

Modelling seasonal influenza in England: Approaches to capture immunity propagation

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The broader project

MEMVIE: Mathematical and Economic Modelling for Vaccination and Immunisation Evaluation

- Provide a complementary **second opinion** on the work presented to the Joint Committee of Vaccination and Immunisation (JCVI).

FUNDED BY



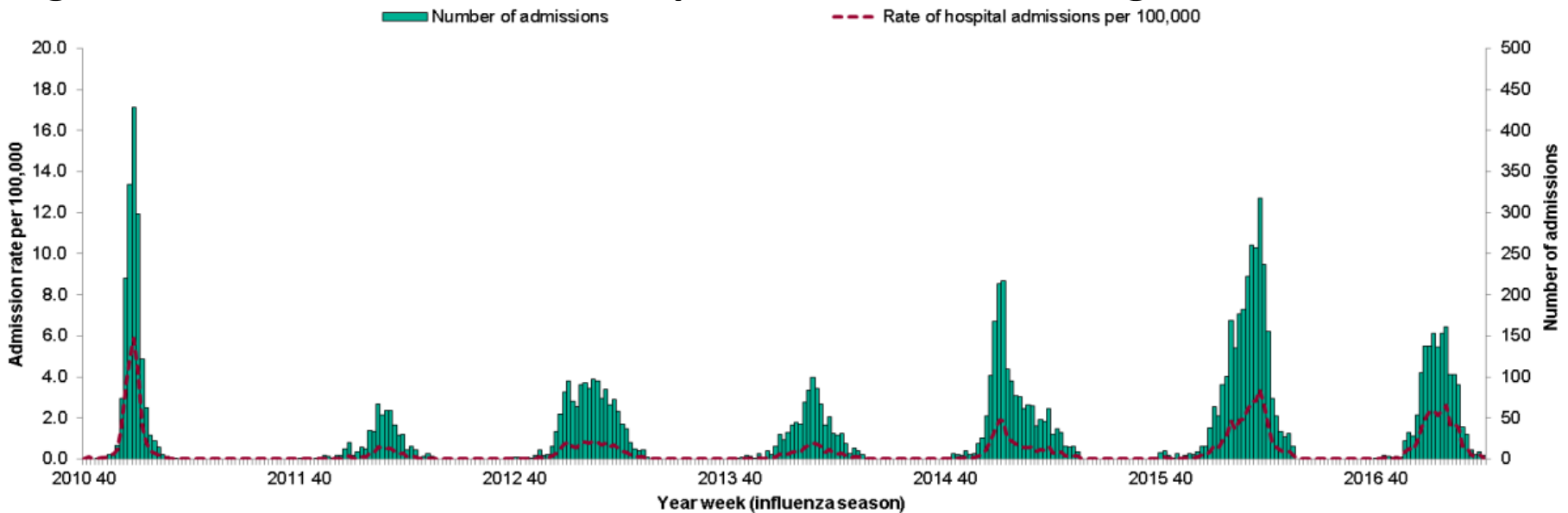
- Pertussis (whooping cough)
- Pneumococcal disease
- Human papillomavirus (HPV)
- Seasonal influenza

Project webpage:

https://warwick.ac.uk/fac/cross_fac/zeeman_institute/zeeman_research/epidemiology/humans/memvie/

Seasonal influenza is a considerable burden on public health

Figure: Influenza confirmed hospital admissions in England, 2010 to 2017




Source: Reproduced from the Public Health England report “Surveillance of influenza and other respiratory viruses in the UK: Winter 2016 to 2017”.

- Vaccination can offer some protection against infection.
 - Two influenza A subtypes: A(H1N1)pdm09, A(H3N2),
 - Two influenza B lineages: B/Victoria, B/Yamagata

Use of modelling to inform policy

Assessing Optimal Target Populations for Influenza Vaccination Programmes: An Evidence Synthesis and Modelling Study

Marc Baguelin , Stefan Flasche, Anton Camacho, Nikolaos Demiris, Elizabeth Miller, W. John Edmunds

Published: October 8, 2013 • <https://doi.org/10.1371/journal.pmed.1001527>

- Prior models typically treat each influenza season and each strain circulating within that season **independently**.

Our study objectives

(1) Data amalgamation

- Gather relevant influenza vaccine and epidemiological data for England (post-2009 influenza pandemic).

(2) Mathematical model development

- SEIR-type seasonal influenza transmission model, incorporating multiple strains and immunity propagation.

(3) Parameter inference

- Calibrate model to data using Approximate Bayesian Computation.
- Quantify extent of immunity propagation.

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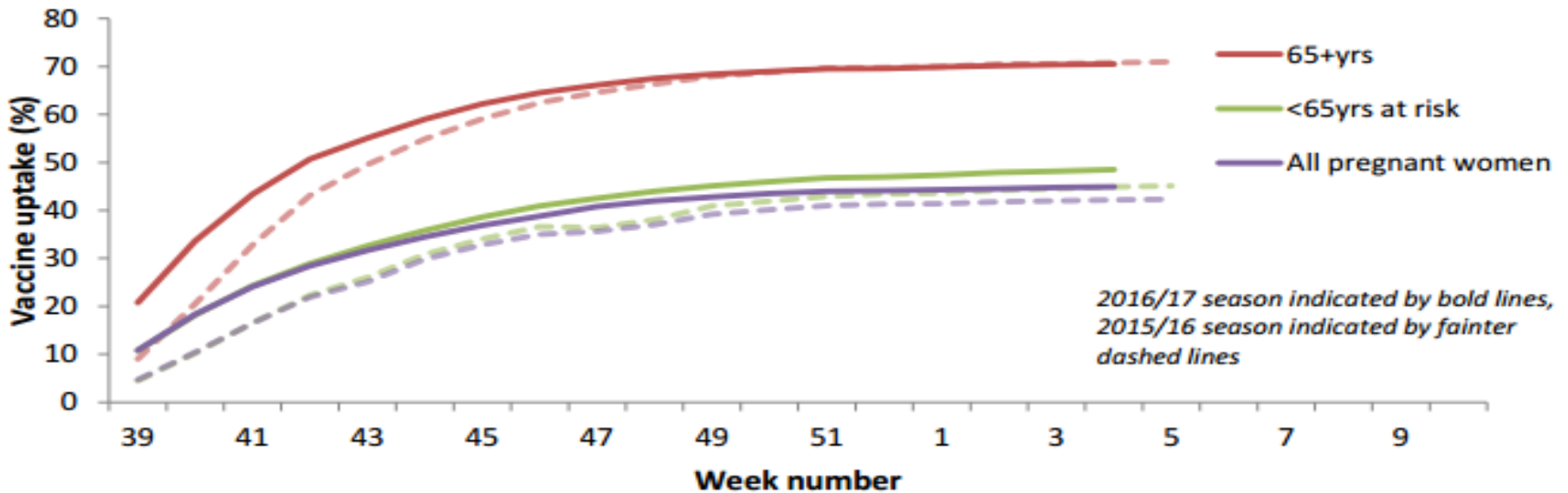
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Data: Vaccine efficacy & uptake

- Efficacy & uptake data from Public Health England

Figure: Vaccine uptake in 2016/17 influenza season



Source: PHE Weekly National Influenza Report (25 May 2017)

Data: Influenza attributed GP visits

GP consultation rate for strain m in season $y = \dots$

Data: GP visits for ILI

GP consultation rate for strain m in season $y = \text{GP ILI consultation rate} \times \dots$

Week	Age	Chronic Disease	Population	Num. of patients with ILI
01/2018	1	1	68,437	10
01/2018	1	0	578,907	13
01/2018	2	1	89,396	17
01/2018	2	0	743,470	28
01/2018	3	1	28,957	25
01/2018	3	0	956,278	13

Data source:

