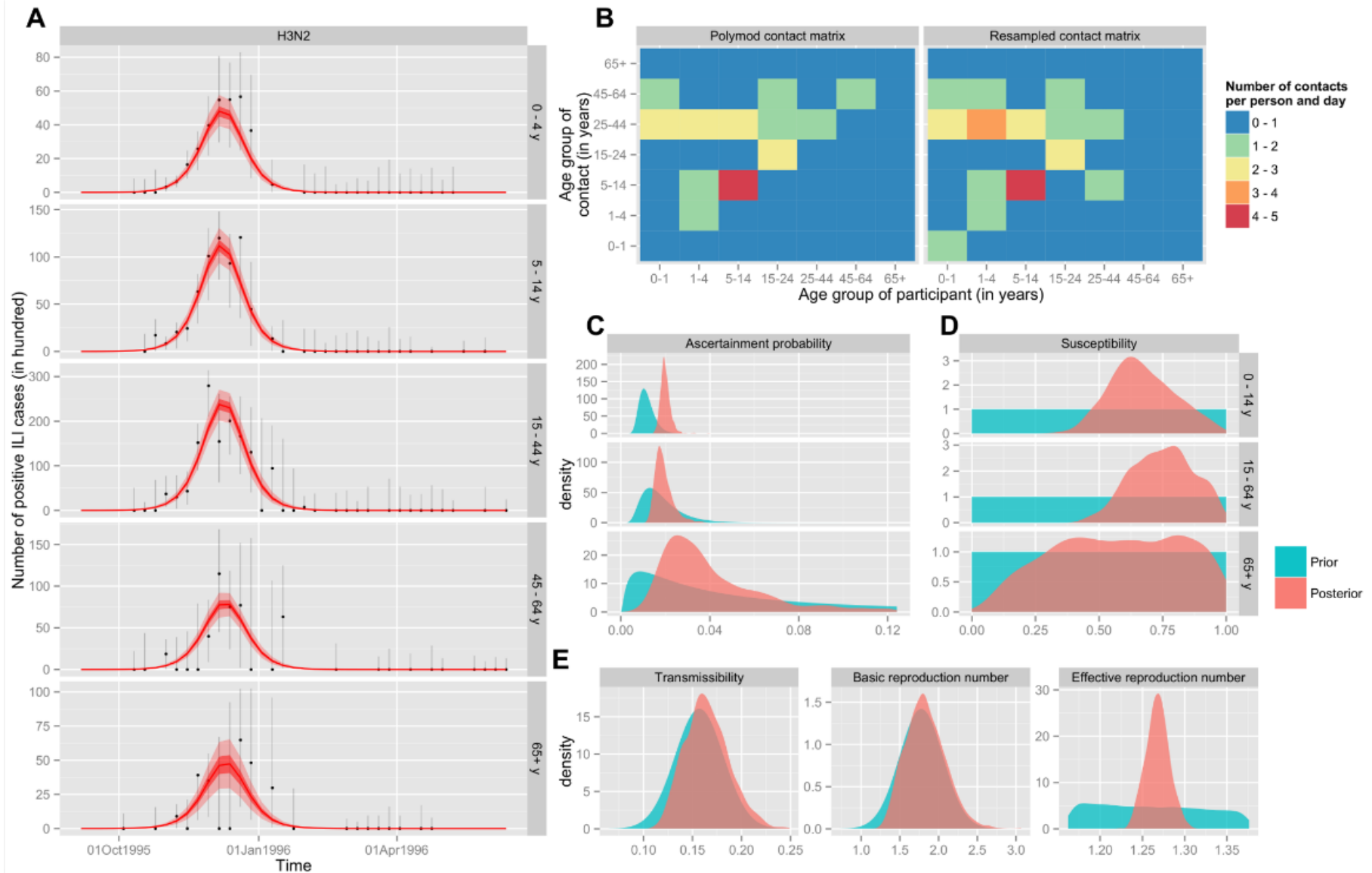
Priors

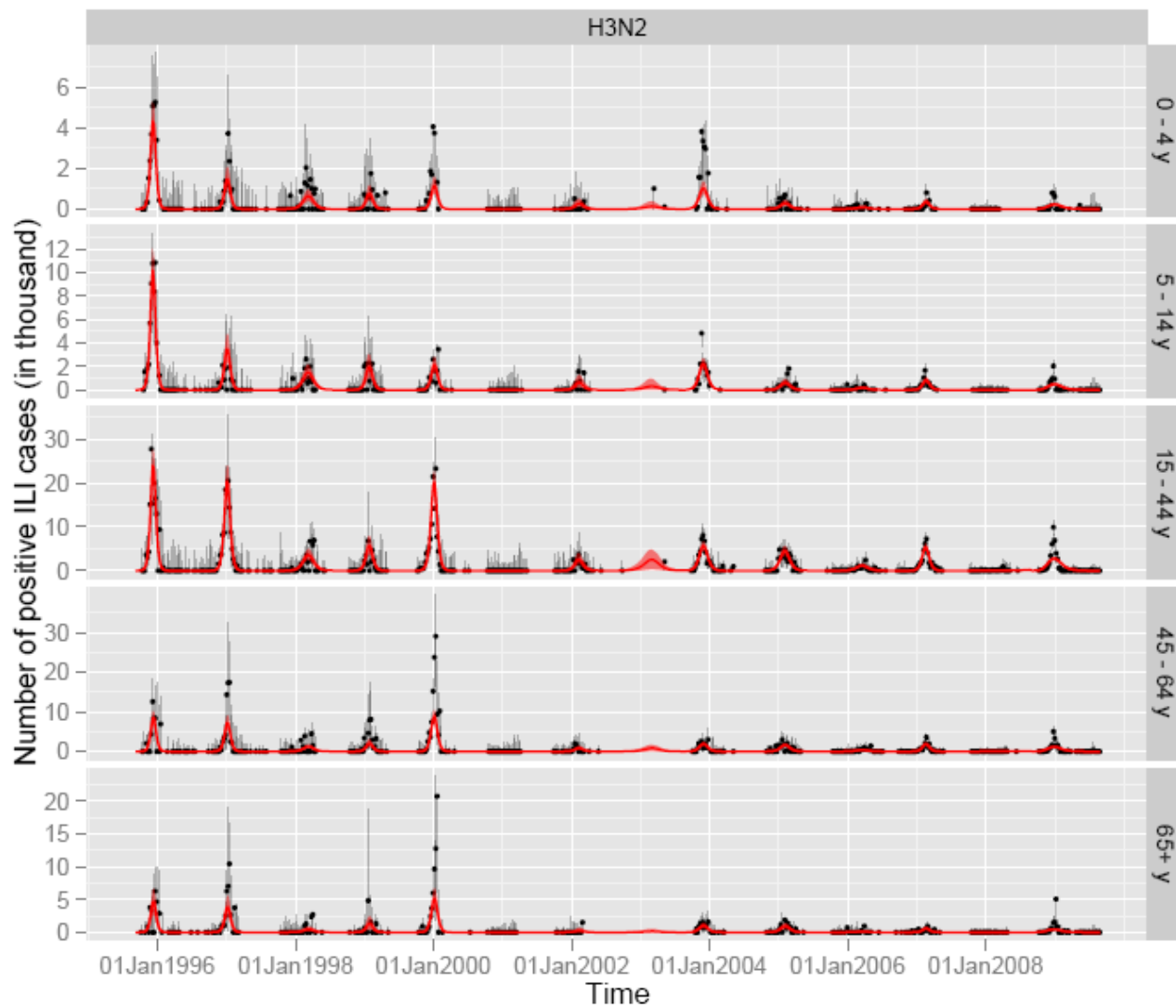
- For one season (2003/04 H3N2), we have serology, so we can derived priors for ε .
- We can also derive priors for σ for this particular season
- Which can be turn into (slightly inflated) prior for q (transmissibility) for the other strains/seasons

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





And finally the decision!



