Modelling varicella and zoster in Europe: can we cope with the current decision paralysis on mass immunization ?

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Predictive Models for Biomedicine & Enviroment

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VARICELLA

Varicella infection has a worldwide distribution. In absence of intervention:

- 80% of children under 10 years have had varicella
- 95% of adults are immune

Caused by VZV (a DNA virus of the Herpes group)

- Transmission by direct contact with an infective subject
- Duration infective phase: about 7 days
- Permanent immunity after recovery
- Main complications: varicella pneumonia and Encephalitis

Rates of mortality vary strongly with age:

- children less than 1: 6-8 per 100,000
- 1-14 years: 0.75 per 100,000
- 15-19 years: 2.72 per 100,000
- 30-49 years: 25.2 per 100,000
- Encephalitis occurs in older teenagers and adults in 1 per 3,000
- 30% of children with leukemia who acquire varicella have severe infections (21% mortality)

Varicella & Zoster

Development of zoster

- after recovery the virus remains latent in specific body sites (the dorsal root ganglia) and can reactivate at later ages, causing herpes zoster (HZ).
- HZ causes significant morbidity (can evolve in the very long and painful post-herpetic neuralgia) and mortality.

Mechanisms underlying the development of zoster and the relation between zoster and varicella

- poorly understood
- the prevailing view is that reactivation occurs endogenously due to the decline of Cell Mediated Immunity (e.g. by aging, other diseases, chemotherapy, etc).
- after Hope-Simpson (1956) some evidence has accumulated that re-exposition to VZV might be protective against zoster by boosting of Cell Mediated Immunity

[Brisson et al., Vaccine, 2002] [Thomas et al., Lancet, 2002] [Ogunjimi et al., Viral Immun, 2011]

Current situation

- A live attenuated varicella virus (Oka) vaccine is available since 1970.
- Safety, immunogenicity, and effectiveness in protecting against infection and disease documented by a number of studies.
- US: mass routine immunization of children since 1995.

However: introduction of mass immunization against VZV in Europe is currently under paralysis (mass programs in place only in Germany and Sicily).

Varicella vaccination & the decision paralysis

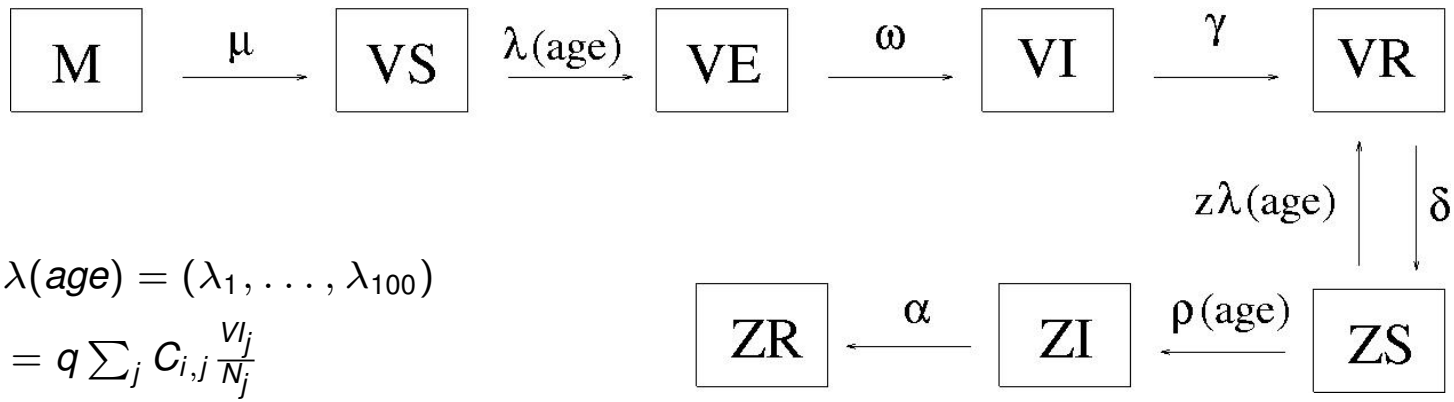
Current situation:

