PHARMACOMETRICS: A SHOT IN THE ARM FOR VACCINE DISCOVERY AND DEVELOPMENT

~OR~

VACCINES ARE NOT IMMUNE TO THE CHARMS OF PHARMACOMETRICS

PAGE 2019 Meeting, Stockholm, Sweden

June 12, 2019

Jeff Sachs

Pharmacokinetics, Pharmacodynamics, and Drug Metabolism
– Quantitative Pharmacology and Pharmacometrics,
Merck & Co., Inc., Kenilworth, NJ, USA

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Outline

Motivation
- Motivation – Impact of vaccines
- Potential impact for PMX

Background
- Vaccines & Immunology

PMX
- Applications
- Their impact

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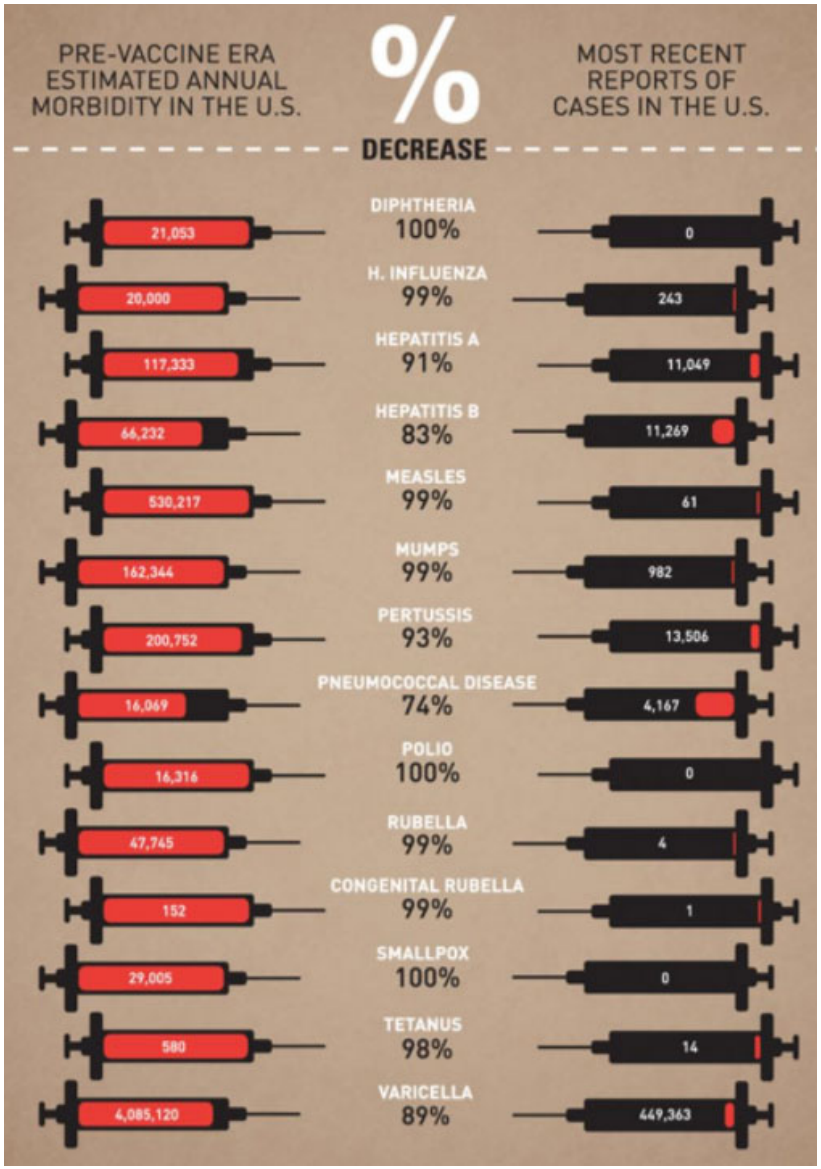
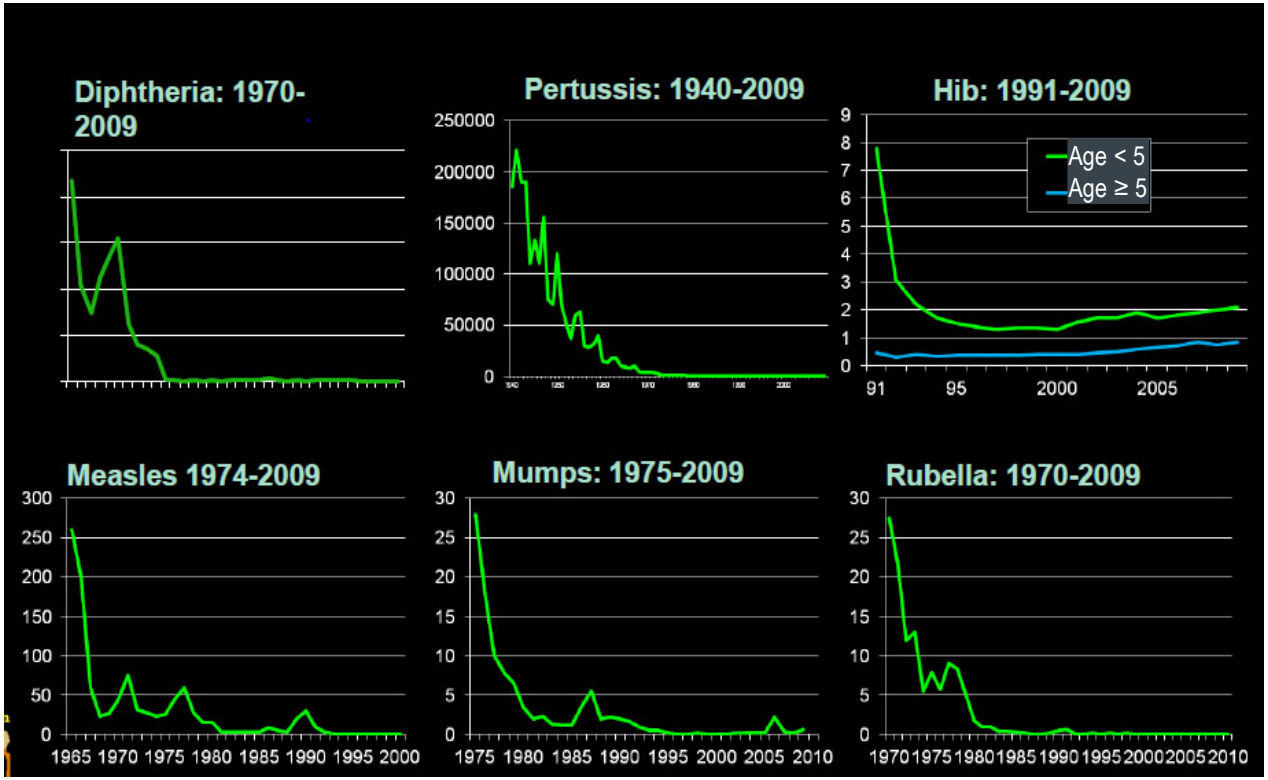


