

The Challenges of Epidemiological Modelling of the COVID-19 Pandemic

**BBS Meeting
July 27, 2021**

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Context

- **Transmission models of infectious diseases** very useful to
 - better understand population-level dynamics of infectious diseases
 - project future epidemiology under different interventions and “scenarios”
- Unprecedented number of transmission models developed during COVID-19 pandemic.
- More exposure of general public to transmission models than ever before.
- Great implications of model projections world-wide:
 - plan health care management (e.g. hospital occupancy)
 - inform decision makers about mandates and policies (lockdown, social distancing, ...)
 - inform general public about future evolution of the pandemic
- Challenging:
 - fast moving
 - still much uncertainty

Aim of this presentation

- **Present key aspects of epidemiological transmission models**, illustrated with COVID-19.

The models presented are for illustration purpose. No ambition to be exhaustive here!

- **Highlight a few challenges** to make middle-to-long term projections.
- This presentation is **NOT** aiming at
 - presenting model projections
 - discussing validation of model projections.

Type of models

- **Forecast vs Prediction**

- Forecast models: shorter term – often more of statistical/probabilistic type.
- Prediction in middle-to-longer term: require to account for “mechanistic” aspects.

- **Focus here is on “mechanistic” models**, they can be

- “Compartmental”
- Agent-based (ABM) model, microsimulations, ...

In this presentation we will illustrate with compartmental models but many key aspects may hold true for ABM models as well.

Key features of mechanistic transmission models

- **Natural history** of the infection/disease
- **Transmission**
 - The *Force of Infection*
 - The *Basic reproduction number*
- **Heterogeneities**
- **Modelling interventions**: non-pharmaceutical interventions (NPI's), vaccination
- **Data & models**

Compartmental models

- The compartmental structure **represents** the **natural history of the infection**
- Key features of compartmental transmission models:
 - **Compartments: represent** different **infection/disease states** in which individuals can be.
 - model states are mutually exclusive.
 - number of individuals in a given compartment is a prevalence
 - **Flows: represent transitions** between compartments (states) over time,
 - characterized by *per-capita* flowing rates between compartments.

COVID-19 's natural history

COVID-19 models are of the “SEIRS” type

FOI: “Force of infection”

p_I: percentage of infections symptomatic

d_E: mean duration of exposed

d_A: mean duration infectiousness asymptomatic

d_I: mean duration infectiousness symptomatic

d_R: mean duration of natural immunity

Model states (compartments)

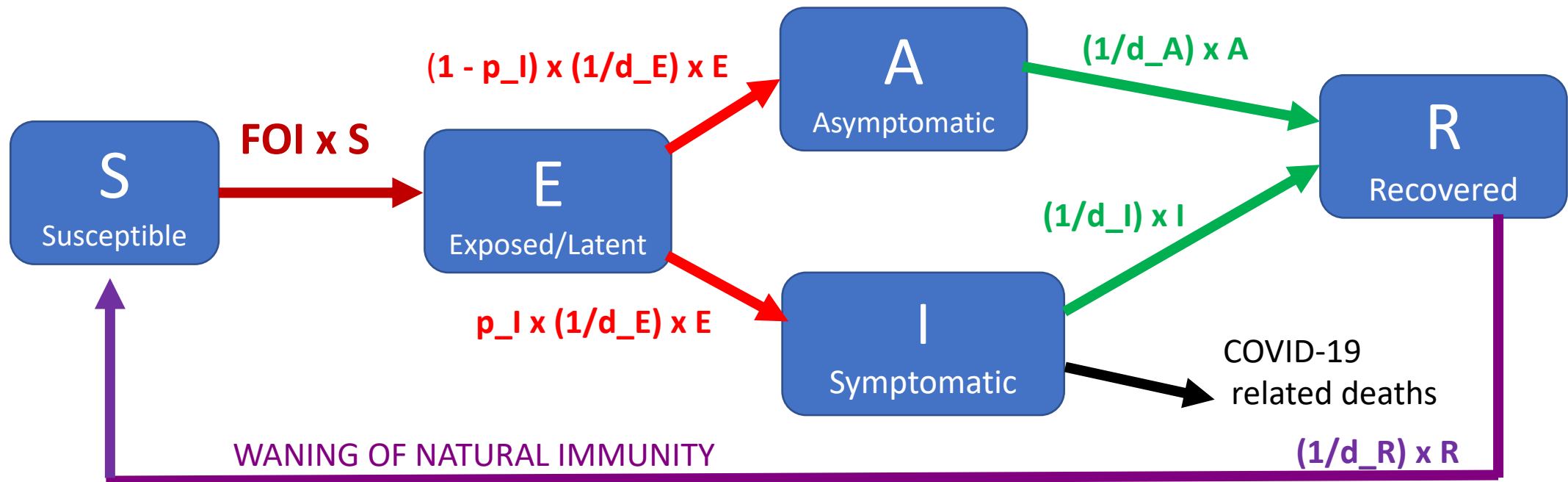
S : susceptible to be infected

E : exposed (latent) - Infected & not yet infectious

A : infected & infectious but Asymptomatic

I : infected & infectious and Symptomatic

R: recovered



Force of infection and *Basic reproduction number*

The “**force of infection**” (FOI) is the per susceptible rate to be infected.