- One cause of the paralysis: the ambiguous responses of mathematical models depending on the postulated relationship between varicella and zoster epidemiology [Bilcke et al., 2011].
- Models postulating a large protective effect of re-exposition to VZV immunity unavoidably predict a perverse impact of varicella mass vaccination on zoster in the short-medium term.
- Models postulating a low impact of boosting of VZV immunity on zoster suggest that VZV vaccination is cost-effective.
- Though new immunological studies have been undertaken to better document [Ogunjimi et al., 2011] the role of re-exposition to VZV on Cell Mediated Immunity, this does not clarify the population effect of boosting.
- Some moderate evidence of increase in zoster incidence in sites where mass vaccination is in place (US, Canada), though still unclear whether this is the consequence of vaccination.
- In recent times also a vaccine against zoster has been licensed having the potential to mitigate the possible perverse effects of varicella vaccine on zoster. A first modeling study available [Van Hoek et al., 2010] but more robust estimates of the vaccine features are needed.

However many problems remain.
In particular the fact that varicella disease is perceived as ”minor”, i.e. characterized by a very small perceived risk of serious disease compared to other infections, which threatens the possibility to achieve and maintain adequate vaccine uptakes.

The Model

- RAS - Realistic age-structured
- model for pre-vaccination dynamics (equilibrium)



where $\lambda(age) = (\lambda_1, \ldots, \lambda_{100})$

and $\lambda_i = q \sum_j C_{i,j} \frac{VI_j}{N_j}$

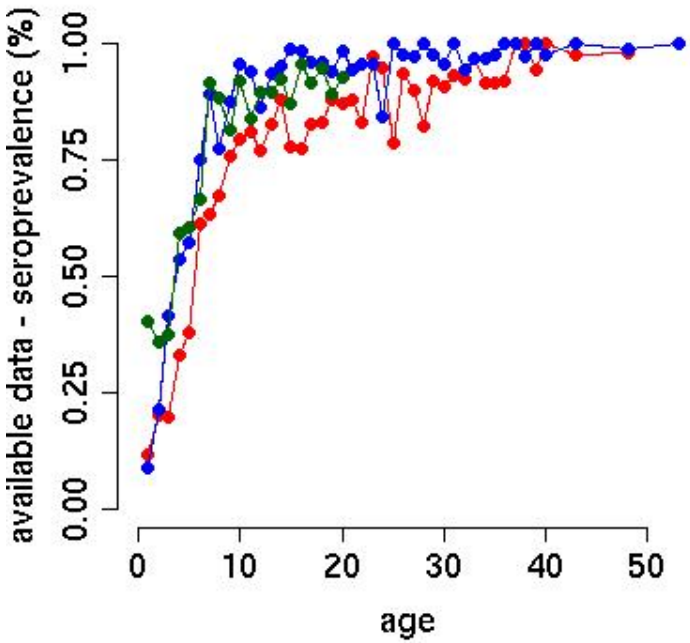
$\rho(\text{age}) = \omega e^{-\phi(\text{age})} + \pi(\text{age})^{\eta}$

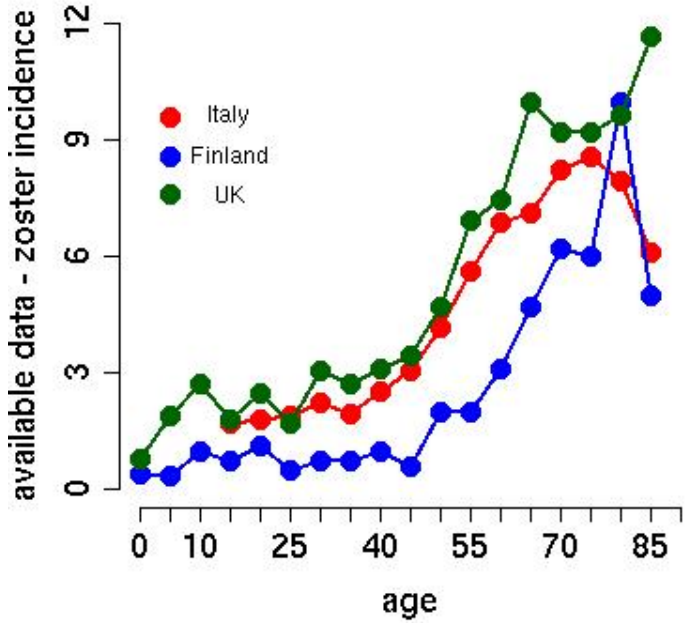
Investigation strategy

- a relevant effort for estimating contact patterns: modeled by the artificial matrices computed using routine sociodemographic data and now available for 26 countries
- 1st. goal: capture varicella transmission using serological data
- reproduce zoster data conditionally on estimates on varicella transmission
- 2st. goal: investigate the impact of different vaccination programs by sensitivity and uncertainty analysis

