SIRS model with gradual waning of immunity

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Stochastic SIRS model with demography

- $\rightarrow$ Population of n individuals. Susceptible individuals born at constant rate μn, and each individual lives an exponentially distributed time with mean $1/\mu$
- $\rightarrow$ Upon infection, each infected
  - remains infectious for a duration $\sim \text{Exp}(\gamma)$
  - makes infectious contacts with each person in the population at the points of a homogeneous Poisson process with rate β/n
- $\rightarrow$ Contacted individuals, if susceptible, become infected
- $\rightarrow$ Recovered individuals are immune to further infection
- $\rightarrow$ Recovered individuals becomes susceptible after a duration $\sim \text{Exp}(\omega)$

Notation: $S(t)$ the number of susceptible individuals, $I(t)$ the number of infected individuals, and $R(t)$ the number of recovered individuals.

The corresponding SIRS deterministic model

When n is large, the process $(S(t)/n, I(t)/n, R(t)/n)$ converges to $(s(t), i(t), r(t))$ solution to

$$\begin{aligned} s'(t) &= \mu - \beta s(t)i(t) + \omega r(t) - \mu s(t), \\ i'(t) &= \beta s(t)i(t) - (\gamma + \mu)i(t), \\ r'(t) &= \gamma i(t) - (\omega + \mu)r(t). \end{aligned}$$

- Andersson H, & Britton T. (2000). *Stochastic epidemic models and their statistical analysis* (Vol 151). Springer New York
- Diekmann, O., Heesterbeek, H., & Britton, T. (2013). *Mathematical tools for understanding infectious disease dynamics* (Vol. 7). Princeton University Press.

Immunity waning in the SIRS model

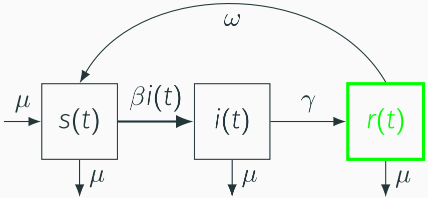


Figure 1: Diagram of standard SIRS epidemic model

$\rightarrow$ Population and individual immunity waning!

Waning of the protection over time

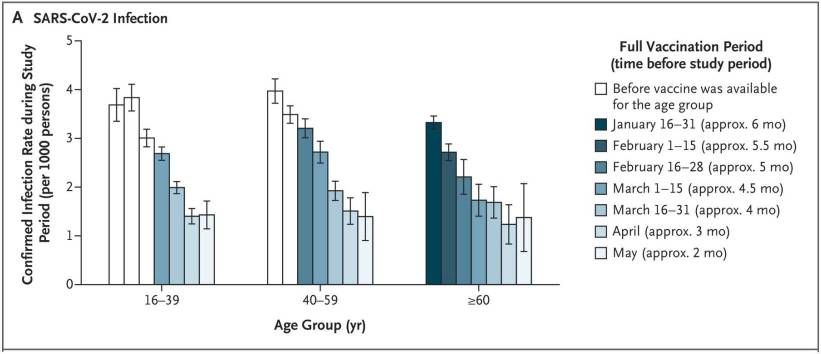


Figure 2: The rates of reported infection (in July 2021) per 1000 persons.

Goldberg, Yair, et al. "Waning immunity after the BNT162b2 vaccine in Israel." *New England Journal of Medicine 385*(24), (2021): e85.

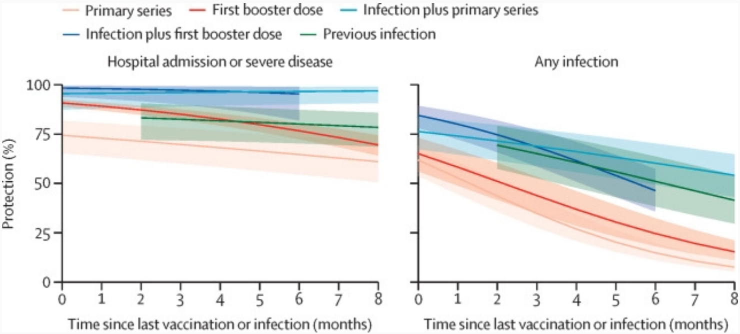


Figure 3: Protection against omicron variant conferred by different combinations of SARS-CoV-2 infection and vaccination over time.

