IDM INSTITUTE FOR DISEASE MODELING

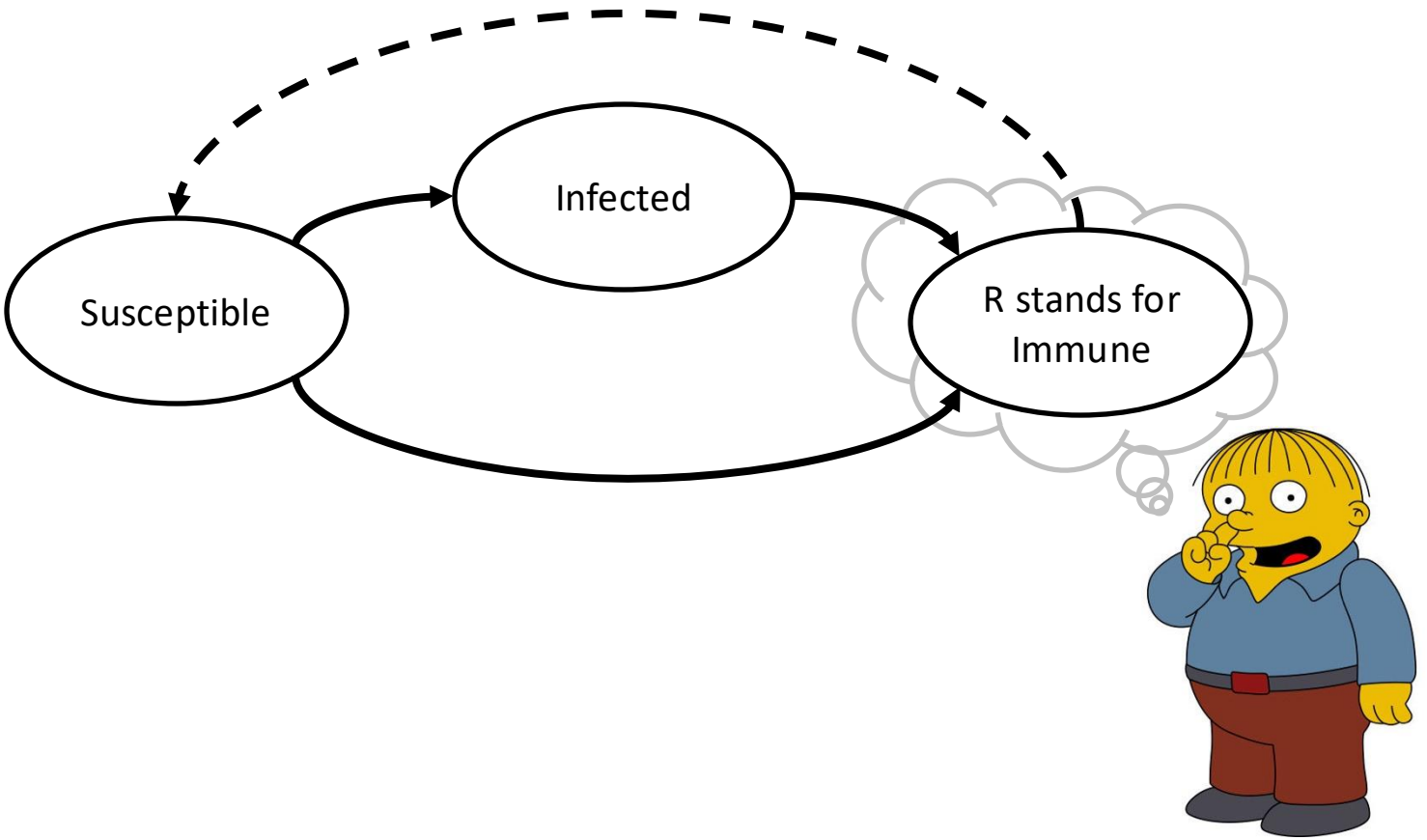
Better defaults for ~~acquired~~ immunity modeling

Mike Famulare

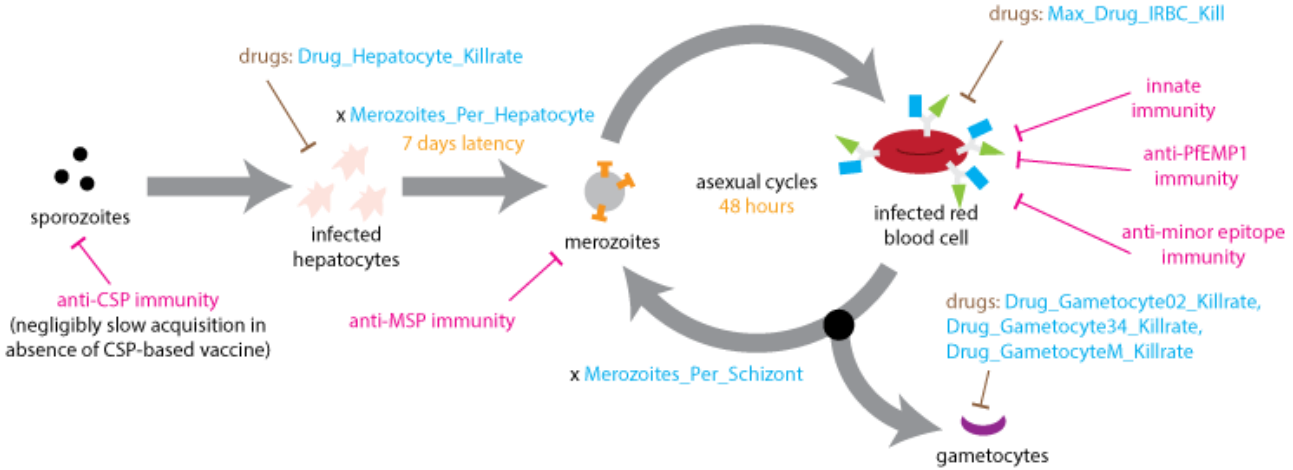
April 11, 2024

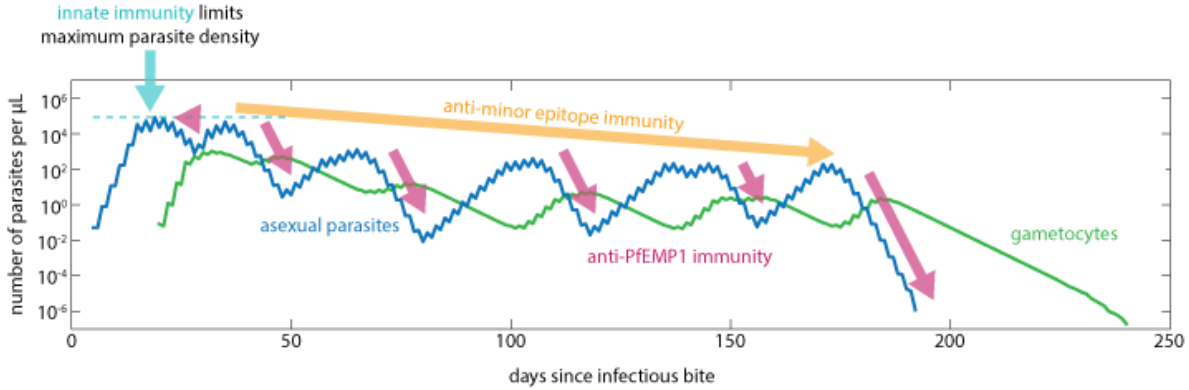
BILL & MELINDA GATES *foundation*

SIRS



Malaria


drugs: Max_Drug_IRBC_Kill
drugs: Drug_Hepatocyte_Killrate
x Merozoites_Per_Hepatocyte
7 days latency
innate immunity
anti-PfEMP1 immunity
anti-minor epitope immunity
sporozoites
infected hepatocytes
merozoites
asexual cycles 48 hours
infected red blood cell
anti-CSP immunity (negligibly slow acquisition in absence of CSP-based vaccine)
anti-MSP immunity
drugs: Drug_Gametocyte02_Killrate, Drug_Gametocyte34_Killrate, Drug_GametocyteM_Killrate
x Merozoites_Per_Schizont
gametocytes


innate immunity limits maximum parasite density
anti-minor epitope immunity
asexual parasites
anti-PfEMP1 immunity
gametocytes
number of parasites per µL
days since infectious bite

Scope of today's talk

We can usually do a lot better than binary SIRS for not much more effort, particularly for disease with separations of timescales between infection and immune dynamics.

