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(Inference For Epidemic-related Risk)

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Statistical inference for models of close-contact infection transmission: An application to varicella in Italy

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Outline

- Estimating transmission
  - The problem
  - Traditional approaches
  - Approaches based on social contact data

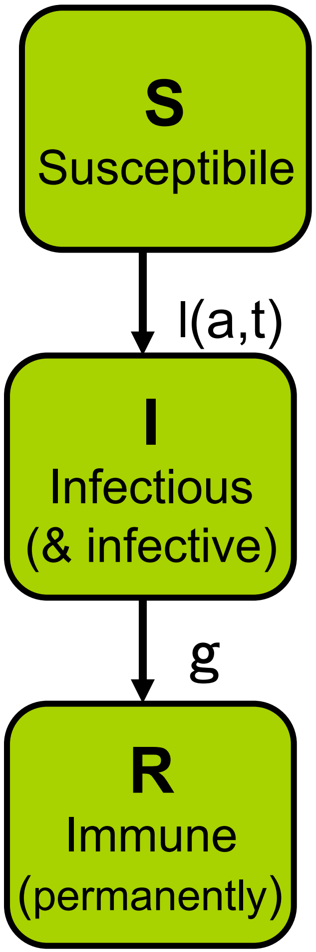
- Inference on transmission parameters
  - A sample of problems: VZV in Italy as case-study.
  - Non-parametric bootstrap inference on transmission parameters.

- Discussion

Dynamic infection transmission models
(infections imparting permanent immunity)

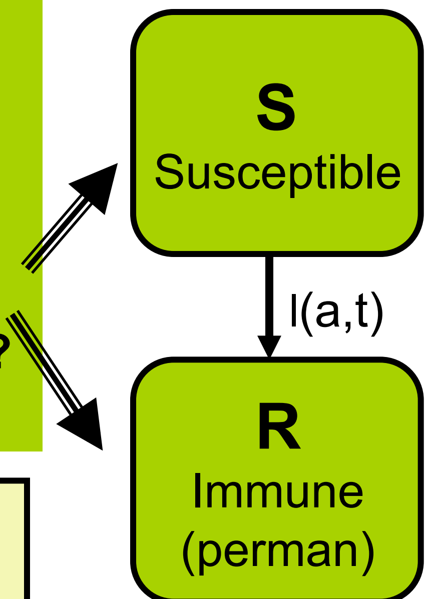
SIR model

l(a,t) = **Force** (“hazard rate”) **of infection**, age–specific
g= force of recovery ➔D=1/g= expected duration infective phase (7 days for VZV)



Disregarding the short infective phase (7days) the FOI “separates” two long phases of host life:
- ❖ the initial susceptible phase
- ❖ the final immunity phase.

Why not to consider an (simpler) SR model ?
(boiling down in a standard survival analysis)



Because evaluation of fundamental parameters (R_0) & policy applications (eg simulating impact of vaccination policies) require using the whole model !

Model equations at equilibrium (eg pre-vaccination period)

$$S'(a) = -\lambda(a)S(a) \qquad S(0) = 1$$
$$I'(a) = \lambda(a)S(a) - \gamma I(a) \qquad I(0) = 0$$
$$R(a) = 1 - S(a) - I(a)$$

S(a) = **Susc fraction aged a**
I(a) = **Infective fraction aged a**
R(a)= **Immune** fraction at age a

Equilibrium FOI :

$$\lambda_i = \sum_{j=1}^{m} q_{ij} C_{ij} \bar{I}_j$$

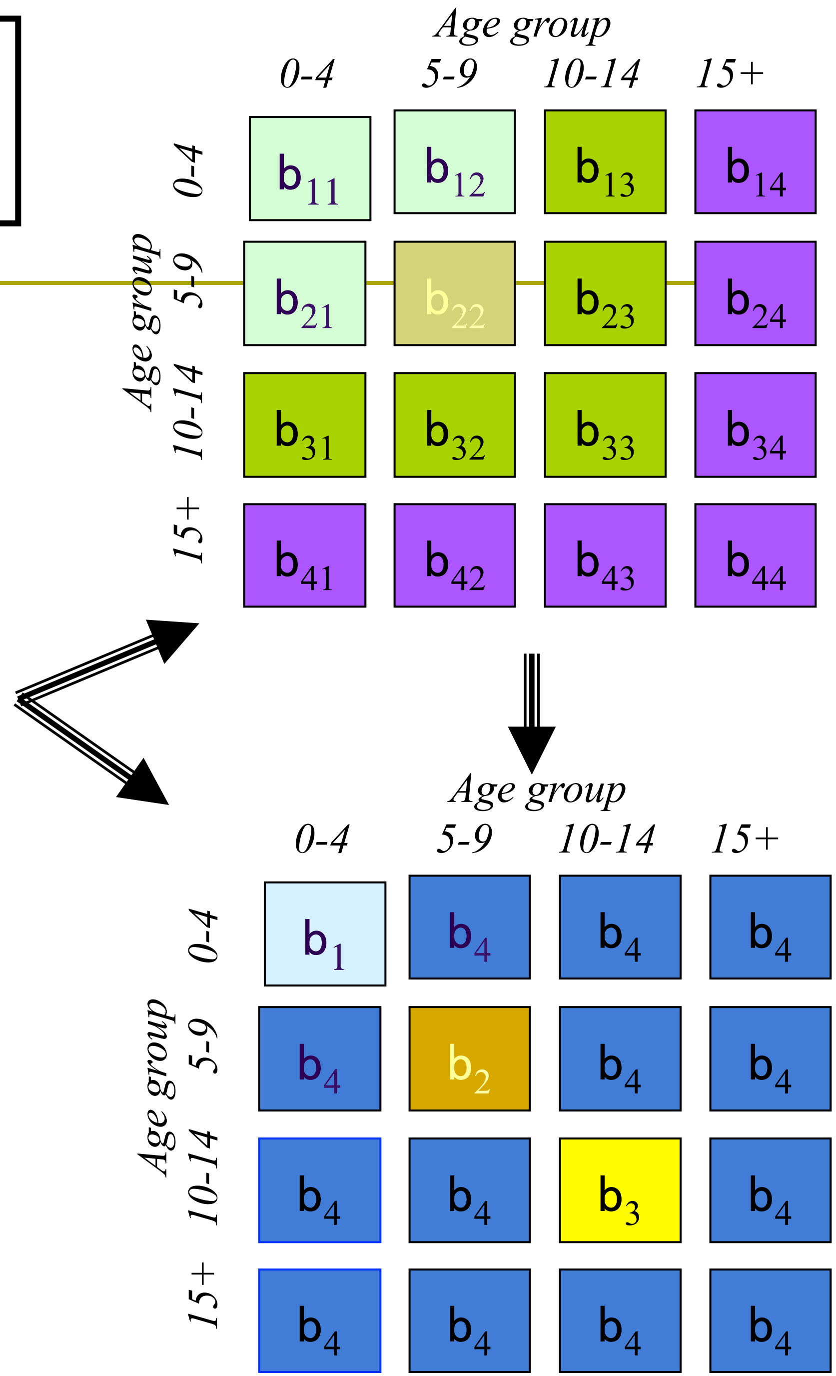
q_{ij}=transmission coefficient per single social contact (age-specific)