The FOI is at the core of the non-linear population dynamics of infectious diseases

$$FOI = t \times c \times \frac{I}{N}$$

t : transmission rate per contact per unit of time
c : mean number of contacts of an individual
I : number of infectious individuals
N : total population

infection-related

socio-demographic

prevalence of infectious

→ incidence of new infections = FOI x S

- The **Basic reproduction number (R₀) is a key quantity**, defined as the mean number of new infections generated by one infectious individual in a fully susceptible population.

$$R_0 = t \times c \times d$$

t and c as above

d: mean duration of infectiousness

Heterogeneities for COVID-19

- **Age:**
 - *Who has contact with whom* shown to be age-dependent through contact survey studies (e.g. Polymod study in the EU): relevant for person-to-person transmission in general.
 - Severity of disease: risk of disease and severity age-dependent.
 - Death (Case fatality rate and Infection fatality rate) strongly age-dependent.
- **Location:**
 - Countries
 - Regions (e.g. Different policies in different provinces)
- **Underlying conditions, comorbidities**
- **SARS-COV-2 variants**
- **Vaccine acceptance**
- **Socio-economic status**
- ...

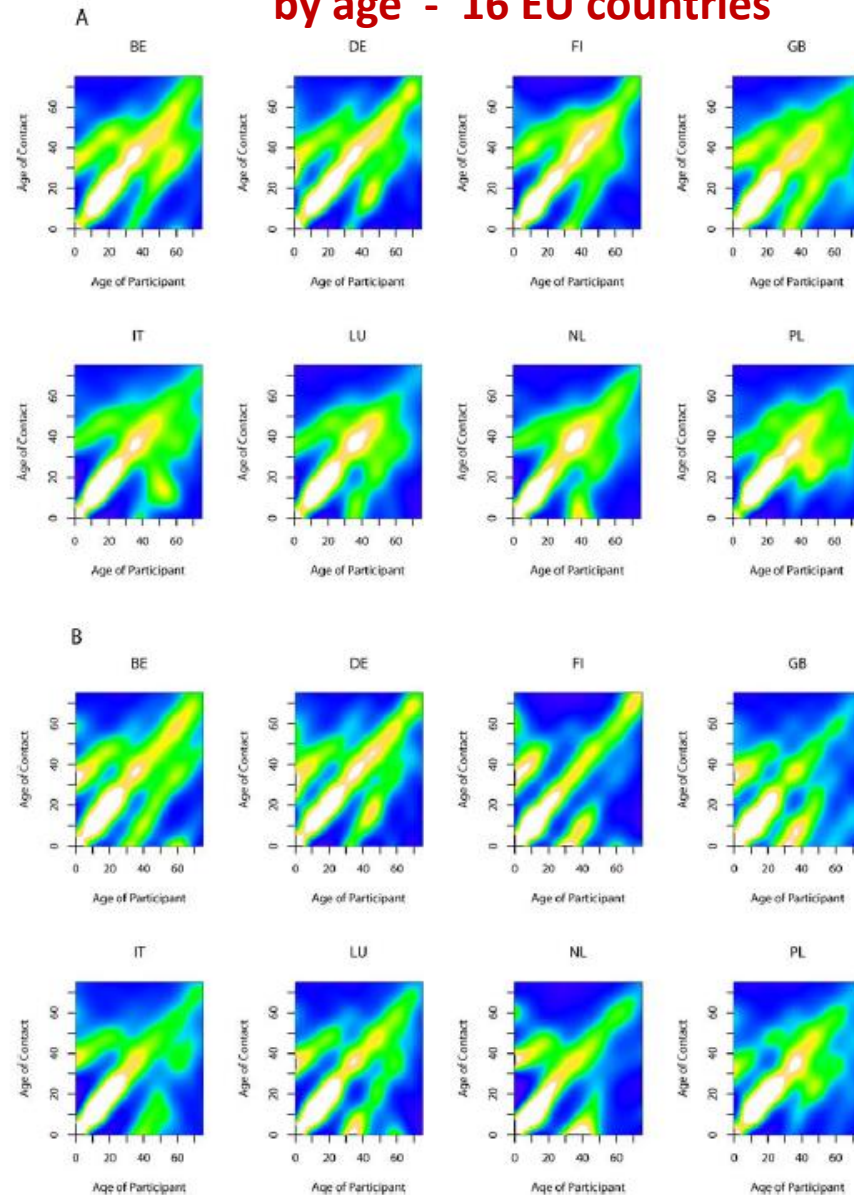
Contact between age groups

Empirical studies (e.g. *Polymod* contact survey, Mossong et al, 2008)

- can inform “who as contact with whom” between age groups.
- have shown:
 - **important assortativity of contacts:** more contact with people of similar age.
 - more contacts in younger people.
 - difference between countries
 - quite similar general pattern though.