- any acute infectious disease (polio, measles, RSV, rotavirus, acute typhoid, covid, flu, dengue…)
- Outcomes on different scales (HPV, TB, typhoid carriers, long-COVID, EBV->MS…)

Less applicable: anything where immune and pathogen dynamics interact and show predator-prey-like dynamics on similar scales

- Malaria, HIV…

Not gonna talk about cross-immunity or host heterogeneity today

Key principles for better immunity modeling

1. Immunity always means multiple things
2. Protection is always a function of correlates, known or not
3. Almost all immunity is leaky
4. Waning is never exponential
5. You probably don’t care about priming and boosting

Key principles for better immunity modeling

1. Immunity always means multiple things
2. Protection is always a function of correlates, known or not
3. Almost all immunity is leaky
4. Waning is never exponential
5. You probably don’t care about priming and boosting

If you think through all this before running a model, your work will be better.
(Even if you end up doing the thing you usually do anyway.)

Key principles for better immunity modeling

1. Immunity always means multiple things
2. Protection is always a function of correlates, known or not
3. Almost all immunity is leaky
4. Waning is never exponential
5. You probably don't care about priming and boosting

If you think through all this before running a model, your work will be better.
(Even if you end up doing the thing you usually do anyway.)

If you advise PST partners to expect more from modeling grantees, they'll better understand the anticipatable impacts and uncertainties in their strategies.

1. Immunity always means multiple things

- Immune to what?
  - Infection
  - symptoms
  - hospitalization
  - death
  - carrier status
  - long-term sequela
  - transmitting if infected
  - …

- Why?
  - Different outcomes are conditionally dependent on each other
  - Different consequences in different body compartments
  - Outcomes often depend on other covariates

Vaccine efficacy is many things

Relative Risk

$$RR_{outcome} = \frac{P(outcome|vaccinated)}{P(outcome|not\ vaccinated)}$$

Vaccine Efficacy is relative risk reduction (in a population with identical exposure)

$$VE_{outcome} = 1 - RR_{outcome}$$

Vaccine efficacy is many things

Relative Risk

$$RR_{outcome} = \frac{P(outcome|vaccinated)}{P(outcome|not\ vaccinated)}$$

Vaccine Efficacy is relative risk reduction (in a population with identical exposure)

$$VE_{outcome} = 1 - RR_{outcome}$$

Conditional relative risks multiply

$$RR_{symptoms} = \frac{P(symp|inf, vax)P(infected|vax)}{P(symp|inf, no\ vax)P(infected|not\ vax)}$$

$$RR_{symptoms} = RR_{symp|inf}RR_{inf}$$

Vaccine efficacy is many things

Relative Risk

$$RR_{outcome} = \frac{P(outcome|vaccinated)}{P(outcome|not\ vaccinated)}$$

Vaccine Efficacy is relative risk reduction (in a population with identical exposure)

$$VE_{outcome} = 1 - RR_{outcome}$$

Conditional relative risks multiply

$$RR_{symptoms} = \frac{P(symp|inf, vax)P(infected|vax)}{P(symp|inf, no\ vax)P(infected|not\ vax)}$$

$$RR_{symptoms} = RR_{symp|inf}RR_{inf}$$

Vaccine efficacy for an endpoint is a composite

$$VE_{symptoms} = 1 - \left(1 - VE_{symp|inf}\right)\left(1 - VE_{inf}\right)$$

Vaccine efficacy is many things

Relative Risk

$$RR_{outcome} = \frac{P(outcome|vaccinated)}{P(outcome|not\ vaccinated)}$$

Vaccine Efficacy is relative risk reduction (in a population with identical exposure)

$$VE_{outcome} = 1 - RR_{outcome}$$

Conditional relative risks multiply

$$RR_{symptoms} = \frac{P(symp|inf, vax)P(infected|vax)}{P(symp|inf, no\ vax)P(infected|not\ vax)}$$

$$RR_{symptoms} = RR_{symp|inf}RR_{inf}$$

Vaccine efficacy for an endpoint is a composite

$$VE_{symptoms} = 1 - \left(1 - VE_{symp|inf}\right)\left(1 - VE_{inf}\right)$$

Efficacy against infection is subtle

$$RR_{inf} = \frac{P(inf|vax\ worked)P(vax\ worked|vax) + P(inf|no\ vax)\left(1 - P(vax\ worked|vax)\right)}{P(inf|no\ vax)}$$

$$VE_{inf} = 1 - RR_{inf}$$

Vaccine efficacy modeling recommendations

- Clinical trials often report only one endpoint, which is rarely the only endpoint relevant for our work.

- Use your knowledge of biology and the policy landscape to *decide thoughtfully*
  - Can I safely assume the VE in my model is the one in the paper(s)?
  - If not, do the data exist re-estimate VE appropriately for my needs?
  - Either way, do I have to propagate the uncertainty in the unmeasured aspects of vaccine protection to get the policy advising right?

- Help your PST partners understand when types of VE not measured in a typical clinical trial will matter when a successful vaccine is rolled out.
  - Motivate better trials.

2. Protection is always a function of correlates, known or not

Table 1. Terminology for Immune Correlates of Protection

Plotkin and Gilbert 2010

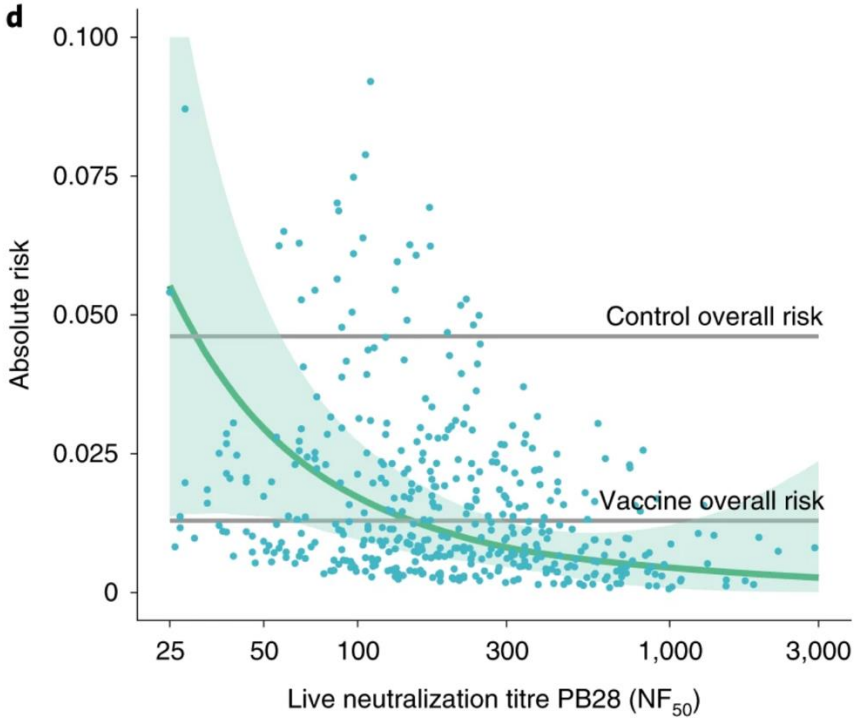
Term	Synonyms	Definition
CoP (correlate of protection)	Predictor of protection	An immune marker statistically correlated with vaccine efficacy (equivalently predictive of vaccine efficacy) that may or may not be a mechanistic causal agent of protection[a]
mCoP (mechanistic correlate of protection)	Causal agent of protection; protective immune function	A CoP that is mechanistically and causally responsible for protection
nCoP (nonmechanistic correlate of protection)	Correlate of protection not causal; predictor of protection not causal	A CoP that is not a mechanistic causal agent of protection

[a] A correlate of protection can be used to accurately predict the level of vaccine efficacy conferred to vaccine recipients (individuals or subgroups defined by the immune marker level).