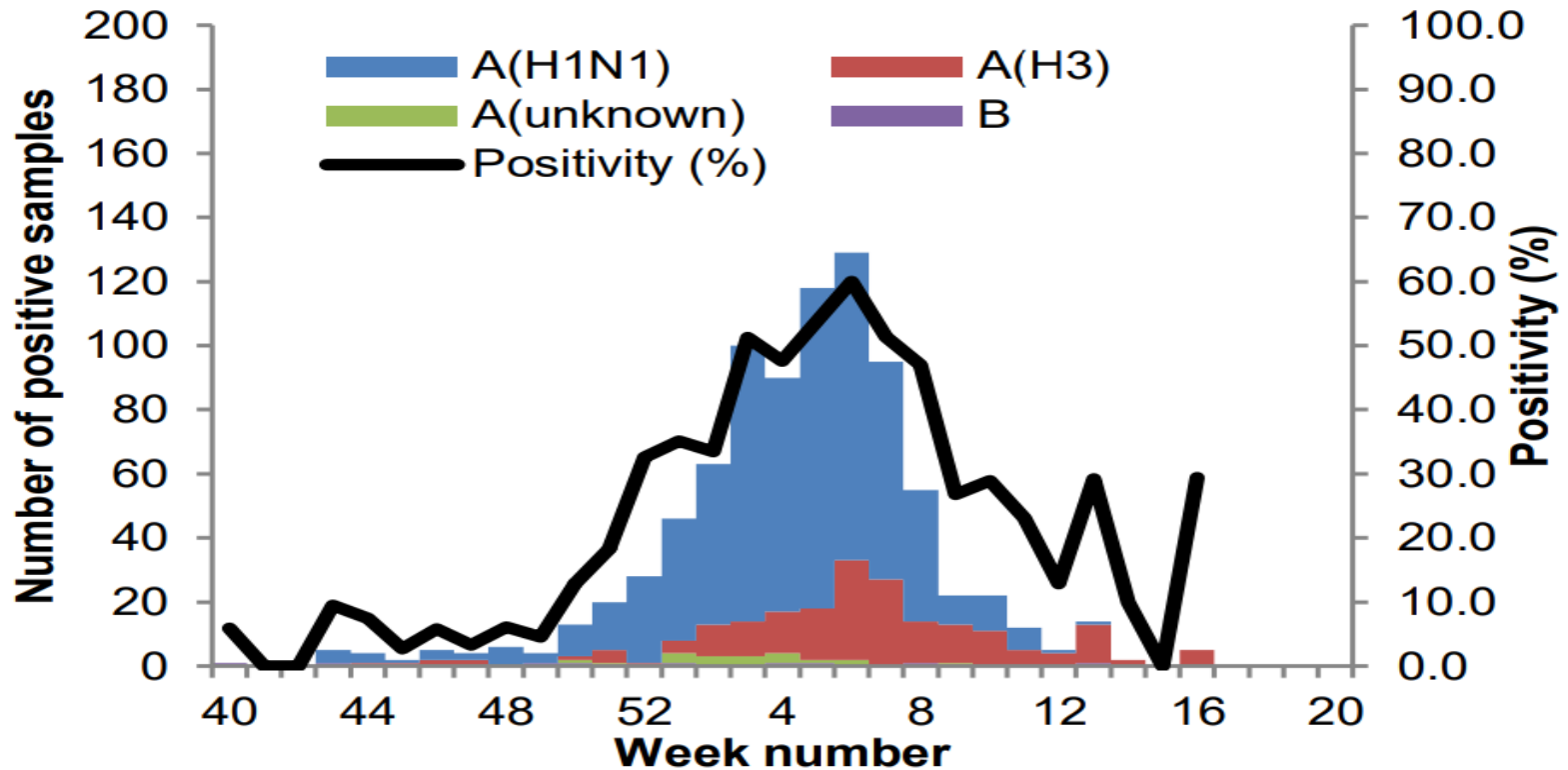
Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) network: www.rcgp.org.uk/rsc

Data: Virological positivity

GP consultation rate for strain m in season $y =$ GP ILI consultation rate $\times \dots$
Proportion of ILI samples influenza positive $\times \dots$

Data: Virological positivity

Figure: Number of influenza positive samples and % positive (2017/18 influenza season).



Data source:

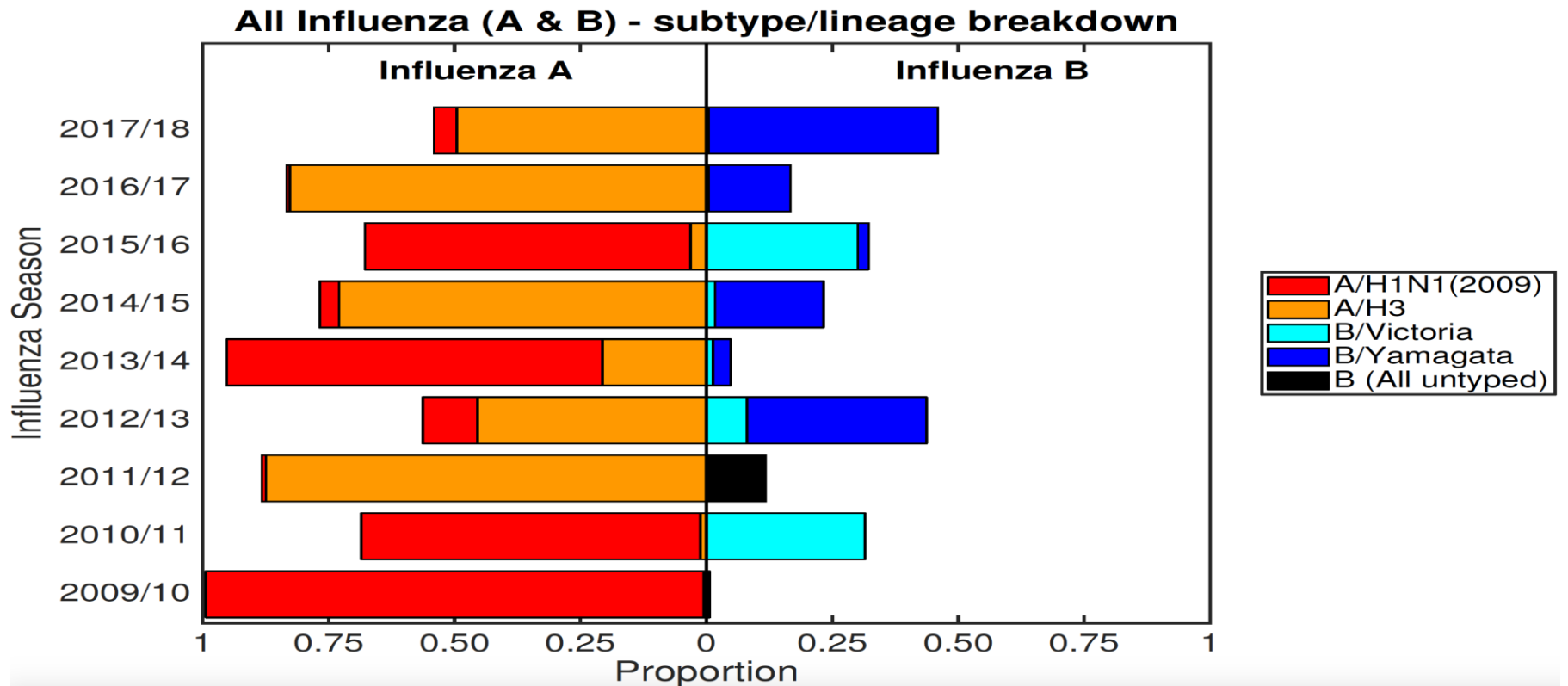
Figure reproduced from Public Health England weekly national influenza reports.

Data: Circulating strain composition

GP consultation rate for strain m in season $y =$ GP ILI consultation rate $\times \dots$
Proportion of ILI samples influenza positive $\times \dots$
Proportion of influenza viruses in circulation of strain type m

Data: Circulating strain composition

Figure: Virologically sampled influenza cases attributed to each strain.