Objectives of the project

- target: modeling the impact of VZV vaccination on the European scale
- goal: evaluating the epidemiological impact and cost-effectiveness of VZV vaccination





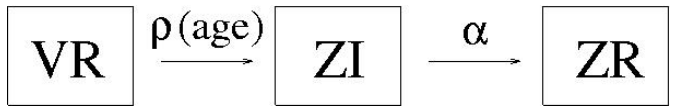
Available Data:

- Age specific varicella seroprevalence: 13 European countries (ESEN2)
- Age specific varicella incidence (EUVAC.NET data)
- Age specific zoster incidence: currently IT, FI, UK
- Age specific contact patterns: Polymod data [Mossong et al., PLoS Med, 2008], Time-Use data [Zagheni et al., AJE, 2008], Artificial matrices [Iozzi et al., PLoS CB, 2010], [Fumanelli et al., submitted, 2011]

How is possible to reconstruct zoster data?

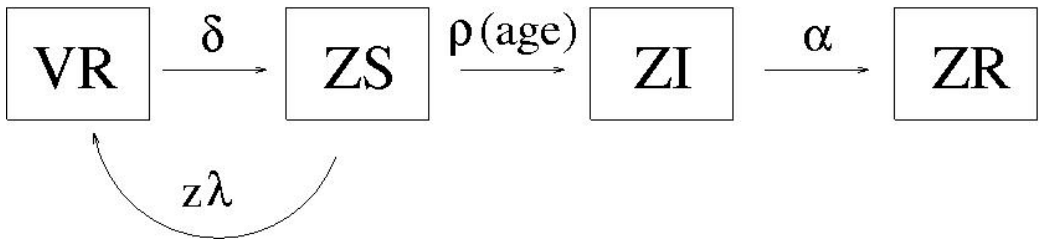
1st The simplest model for zoster incidence

- good fit BUT we know that zoster doesn't work like this
- no way to consider the effect of varicella vaccination on boosting



2nd The prevailing view about natural progress from varicella to zoster

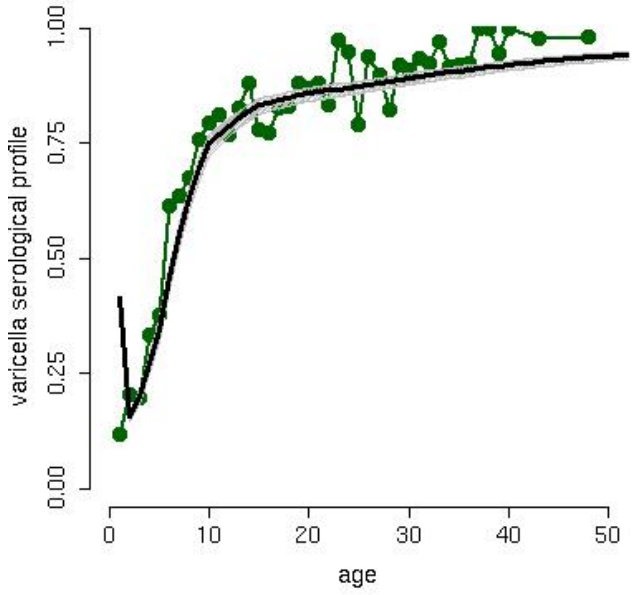
- considers also intermediate processes (development of susceptibility to zoster & the boosting hypothesis)
- hardly identifiable [Jacquez, 1998] from zoster data only, due to the lack of information on intermediate process