Many Diseases Have Been Prevented



Halsey, NA, *How Vaccines Cause Adverse Events, ADVAC Course Annecy France 2018*

https://www.forbes.com/sites/matthewherper/2013/02/19/a-graphic-that-drives-home-how-vaccines-have-changed-our-world/ - 1a58e6dd3302

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Polio

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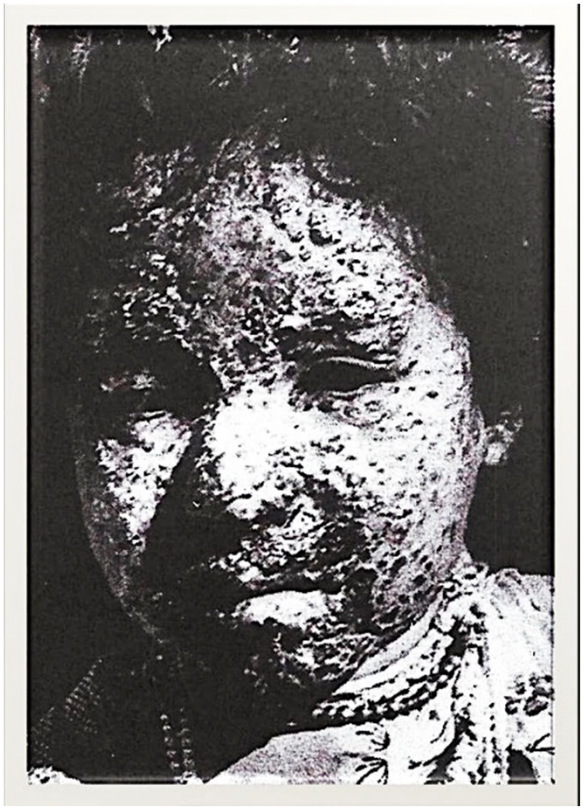
Historical Perspective: Smallpox



Bazin, H., *Vaccination: a History*

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Don't Count Your Children Until The Measles Have Come Through
– African saying

*MMWR / November 11, 2016, 65 (44) 1228-1233

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The Modern Toll of Measles

EU region
2018
83,000 cases
50,000 hospitalized
72 deaths[1]

EU region
1Jan18 – 8May19
100,000 cases
>90 deaths[2]

Philippines
1Q 2019
33,000 cases
> 450 deaths[3]

[1] European Region statistics. From "Measles in Europe: record number of both sick and immunized," WHO Regional Office for Europe, Copenhagen, 7 February 2019
[2] http://www.euro.who.int/en/media-centre/sections/press-releases/2019/over-100-000-people-sick-with-measles-in-14-months-with-measles-cases-at-an-alarming-level-in-the-european-region,-who-scales-up-response
[3] https://www.npr.org/2019/05/19/724747890/measles-outbreak-in-the-philippines