25 July 2012 Last updated at 09:31

787 Share    

Fergus Walsh

Medical correspondent

More from Fergus



Flu vaccines for all children

 COMMENTS (511)

All two to 17-year-olds in the UK are to be offered annual flu vaccinations.

If 30% take up the offer, there will be 11,000 fewer hospitalisations and 2,000 fewer deaths each year, the chief medical officer for England says.

The children will be immunised using a nasal spray rather than an injection, starting in 2014 at the earliest.



Nasally introduced flu vaccine

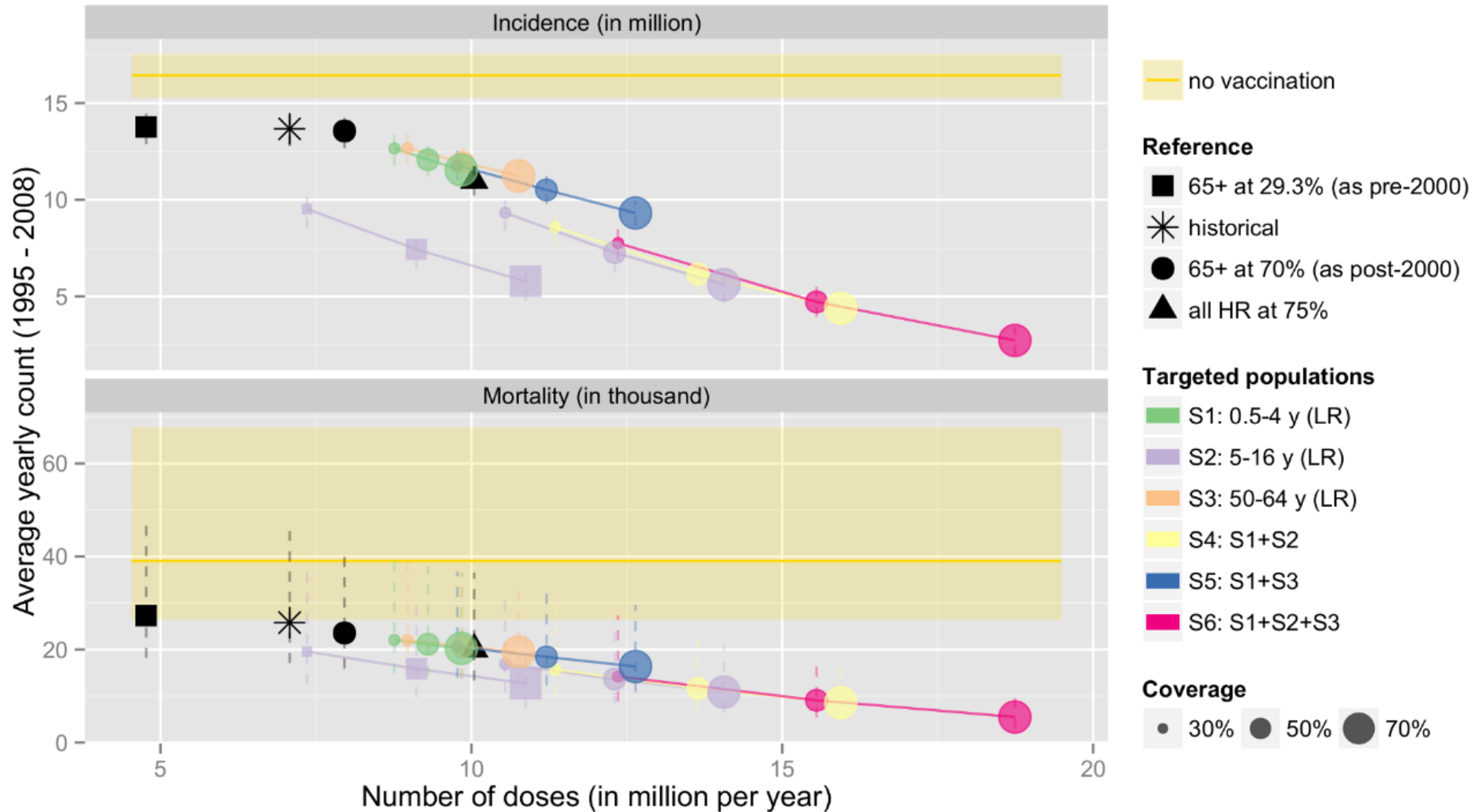
Discussion/Further research

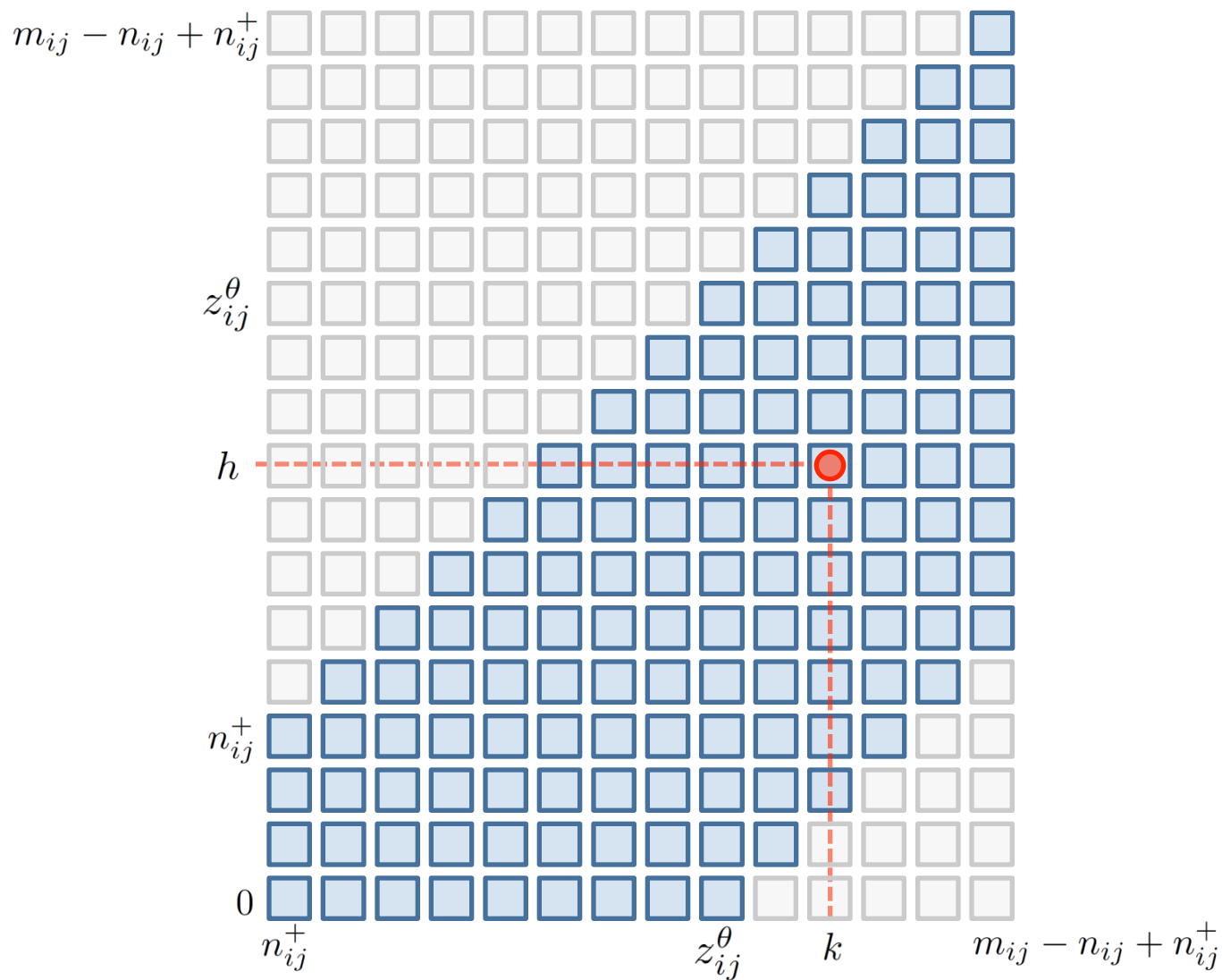
- Sequential year + interaction between strains
- Inference using contact survey, more theoretical work needed
- Adaptive McMC global, use more local methods
- Integrates other data sources (hospitalization, mortality, molecular...)