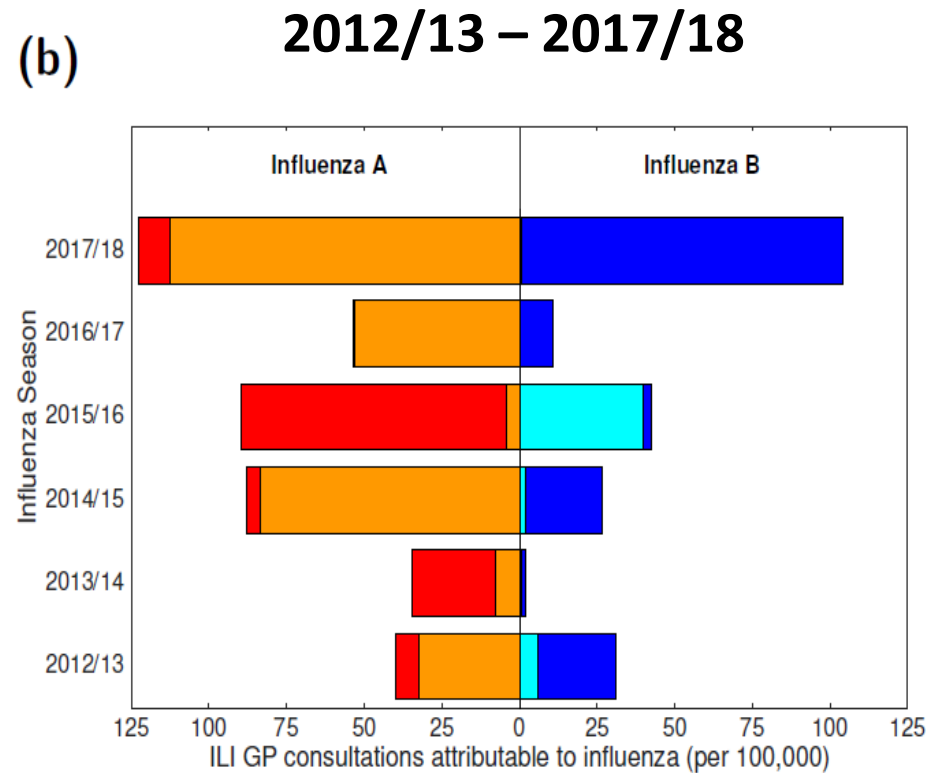
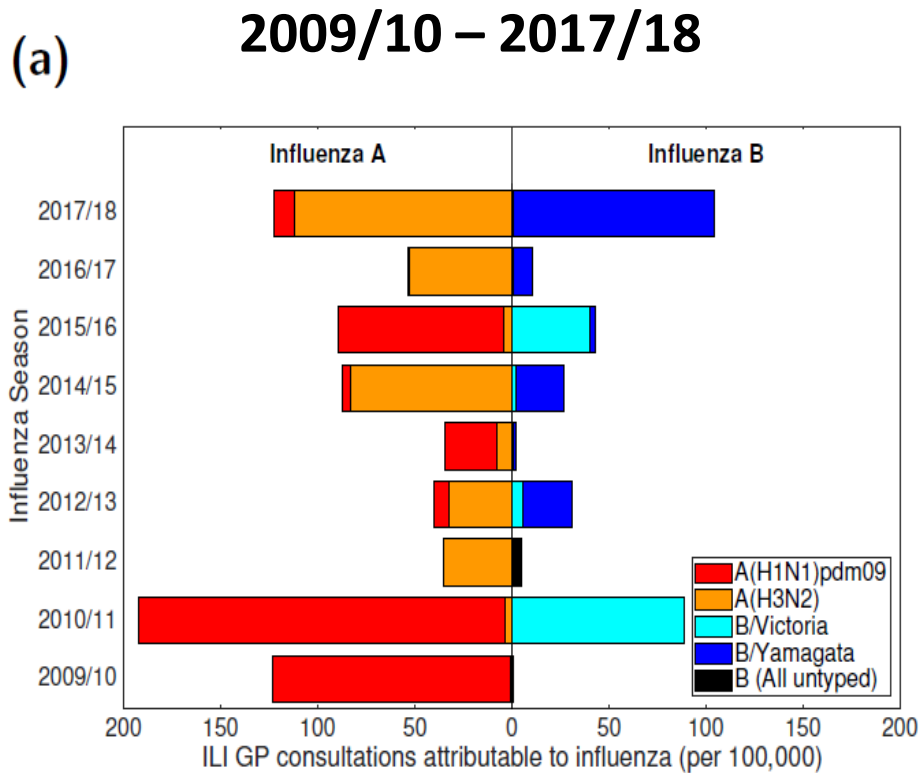


Data source:

WHO FluNet (https://www.who.int/influenza/gisrs_laboratory/flunet/en/)

Data: Influenza attributed GP visits

Figure: Empirical, strain-stratified data for ILI GP consultations attributable to influenza per 100,000 population.



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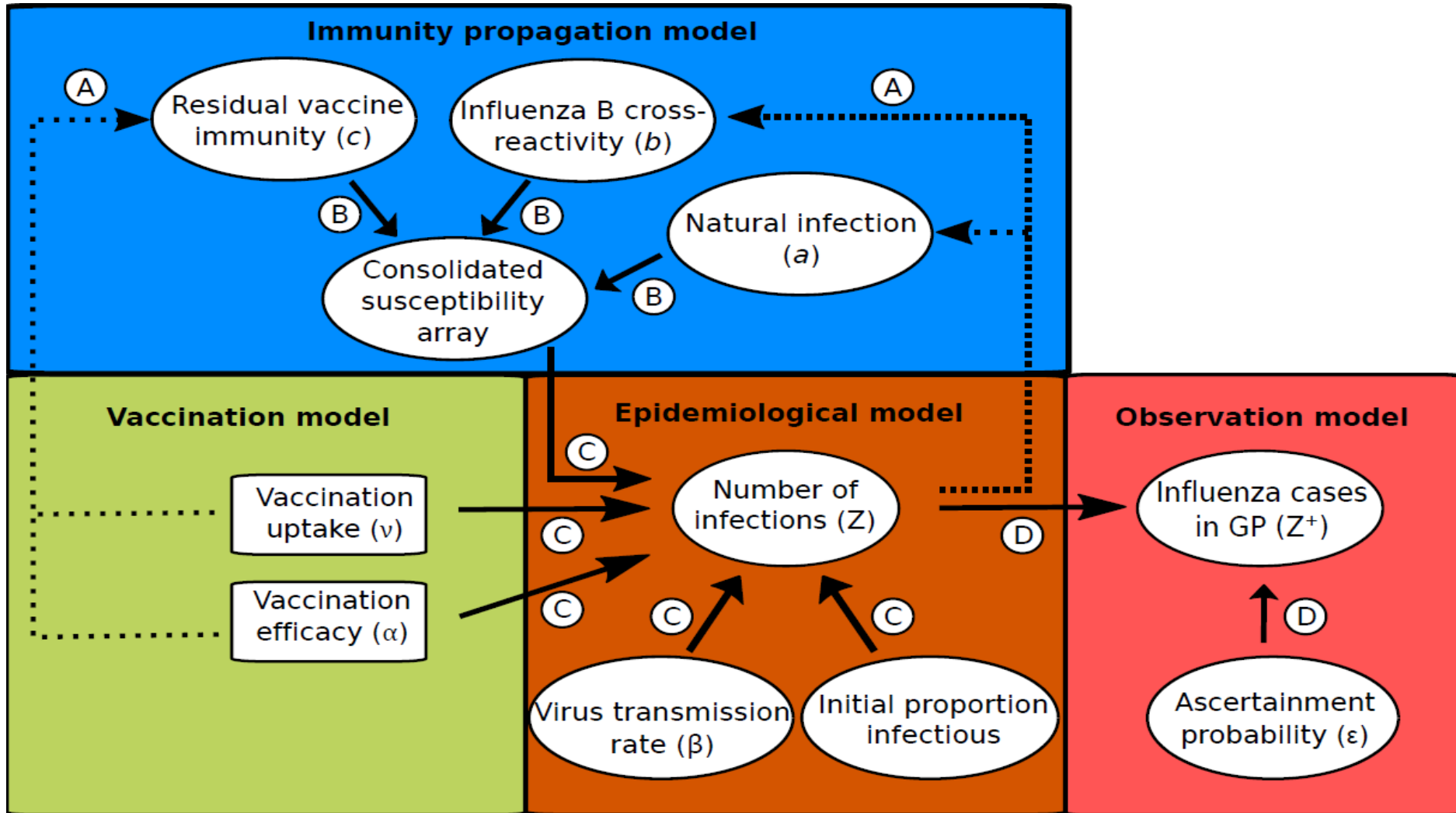
(2) Mathematical model development

- SEIR-type seasonal influenza transmission model, incorporating multiple strains and immunity propagation.