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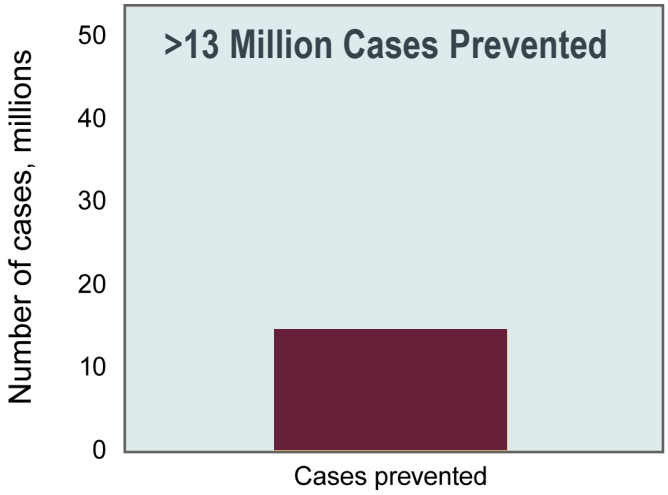
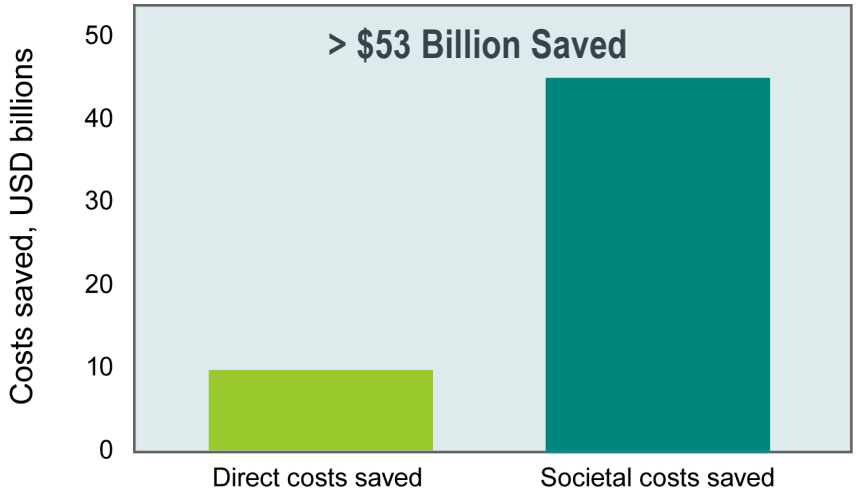
Health and Economic Impact of Preventing Disease with Vaccination…

Just One Country: USA

Just One Year's Cohort: Children born in 2001





Adapted from: Zhou F et al. Arch Pediatr Adolesc Med. 2005;159:1136–1144.

All costs are given in US dollars (USD).
Direct program costs included vaccines, administration, parent travel, and direct costs for the management of adverse events. Societal costs included direct program costs and parent time lost for vaccination and the management of adverse events.

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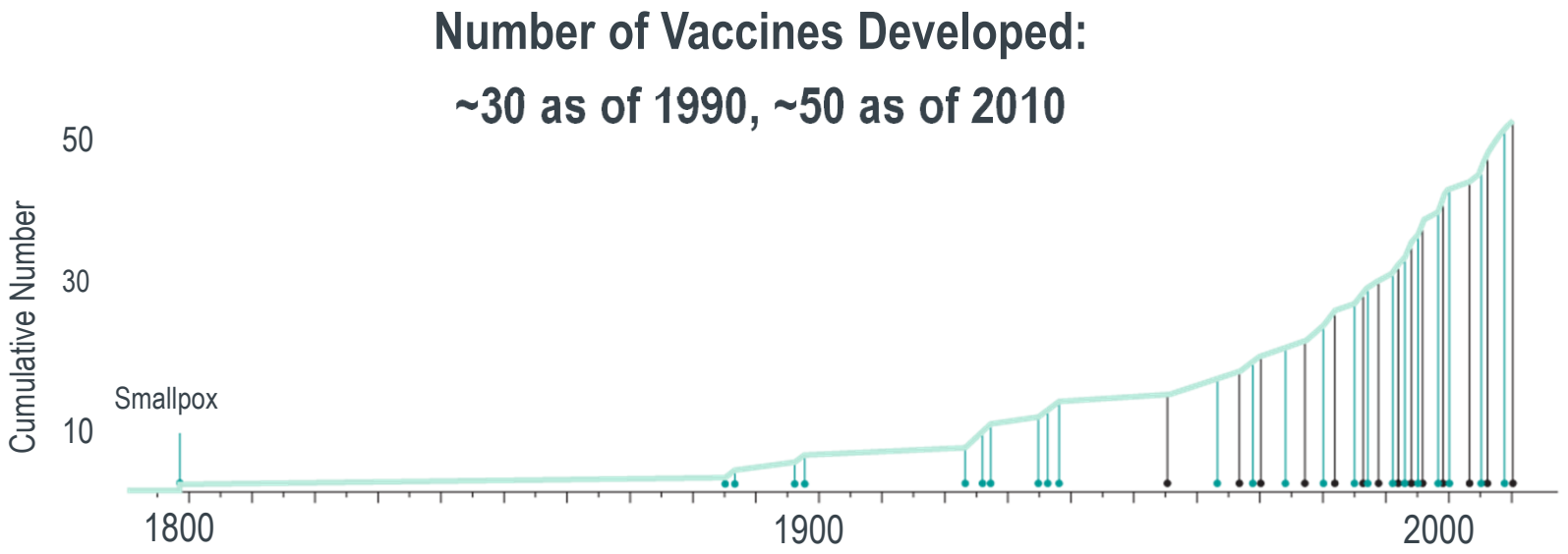
About 50 Vaccines Developed to Date