C_{ij}= mean number of contacts p.u.t between individuals i and j

2m^2 parameters to be estimated (m=number age groups) !

Traditional approach to estimating transmission

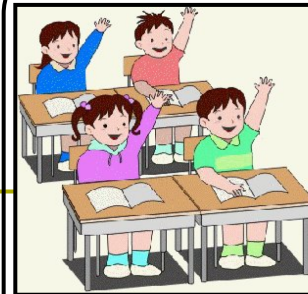
- **Indirect approach** via estimating the FOI from seroprevalence data.
- Use hypotheses ("WAIFW" matrices) to reduce number of unknown parameters from m^2 to m.
- Find transmission rates by solving the (linear) system of equations: $$\lambda_i = \sum_{j=1}^{m} \beta_{ij} \bar{I}_j$$
- **<u>No statistics !</u>**

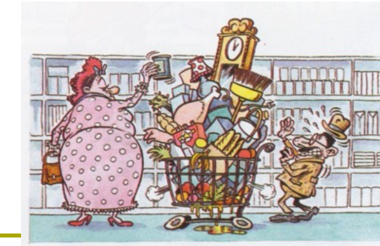
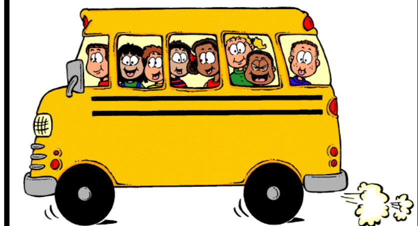


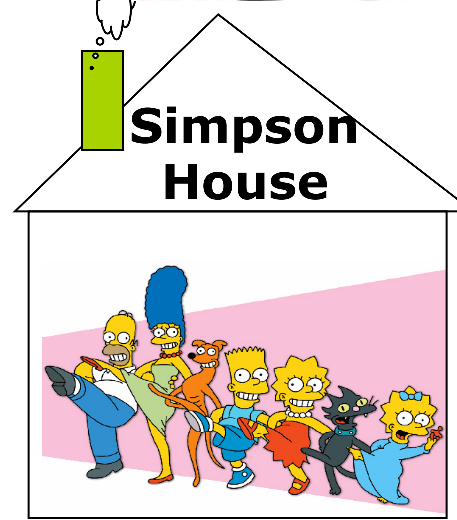
Social contact data

- POLYMOD project (FP6). Direct collection of contact data by contact survey in 8 European countries. (Mossong *et al.* 2008).
- **Definition of "at risk contact"**:
  - "Face to face" conversation.
  - Physical ("skin to skin") contact.
- **Diary-based survey.** Participants reported in a diary all different persons with whom an "at risk contact" occurred in a randomly assigned day. Also reported:
  - age/sex/location of the contact
  - Type (physical/non physical)
  - Duration, etc.