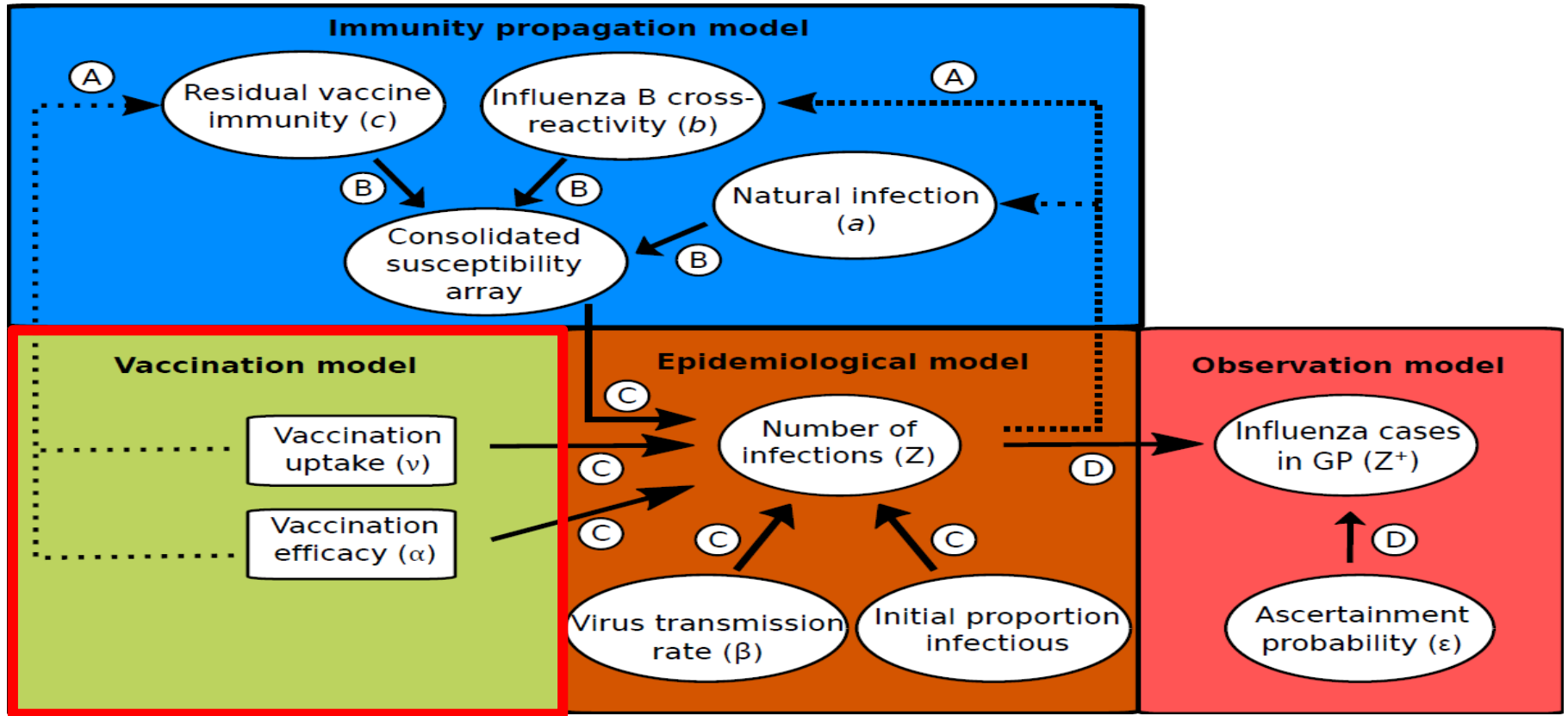
(3) Parameter inference

- Calibrate model to data using Approximate Bayesian Computation.
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Full model schematic

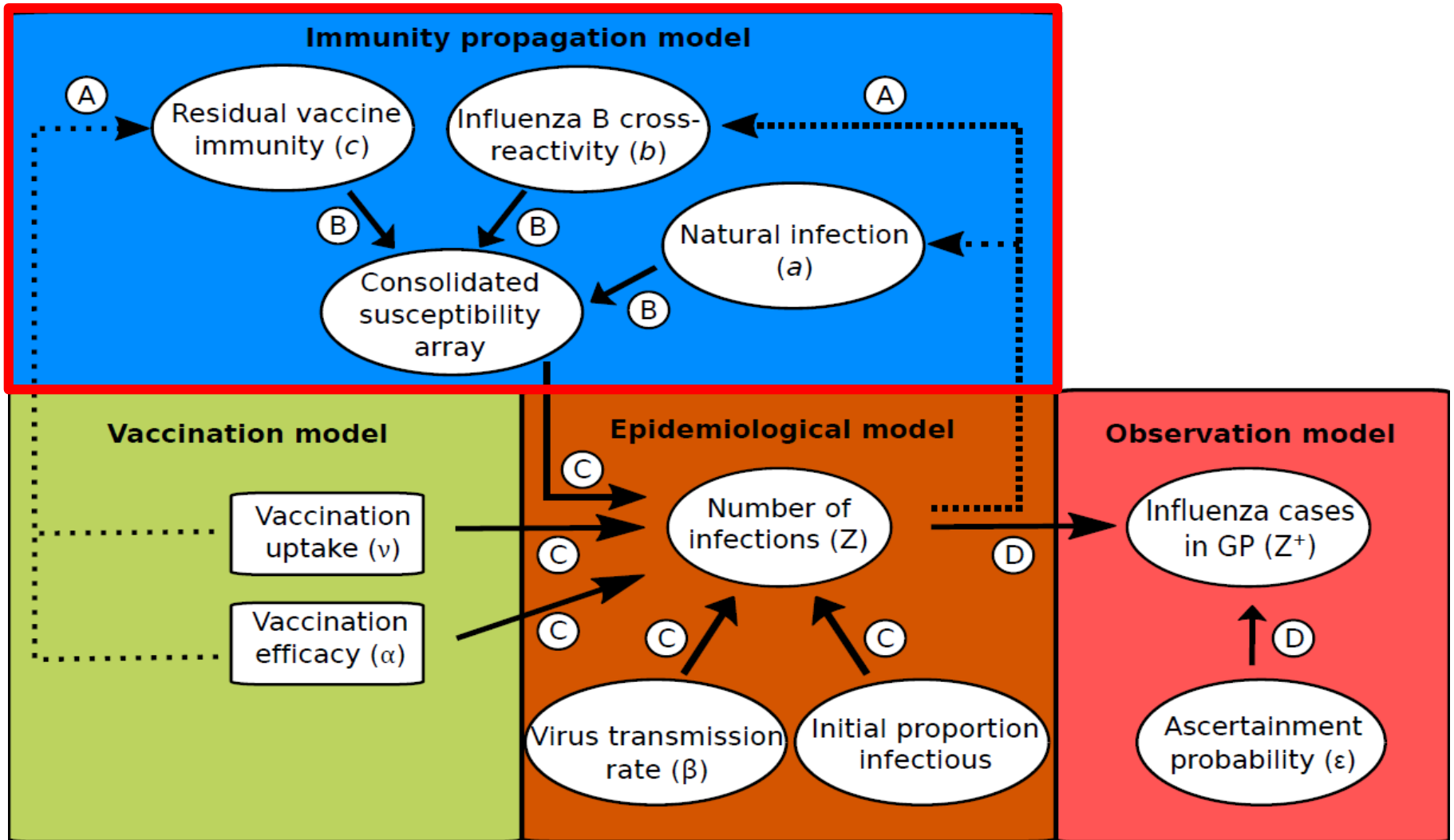


Vaccination model



- Assumed a 'leaky' vaccine; reducing the overall susceptibility of the given group receiving vaccination.

Immunity propagation model



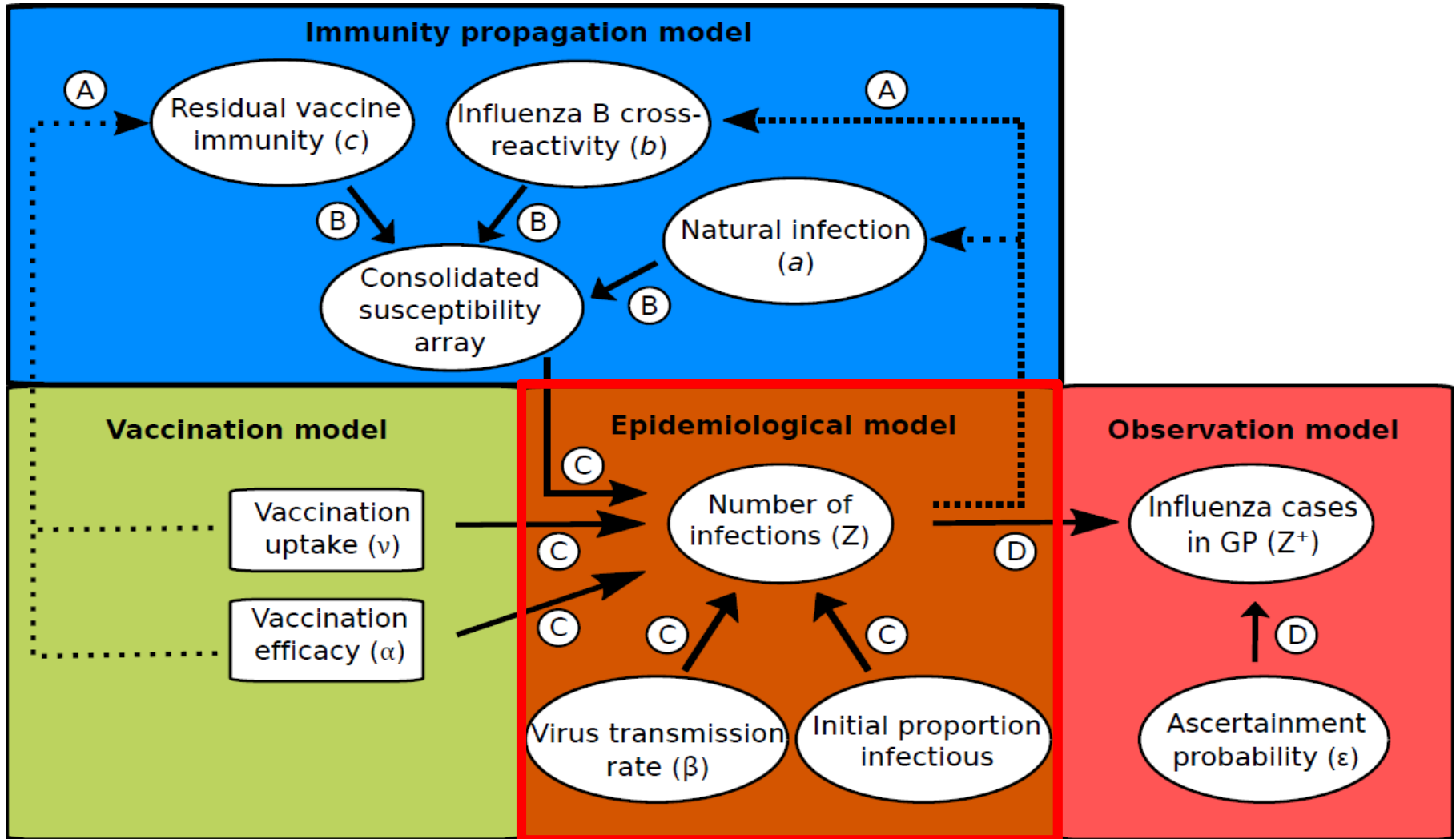
Immunity propagation model

Figure: Interaction between exposure history and susceptibility.