Adapted from: IOM (Institute of Medicine), Ranking vaccines: A prioritization framework: Phase I: Demonstration of concept and a software blueprint. Washington, DC, *The National Academies Press,* 2012, p. 19.

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…But Expensive and Takes Too Long

- **Cost** of a vaccine from discovery through Ph. 2a: **$0.4 Billion** (range $0.1-1B)*
- **Time** for a vaccine from discovery through Ph. 2a: **7 years** (range 4-15 years)*
- Vaccines too often in development for ~20 years

(Typically)

- **In Phase 3, 18,000 subjects total, 3 years** (range 1-5)
- **Time: enrollment + low incidence rate**

*Gouglas, D., TT Le, et al., Estimating the cost of vaccine development against epidemic infectious diseases: a cost minimisation study, Lancet Glob. Health, 2018;6:e1386–96

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“Vaccine”

Vaccine (for today): Active Stimulator Of Immune Memory and Antibody Production for Prevention of an Infectious Disease.

Jeryl Lynn Hilleman with her sister, Kirsten, in 1966 getting the mumps vaccine developed by their father.

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What is Special About Vaccines and Pharmacometrics?

Why were Vaccines not on our radar??

- PK* Rare
- Little DDI* (concomitant vaccination)
- Traditional clinical pharmacology analyses not typical
  - except safety & Tox

→ not part of our traditional purview.

*PK: pharmacokinetics, DDI: drug-drug interaction

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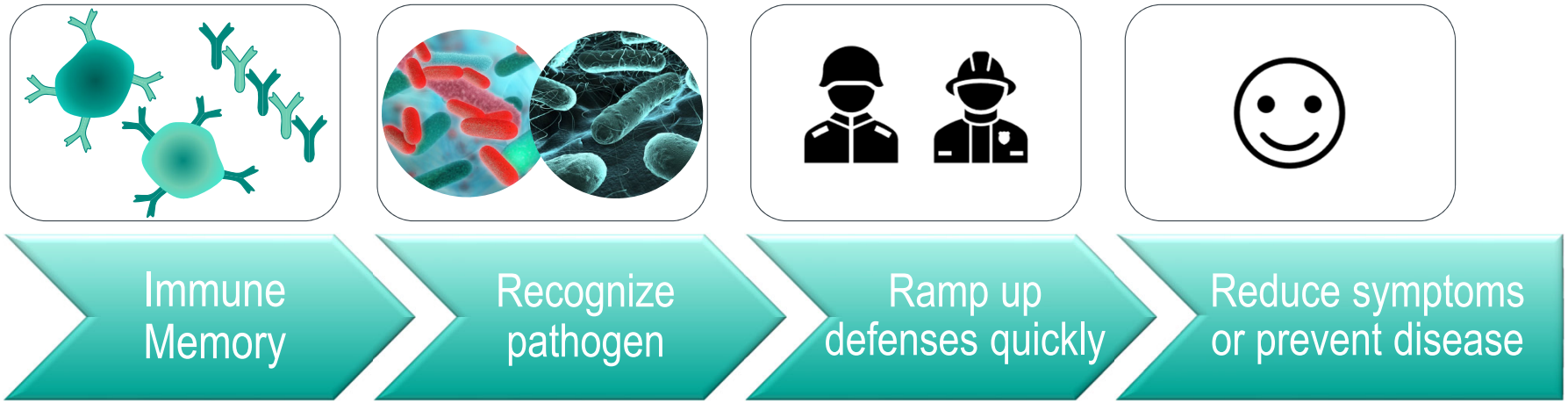
The Very BASICS: VACCINES and IMMUNOLOGY

Active Immunization – How it works



- Measuring Immune response: “Titer” ~ Target engagement
  - Quantity and quality of antibodies
- More is better