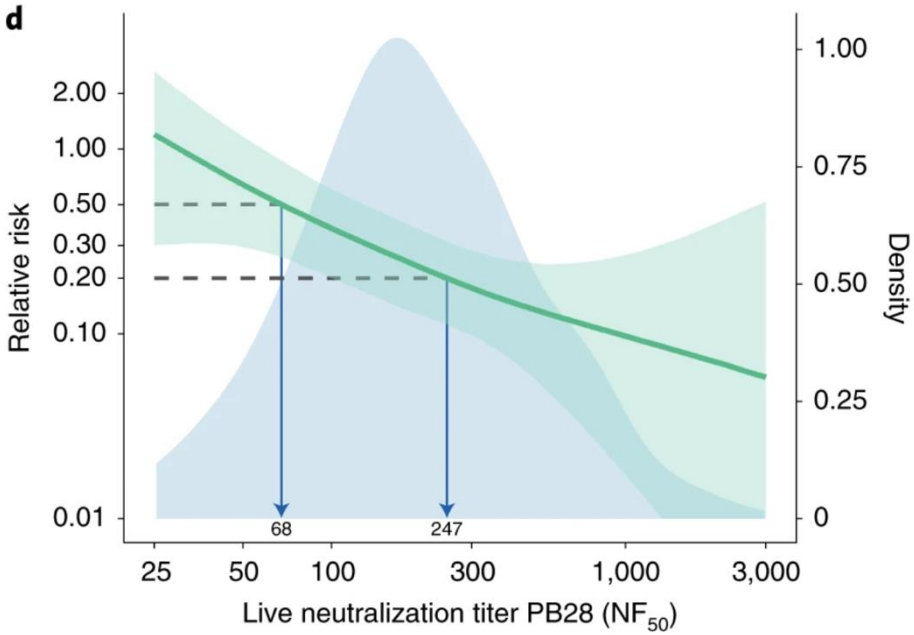
Correlates of Protection are always continuous quantities, and because immunity is always leaky, VE always varies continuously with CoP.

Thus it is really annoying that most studies focus on thresholds of protection as a binary classifier.

Example CoP: symptomatic COVID, AZ vaccine



Feng *et al* 2021



$$RR_{symp\ inf}(NF_{50}) = \frac{AR_{vax}(NF_{50})}{AR_{no\ vax}}$$

$$VE_{symp\ inf}(NF_{50}) = 1 - RR_{symp\ inf}(NF_{50})$$

Modeling VE with a Correlate of Protection

Vaccinology studies (usually)

$$\log(RR_{outcome}) = \alpha - \beta \log(\mathrm{CoP})$$
$$VE_{outcome} = 1 - e^{\alpha}(\mathrm{CoP})^{-\beta}$$

VE can go negative.
Useful in studies since you have to watch if the vaccine is harmful.

Modeling VE with a Correlate of Protection

Vaccinology studies (usually)	$\log(RR_{outcome}) = \alpha - \beta \log(\text{CoP})$ $VE_{outcome} = 1 - e^{\alpha}(\text{CoP})^{-\beta}$	VE can go negative. Useful in studies since you have to watch if the vaccine is harmful.
If you can safely assume VE>0	$\text{logit}(VE_{outcome}) = \alpha + \beta \log(\text{CoP})$	VE bounded between 0 and 1. More efficient statistically and correct biologically if you know VE>0 always.

Modeling VE with a Correlate of Protection

Vaccinology studies (usually)	$\log(RR_{outcome}) = \alpha - \beta \log(\text{CoP})$ $VE_{outcome} = 1 - e^{\alpha}(\text{CoP})^{-\beta}$	VE can go negative. Useful in studies since you have to watch if the vaccine is harmful.
If you can safely assume VE>0	$\text{logit}(VE_{outcome}) = \alpha + \beta \log(\text{CoP})$	VE bounded between 0 and 1. More efficient statistically and correct biologically if you know VE>0 always.
Vaccine efficacy for an endpoint is a composite	$VE_{symp}(\text{CoP})$ $= 1 - \left(1 - VE_{symp\|inf}(\text{CoP})\right)\left(1 - VE_{\text{inf}}(\text{CoP})\right)$	Nonlinear regression, but more correct over range of possible CoP

Modeling VE with a Correlate of Protection

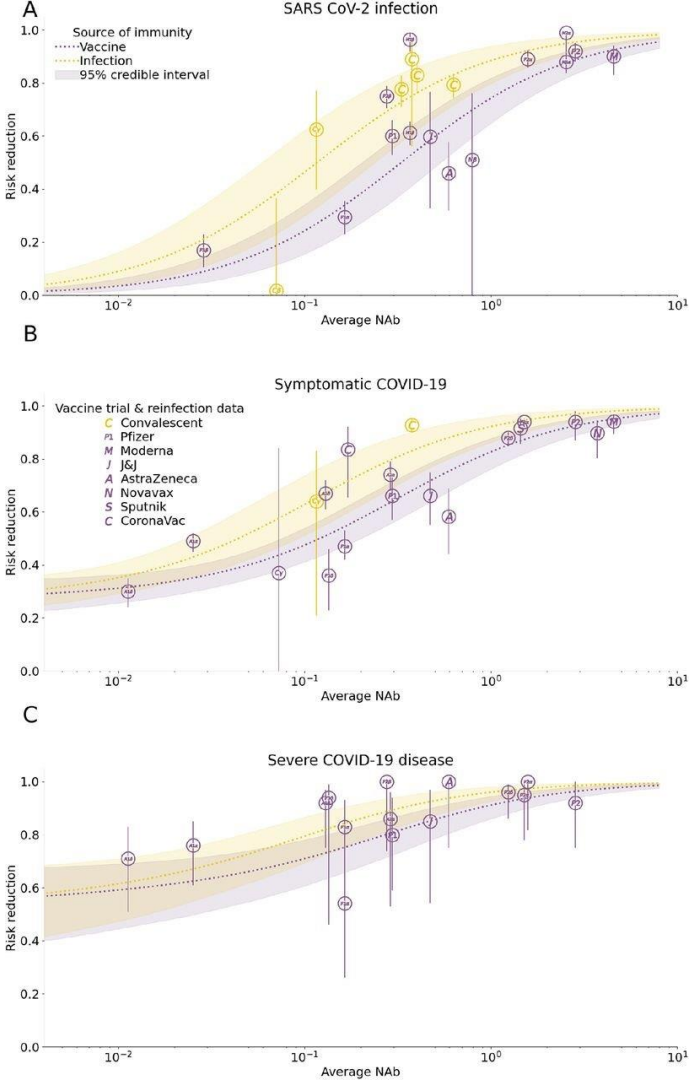
Vaccinology studies (usually)	$\log(RR_{outcome}) = \alpha - \beta \log(\text{CoP})$ $VE_{outcome} = 1 - e^{\alpha}(\text{CoP})^{-\beta}$	VE can go negative. Useful in studies since you have to watch if the vaccine is harmful.
If you can safely assume VE>0	$\text{logit}(VE_{outcome}) = \alpha + \beta \log(\text{CoP})$	VE bounded between 0 and 1. More efficient statistically and correct biologically if you know VE>0 always.
Vaccine efficacy for an endpoint is a composite	$VE_{symp}(\text{CoP})$ $= 1 - \left(1 - VE_{symp\|inf}(\text{CoP})\right)\left(1 - VE_{\text{inf}}(\text{CoP})\right)$	Nonlinear regression, but more correct over range of possible CoP
If you suspect the range of possible VE is narrower than 0 to 1 for any value of the CoP	$\text{logit}\left(\frac{VE_{outcome}}{VE_{max} - VE_{min}}\right) = \alpha + \beta \log(\text{CoP})$	Probably already doing nonlinear regression. But think carefully about identifiability and if you're not doing something else wrong. CoPs are imperfect. Biology is weird sometimes.

Covid example where the nonlinear regression helps

- [Jamie Cohen *et al* 2023]

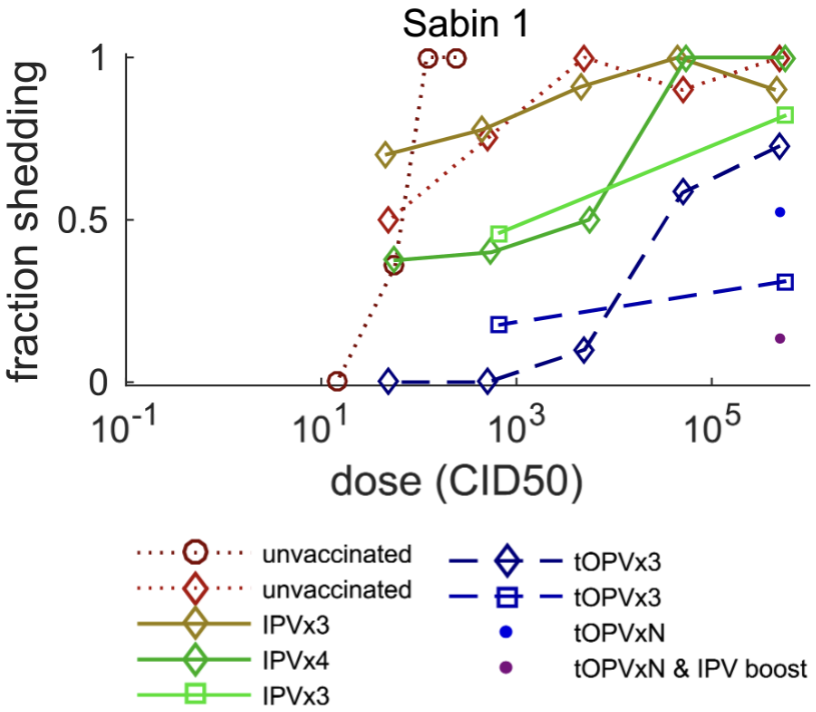
- Conditional cascade fits to VE for infection, symptoms, and severe disease
  - Intercepts for vaccine and infection

- Useful things you don't get if you just do independent regressions
  - Marginal efficacies for symptoms and severe disease asymptote above 0, consistent with existence of other as-yet-unidentified CoPs
  - Waning models don't go to zero for severe disease (big problem with some others)
  - No dumb arguments about "efficacy against severe disease doesn't wane" vs "no, it does!"