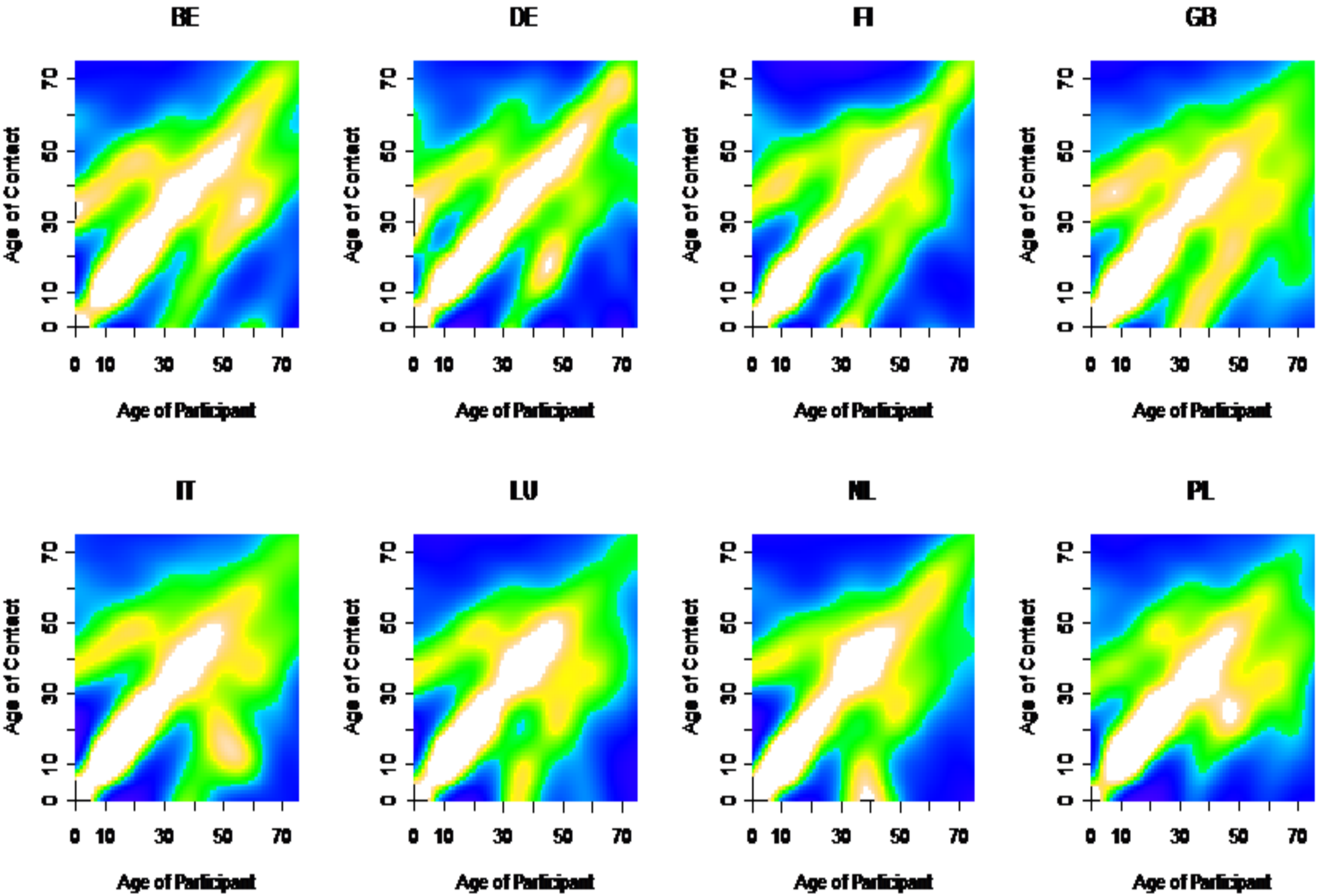
- Also possible to use artificially generated contact data (Del Valle *et al.*, 2007; Iozzi *et al*., 2010).





Source: Mossong et al. 2008



The "social contact" approach to estimating transmission

- Choice of one (or more) contact matrix

- "Social contact hypothesis": reduction of q parameters space by using 1 (constant) "transmission" parameter *q* for each chosen contact matrix

The statistical model: nonlinear regression model linking serological likelihood & contact data

- **Individual immune status**
- **Serological likelihood:**
  - k age groups (k=1…K>m), n_k observations
  - y_k =n. immune individuals
  - π_k =success probability (expected seroprev). It depends on unknown (q_1,..,q_s.) & known pars (C_{ij})
- **(the link)** The expected seroprevalence computed by solving the mathematical model over serological age groups taking contacts as known parameters.

$$Y_i = \begin{cases} 1 & immune \\ 0 & susceptibile \end{cases} \quad i = 1,\ldots,n$$

$$L = L(q_1,\ldots,q_s) = \prod_{k=1}^{K} L_k(q_1,\ldots,q_s)$$

$$L_k = \prod_{i=1}^{n_k} (\pi_k(q_1,\ldots,q_s))^{y_k} (1-\pi_k(q_1,\ldots,q_s))^{n_k - y_k}$$

$$\pi_k = R_k = 1 - \frac{1}{\lambda_k h_k}\left(\prod_{j=1}^{k-1} e^{-\lambda_j h_j}\right)\left(1 - e^{-\lambda_k (a_k - a_{k-1})}\right)$$

$$\lambda_i = \sum_{j=1}^{m} q_{ij} C_{ij} \bar{I}_j = \lambda_i(q_1 \ldots q_s)$$

The estimation problem

Maximise the log-likelihood of the observed seroprofile

$$\log(L) = \sum_{k=1}^{K} \sum_{i=1}^{n_k} \left[y_k \log \pi_k + (n_k - y_k) \log(1 - \pi_k) \right]$$

$$\pi_k = \pi_k(q_1, \ldots, q_s) = 1 - \frac{1}{\lambda_k h_k} \left(\prod_{j=1}^{k-1} e^{-\lambda_j h_j} \right) \left(1 - e^{-\lambda_k (a_k - a_{k-1})} \right)$$

Subject to:

- The chosen contact matrix & age grouping

$$C = \begin{pmatrix} C_{11} & C_{12} & C_{13} \\ C_{21} & C_{22} & \ldots \\ \ldots & \ldots & \ldots \end{pmatrix}$$