More recently: models of contacts based on empirical data have been developed for many countries (e.g. Prem et al, 2017, in 152 countries)

Heat plots of mean number of contacts between participant and contact by age - 16 EU countries



Polymod study
From Mossong et al,
PLoS Medicine, 2008

The *force of infection* revisited

Heterogeneity of contacts between age groups can be accounted for with contact matrices:

$$FOI_i = t \sum_{j=1}^N c_{ij} \frac{I_j}{N_j}$$

- t : transmission rate per contact per unit of time
- C_{ij} : mean number of contacts of individuals of age i with individuals of age j
- I_j : number of infectious individuals of age j
- N_j : population of age j

One way to model Non-pharmaceutical Interventions (NPI's):

- use setting-specific contact matrices (home, school, work, others). See for example: Prem et al, 2017.
- reduce transmission by setting over time (see for examples: Davies et al, 2020, Abrams et al, 2021)

$$FOI_i = t \sum_{j=1}^N \left(w_H(t) c_{ij}^H + w_S(t) c_{ij}^S + w_W(t) c_{ij}^W + w_O(t) c_{ij}^O \right) \frac{I_j}{N_j}$$

$c_{ij}^H, c_{ij}^S, c_{ij}^W, c_{ij}^O$: mean number contacts between age i and age j at home (H), school (S), work (W), other settings (O)
 $w_H(t), w_S(t), w_W(t), w_O(t)$: time-varying weights decreasing transmission by setting.

Challenges related to transmission

- The transmission usually estimated (derived) from the *basic reproduction number*.

Estimates of R_0 available since beginning of the pandemic, but projections may have to account for evolution in transmissibility (e.g. new SARS-COV-2 variants)

- Modeling NPI's very challenging:
 - time-varying
 - same NPI's may have different effects in different countries wrt “compliance” (e.g. China vs U.S.)
 - uncertainty about potential NPI's in the future

Models & Data

- In order to estimate some model parameters or to refine them, most models need to **be calibrated to observed population-level data**.
- Type of data used for calibration for COVID-19: **cases, hospitalizations, deaths, ...**
 - **COVID-19 cases:**
 - only tested cases are reported (different testing strategies in different countries)
 - fewer asymptomatic infections are reported
 - also substantial **under-ascertainment of symptomatic cases**,
which is time- and country/region-specific
 - **COVID-19 hospitalizations**
 - **COVID-19 deaths:** usually more reliable, but not everywhere

Under-ascertainment of COVID-19 symptomatic cases

Case reports under-estimate
true burden of
symptomatic infections:

Model-based estimation (Russell et al, 2020)

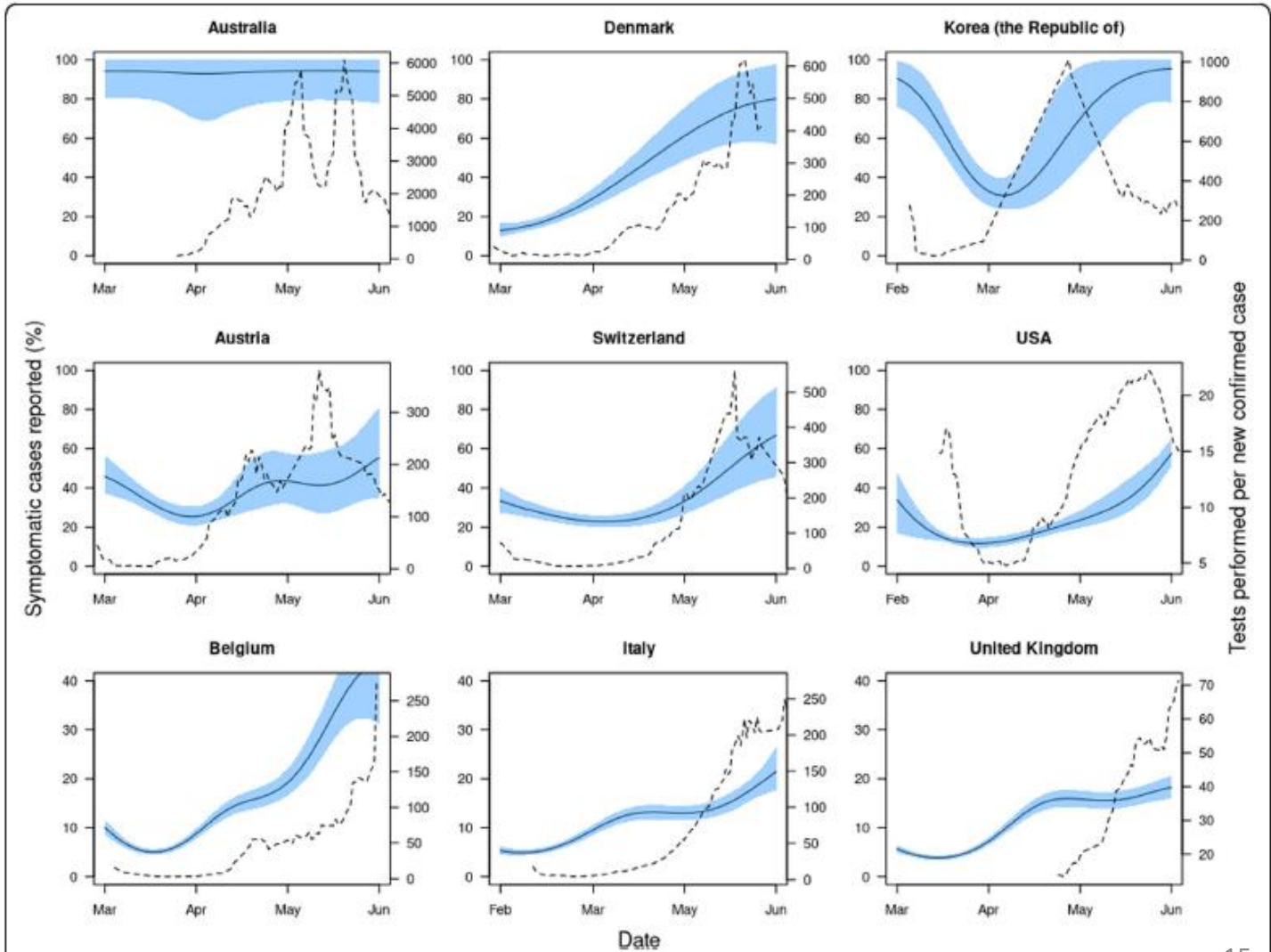
Estimated under-ascertainment:

- solid: median
- blue band: 95% CI

Dashed: new tests per new case

From Russell et al,
BMC Medicine, 2020

Estimated percentage of symptomatic cases reported
Examples in 9 different countries

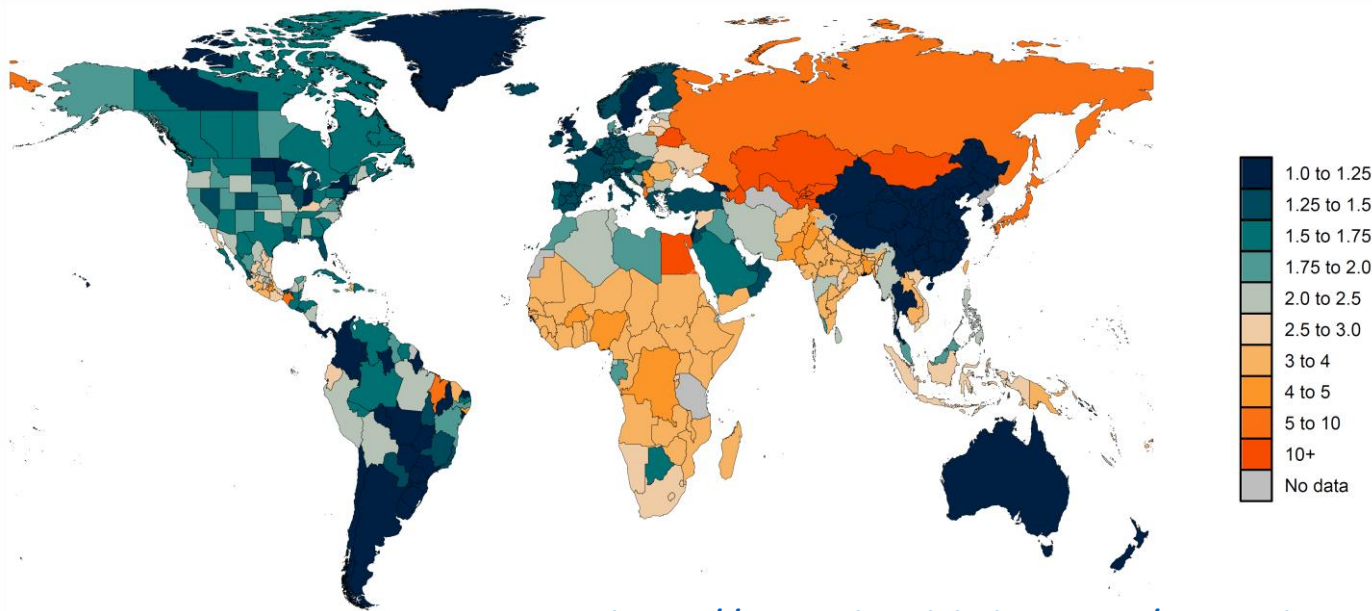


To what extent are COVID-19 under-reported?

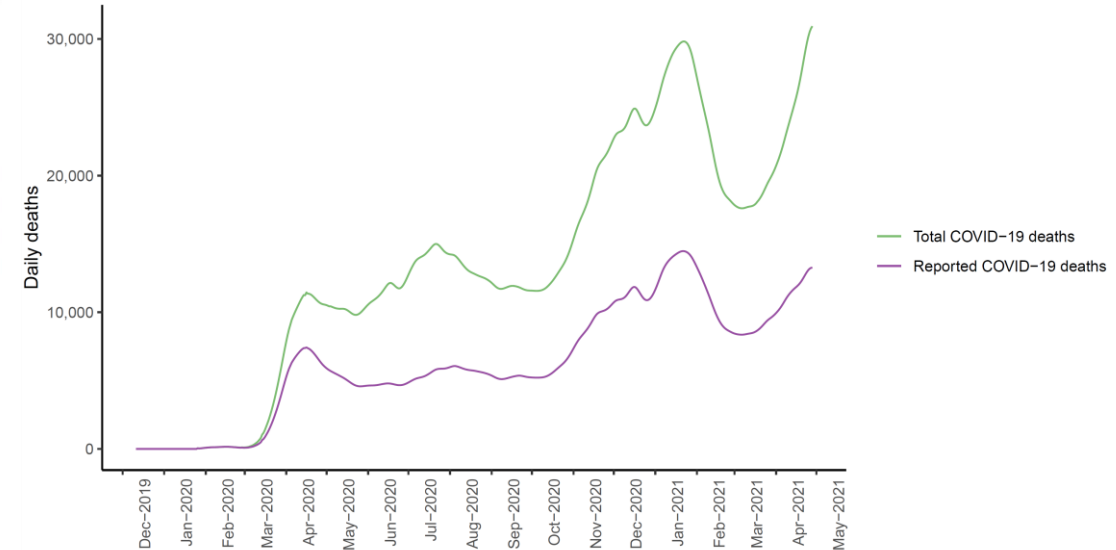
Excess mortality: difference in total number of deaths in a crisis compared to those expected under normal conditions.