Bobrovitz, Niklas, et al. "Protective effectiveness of previous SARS-CoV-2 infection and hybrid immunity against the omicron variant and severe disease: a systematic review and meta-regression." *The Lancet Infectious Diseases* (2023).

Decay of Neutralization antibodies

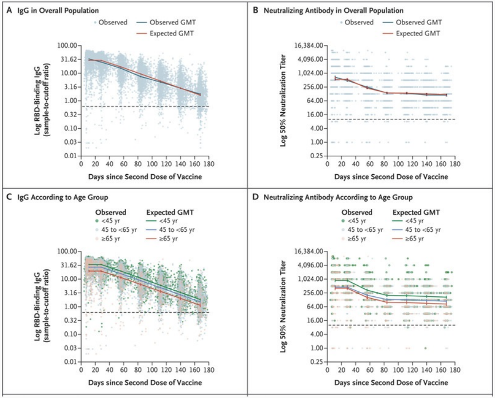


Figure 4: Distribution of Antibodies 6 Months after Receipt of Second Dose of the BNT162b2 Vaccine.

Levin, Einav G., et al. ”Waning immune humoral response to BNT162b2 Covid-19 vaccine over 6 months.” *New England Journal of Medicine 385*(24), (2021): e85.

Relationship between NAb titers and protection

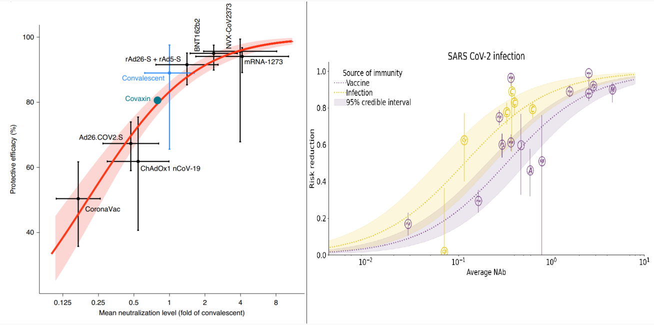
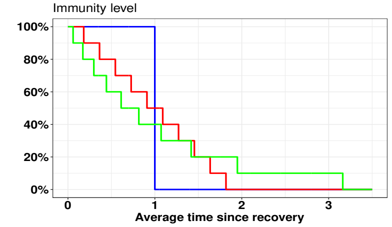


Figure 5: The relationship between neutralization and protection.

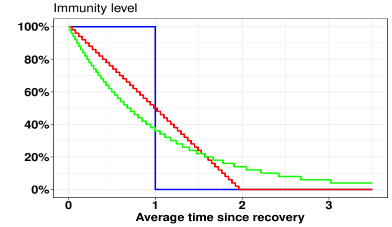
- Khoury, David S., et al. ”Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection.” *Nature medicine 27*(7), (2021): 1205-1211.
- Cohen, Jamie, et al. ”Quantifying the role of naturally-and vaccine-derived neutralizing antibodies as a correlate of protection against COVID-19 variants.” medRxiv 2021.05.31.21258018 (2021).
- Report 48 - The value of vaccine booster doses to mitigate the global impact of the Omicron SARS-CoV-2 variant. *Imperial College London*, Dec 2021.

Gradual waning of Immunity

Contrary to the extreme assumption $R \to S$, assume that recovered individuals lose immunity gradually: Losing a portion in each step, until all immunity is lost in a total of $k > 1$ steps



$k = 10$ steps



$k = 50$ steps

$\to$ Standard SIRS ($k = 1$) and continuous waning model ($k \to \infty$)

Stochastic SIR$^{(k)}$S model

Consider the stochastic SIRS setting, and

→ Recovered individuals lose an immunity portion $\frac{1}{k}$ after an exponential time,

→ Total immunity duration e.g. is Gamma-distributed,

Notations:

→ $R_0(t)$ being the number of perfectly immune individuals, $R_1(t)$ the number of $\frac{1}{k}$-susceptible individuals, ... , $R_k(t)\,(= S(t))$ fully susceptibles