Immunogenicity ≠ efficacy

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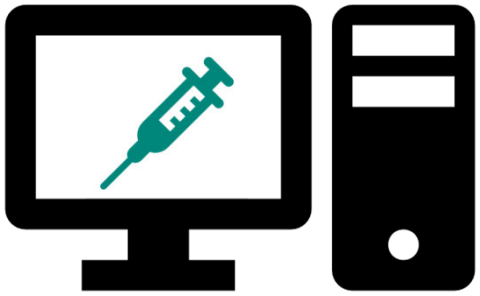
Overview of PMX and Vax

Modeling and Simulation in Vaccines



Computational vaccinology:

~~Epidemiology Health Econ~~

~~PKPD of mAb ("passive immu-nization")~~

~~immuno-genicity = *F*(antigen sequence)~~

~~chem eng. & SYS BIO for bioprocess~~

~~QSP/PKPD in Chemo-prophylaxis~~

Vaccine Pharmacometrics

(Today's focus)

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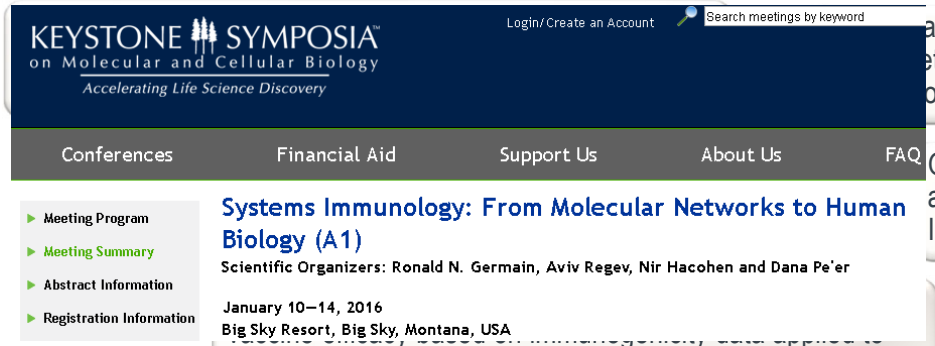
Rich History of Published Work (not a complete list!)



al. (2015) Mathematical modeling provides
etails of the human immune response to
on. *Front Cell Infect Microbiol.* 4:177

Gómez-Mantilla JD, et. al. ADME processes in vaccines and PK/PD approaches for vaccination optimization. In: ADME and tPK/PD. Wiley; 2016.

Rhodes SJ, et al. (2016) The TB vaccine H56 + IC31 dose-

influenza vaccines administered by the intradermal or

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Modelling dose responses following vaccination: lessons from the PK/PD field

Rockville, Maryland, May 29, 2014
Organizers:

BMGF: Steve Kern
LSHTM: Richard White, Sophie Rhodes
Imperial College: Gwen Knight
AERAS: Tom Evans, Lewis Schrager

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18

EXAMPLES

Phase	Key Question	Method(s)	Decision(s) / Impact

Seven Examples

Capability Demonstration
Program Impact

Enabling Translation

Understanding TE* Biomarkers Using Past Data

Leveraging TE* Biomarkers for Trial Design

Making Earlier Decisions with Quantified Risk

Supporting Regulatory Interaction

*TE: Target Engagement (stimulating protective immune response)

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Phase	Key Question	Method(s)	Decision(s) / Impact
1/2	**What N (# subjects) will let us tell if vaccines A and B are different?**	Phenomenological model Clinical trial simulation	Trial design, program strategy for sequence of trials

Wrong Question!

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What can we learn about dose-level & formulation impact on immunogenicity?
How can we use past data to inform the trial design?
How can we integrate data across trials in the future?

How many arms (and which ones) were needed to address information desired in the first question?

~400 Million

Number of arms the team had planned:

3

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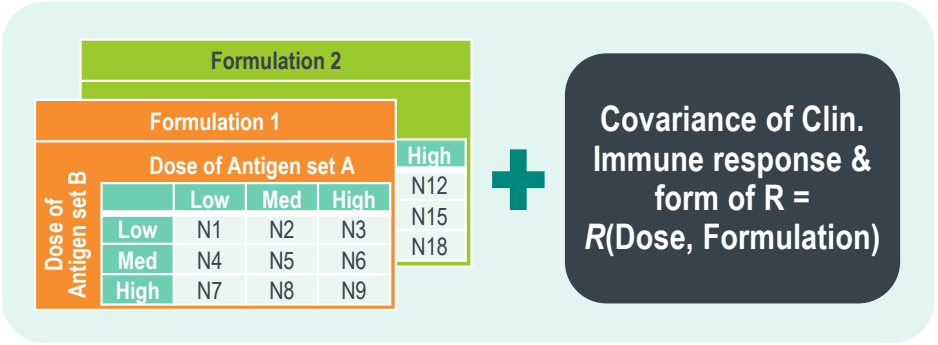
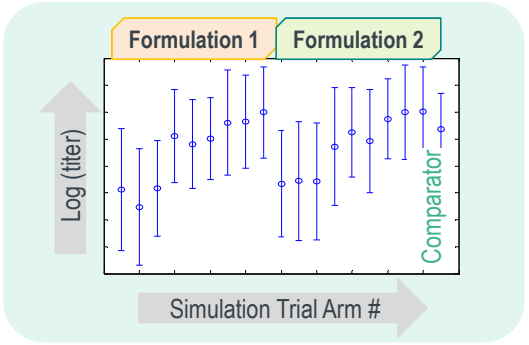
Trial Design by *Phenomenological* Simulation