3. Almost all immunity is leaky

- Immunity is almost always a function of dose.
- It is almost always possible in principle to deliver a big enough dose in the right way to overcome immunity
- Binary (”sterilizing”) immunity is an approximation whose validity depends on
  - Setting
    - Force of infection, “vaccine take”, delivery, cold chain, co-morbidities etc
  - Time since vaccination (waning)
  - Disease outcome being considered



Famulare *et al 2016*

Recommendations to deal with leaky immunity

- If your thoughtful understanding of biology and policy says you can get away with it, modeling immunity as binary is great.

- If you can't get away with binary immunity, build a leaky model, fit it to data (more ahead), and propagate policy-relevant uncertainty.

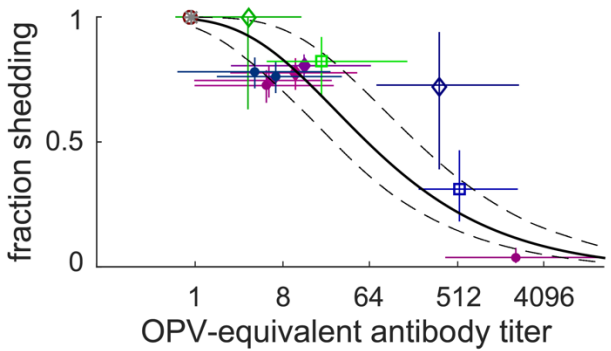
Recommendations to deal with leaky immunity

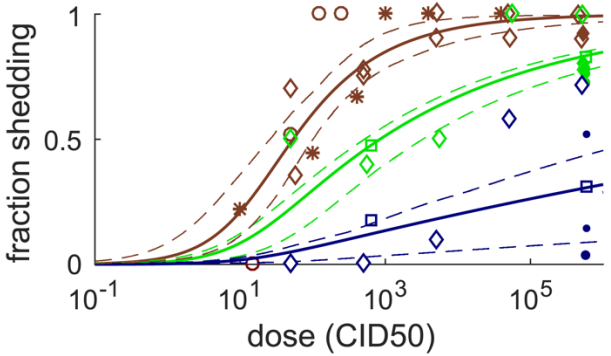
- If your thoughtful understanding of biology and policy says you can get away with it, modeling immunity as binary is great.

- If you can't get away with binary immunity, build a leaky model, fit it to data (more ahead), and propagate policy-relevant uncertainty.

- Observations: I haven't done simulation studies (should! will?¡), but
  - binary with waning is often fine when modeling large pops without age structure
  - *A priori* it's a problem in highly-structured populations with complex immune histories and contact patterns (like households)
    - You can be saved if $VE_{transmission|inf}$ is high even if VE_{inf} isn't, but the reliability of that implicit assumption is sensitive to contact patterns and FOI

Good default: approximate beta-Poisson with immunity



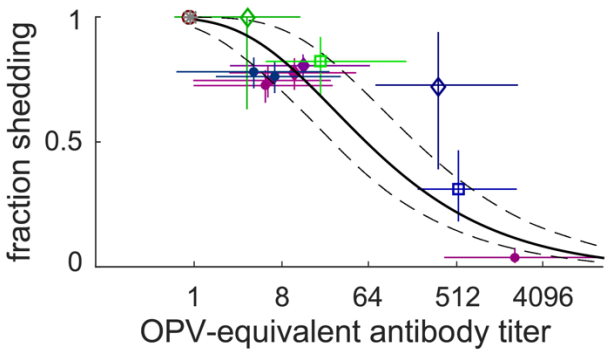


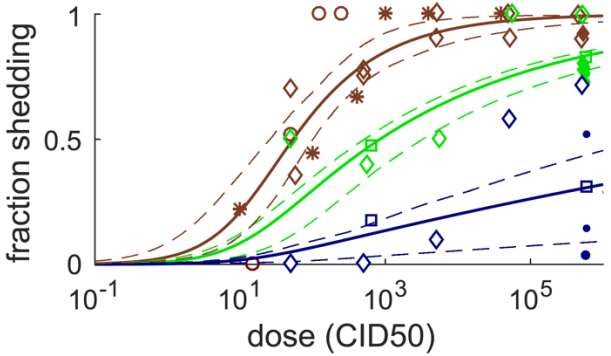
Simplest sensible dose response model

$$P(\text{infected}|\text{dose}, \text{CoP}) = p_{max}\left(1 - \exp\left(-\frac{\text{dose}}{D}\right)\right)$$

All infectious units and people are identical.

Good default: approximate beta-Poisson with immunity





Simplest sensible dose response model

$$P(\text{infected}|\text{dose}, \text{CoP}) = p_{max}\left(1 - \exp\left(-\frac{\text{dose}}{D}\right)\right)$$

All infectious units and people are identical.

Better dose response model (approx. beta-Poisson aka exact gamma-Poisson, with immunity)

$$P(\text{infected}|\text{dose}, \text{CoP}) = p_{max}\left(1 - \left(1 + \frac{\text{dose}}{\beta}\right)^{-\alpha/(\text{CoP})^{\gamma}}\right)$$

Interpretation: infectious units and people vary, and immunity reduces probability infectious unit is viable

$\alpha \ll \beta$ is typical

Modeling the effects of exposure dose on VE

Dose response model

$$P(\text{infected}|\text{dose}, \text{CoP}) = p_{max}\left(1 - \left(1 + \frac{\text{dose}}{\beta}\right)^{-\alpha/(\text{CoP})^{\gamma}}\right)$$

Interpretation: infectious units and people vary, and immunity reduces probability infectious unit is viable

$\alpha \ll \beta$ is typical

Vaccine efficacy

$$VE_{inf}(\text{dose}, \text{CoP}) = 1 - \frac{P(\text{infected}|\text{dose}, \text{CoP})}{P(\text{infected}|\text{dose}, \text{CoP}_{\text{min}})}$$

Dose-dependent vaccine efficacy

Modeling the effects of exposure dose on VE

Dose response model

$$P(\text{infected}|\text{dose},\text{CoP}) = p_{max}\left(1 - \left(1 + \frac{\text{dose}}{\beta}\right)^{-\alpha/(\text{CoP})^{\gamma}}\right)$$

Interpretation: infectious units and people vary, and immunity reduces probability infectious unit is viable

$\alpha \ll \beta$ is typical

Vaccine efficacy

$$VE_{inf}(\text{dose},\text{CoP}) = 1 - \frac{P(\text{infected}|\text{dose},\text{CoP})}{P(\text{infected}|\text{dose},\text{CoP}_{\text{min}})}$$

Dose-dependent vaccine efficacy

VE if dose is small (linear dose regime)

$$VE_{inf}(\text{small dose},\text{CoP}) \approx 1 - \left(\frac{\text{CoP}_{\text{min}}}{\text{CoP}}\right)^{\gamma}$$

VE is independent of exposure dose at small doses

Modeling the effects of exposure dose on VE

Dose response model

$$P(\text{infected}|\text{dose},\text{CoP}) = p_{max}\left(1 - \left(1 + \frac{\text{dose}}{\beta}\right)^{-\alpha/(\text{CoP})^{\gamma}}\right)$$

Interpretation: infectious units and people vary, and immunity reduces probability infectious unit is viable

$\alpha \ll \beta$ is typical

Vaccine efficacy

$$VE_{inf}(\text{dose},\text{CoP}) = 1 - \frac{P(\text{infected}|\text{dose},\text{CoP})}{P(\text{infected}|\text{dose},\text{CoP}_{\min})}$$

Dose-dependent vaccine efficacy

VE if dose is small (linear dose regime)

$$VE_{inf}(\text{small dose},\text{CoP}) \approx 1 - \left(\frac{\text{CoP}_{\min}}{\text{CoP}}\right)^{\gamma}$$

VE is independent of exposure dose at small doses

VE if dose is small and VE isn't small

$$\text{logit}\left(VE_{inf}(\text{small dose},\text{CoP})\right) \approx -\gamma\log(\text{CoP}_{\min}) + \gamma\log(\text{CoP})$$

We're back to Vaccinology 501: if doses are small, VE is independent of dose and logit in log CoP.