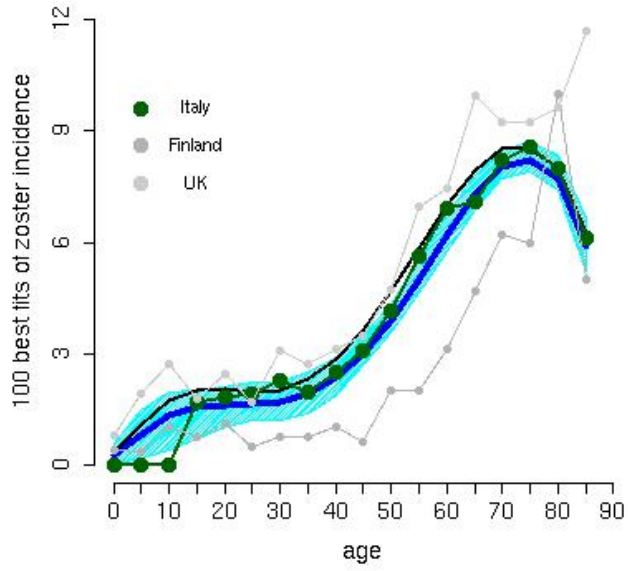


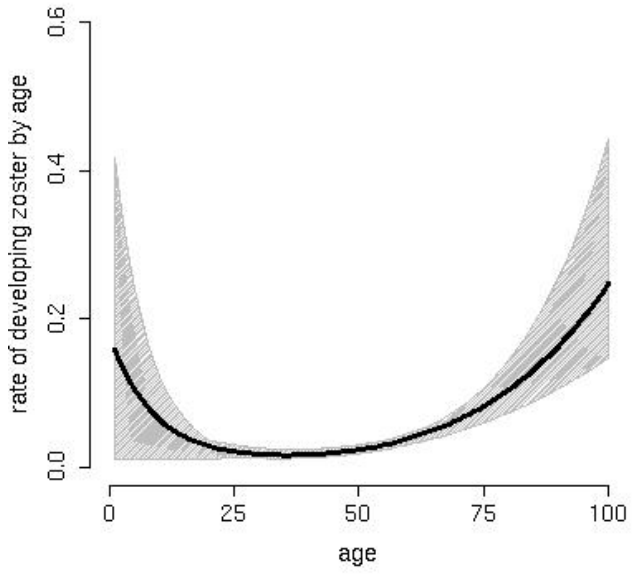
Change of perspective needed?

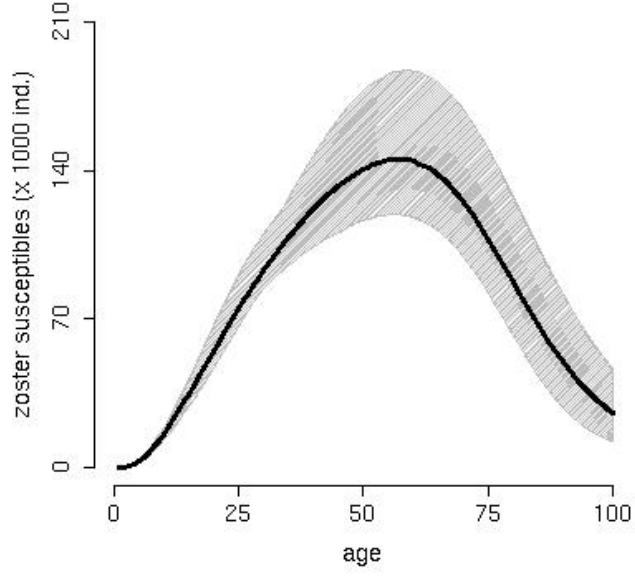
- renouncing to the idea of robustly estimating of single parameters & (intermediate) processes
- considering instead ALL parameters configurations consistent with zoster data
- identifying robust implications for vaccination programs among these different configurations (consider plausible scenario where robustness is absent)