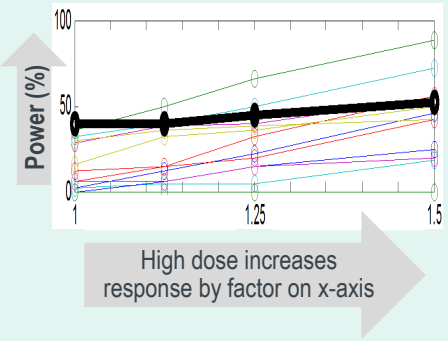


Covariance of Clin. Immune response & form of R = *R*(Dose, Formulation)

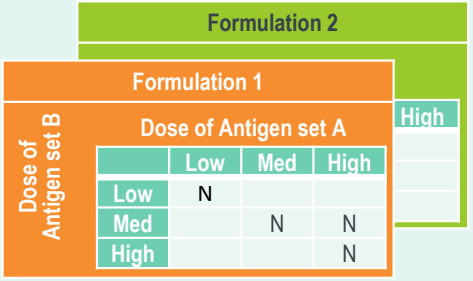
Simulate each of the 18 possible arms



Estimate power to detect dose / formulation effects



Choose trial arms & sizes



Thanks: Kapil Mayawala, Jon Hartzel

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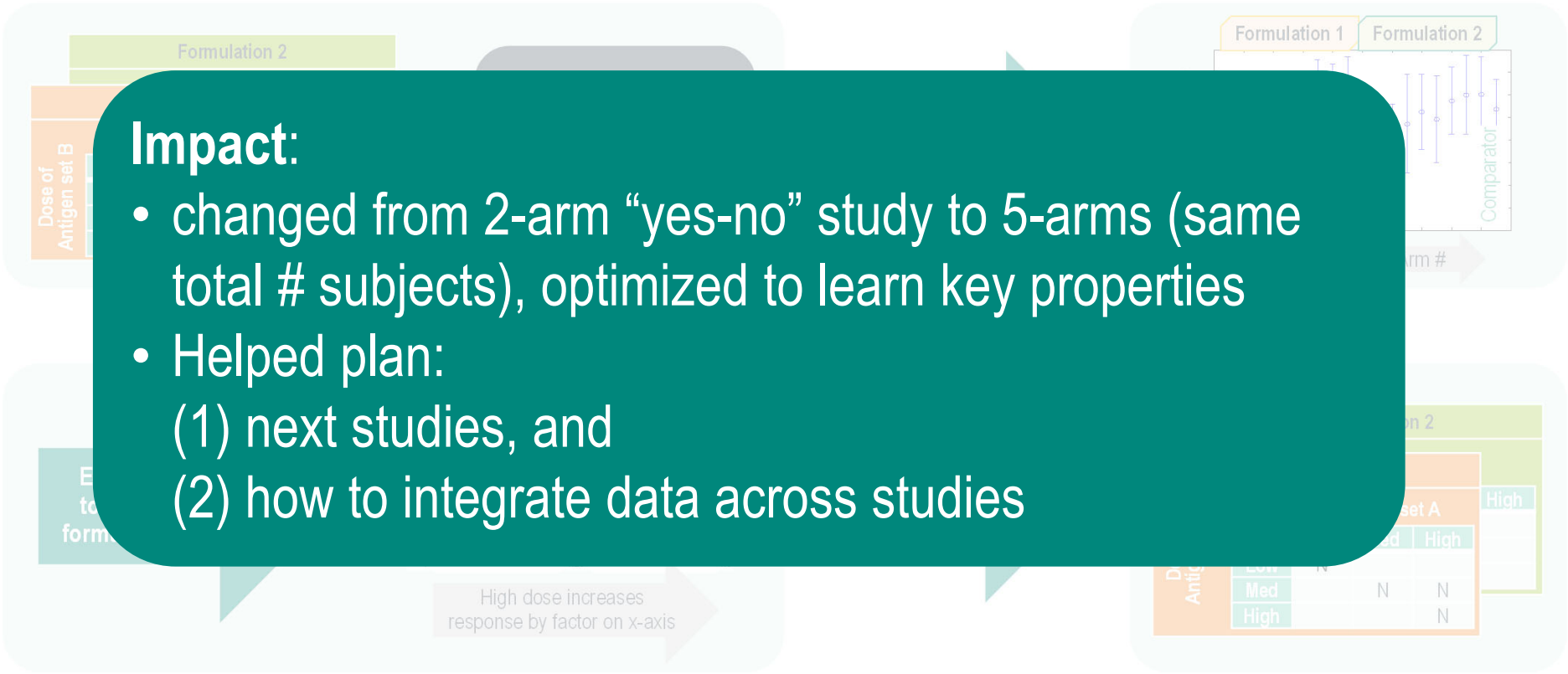
Trial Design by *Phenomenological* Simulation