As an example: IHME estimates 7.1 million COVID-19 deaths by May 13, 2021, which is more than 2 x higher than reported number of deaths (3.33 million).

Ratios of estimated total COVID-19 deaths to reported COVID-19 deaths



Reported and adjusted daily deaths for the world

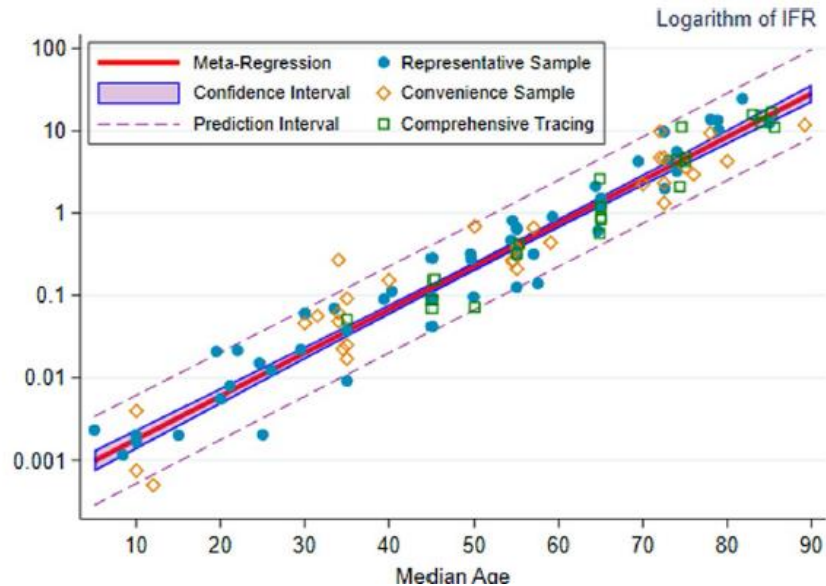


[IHME: http://www.healthdata.org/special-analysis/estimation-excess-mortality-due-covid-19-and-scalars-reported-covid-19-deaths](http://www.healthdata.org/special-analysis/estimation-excess-mortality-due-covid-19-and-scalars-reported-covid-19-deaths) (downloaded July 1, 2021)

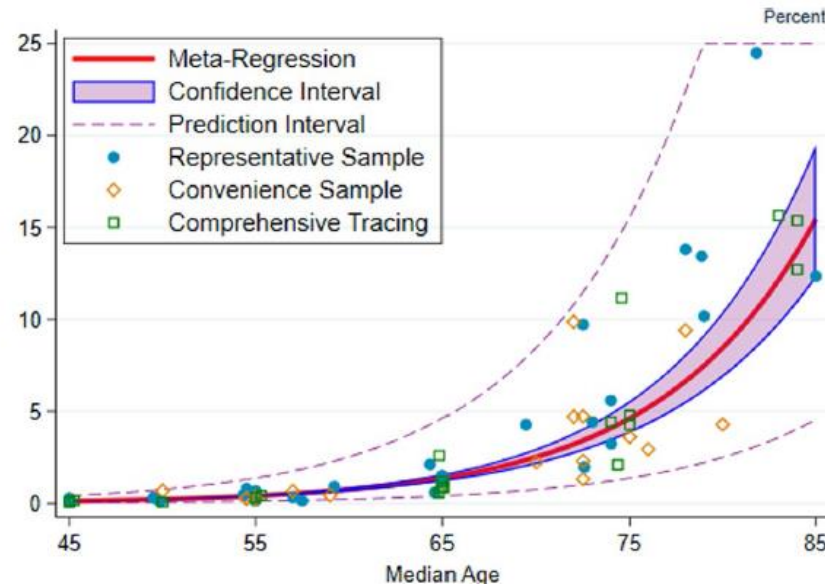
Using deaths counts for model calibration

- Many models calibrated on deaths counts (and/or hospitalizations)
- **Deaths related to infections through estimates of the Infection fatality rate** (IFR) = percentage of COVID-19 infections that lead to COVID-19 deaths
- IFR is strongly age-specific
- Calibration of deaths projected by a model to deaths counts allows to estimate **all** infections