Acknowledgements

- Douglas Fleming (RCGP)
- Liz Miller, Albert-Jan van Hoek (HPA)
- Dave Lunn (MRC BioStat Unit)

Results: extending vaccination

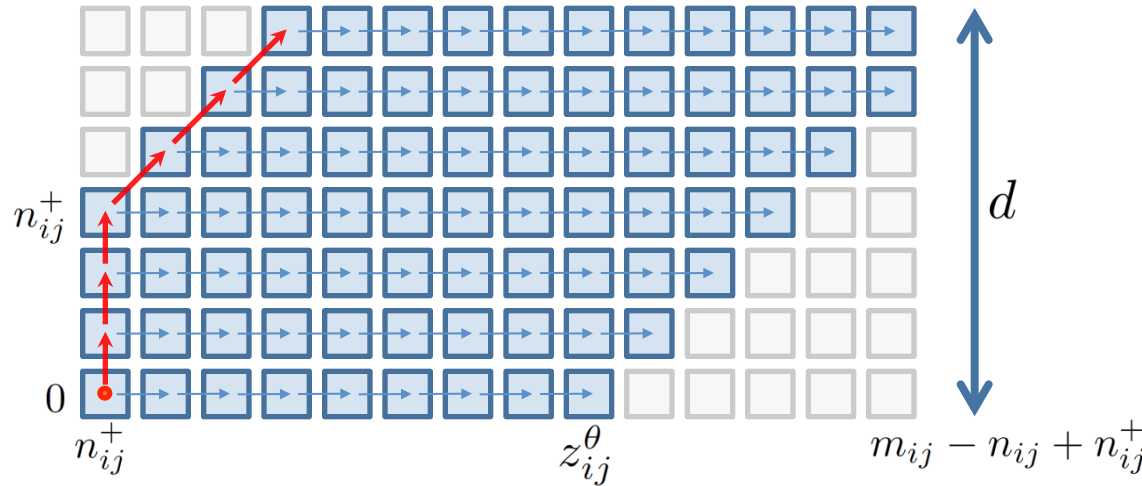




up to a constant

$$a_{kh}^{ij} = \frac{k!(m_{ij} - k)!z_{ij}^\theta!}{(k - n_{ij}^+)!(m_{ij} + n_{ij}^+ - k - n_{ij})!(k - h)!(z_{ij}^\theta - k + h)!} \epsilon_i^k (1 - \epsilon_i)^{z_{ij}^\theta - k + h} \frac{(\psi N_{ij}^{mon})^h}{h!} e^{-\psi N_{ij}^{mon} \epsilon_i}$$

Truncation and recursive calculation



$$\begin{cases} a_{k,h}^{ij} = \frac{k-h+1}{z_{ij}^\theta - k + h} \frac{\psi N_{ij}^{mon}}{h} (1 - \epsilon_i) a_{k,h-1}^{ij} & \text{vertical increment} \\ a_{k,h}^{ij} = \frac{k(m_{ij} + n_{ij}^+ - k - n_{ij} + 1)(z_{ij}^\theta - k + h + 1)}{(m_{ij} - k + 1)(k - n_{ij}^+)(k - h)} \frac{\epsilon_i}{1 - \epsilon_i} a_{k-1,h}^{ij} & \text{horizontal increment} \\ a_{k,h}^{ij} = \frac{k(m_{ij} + n_{ij}^+ - k - n_{ij} + 1)}{(m_{ij} - k + 1)(k - n_{ij}^+)} \frac{\psi N_{ij}^{mon} \epsilon_i}{h} a_{k-1,h-1}^{ij} & \text{diagonal increment} \end{cases}$$