Impact:

- changed from 2-arm "yes-no" study to 5-arms (same total # subjects), optimized to learn key properties
- Helped plan:
  (1) next studies, and
  (2) how to integrate data across studies

Thanks: Kapil Mayawala, Jon Hartzel

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Phase	Key Question	Method(s)	Decision(s) / Impact
2	**What disease assay(s) should we use and how often?**	QSP and Bayesian probabilistic	Saved $, increased POS Choice of assay, frequency

- Measuring vaccine efficacy requires counting number of disease cases.
- What happens if the counting (assay) process is not perfect?
- What assays should we use and how often?

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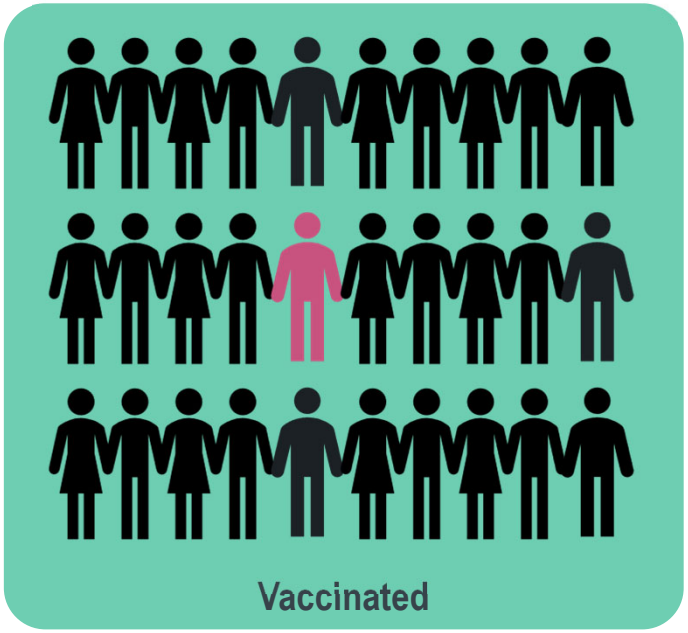
Efficacy = Proportional Risk Reduction

10% of placebo subjects get sick,

3% vaccinated subjects get sick

Efficacy = (10% - 3%) / 10% = 0.7 = “70% efficacy”



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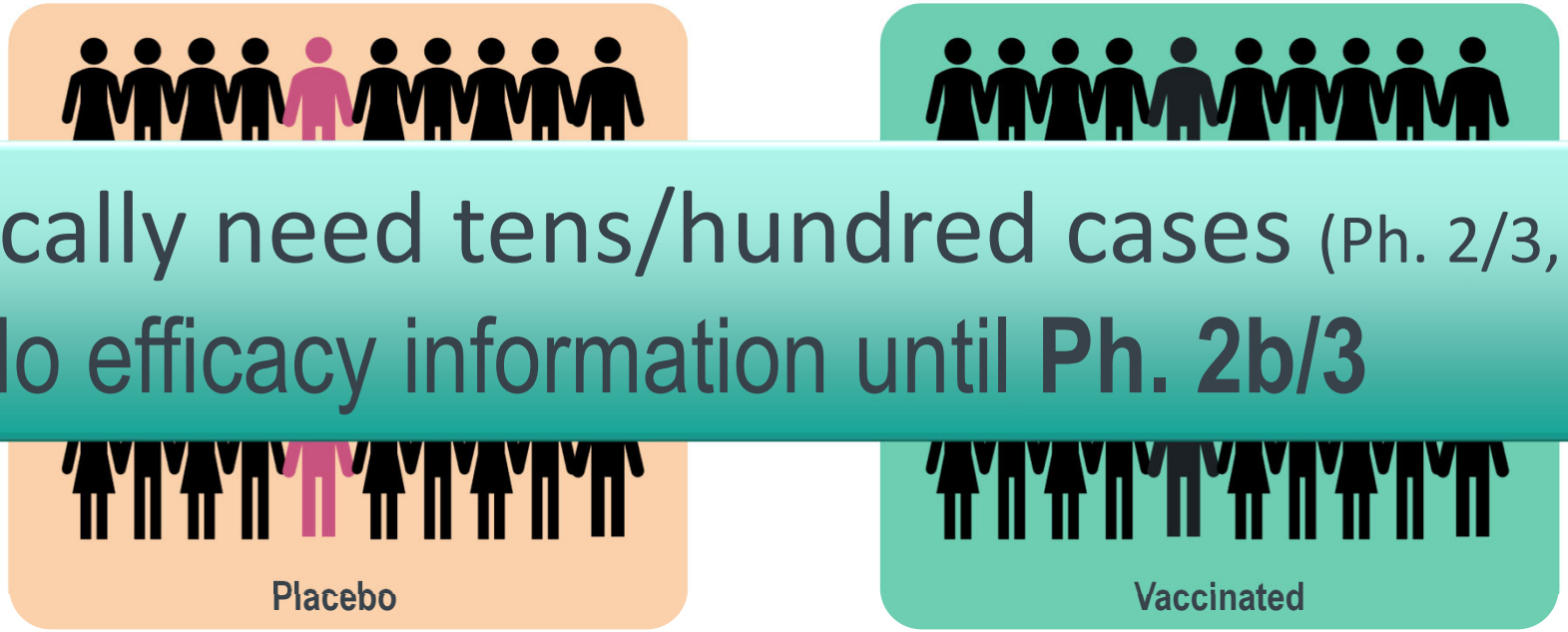