Vaccine efficacy studies (usually)	$\log(RR_{outcome}) = \alpha - \beta\log(\text{CoP})$ $VE_{outcome} = 1 - e^{\alpha}(\text{CoP})^{-\beta}$
If you can safely assume VE>0	$\text{logit}(VE_{outcome}) = \alpha + \beta\log(\text{CoP})$

Recommendations to deal with dose-dependent immunity

- If you see different VE in cohorts with similar CoP responses, that's a good clue you have large exposure and/or comorbidity variation among cohorts.
  - R0 and VE against infection will typically be inversely correlated.
  - Large R0 variation all but guarantees variation in VE against infection for any pathogen.

- Even if you don't have data on dose response, studying VE across settings can help you partially identify it. That's something you can feed forward into the transmission parts of a model, to get an *ecologically self-consistent* model of transmission and vaccination.

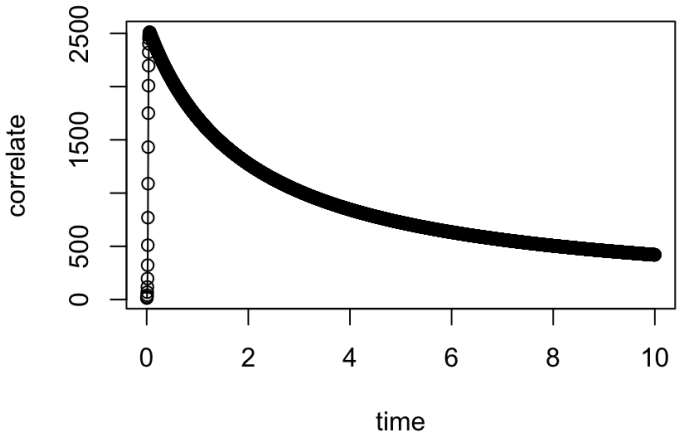
In addition to correlates of protection, there are *correlates of transmission*.

- Given leaky immunity, amount shed typically varies with CoP
- $(\text{Measure of shedding}) = (\text{Measure of shedding})_{max}\left(1 - k\log(\text{CoP}_{pre})\right)$
- Measures of shedding
  - Duration
  - Concentration excreted
- True for polio, COVID, flu…
- VE for transmission depends on individual correlates and transmission ecology, but this talk is already way too dense so we end this here.
  (Need to write a paper introducing this term and concept to the literature in a general way.)

4. Waning is never exponential

- Typical correlate rises rapidly upon immunization and falls (wanes) over time
- Separation of timescales: unless modeling interaction of immune response dynamics and infection, you can model this is a discrete jump and continuous decay thereafter.
- Simplest dynamics $\frac{d}{dt}(\mathrm{CoP}) = -w * \mathrm{CoP}$.

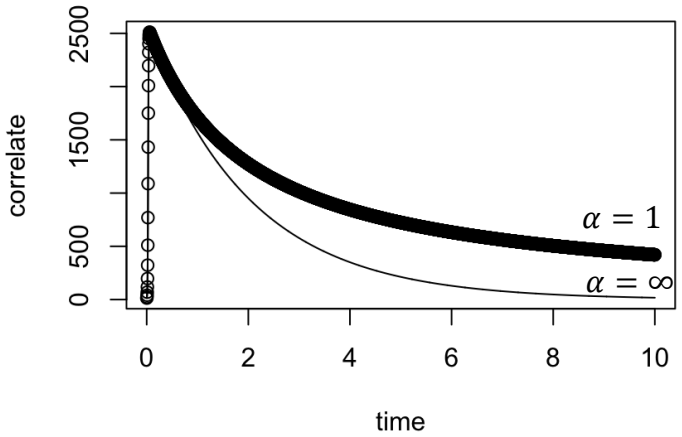
  Or $\mathrm{CoP(t)} = \left(\mathrm{CoP}_{peak} - \mathrm{CoP}_{min}\right)e^{-wt} + \mathrm{CoP}_{min}$



4. Waning is never exponential

- Typical correlate rises rapidly upon immunization and falls (wanes) over time
- Separation of timescales: unless modeling interaction of immune response dynamics and infection, you can model this is a discrete jump and continuous decay thereafter.
- Simplest dynamics $\frac{d}{dt}(\mathrm{CoP}) = -w * \mathrm{CoP}$.

  Or $\mathrm{CoP(t)} = \left(\mathrm{CoP}_{peak} - \mathrm{CoP}_{min}\right)e^{-wt} + \mathrm{CoP}_{min}$

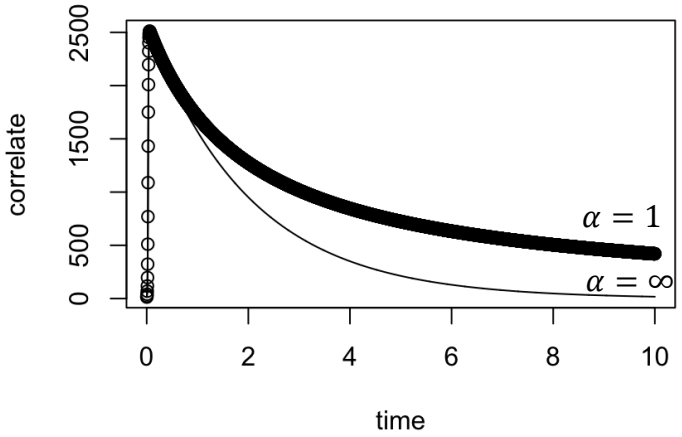


- *Do you really believe every single B-cell/antibody/T-cell/cytokine/??? decays at the exact same rate? That there is zero long-term response?* ***NO!***

4. Waning is never exponential

- Typical correlate rises rapidly upon immunization and falls (wanes) over time
- Separation of timescales: unless modeling interaction of immune response dynamics and infection, you can model this is a discrete jump and continuous decay thereafter.
- Simplest dynamics $\frac{d}{dt}(\mathrm{CoP}) = -w * \mathrm{CoP}$.

  Or $\mathrm{CoP(t)} = \left(\mathrm{CoP}_{peak} - \mathrm{CoP}_{min}\right)e^{-wt} + \mathrm{CoP}_{min}$



- *Do you really believe every single B-cell/antibody/T-cell/cytokine/??? decays at the exact same rate? That there is zero long-term response?* ***NO!***

- A better model is thus $\mathrm{CoP(t)} = \mathrm{CoP}(0)\int dw\, P(w)e^{-wt}$.
  Assume $P(w)$ is Gamma-distributed because it's easy and doesn't much matter

$$\mathrm{CoP}(\text{time } t \text{ since last immunization}) = \begin{cases} \mathrm{CoP}_{peak} & t < \tau_{peak} \\ \mathrm{CoP}_{min} + \left(\mathrm{CoP}_{peak} - \mathrm{CoP}_{min}\right)\left(1 + \dfrac{t - \tau_{peak}}{\alpha T_{decay}}\right)^{-\alpha} & t \geq \tau_{peak} \end{cases}$$

Recommendations for modeling waning

- The standard exponential model is actually a strong and biologically-unrealistic assumption (zero variation in cellular/molecular response ($\alpha = \infty$), zero long-term adaptation)

- **So you should always fit the power law in place of the exponential.**

- With the follow-up durations in typical clinical trials, you may not be able to identify the dispersion parameter. In that case, based on surveying across some pathogens, *you're better off assuming* $\alpha \approx 1$.
    - Polio $\alpha = 0.9$, COVID $\alpha \approx (0.7, 1.1)$, (measles $\alpha \approx 0.07$)
  - Will match observed short-term dynamics, but very likely to better predict long-time behavior even in absence of data.
  - Obviously, basing on data or calibration is best.