- $q_i > 0$ (positivity)
- R0>1

$$Dq \|C\| > 1$$

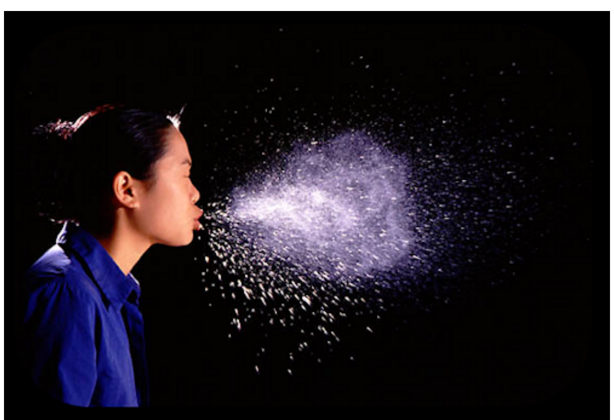
(pre-condition to have an endemic state and therefore to "observe a seroprofile"!)

- FOI equilibrium (discretised integral) equation

$$\lambda_i = \sum_{j=1}^{n} q_{ij} C_{ij} I_j = D \sum_{j=1}^{n} q_{ij} C_{ij} \frac{\prod_{h=1}^{j-1} e^{-\lambda_h h_h} \left(1 - e^{-\lambda_j h_j} \right)}{h_j}$$

Applications: estimating varicella transmission in Italy

- **Etiological agent:** "VZ" virus (herpes virus 3 family (HHV-3).
- **A childhood infectious disease** in industrialised countries.
- **Transmission** via close person-to-person contacts with infective subjects.
- **Duration infectious phase**: about 7 days.
- **Permanent immunity** after recovery.
- However the virus remains latent in the dorsal ganglia, and can reactivate at later ages when immunocompetency declines, causing **herpes zoster** ("shingles").



Experiments

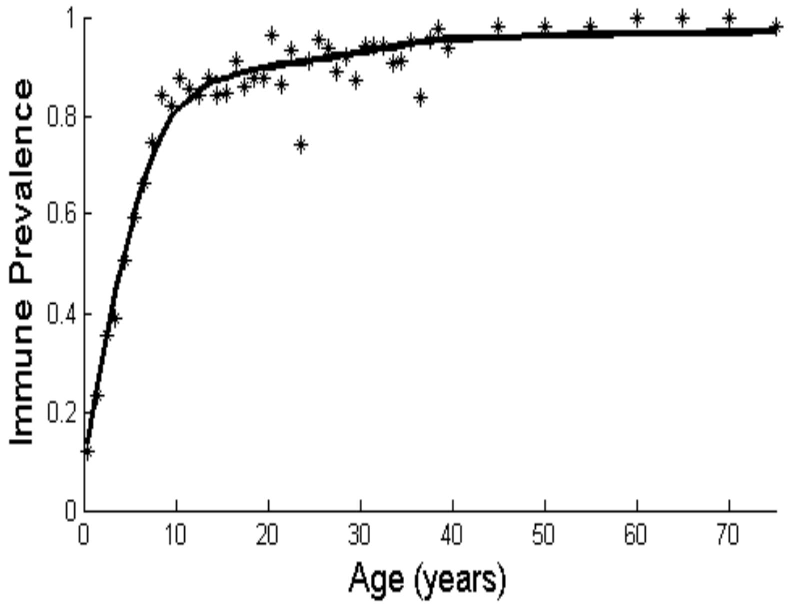
- Estimating simple 1-q models also considered in similar studies (Melegaro *et al.*, *submitted*; Goeyvaerts *et al.*, 2010)
  - M1: "all reported contacts"
  - M2: "physical contacts only"
  - M3: "physical contacts of prolonged duration (>15 min)"

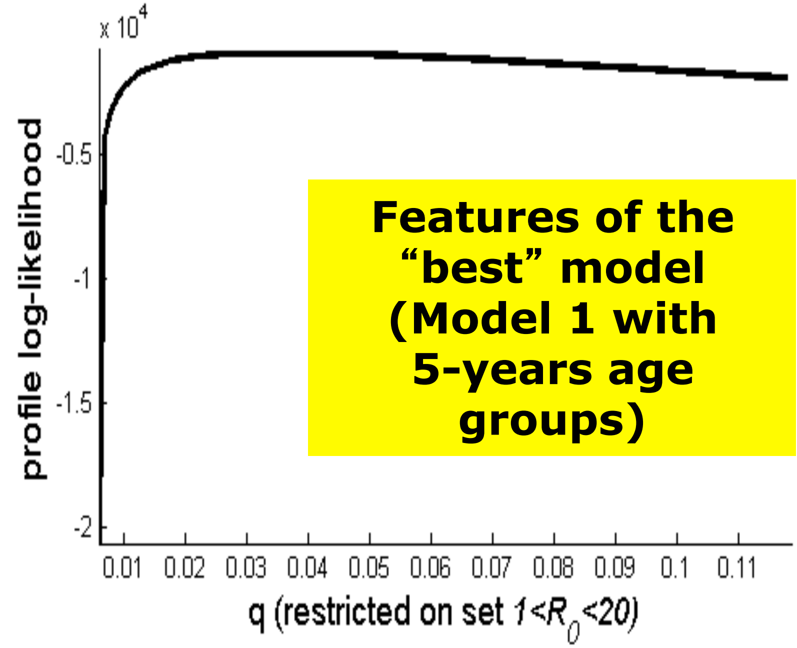
- Bootstrap inference
  - Non-parametric (=re-sampling individuals)
    - serological data
    - contact data
  - "design consistent"
  - Evaluating relative contributions of the two sources of uncertainty
    - separate re-sampling of each source
    - joint re-sampling
  - performances of different types of bootstrap CI (e.g., looking at "real" vs. "nominal" coverage).