→ We call the model a SIR$^{(k)}$S model

Stochastic and deterministic SIR$^{(k)}$S model

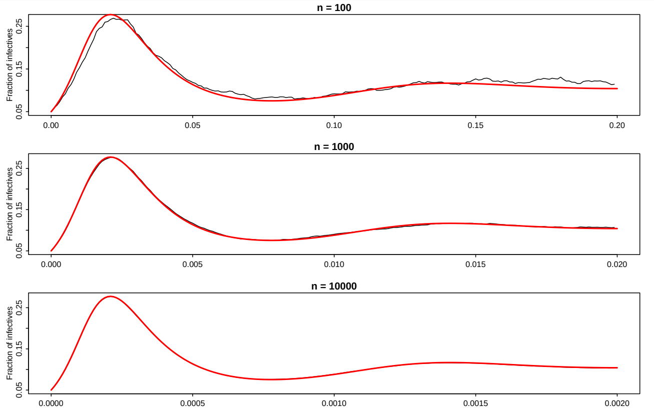


Figure 6: Black line: mean of $I(t)/n$ over 1000 stochastic simulations of an SIR$^{(5)}$S model. Red line: deterministic path of the large population limit SIR$^{(5)}$S model.

Gradual waning of immunity

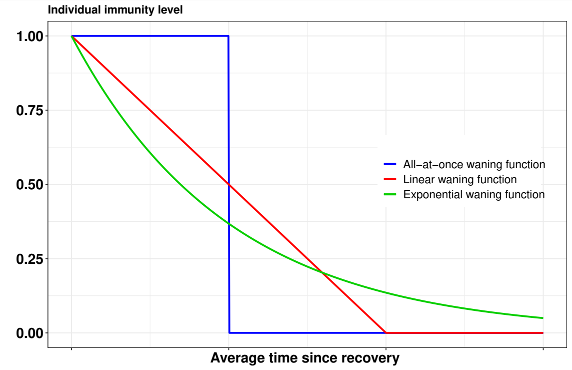


Figure 7: Different modes of waning of immunity on individual level.

→ Continuous waning of immunity!
→ Comparison of different waning by have fixed cumulative immunity.

Immunity waning in k steps

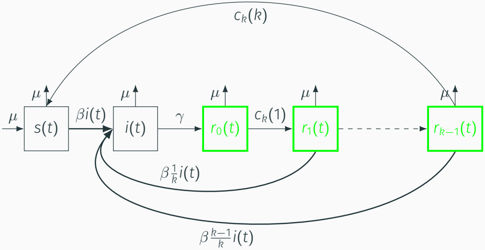


Figure 8: Diagram of the SIR$^{(k)}$S epidemic model.

→ Parametrization of the model: immunity portion to be lost, different waning rates

→ Standard SIRS ($k = 1$) and continuous waning model ($k \to \infty$)

Comparison of the models

We now have three models

- Standard SIRS model
- $SIR^{(k)}S$ with linear waning of immunity
- $SIR^{(k)}S$ with exponential waning of immunity

Calibration: same cumulative immunity

When there is no vaccination, **the basic reproduction number is the same.**

$$R_0 = \frac{\beta}{\mu + \gamma}.$$

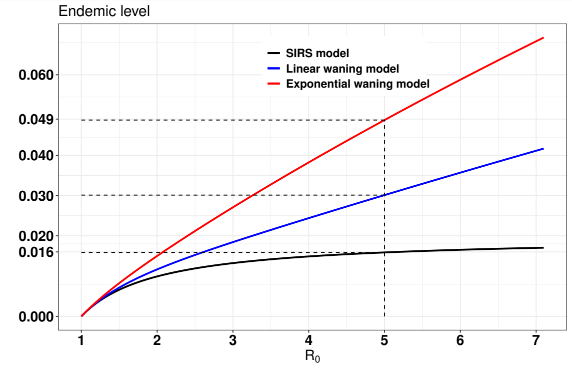


Figure 9: Endemic levels from the standard model and the $SIR^{(k)}S$ model with linear and exponential waning functions, for different values of R_0.

In case $R_0 = 5$ and $\omega^{-1} = 1$ year and $\mu^{-1} = 80$ years, the exponential waning function results in **three times higher** endemic level, compared to the standard SIRS model.

With vaccination

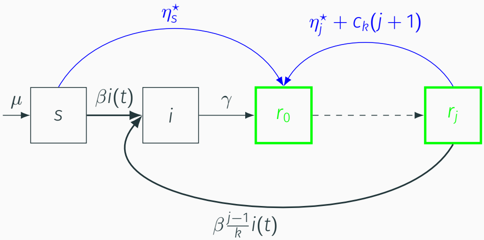


Figure 10: Diagram of the SIR$^{(k)}$S epidemic model with vaccination.