Log10 (IFR) vs Age



IFR vs Age



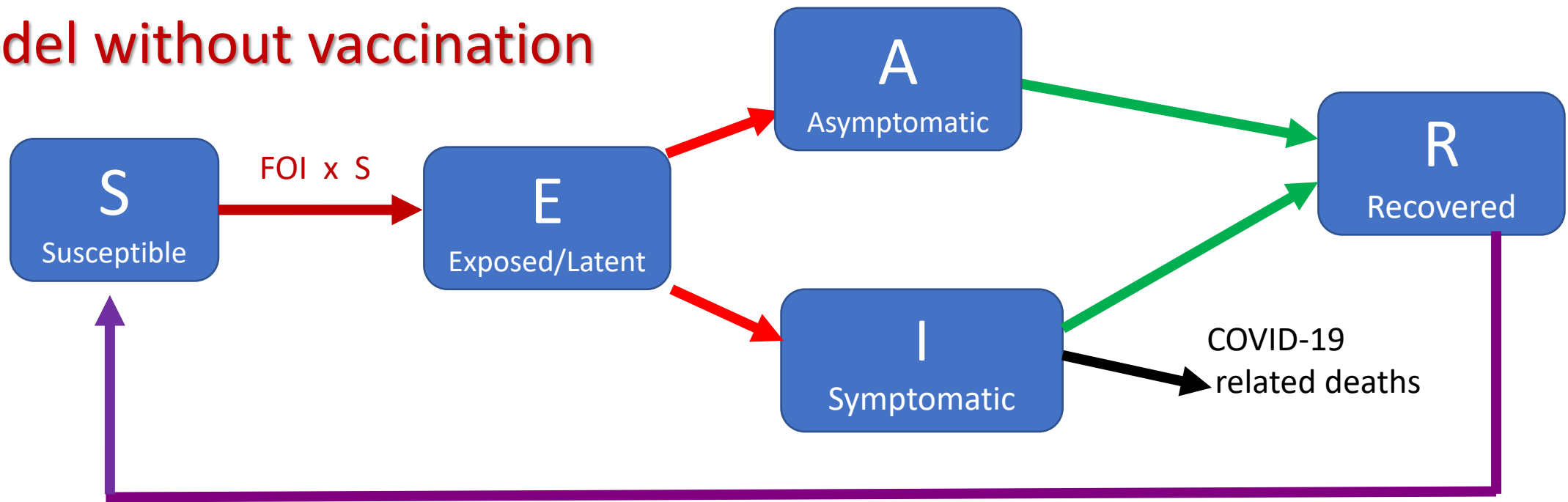
From Levin et al,
European Journal of
Epidemiology, 2020

Modeling vaccination

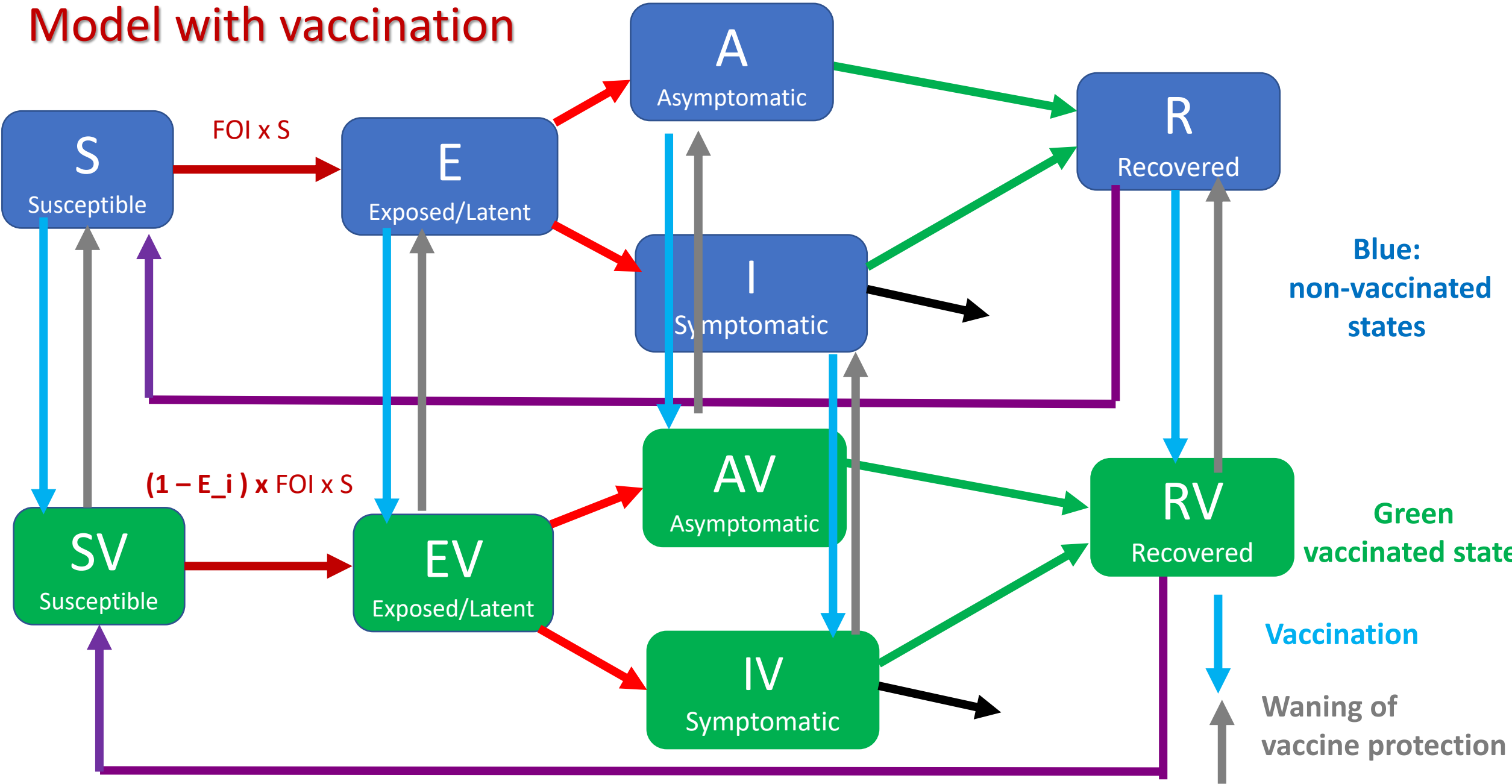
Vaccines can potentially have multiple effects:

- **direct effect on disease** (primary endpoint in vaccine trials)
 - Could be different on different levels of severity
- **reduce the *force of infection*:**
 - Can generate additional *herd protection* (indirect) effects
- **reduce infectiousness if nevertheless infected**
 - Can generate additional *herd protection* (indirect) effects

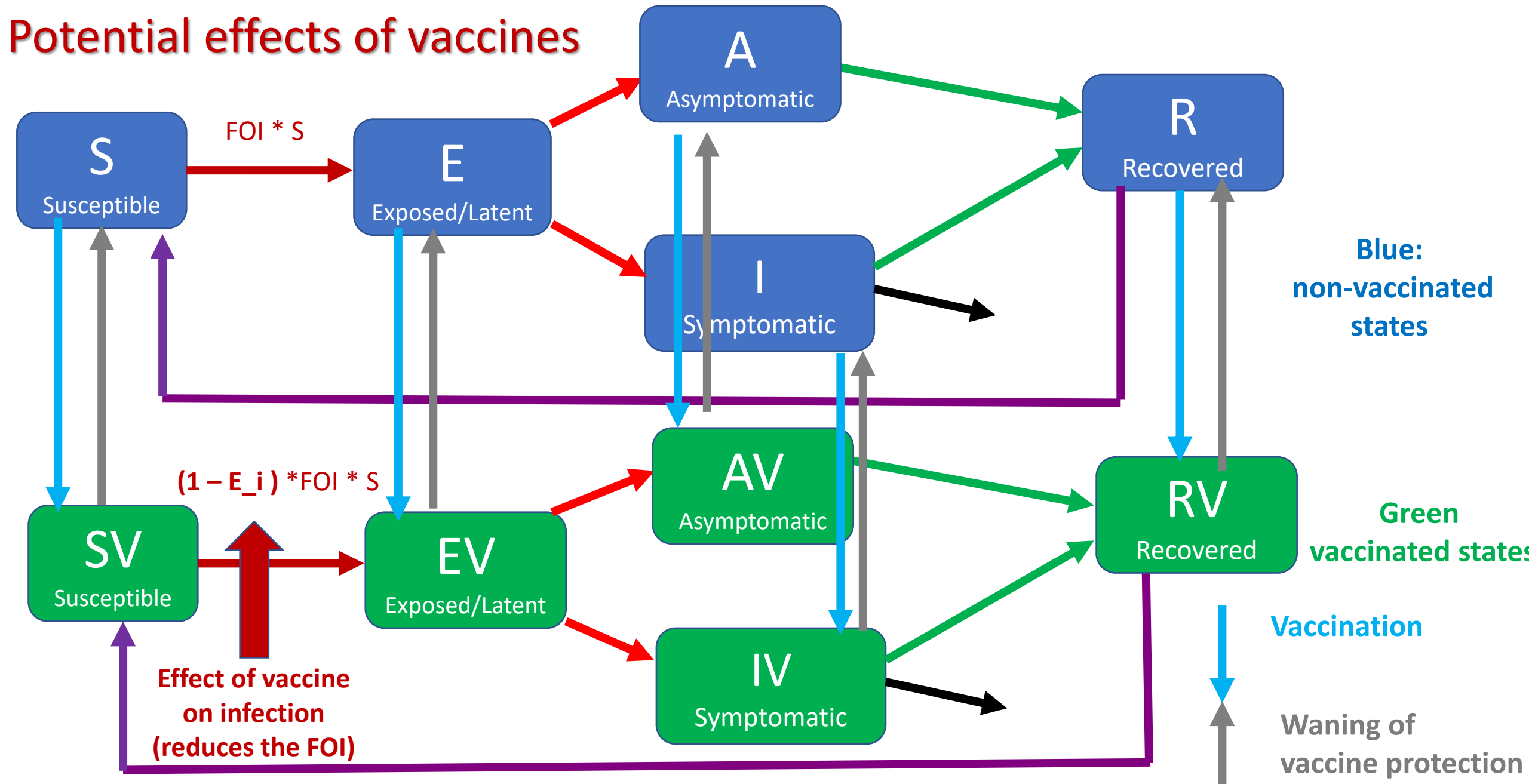
Model without vaccination



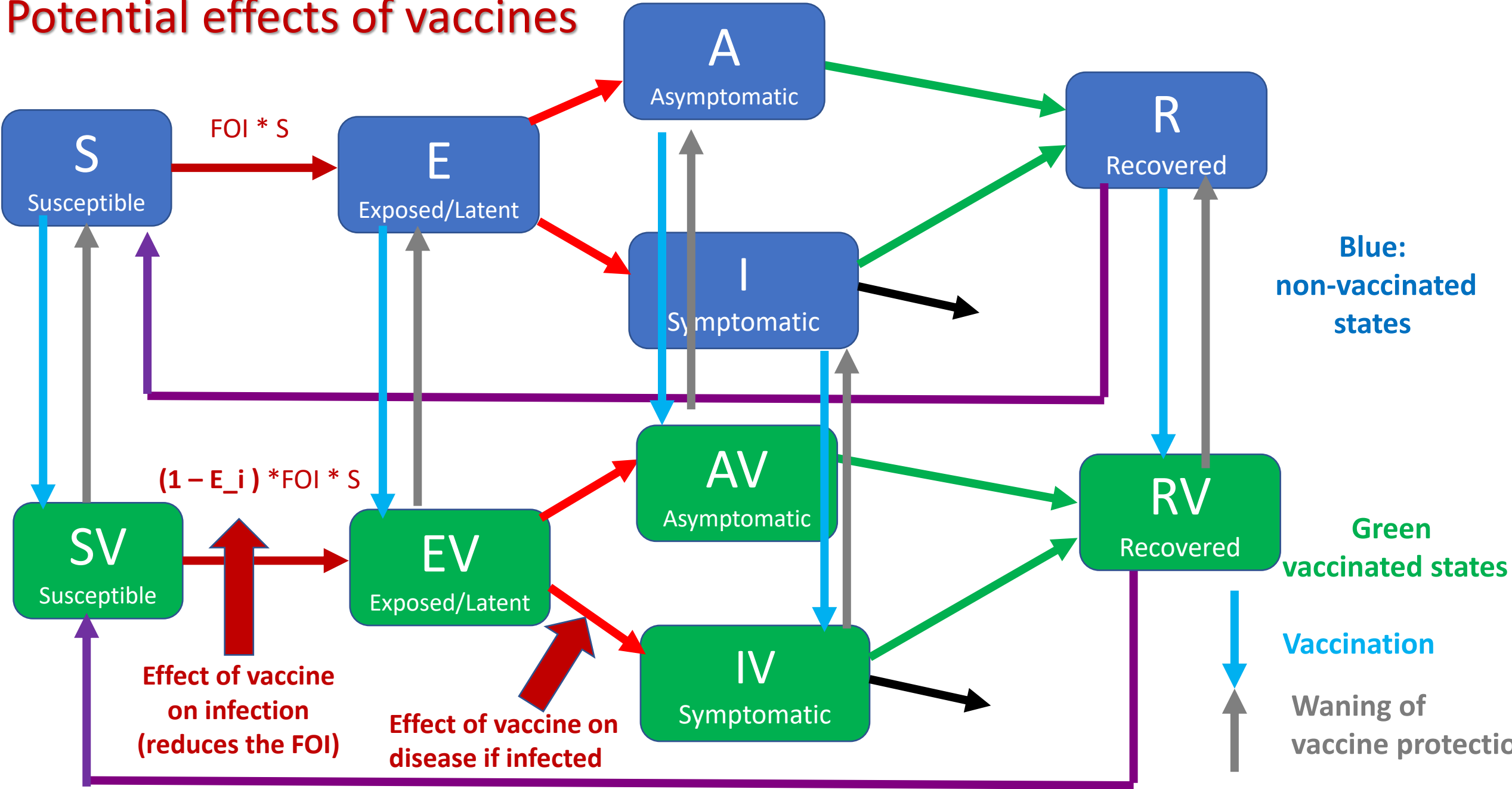
Model with vaccination



Potential effects of vaccines



Potential effects of vaccines



Challenges related to modelling vaccination

- Preliminary data indicates COVID-19 vaccines also have the potential to reduce the risk to be infected and infectiousness if infected, which can generate indirect “herd protection” effects.

Primary endpoint of trials on disease. Desirable to have more data to estimate those other important outcomes as well.

- **Duration of vaccine protection not well known yet (need longer follow-up)**, with subsequent impact on modelling re-vaccination strategies
- Effects of **vaccines against new variants might need periodic re-assessments.**
- Uncertainties about **who will be vaccinated and vaccination coverage** in the future:
 - Target populations
 - Vaccine availability
 - Different vaccines with different characteristics (number of doses, efficacies, ...)
 - Vaccine acceptance.

Conclusions