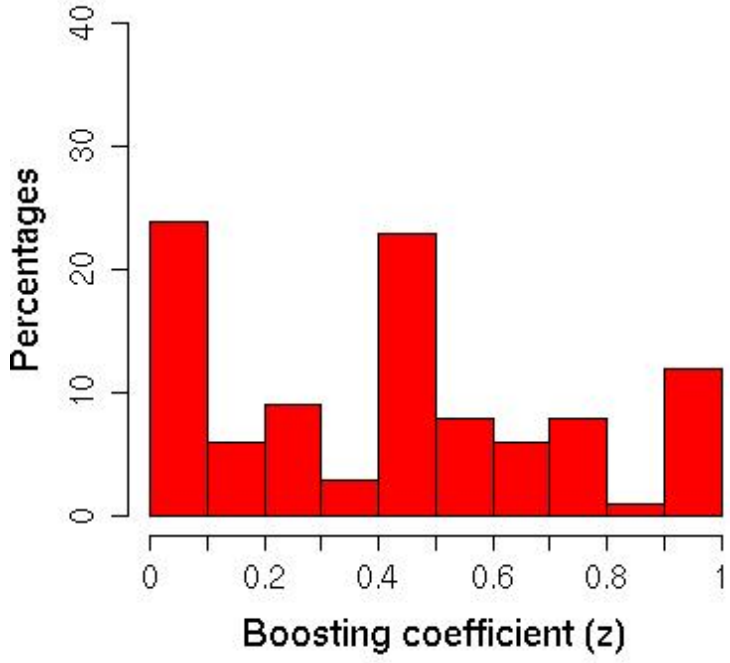
A PILOT COUNTRY: ITALY

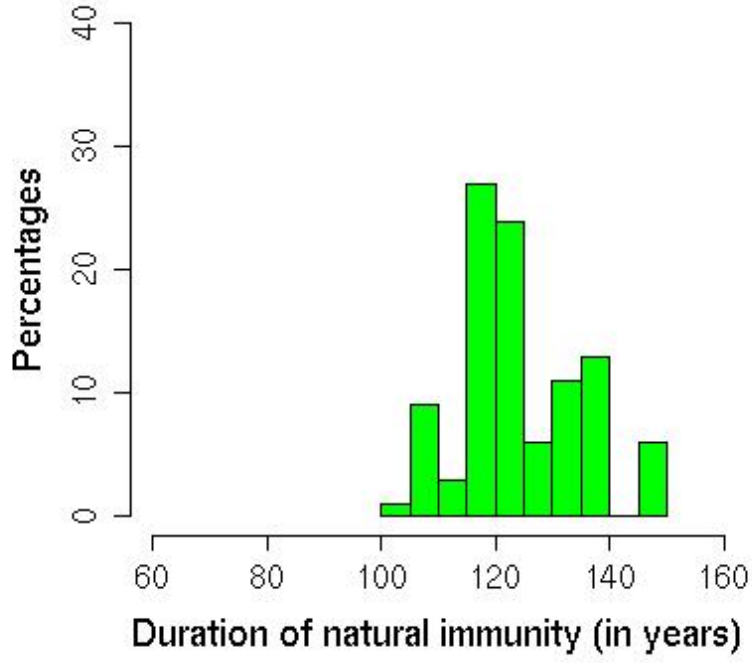








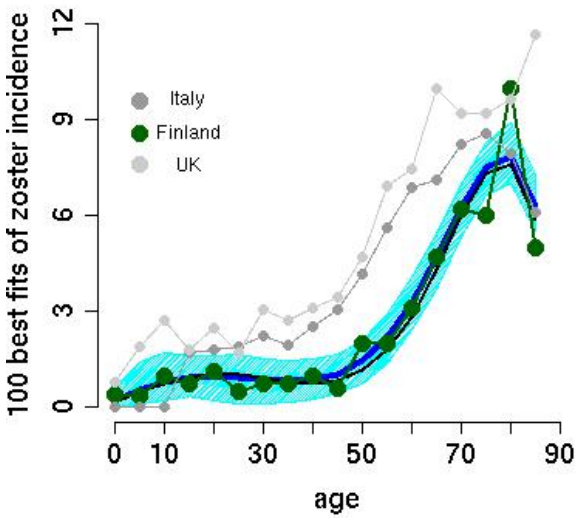


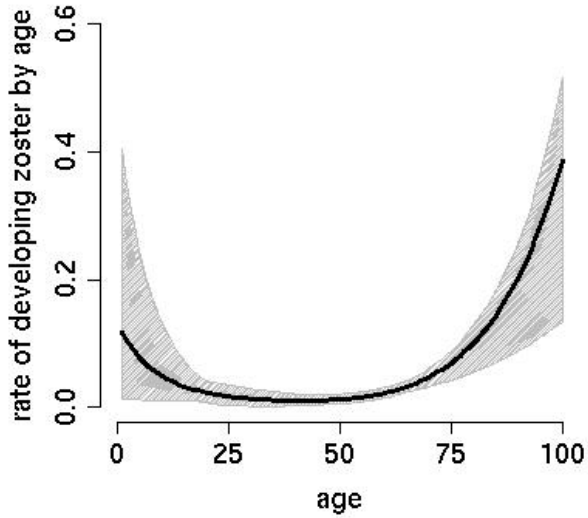


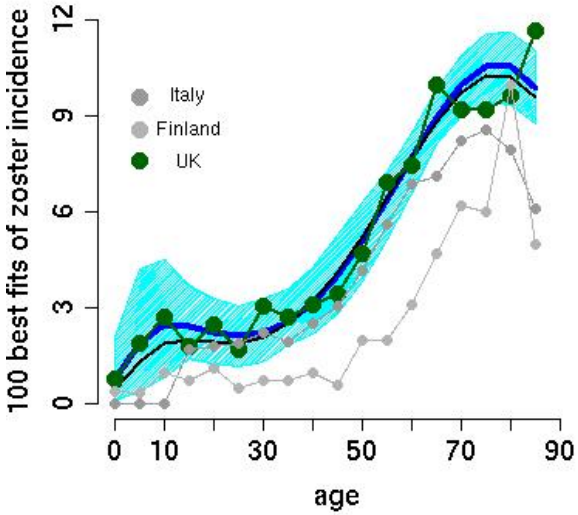
REMARK

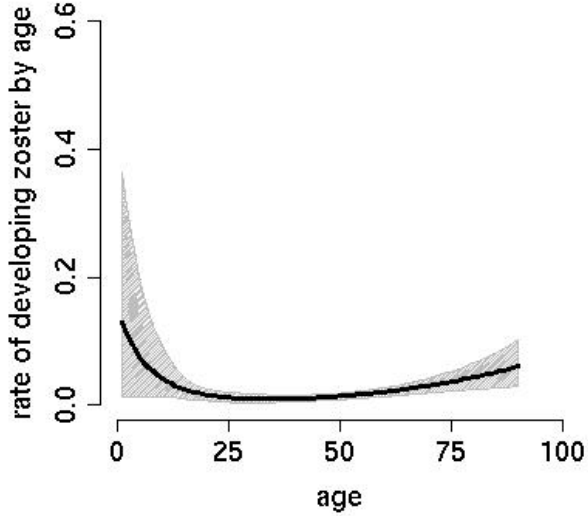
- Our results show that many different configuration of parameters can reproduce available zoster data, some very different from estimates found in the literature.
- Past works have estimated the average duration between varicella infection and zoster susceptibility as 20 years [Brisson et al., Vaccine, 2002], a value used in many subsequent work [Van Hoek et al., Vaccine 2011]
- Nonetheless: values of $1/\delta$=120 years are not to be considered trivial: they suggest that the process of developing susceptibility to zoster is in average longer than human life, or that some heterogeneity exists: e.g. only a fraction of those immune to varicella actually develop susceptibility to zoster ($\simeq$ 33% lifetime zoster risk)