→ Perfect vaccine with continuous waning,

→ Vaccine-induced immunity wanes just like infection induced immunity!

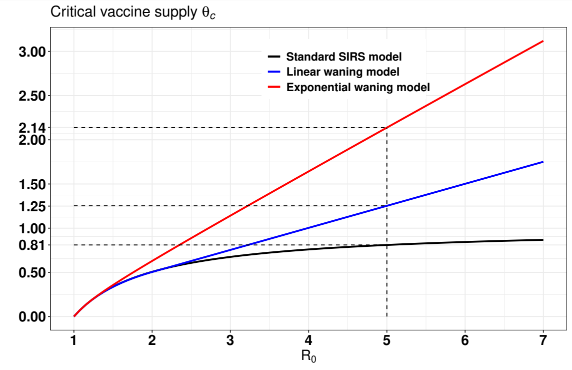


Figure 11: Critical amount of vaccines, θ_c, needed to reach herd immunity.

Compared to SIRS model, **the model with linear waning requires 55% more vaccines, and the exponential waning model requires 164% more vaccinations**, when $R_0 = 5$ and $\omega^{-1} = 1$ year.

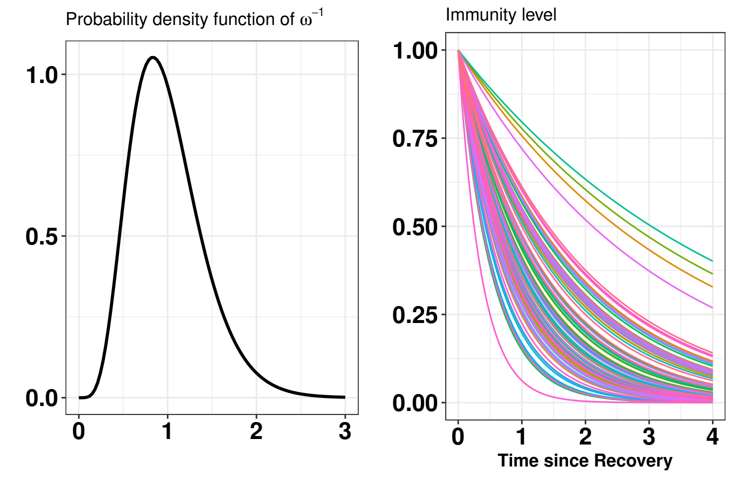
- → Previous results, e.g. Ball (1985), Britton, Ball, and Trapman (2020), proved that heterogeneity **reduces** the epidemic size and the critical vaccine coverage!

How can new model then result in **increase** in endemic level?

- → New model makes distribution more **homogeneous** than the extreme 0-1 immunity of SIRS

Limitation: Heterogeneity is also needed!

Heterogeneity in immunity waning



→ Exponential waning

→ Random waning rate, e.g. $p(\omega^{-1}) \sim$ Gamma with mean = 1 year and a standard deviation = 2 months

- For simplicity we focus on a two-point distribution, 50% of each type, such that the mean cumulative immunity remains the same ;

$$\omega_1^{-1} = \omega_0^{-1}(1-\alpha),$$
$$\omega_2^{-1} = \omega_0^{-1}(1+\alpha),$$

with α is the coefficient of variation of immunity distribution.

Immunity waning in the SIRS model

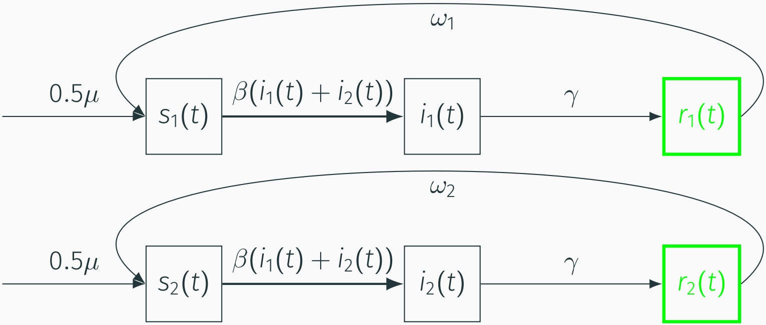


Figure 12: Diagram of heterogeneous SIRS epidemic model with two immune subpopulations.