		Strain susceptibility			
		A(H1N1)pdm09	A(H3N2)	B/Victoria	B/Yamagata
Exposure history (h)	Naïve	1	1	1	1
	A(H1N1)pdm09	a	1	1	1
	A(H3N2)	1	a	1	1
	B/Yamagata	1	1	a	b
	B/Victoria	1	1	b	a
	Vacc. (V)	$c_{A(H1N1)}$	$c_{A(H3N2)}$	$c_{B/Victoria}$	$c_{B/Yamagata}$
	A(H1N1)pdm09 & V	$\min(a, c_{A(H1N1)})$	$c_{A(H3N2)}$	$c_{B/Victoria}$	$c_{B/Yamagata}$
	A(H3N2) & V	$c_{A(H1N1)}$	$\min(a, c_{A(H3N2)})$	$c_{B/Victoria}$	$c_{B/Yamagata}$
	B/Victoria & V	$c_{A(H1N1)}$	$c_{A(H3N2)}$	$\min(a, c_{B/Victoria})$	$\min(b, c_{B/Yamagata})$
	B/Yamagata & V	$c_{A(H1N1)}$	$c_{A(H3N2)}$	$\min(b, c_{B/Victoria})$	$\min(a, c_{B/Yamagata})$

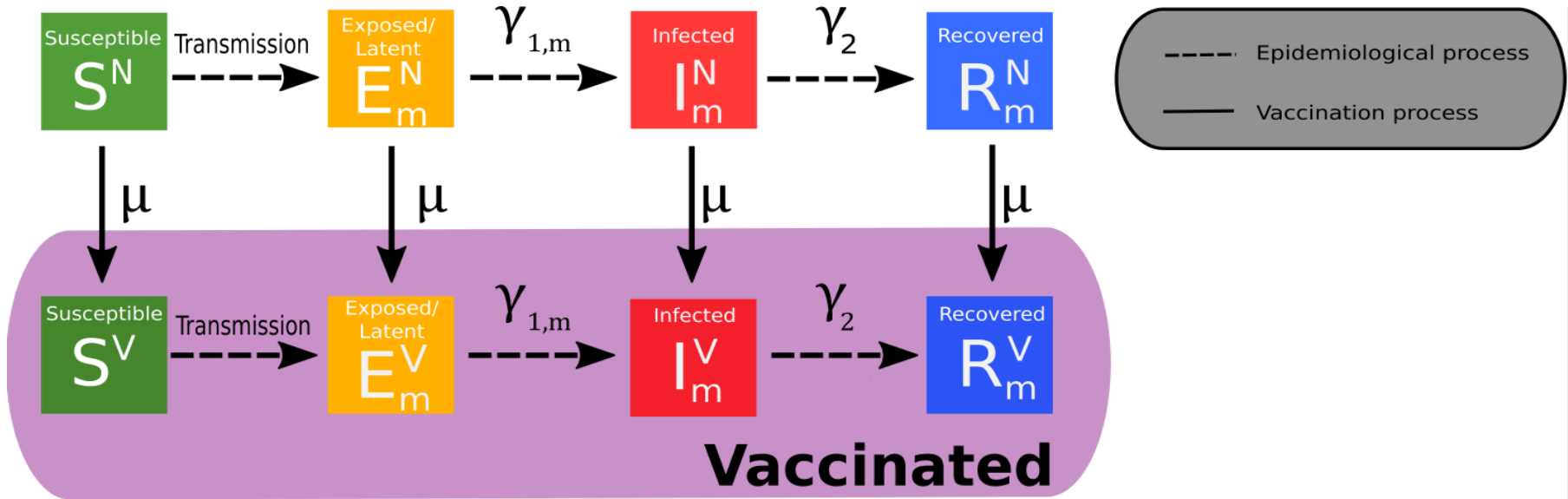
➤ Vaccine immunity carried over: $c_m^y = 1 - \xi \alpha_m^{y-1}$; $\xi \in (0, 1)$

Epidemiological model



Epidemiological model

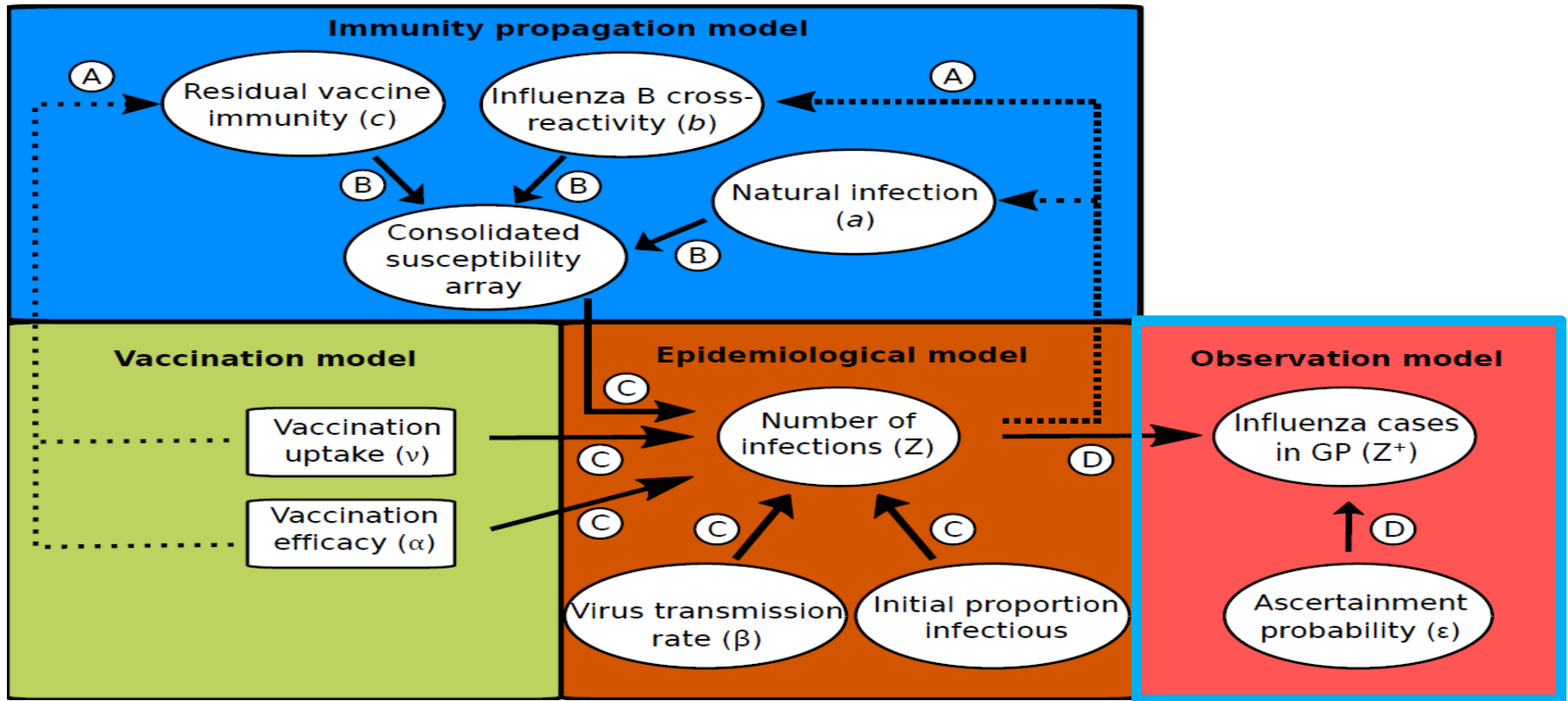
Figure: Vaccination and epidemiological model schematic.



- Track incidence rate (per 100,000) of new strain m influenza infections in season y :

$$Z_m(y) = \left(\int_{y-1}^y \gamma_{1,m} (E_m^N + E_m^V) dt \right) \times 100,000.$$

Observation model



➤ Estimated ascertainable influenza cases:

$$Z_m^+(y) = \epsilon_y Z_m(y).$$

Table: Overview of parameters in the model.