RESULTS ON DIFFERENT COUNTRIES



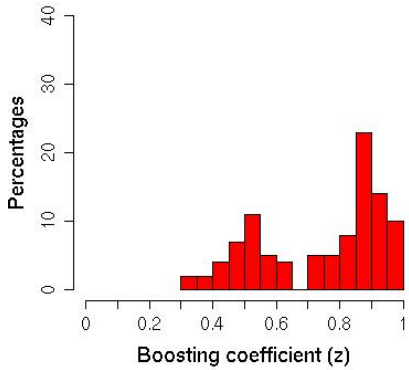


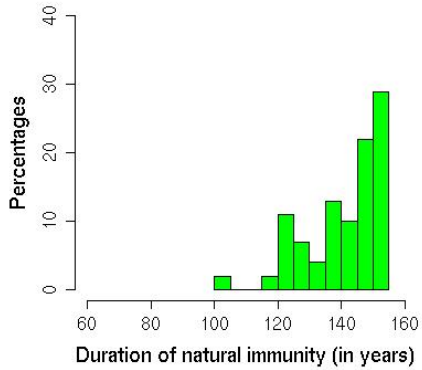


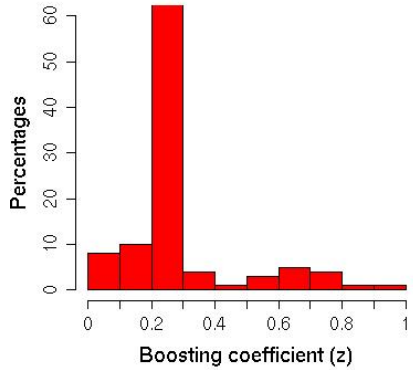


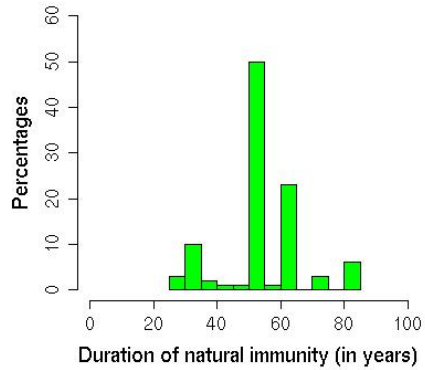
Some predictions (e.g. on risk of developing zoster are sufficiently stable

VERY GOOD FITS BUT...









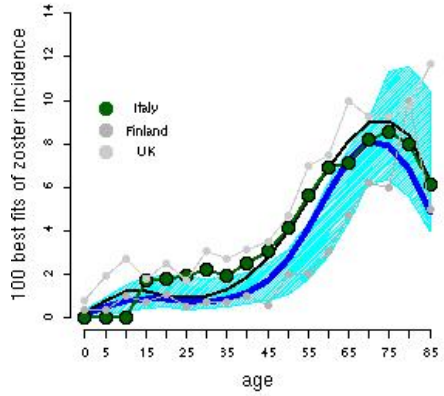
THE PERVERSE EFFECT

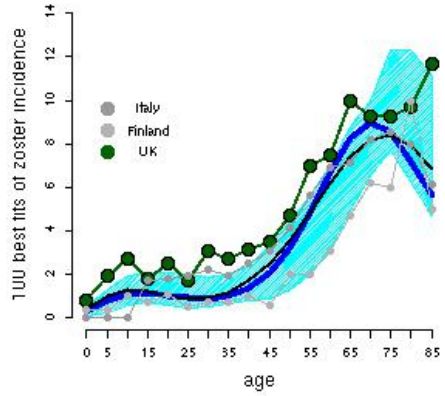
- still: different configuration of parameters can reproduce the same data. This is not unexpected given the lack of identifiability (ok)
- zoster-related parameters show very large inter-country variation (sounds bad)
- IN FACT: those parameters related to inherently biological phenomena (e.g. loss of CI) are expected to be ”invariant” among countries
- idea: try fitting data from several countries simultaneously

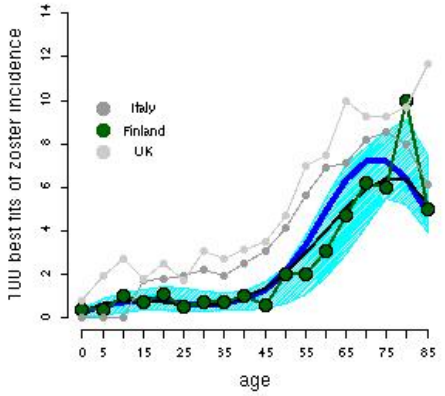
VERY PRELIMINARY RESULTS

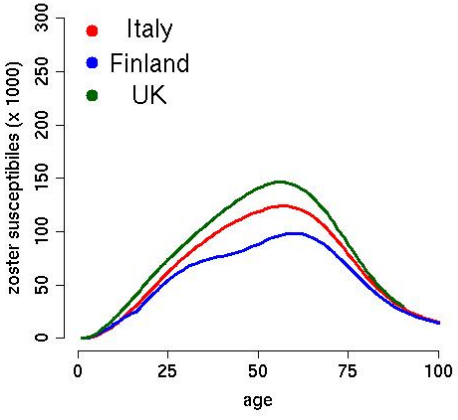
Work in progress: next results are based on a “small” number of runs

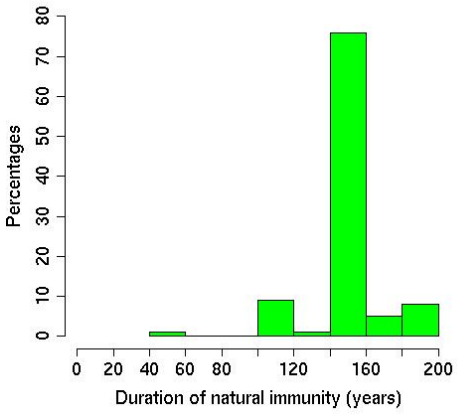
However, things seem to work.