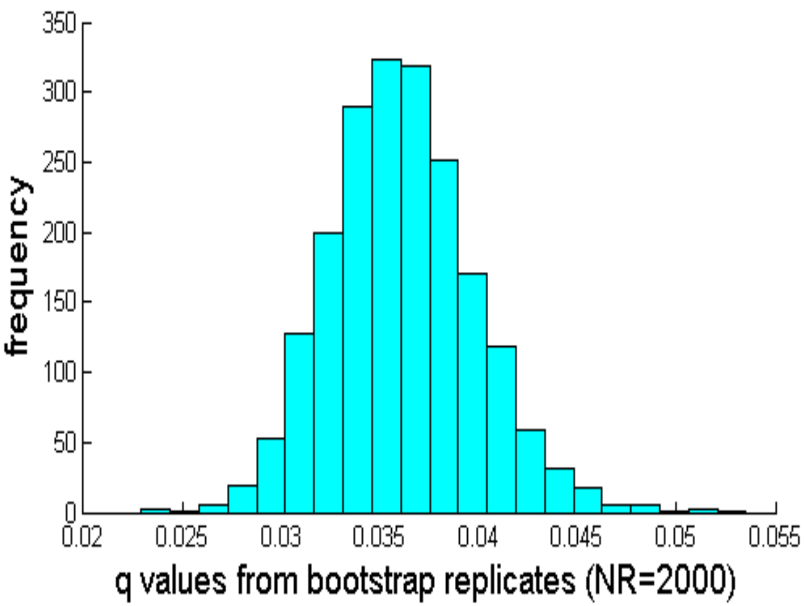
Age grouping	5-years					School	0-2, 3-5, 6-10, 11-13, 14-18, 18-25, etc		
	q	R0	Deviance	AIC		q	R0	Deviance	AIC
Model 1 (1-q)	0,0355	5,97	30,25	1903,10		0,037	6,15	49,38	1922,20
All reported contacts	(0,0339; 0,379)					(0,034;0,0390)			
Model 2 (1-q)	0,049	4,66	32,57	1905,40		0,0510	4,91	60,11	1933,00
Physical contacts only	(0,0465;0,0515)					(0,0484;0,0544)			
Model 3 (1-q)	0,0527	4,18	35,97	1908,80		0,0553	4,49	65,13	1938,00
Physical contacts	(0,0496; 0,0565)					(0,0523;0,0615)			
>15 min									

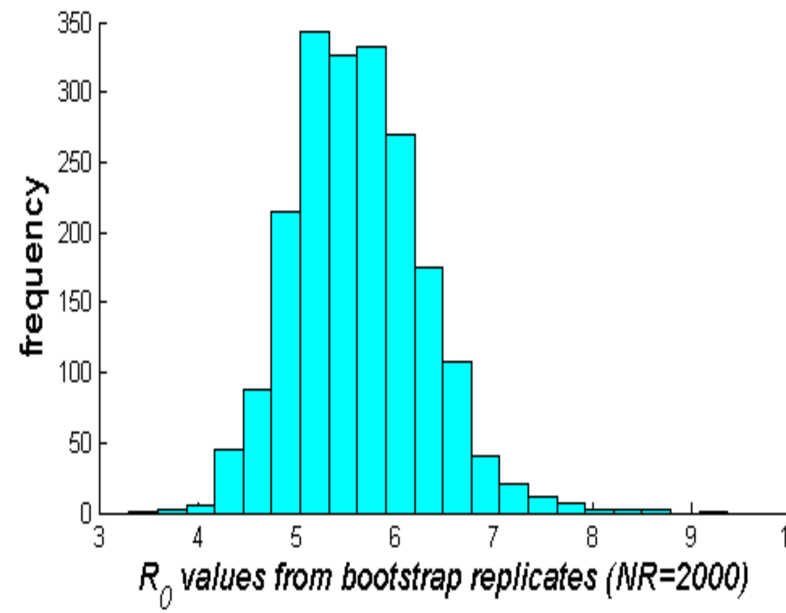
Role of age grouping: 5-years vs school

Features of the "best" model (Model 1 with 5-years age groups)