Description	Notation	Value
Fixed parameters		
Mortality rate (day^{-1})	B,D	$\frac{1}{81 \times 365}$
Rate of latency loss, influenza A subtypes (day^{-1})	$\gamma_{1,A}$	$\frac{1}{1.4}$
Rate of latency loss, influenza B lineages (day^{-1})	$\gamma_{1,B}$	$\frac{1}{0.6}$
Recovery rate (day^{-1})	γ_2	$\frac{1}{3.8}$
Time-varying parameters		
Vaccination rate at time t	$\nu(t)$	—
Vaccine efficacy, season y strain m	α_m^y	—
Inferred parameter description		
Influenza virus transmissibility, strain m	β_m	$\mathcal{U}(0.2632, 0.7896)$
Modified susceptibility given natural infection in prior season	a	$\mathcal{U}(0, 1)$
Modified susceptibility due to type B influenza cross-reactivity	b	$\mathcal{U}(0, 1)$
Proportion of prior season vaccine efficacy carried over	ξ	$\mathcal{U}(0, 1)$
Ascertainment probability in season y	ϵ_y	$\mathcal{U}(0, 0.05)$

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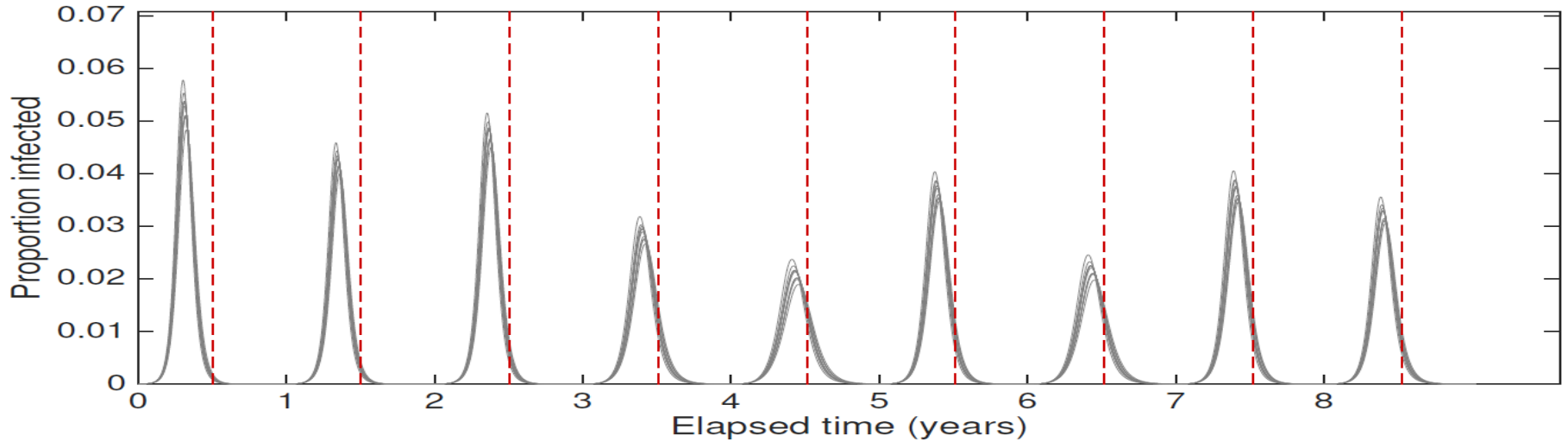
- SEIR-type seasonal influenza transmission model, incorporating multiple strains and immunity propagation.

(3) Parameter inference

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Parameter set summary statistics

➤ Component one: Temporal profile check



➤ Component two: Error metric

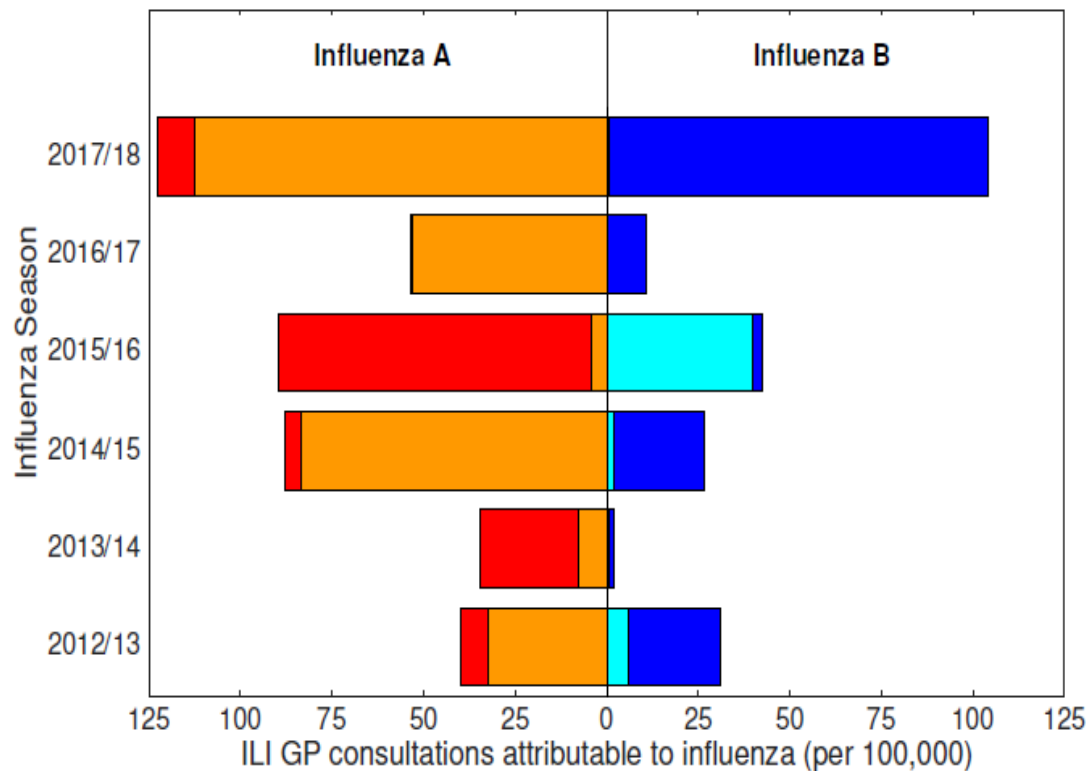
$$\text{DEV} = 2 \sum_y \sum_m \left(C_{m,y} \ln \left(\frac{C_{m,y}}{M_{m,y}} \right) - (C_{m,y} - M_{m,y}) \right)$$

$C_{m,y}$ the observed value for strain m in season y ,

$M_{m,y}$ the model estimate for strain m in season y .

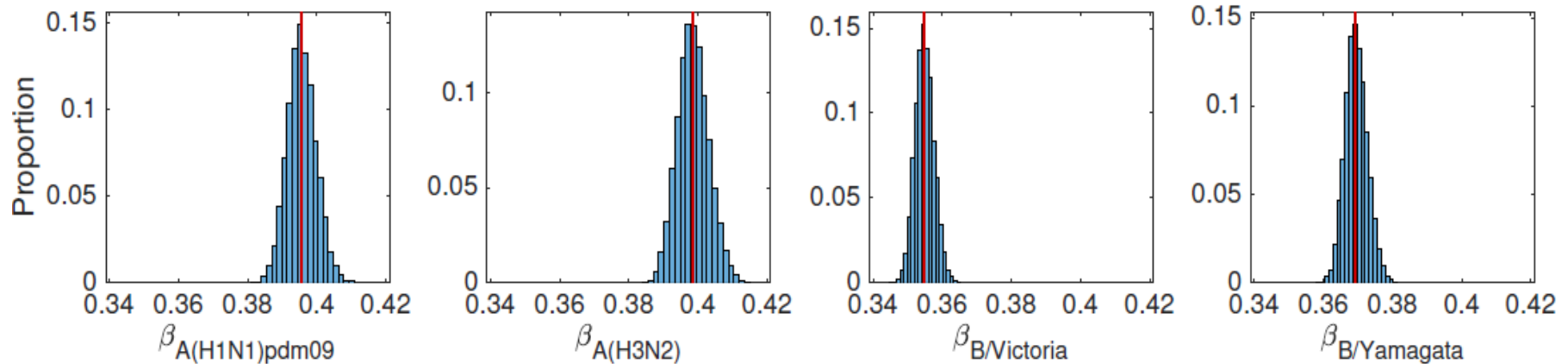
Data: Influenza attributed GP visits

Figure: Empirical, strain-stratified data for ILI GP consultations attributable to influenza per 100,000 population (influenza seasons 2012/13-2017/18).