Modeling VE waning without a CoP

VE with a CoP

$$\text{logit}(VE_{outcome}) = \alpha + \beta \log(\text{CoP})$$

Time dependence of a CoP

$$\text{CoP}(\text{time } t \text{ since last immunization}) = \begin{cases} \text{CoP}_{peak} & t < \tau_{peak} \\ \text{CoP}_{peak}\left(1 + \dfrac{t - \tau_{peak}}{\gamma T_{decay}}\right)^{-\gamma} & t \geq \tau_{peak} \end{cases}$$

Modeling VE waning without a CoP

VE with a CoP

$$\text{logit}(VE_{outcome}) = \alpha + \beta \log(\text{CoP})$$

Time dependence of a CoP

$$\text{CoP}(\text{time } t \text{ since last immunization}) \approx \begin{cases} \text{CoP}_{peak} & t < \tau_{peak} \\ \text{CoP}_{peak}\left(1 + \dfrac{t - \tau_{peak}}{\gamma T_{decay}}\right)^{-\gamma} & t \geq \tau_{peak} \end{cases}$$

VE vs time with a CoP

$$\text{logit}(VE_{outcome}) \approx \alpha - \beta \log\left(\text{CoP}_{peak}\right) - \beta\gamma \log\left(1 + \frac{t}{\gamma T_{decay}}\right)$$

Modeling VE waning without a CoP

VE with a CoP

$$\text{logit}(VE_{outcome}) = \alpha + \beta \log(\text{CoP})$$

Time dependence of a CoP

$$\text{CoP}(\text{time } t \text{ since last immunization}) \approx \begin{cases} \text{CoP}_{peak} & t < \tau_{peak} \\ \text{CoP}_{peak}\left(1 + \dfrac{t - \tau_{peak}}{\gamma T_{decay}}\right)^{-\gamma} & t \geq \tau_{peak} \end{cases}$$

VE vs time with a CoP

$$\text{logit}(VE_{outcome}) \approx \alpha - \beta \log\left(\text{CoP}_{peak}\right) - \beta\gamma \log\left(1 + \frac{t}{\gamma T_{decay}}\right)$$

VE vs time without a CoP

$$\text{logit}(VE_{outcome}) = \acute{\alpha} - \acute{\beta} \log\left(1 + \frac{t}{\acute{\gamma}}\right)$$

Nonlinear regression again, but an easy one

5. You probably don't care about priming and boosting

- Example CoP response across the entire achievable range: poliovirus neutralizing antibody titer

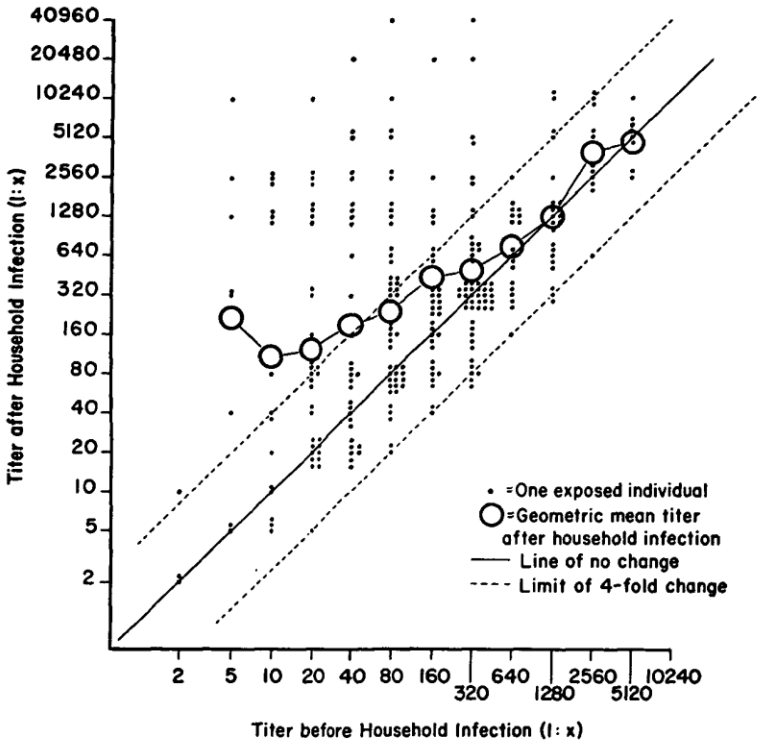


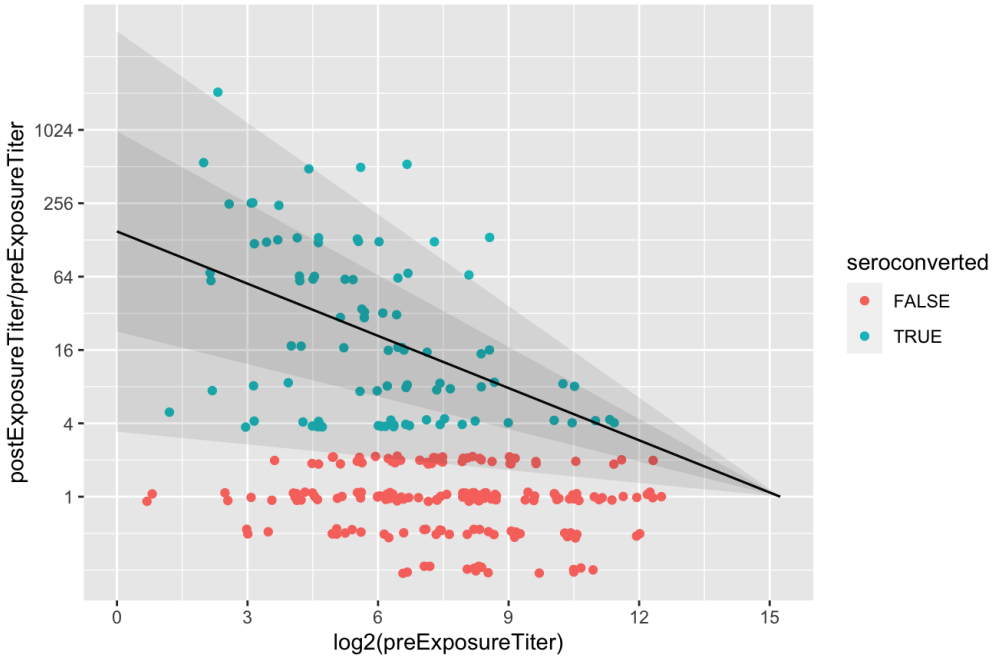
FIGURE 1. Serum neutralization titers of previously immune individuals exposed to reinfection in households of infected index children.

5. You probably don't care about priming and boosting

- Example CoP response across the entire achievable range:
  - poliovirus neutralizing antibody titer

$$\text{Mean}\left[\log\left(\frac{\text{CoP}_{peak}}{\text{CoP}_{pre}}\right)\right] = \mu_o\left(1 - \frac{\log(\text{CoP}_{pre})}{\log(\text{CoP}_{max})}\right)$$

$$\text{sd}\left[\log\left(\frac{\text{CoP}_{peak}}{\text{CoP}_{pre}}\right)\right] = \sigma_o\left(1 - \frac{\log(\text{CoP}_{pre})}{\log(\text{CoP}_{max})}\right)$$

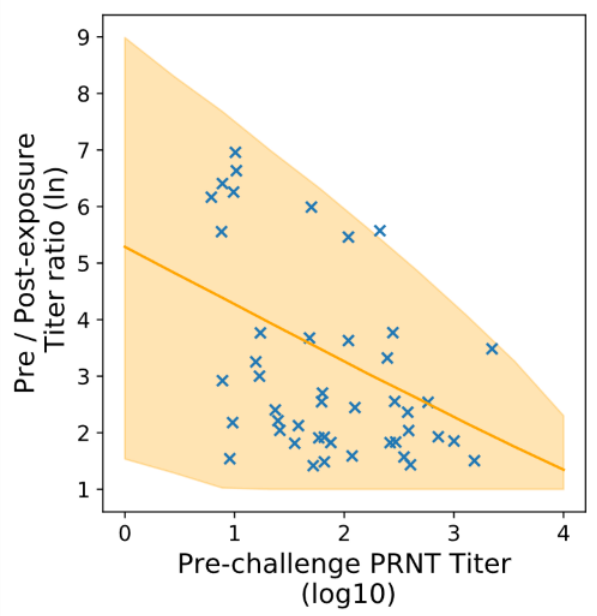


5. You probably don't care about priming and boosting

- Example CoP response across the entire achievable range:
  - measles neutralizing antibody titer

$$\text{Mean}\left[\log\left(\frac{\text{CoP}_{peak}}{\text{CoP}_{pre}}\right)\right] = \mu_o\left(1 - \frac{\log(\text{CoP}_{pre})}{\log(\text{CoP}_{max})}\right)$$

$$\text{sd}\left[\log\left(\frac{\text{CoP}_{peak}}{\text{CoP}_{pre}}\right)\right] = \sigma_o\left(1 - \frac{\log(\text{CoP}_{pre})}{\log(\text{CoP}_{max})}\right)$$