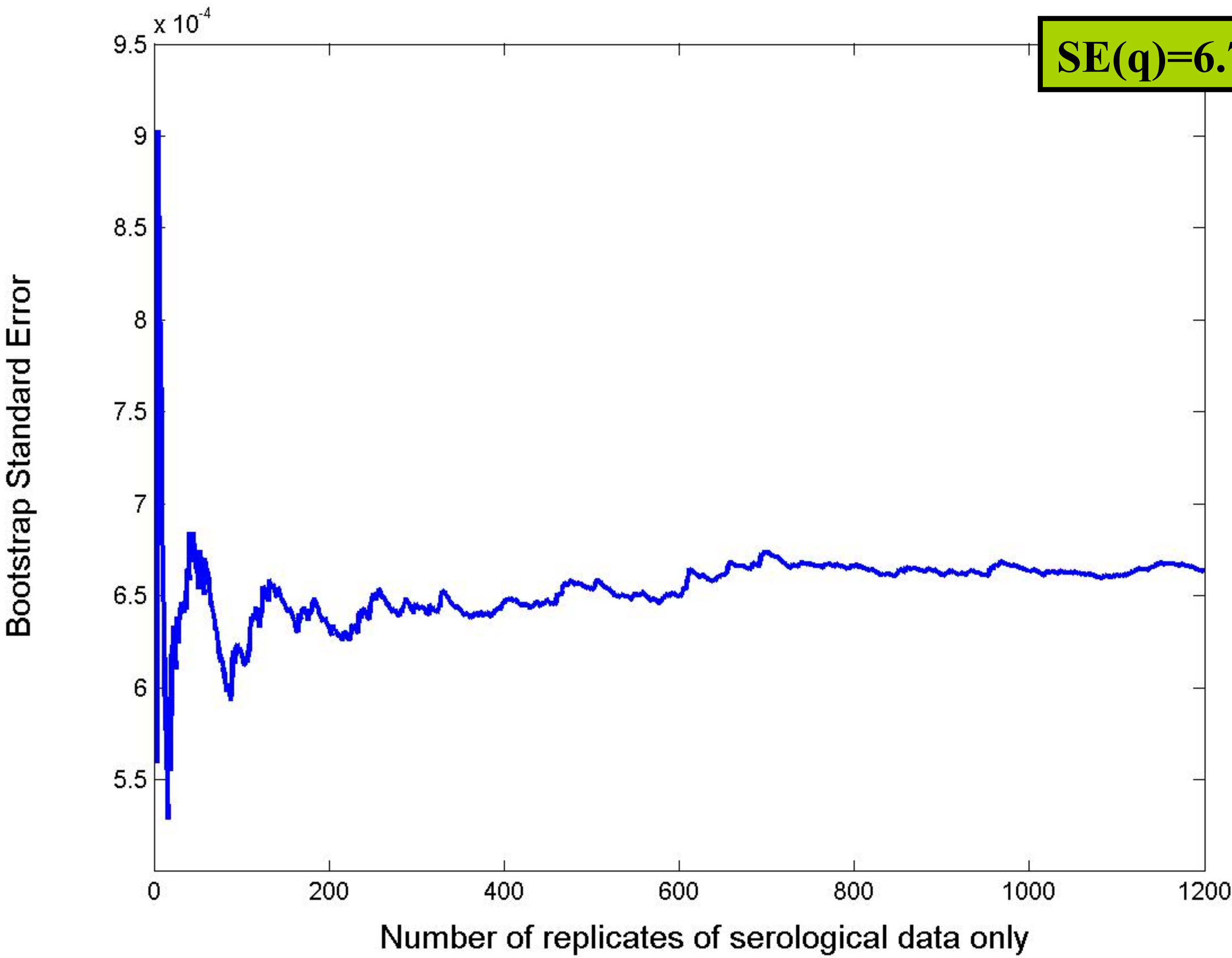






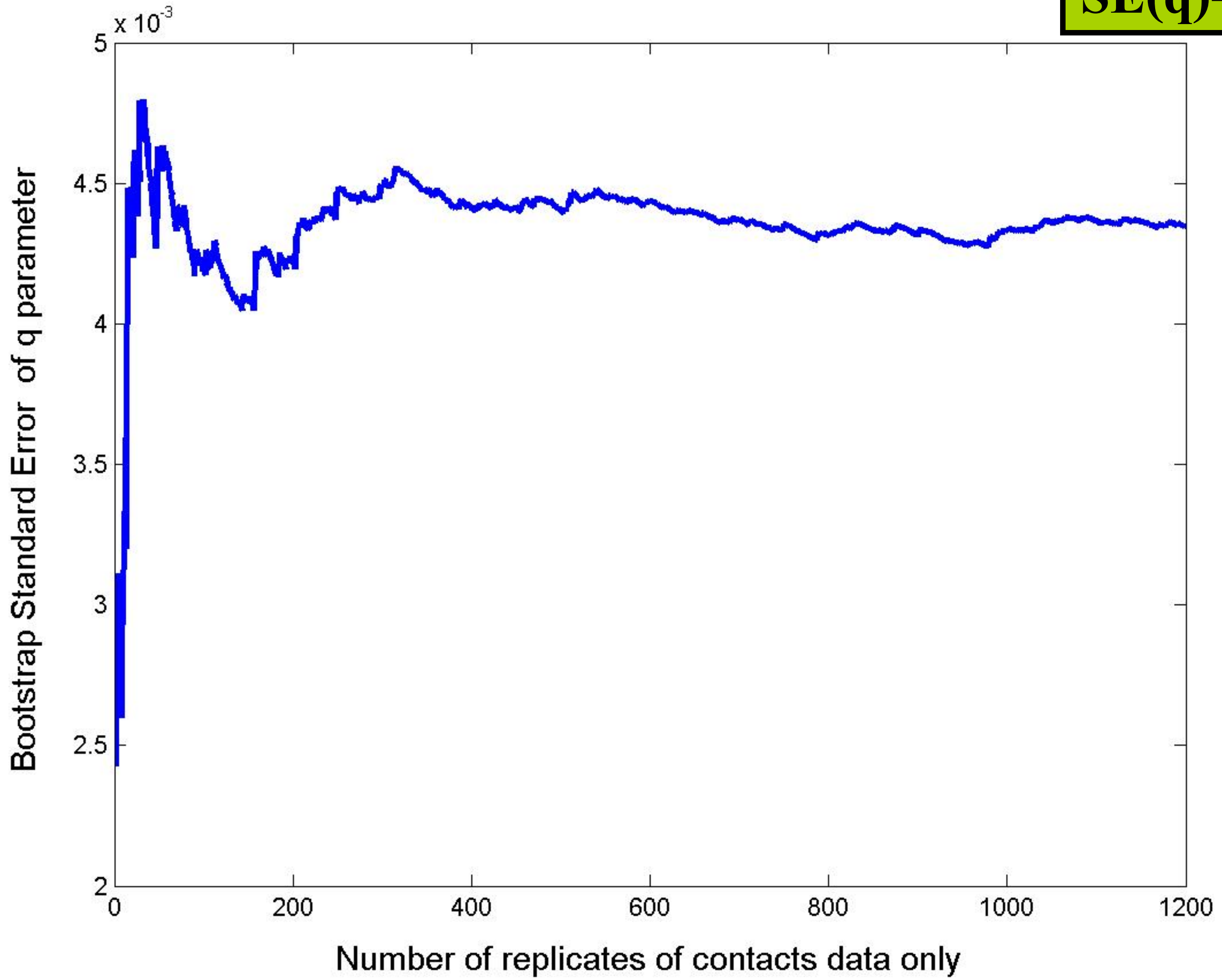
M1 Model, 1-q, “all registered contacts” Bootstrapping (“design-consistent”) serodata only