Parameter fits: Transmissibility

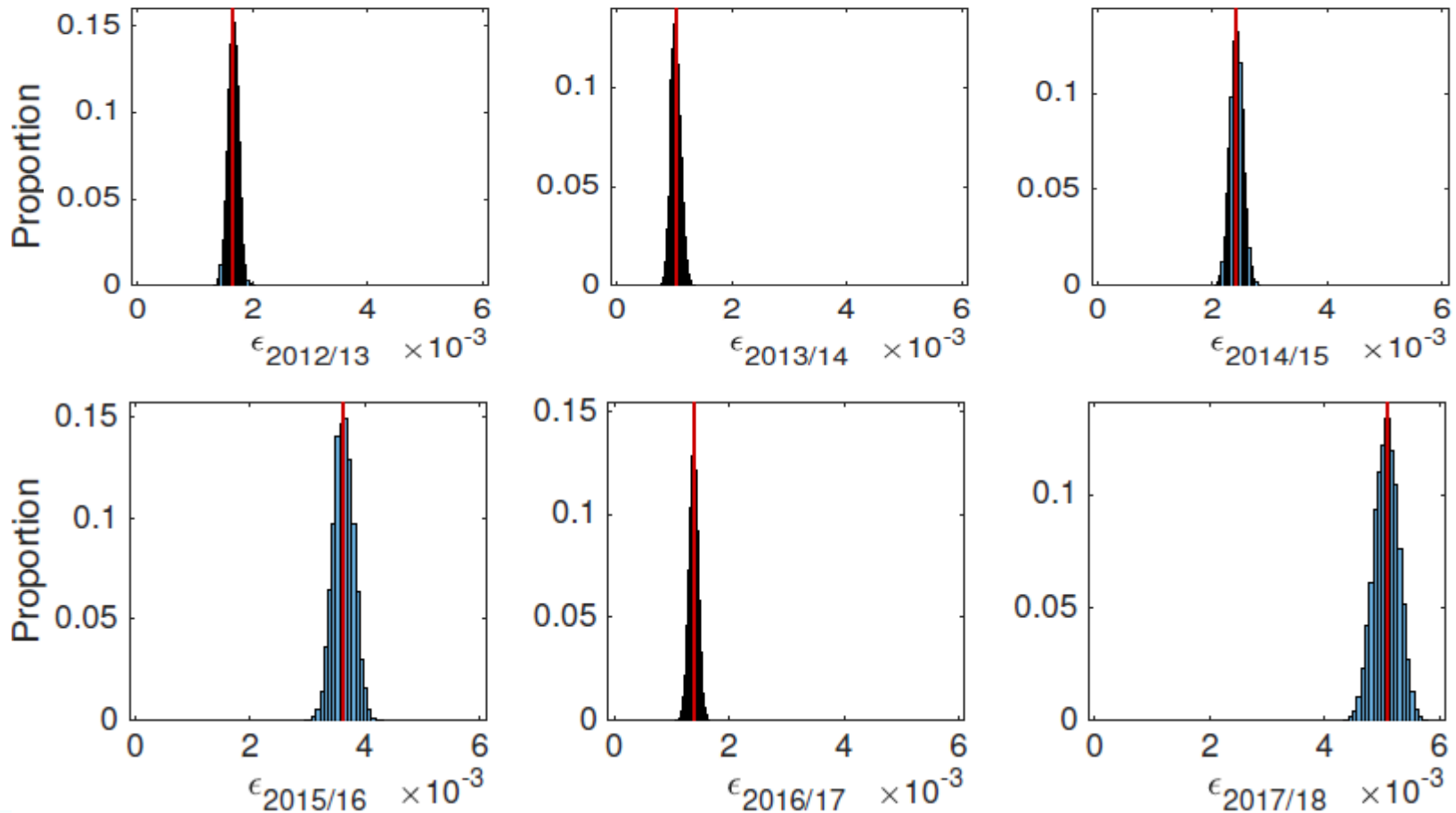
Figure A: Inferred posterior distributions for the transmissibility associated parameters.



- Similar estimates for the two influenza A subtypes.
- Exceed corresponding estimates for the two type B lineages.

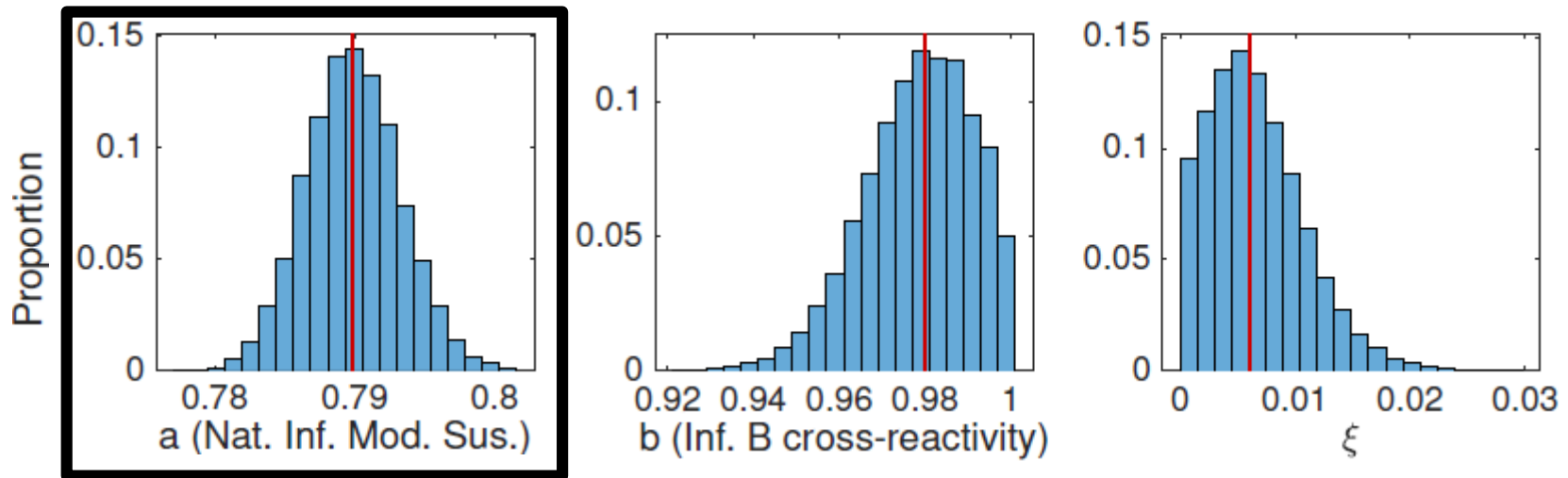
Parameter fits: Ascertainment

Figure B: Inferred posterior distributions for the ascertainment associated parameters.



Parameter fits: Immunity propagation

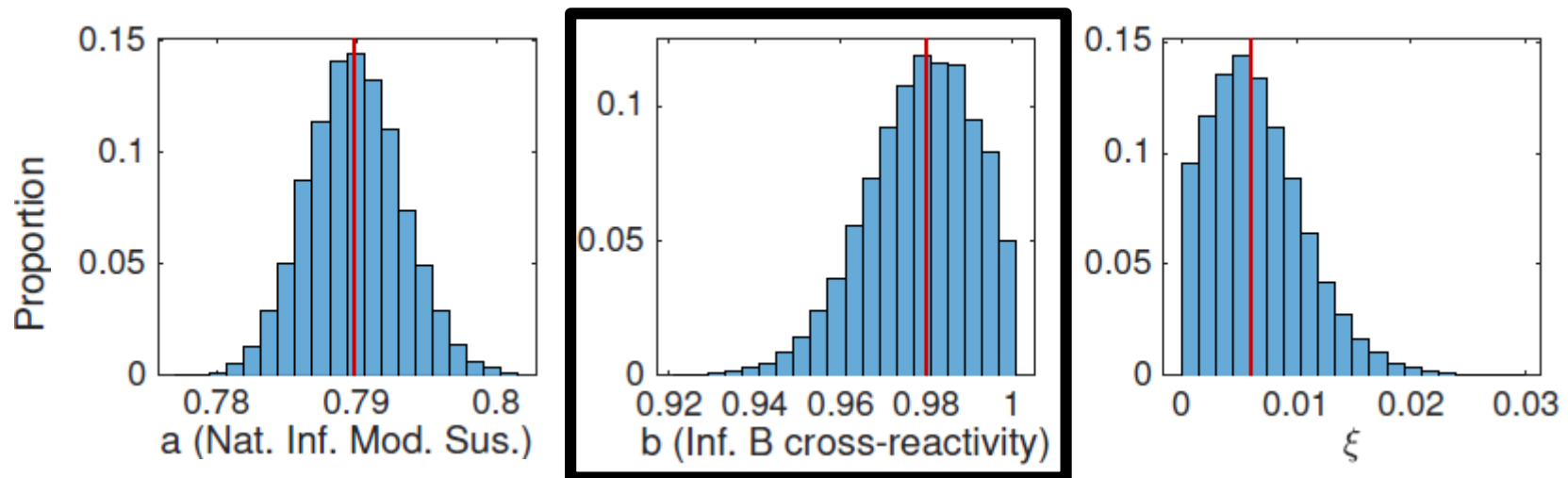
Figure C: Inferred posterior distributions for the immunity propagation associated parameters.



- Observe modulation of susceptibility due to propagation of immunity arising from natural infection.