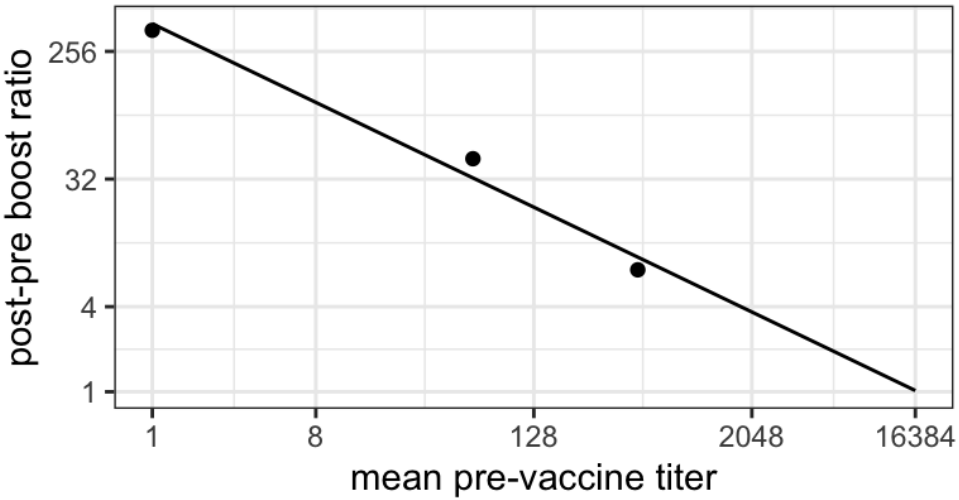
Wong *et al* unpublished

5. You probably don't care about priming and boosting

- Example CoP response across the entire achievable range:
  - COVID neutralizing antibody titer from Pfizer mRNA vaccine

$$\text{Mean}\left[\log\left(\frac{\text{CoP}_{peak}}{\text{CoP}_{pre}}\right)\right] = \mu_o\left(1 - \frac{\log(\text{CoP}_{pre})}{\log(\text{CoP}_{max})}\right)$$

$$\text{sd}\left[\log\left(\frac{\text{CoP}_{peak}}{\text{CoP}_{pre}}\right)\right] = \sigma_o\left(1 - \frac{\log(\text{CoP}_{pre})}{\log(\text{CoP}_{max})}\right)$$



5. You probably don't care about priming and boosting

- Example CoP response across the entire achievable range:
  - Influenza HAI titer from live and inactivated vaccines

$$\text{Mean}\left[\log\left(\frac{\text{CoP}_{peak}}{\text{CoP}_{pre}}\right)\right] = \mu_{vax}\left(1 - \frac{\log(\text{CoP}_{pre})}{\log(\text{CoP}_{max})}\right)$$

$$\text{sd}\left[\log\left(\frac{\text{CoP}_{peak}}{\text{CoP}_{pre}}\right)\right] = \sigma_{vax}\left(1 - \frac{\log(\text{CoP}_{pre})}{\log(\text{CoP}_{max})}\right)$$

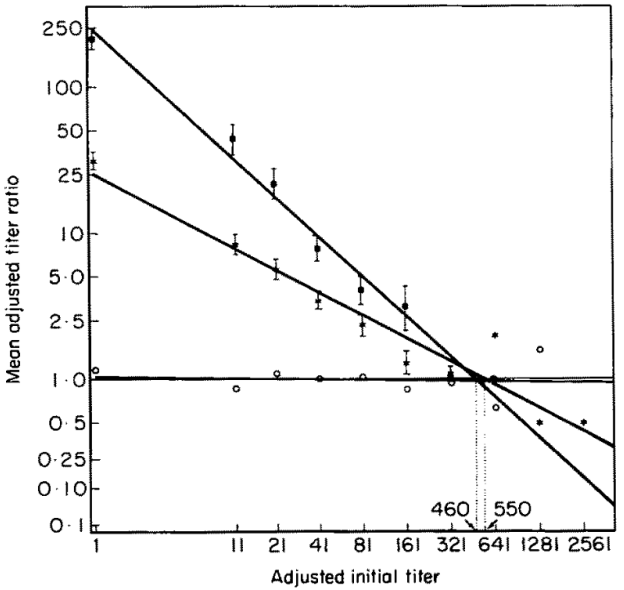


FIG. 4. Immune response profiles for a live versus killed vaccine. The immune response profiles for the live and killed forms of A/England vaccine are shown and are seen to be quite distinct. The zero boost initial titer for each of the two forms is seen to be equivalent, however. ■—■, killed; * — *, live; ○—○, placebo.

Smith *et al* 1984

5. You probably don't care about priming and boosting

- At least for antibody-based CoP, there appears to be a universal model for CoP response across the entire range of achievable immunity

$$\text{Mean}\left[\log\left(\frac{\text{CoP}_{peak}}{\text{CoP}_{pre}}\right)\right] = \mu_{source}\left(1 - \frac{\log(\text{CoP}_{pre})}{\log(\text{CoP}_{max})}\right)$$

$$\text{sd}\left[\log\left(\frac{\text{CoP}_{peak}}{\text{CoP}_{pre}}\right)\right] = \sigma_{source}\left(1 - \frac{\log(\text{CoP}_{pre})}{\log(\text{CoP}_{max})}\right)$$

CoP_{max} is a property of the host immune system and the pathogen

- Shared across infection and different vaccine formulations and schedule
- *If your CoP is a neutralizing antibody titer and your pathogen is a virus, probably* $\text{CoP}_{max} \sim 2^{14} = 10^{4.2}$ (works for polio, COVID, flu, RSV, measles)

μ_{source} and σ_{source} are also properties of the immunizing source

- Fit separately for infection and each vaccine formulation you care about

Recommendations for modeling CoP response

- The mean CoP response is a two-parameter fit
  - You can probably guess the max CoP from looking at peak values right after boosting in people with lots of prior immunity
  - You can get the other parameter from a single trial

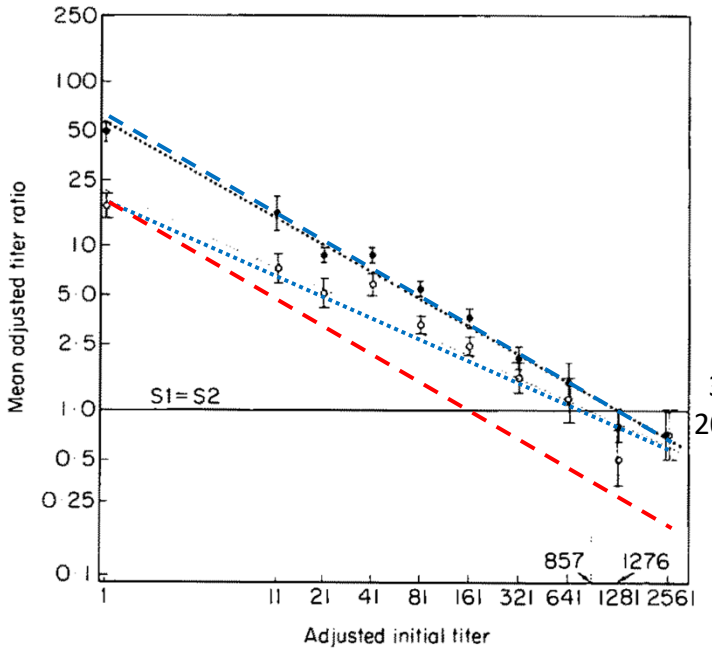
- This is super useful because now, with the waning model, you have a complete model of the immune response and level of protection for many populations
  - Different immune histories and force of infection
  - Revaccination vs first vaccination. How much will adding a dose when help?