SE(q)=6.7*10^(-4)



M1 Model, 1-q, “all registered contacts” Bootstrapping (“design-consistent”) contacts data only

SE(q)=4.4*10^(-3)



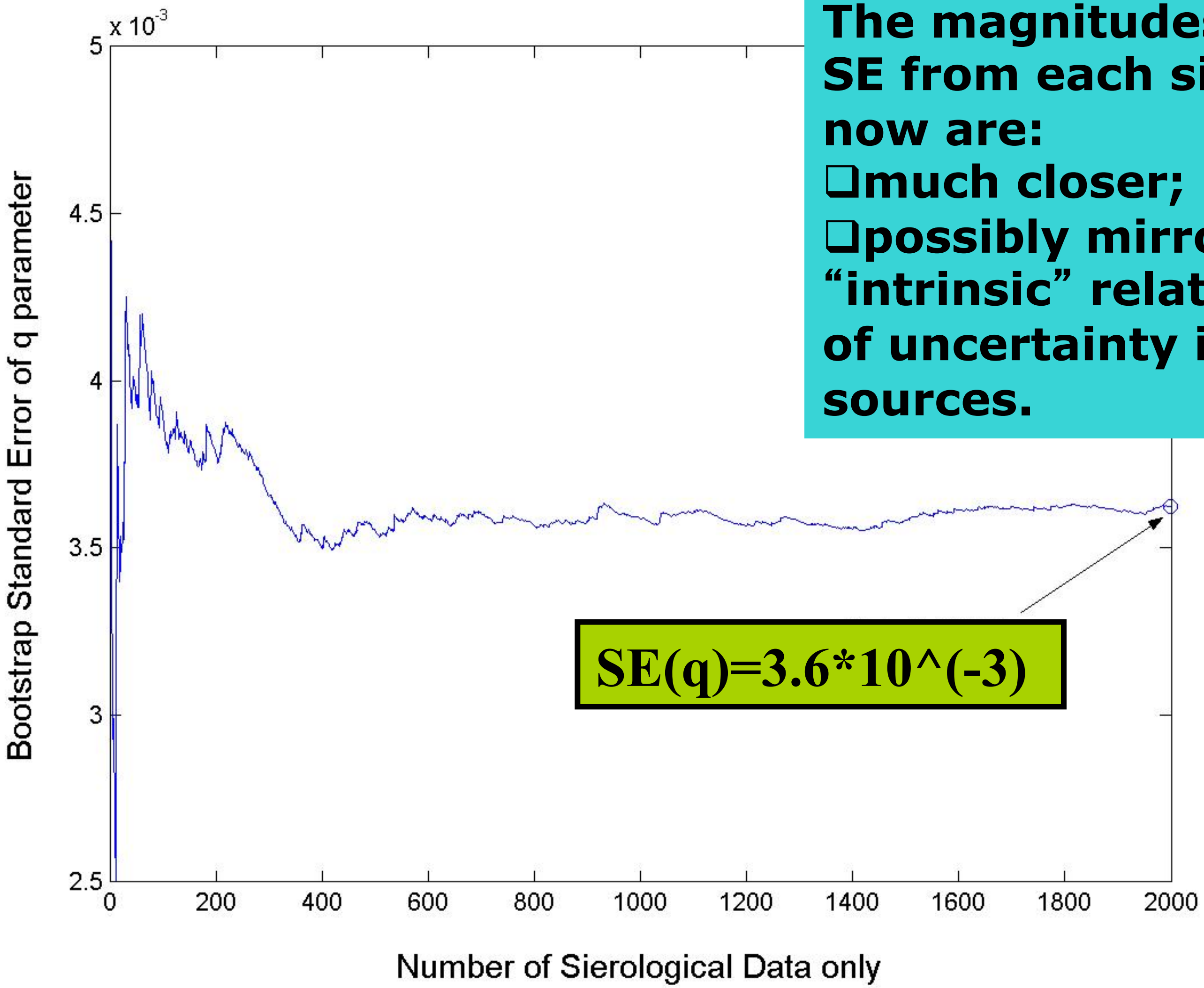
Contacts appear to be the most important source of uncertainty.

The comparison is naive however, given that the two sources concur with largely different numbers of observations: number of serological samples (2446) three times as higher as the number of contact data (845).

Keeping sample size under control:

Keeping fixed the serological proportions per age group, we simulated a serological sample of 845 individuals.