Parameter fits: Immunity propagation

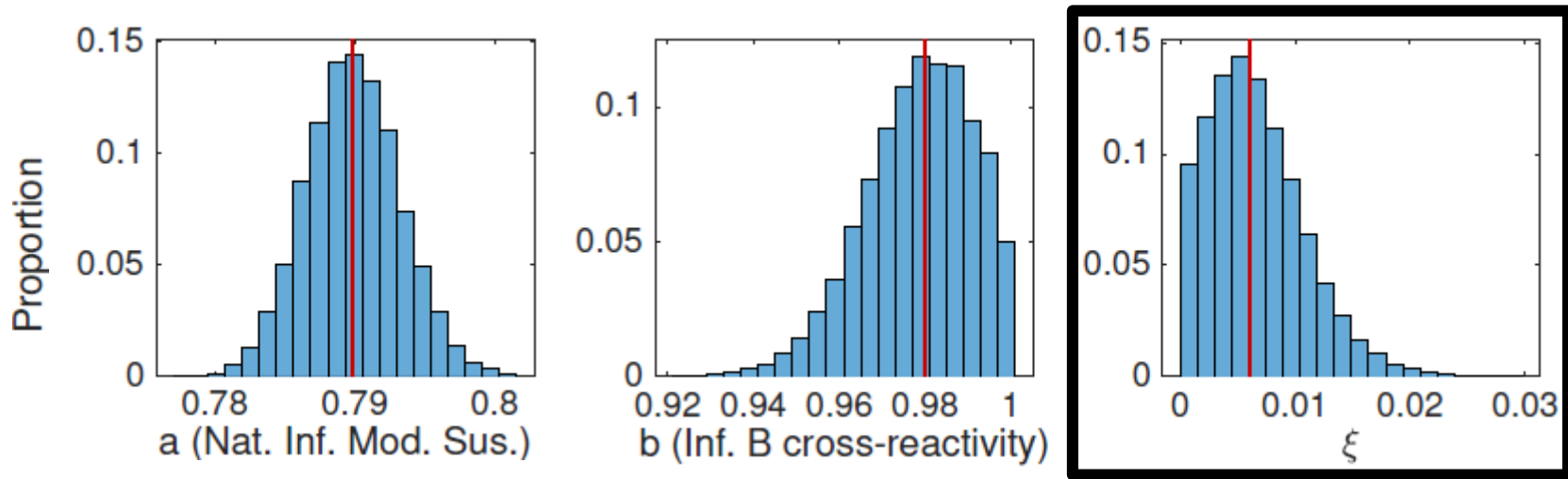
Figure C: Inferred posterior distributions for the immunity propagation associated parameters.



- Minimal propagation of influenza B cross-reactive immunity.

Parameter fits: Immunity propagation

Figure C: Inferred posterior distributions for the immunity propagation associated parameters.



- Very little carry over of prior season vaccine efficacy.
- Corroborates reports vaccine-mediated immunity wanes rapidly.

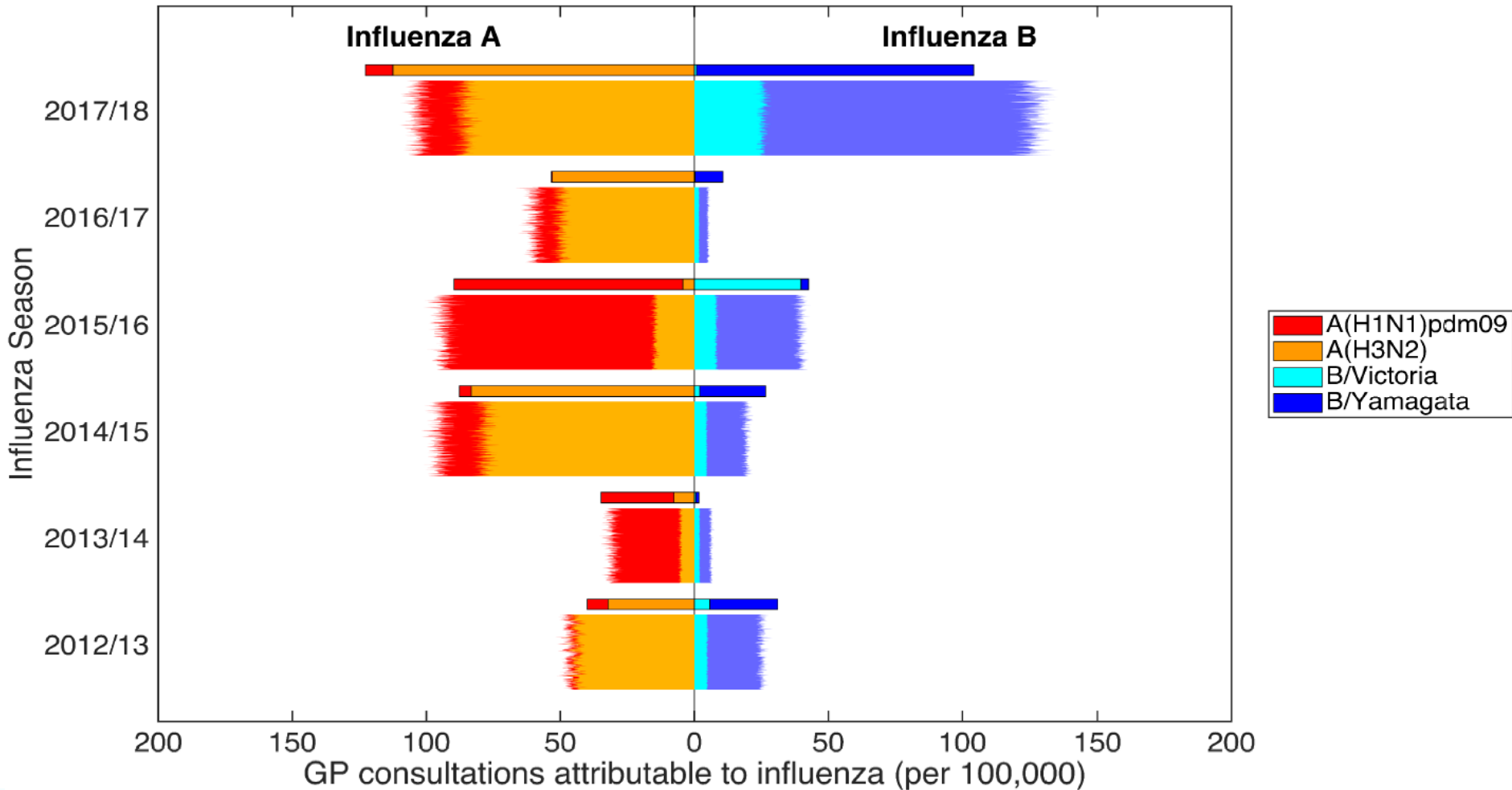
Reference: Kissling E, Rondy M, study team IMM. Early 2016/17 vaccine effectiveness estimates against influenza A(H3N2): I-MOVE multicentre case control studies at primary care and hospital levels in Europe. *Eurosurveillance*. 2017;**22**(7):30464.

Goodness-of-fit verification

- Perform 1,000 independent simulations using parameter sets drawn from the ABC inference procedure.
- Generate variability in epidemic composition due to the posterior distribution for the underlying parameters.
- Compare projected flu attributed GP consultations (per 100,000) to the data.

Goodness-of-fit verification

Figure: Posterior predictive distributions for influenza positive GP consultations per 100,000 population.



Limitations & future work

- Include age structure
 - Age-specific vaccine uptake and efficacy
 - Heterogeneous social contact patterns

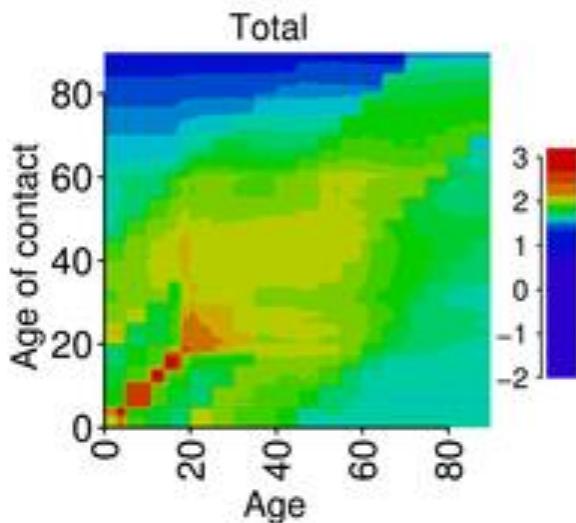


Figure: Representations in logarithmic scale of contact matrices by one-year age brackets for the United Kingdom.

Source: Reproduced from L. Fumanelli *et al.* Inferring the Structure of Social Contacts from Demographic Data in the Analysis of Infectious Diseases Spread. *PLOS Computational Biology* **8**(9): e1002673 (2012) .

Limitations & future work

- Include age structure
 - Age-specific vaccine uptake and efficacy
 - Heterogeneous social contact patterns
- Propagation of immunity limited to a single season
- Appraise cost-effectiveness of prospective vaccination programmes

Summary of advances

(1) Data amalgamation

- Compiled influenza vaccine and epidemiological data subsequent to the 2009 influenza pandemic for England.

(2) Mathematical model development

- Constructed a dynamic multi-strain SEIR-type transmission model for seasonal influenza, with immunity propagation mechanisms between seasons.

(3) Parameter inference

- Propagation of seasonal influenza immunity from one season to the next is weaker if vaccine derived, compared to natural immunity from infection.

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- Ivelina Yonova, Simon de Lusignan (RCGP & University of Surrey)

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