- If you don't have a CoP, you can fit the model with a latent CoP using VE measurements from 1 dose and 2 (or different schedules)

*Asterisk: waning rate may depend on CoP_{peak}

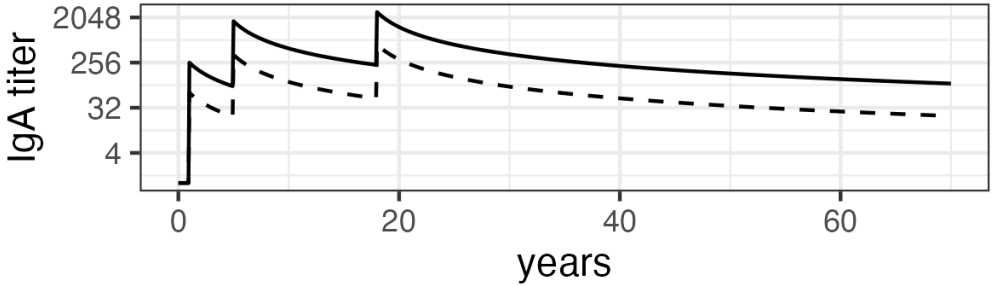
$$\mathrm{CoP}(\text{time } t \text{ since last immunization}) \overset{?}{=} \begin{cases} \mathrm{CoP}_{peak} & t < \tau_{peak} \\ \mathrm{CoP}_{peak}\left(1 + \dfrac{t - \tau_{peak}}{\alpha\left(T_{max} - \Delta T\left(1 - \dfrac{\log(\mathrm{CoP}_{peak})}{\log(\mathrm{CoP}_{max})}\right)\right)}\right)^{-\alpha} & t \geq \tau_{peak} \end{cases}$$

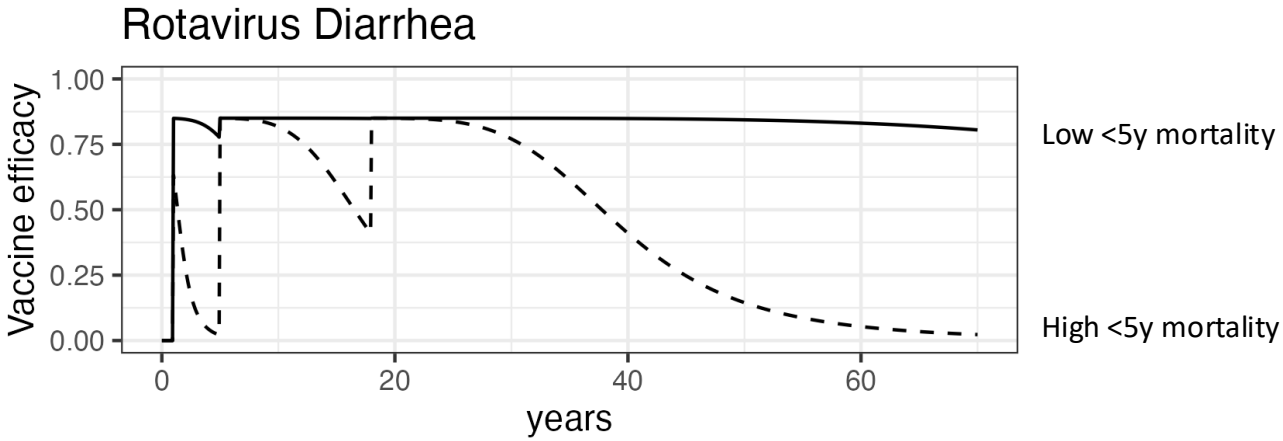
I only came to appreciate this figure yesterday and it's the only figure of its kind I've seen so far. We have COVID data to check, so I will be doing that.



3 weeks after vaccination
20 weeks after

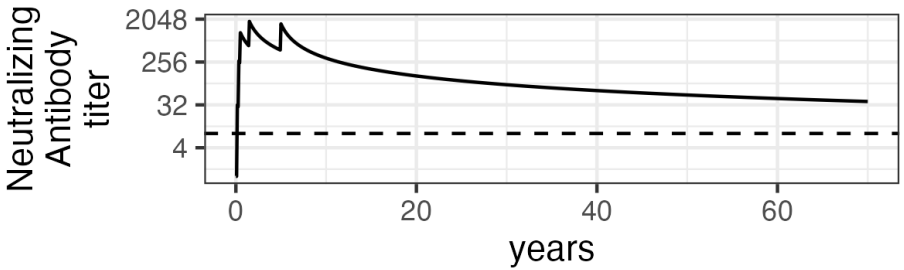
Examples VE vs time curves with one model: rotavirus (toy)

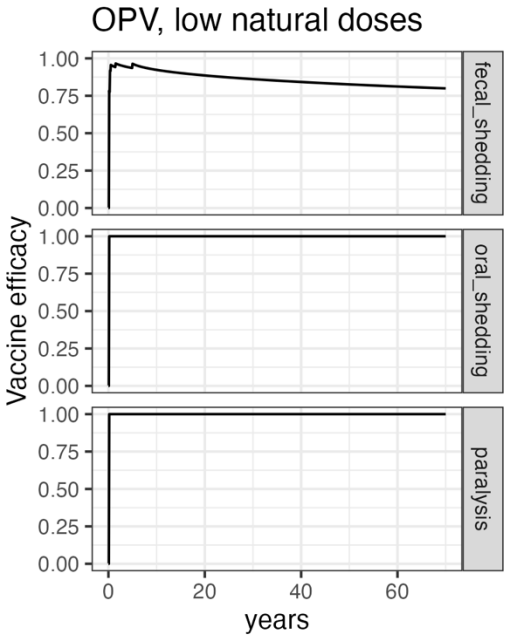


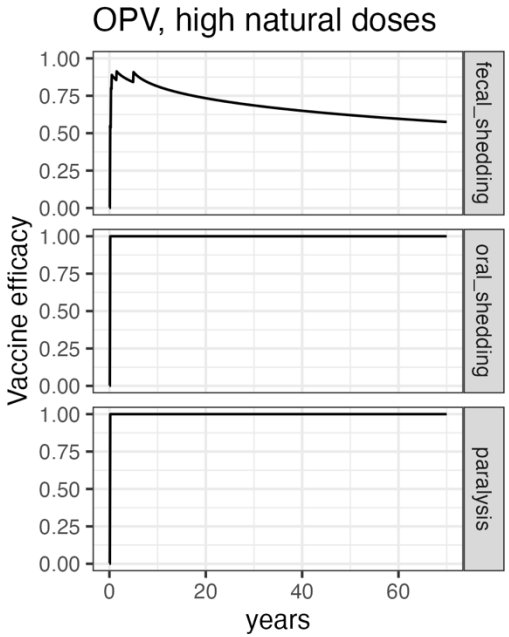


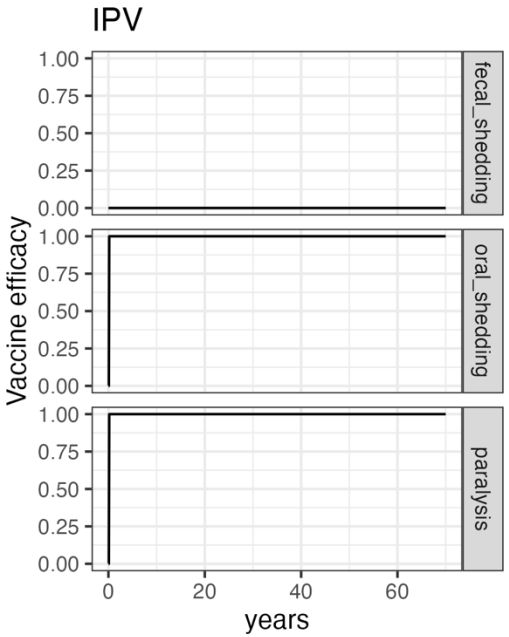
Mockup with Alicia.
Real work still has to be done.

Examples VE vs time curves with one model: Polio









Summary

Vaccine efficacy for an endpoint is a composite

$$VE_{symptoms} = 1 - (1 - VE_{symp|inf})(1 - VE_{inf})$$

If you can safely assume VE>0

$$\text{logit}(VE_{outcome}) = \alpha + \beta \log(\text{CoP})$$

Time dependence of a CoP

$$\text{CoP}(\text{time } t \text{ since last immunization}) = \begin{cases} \text{CoP}_{peak} & t < \tau_{peak} \\ \text{CoP}_{min} + (\text{CoP}_{peak} - \text{CoP}_{min})\left(1 + \dfrac{t - \tau_{peak}}{\alpha T_{decay}}\right)^{-\alpha} & t \geq \tau_{peak} \end{cases}$$

Mean response of a CoP

$$\text{Mean}\left[\log\left(\frac{\text{CoP}_{peak}}{\text{CoP}_{pre}}\right)\right] = \mu_{source}\left(1 - \frac{\log(\text{CoP}_{pre})}{\log(\text{CoP}_{max})}\right)$$

If force of infection is highly variable, think dose response

$$VE_{inf}(\text{dose}, \text{CoP}) = 1 - \frac{P(\text{infected}|\text{dose}, \text{CoP})}{P(\text{infected}|\text{dose}, \text{CoP}_{\text{min}})}$$

Think through the biology and the data, complexify as you can, simplify as you must, propagate uncertainty, and advocate to measure important unknowns.