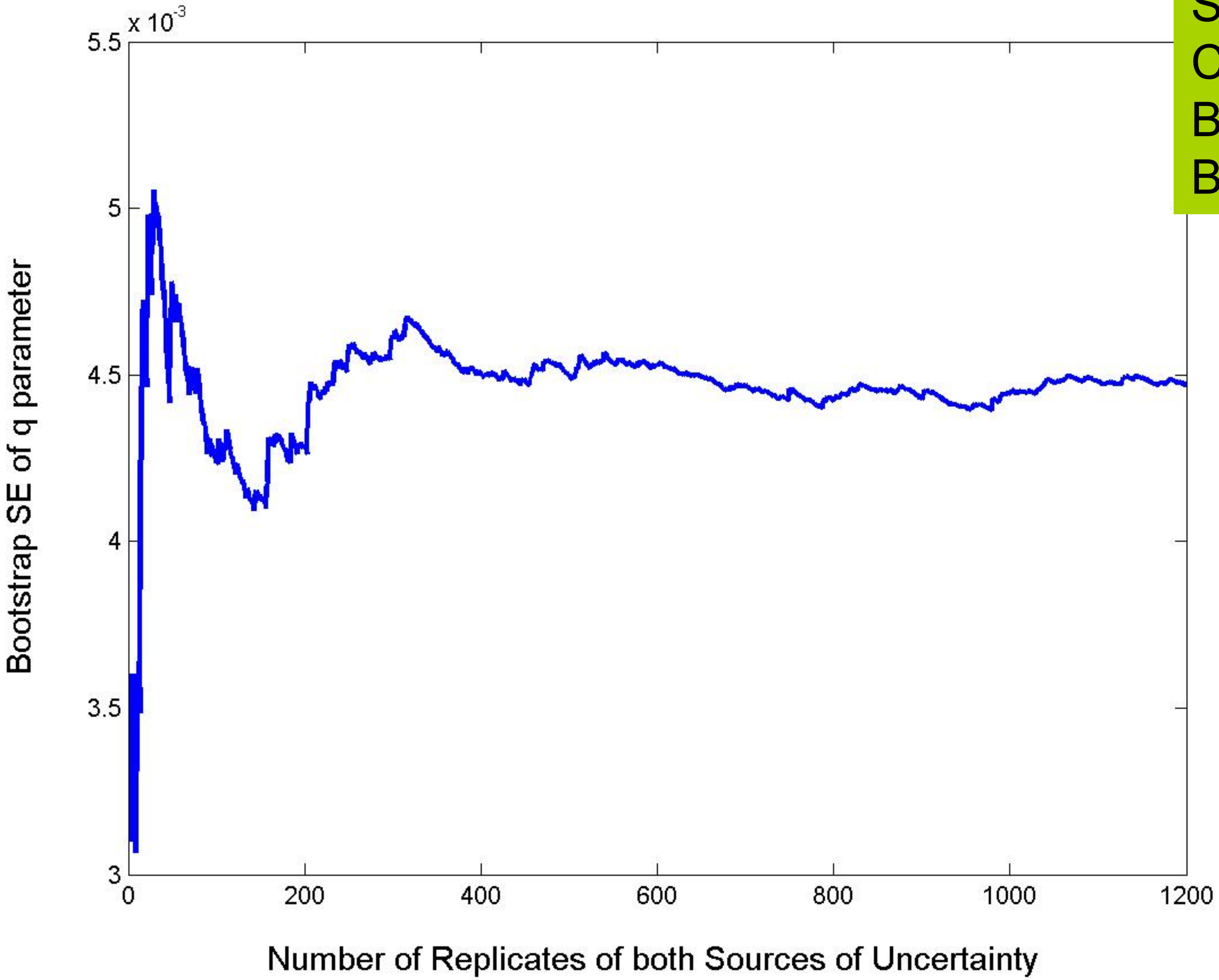
M1 Model, 1-q, "all registered contacts" Bootstrapping sero-data only, but size of serological sample equal to contact sample (other things – e.g., seroprevalence - being equal)



The magnitudes of the "ideal" SE from each single source now are:

- **much closer;**
- **possibly mirroring the true "intrinsic" relative magnitude of uncertainty in the two sources.**

M1 Model, 1-q, "all registered contacts"
Joint bootstrap ("design consistent") of both sources
(1 replicate = 1 resampling from both sources)



SE= 4.5*10^(-3)
CV= 0.1403
BIAS= -1.1*10^(-4)
BIAS/SE= -0.0258

Which bootstrap CI performs better for estimating transmission? (a frequentist experiment: real vs. nominal 95% coverage)

IC	q (Nominal: 1-α=0.95)
Normal	**0.898**
Percentile	**0.937**
BCa (Efron, 1987)	**0.959**

Keeping fixed q, we resampled serological and contact data many times. In this way, we got a series of bootstrap CI's. Then, we computed the proportion of CI's containing the "true" value of q.

Discussion: bootstrap inference & transmission pars

- **Design-consistent bootstrapping per age group provides narrower CI’s with respect to naive resampling (disregarding from the age structure), for any level of nominal coverage.**

- **Contacts appear to be the most important source of uncertainty (under standard sample size).**

- **The bootstrap normal CI shows a real coverage too low, while the BCa CI performs well, as expected.**

Future research

- **Why is a certain contact matrix working better than others? Deepening our understanding of the internal structure of a contact matrix, beyond assortativeness.**

- **Alternative approaches to bootstraap, e.g., MCMC approaches, bayesian melding (Alkema *et al.,* 2007).**

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