- Transmission models useful to better understand the dynamics of the COVID-19 pandemic and project potential future epidemiology under different scenarios/strategies.
- Several challenges though:
 - Reliability of epidemiological data needed for model calibration
 - Model NPI's over time.
 - Uncertainties about natural history, e.g. duration of natural immunity and future evolution of transmissibility with new variants
 - Quantify effects of vaccine, not only on disease but also on infection and infectiousness
 - Uncertainties about duration of vaccine protection.

References

- **Abrams et al.** Modelling the early phase of the Belgian COVID-19 epidemic using a stochastic compartmental model and studying its implied future trajectories. *Epidemics*, 2021.
- **Davies et al.** Effects of non-pharmaceutical interventions on COVID-19 cases, deaths, and demand for hospital services in the UK: a modelling study. *The Lancet*, 2020.
- **Levin et al.** Assessing the age specificity of infections fatality rates for COVID-19: systematic review, meta-analysis and public policy implications. *European Journal of Epidemiology*, 2020.
- **Mossong et al.** Social contacts and mixing patterns relevant to the spread of infectious diseases. *PLoS Medicine* 2008.
- **Prem et al.** Projection social contact matrices in 152 countries using contact surveys and demographic data. *PLoS Computational Biology*, 2017.
- **Russell et al.** Reconstructing the early global dynamics of under-ascertained COVID-19 cases and infections. *BMC Medicine*, 2020.