The long-term prevalence

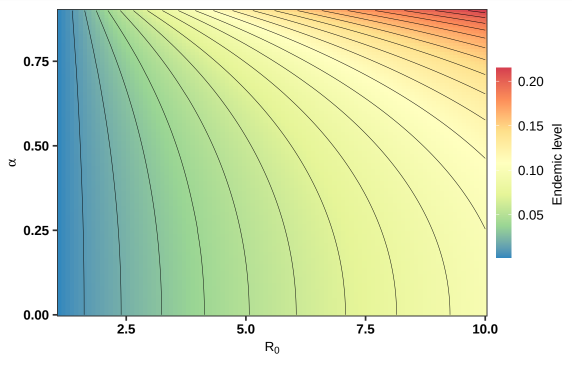


Figure 13: Endemic levels from the heterogeneous SIR$^{(\infty)}$S model with exponential waning.

$\rightarrow$ The more heterogeneous waning (= large α) the higher endemic level

Vaccination in the heterogeneous model

- Perfect vaccine with continuous waning ; natural- and vaccine-derived immunities are the same
- Vaccination strategy: informed (immunity status is known) vs. uninformed (immunity status is unknown)!

Critical vaccine supply

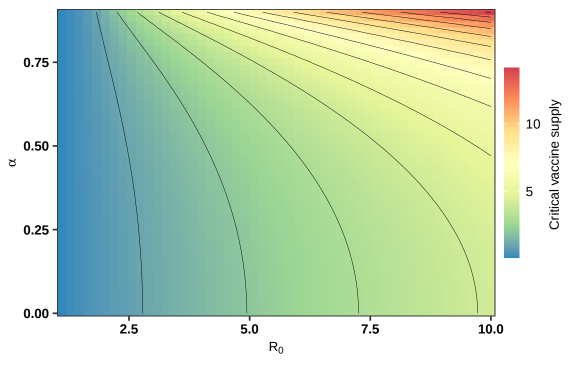
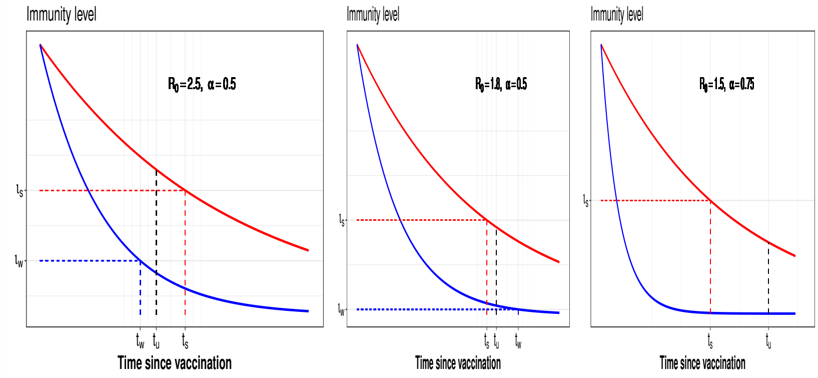


Figure 14: Amount of vaccine per person per year under the uninformed situation.

→ The more heterogeneous waning (=large α) the more vaccines are required for herd immunity

→ Uninformed strategy requires more than the informed strategy! (not illustrated)

Form of optimal vaccination in informed and uninformed situation



- t_S: critical vaccination time of strongly immune individuals (informed)
- t_W: critical vaccination time of weakly immune individuals (informed)
- t_U: critical vaccination time all individuals (uninformed)

Table 1: Critical vaccination strategy when $R_0 = 5$ and $\omega = 1$, with $\alpha = .5$ in the heterogeneous waning case.

	Vaccination frequency	Dose per person per year
SIRS	15 months	0.81
Exp. waning	5.5 months	2.15
Exp. waning: informed	3.8/5.7 months	2.62
Exp. waning: uninformed	4.4 months	2.76

Conclusion and Future directions

An ODE model extending SIRS model to allow individual immunity to wanes in steps.

Higher endemic levels if prevention is not put in place.

Substantially larger vaccine supply is required for herd immunity.

Heterogeneity in immunity waning makes the situation worse!

Uninformed vs informed vaccination strategies

future directions: Imperfect vaccines, Seasonality effects

References

- El Khalifi, M., & Britton, T. (2022). Extending SIRS epidemics to allow for gradual waning of immunity. *Conditionally accepted for JRS Interface, arXiv preprint arXiv:2211.09062*.
- El Khalifi, M., & Britton, T. (2023). Consequences of heterogeneity in a model with continuous waning of immunity. *Manuscript*.

Thank you