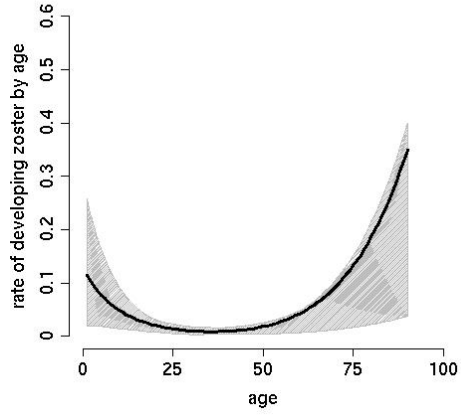

100 best fits of zoster incidence
Italy
Finland
UK
age

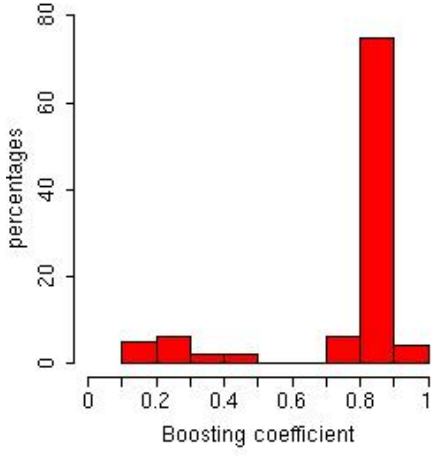

100 best fits of zoster incidence
Italy
Finland
UK
age

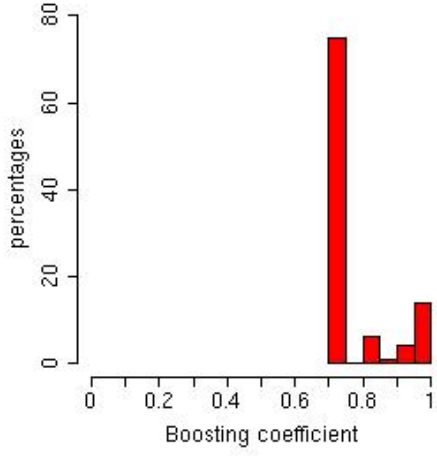

100 best fits of zoster incidence
Italy
Finland
UK
age

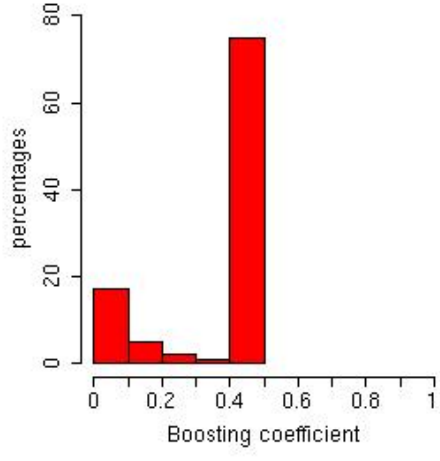

zoster susceptibiles (x 1000)
Italy
Finland
UK
age


Percentages
Duration of natural immunity (years)


rate of developing zoster by age
age


percentages
Boosting coefficient


percentages
Boosting coefficient


percentages
Boosting coefficient

Conclusions

Summary

- single parameters can be hardly identifiable from zoster data only, due to the lack of information on intermediate process
- our approach is based on the idea that the impact of vaccination is to be assessed over the whole set of configurations of parameters consistent with data
- we assume that: parameters related to biological phenomena (e.g. loss of CI) are ”invariant” among countries

PLUS some specific scenarios of interest

- in absence of robust predictions
- for comparison with past work on VZV

Future directions: EVALUATE VACCINATION!

- The model, in the extended version, considers varicella breakthrough and zoster among vaccinees
- we will consider a large set of vaccination strategies and schedules

Thanks for your attention

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