Typically need tens/hundred cases (Ph. 2/3, resp.)
→ No efficacy information until **Ph. 2b/3**

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Efficacy = Proportional Risk Reduction

13% ~~10%~~ of placebo subjects get sick,

6% ~~3%~~ vaccinated subjects get sick

~~Efficacy = (10% - 3%)/10% = 0.7 = "70% efficacy"~~

Efficacy = (13% - 6%)/13% = 0.54 = "54% efficacy"

+3%

+3%

Impact of False Positives

Repeat testing → ☹

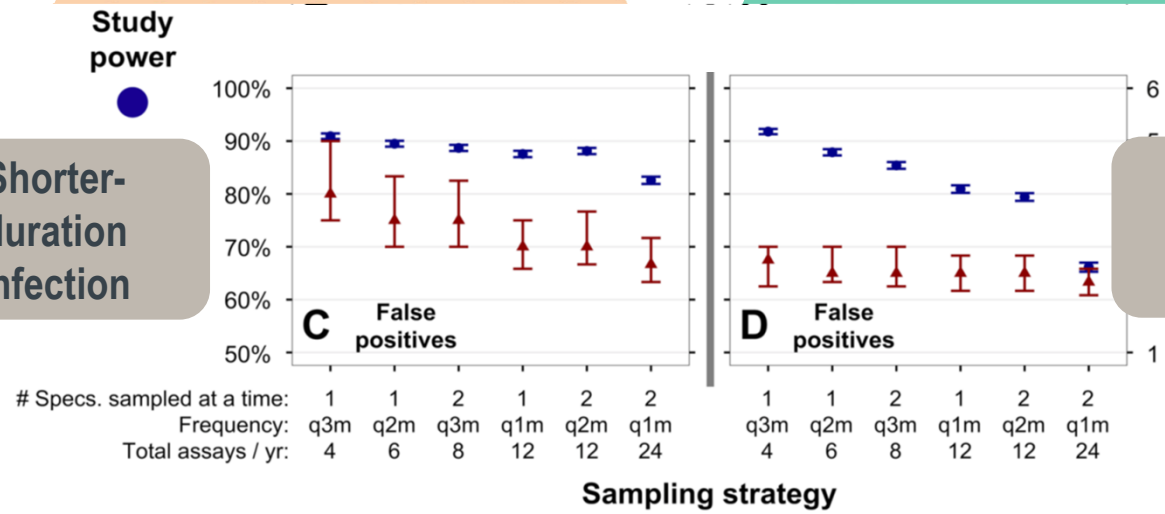
Smart testing → ☺

+ Pathogen Dynamics

Ph. 2/3 Design
More assays:
Trade Time for power
Duration of detectability matters

Shorter-duration infection

Longer-duration infection



Daniel Rosenbloom, Nitin Mehrotra

Radha Railkar, Daniel Rosenbloom, Casey Davis

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Efficacy = Proportional Risk Reduction

Impact:

- Saved $,
- increased POS (per subject)
- Choice of assay(s) and their frequency

Impact of False Positives

peat testing → ☹
nart testing → ☺

+ Pathogen Dynamics

Ph. 2/3 Design
More assays:
Trade Time for power
Duration of detectability matters

Radha Railkar, Daniel Rosenbloom, Casey Davis

Daniel Rosenbloom, Nitin Mehrotra

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Phase	Key Question	Method(s)	Decision(s) / Impact
(na)	**Can we model enough of the immune system to be predictive?**	QSP	Capability development

How can we use preclinical data to help design vaccines and to predict the right dose-level or regimen?

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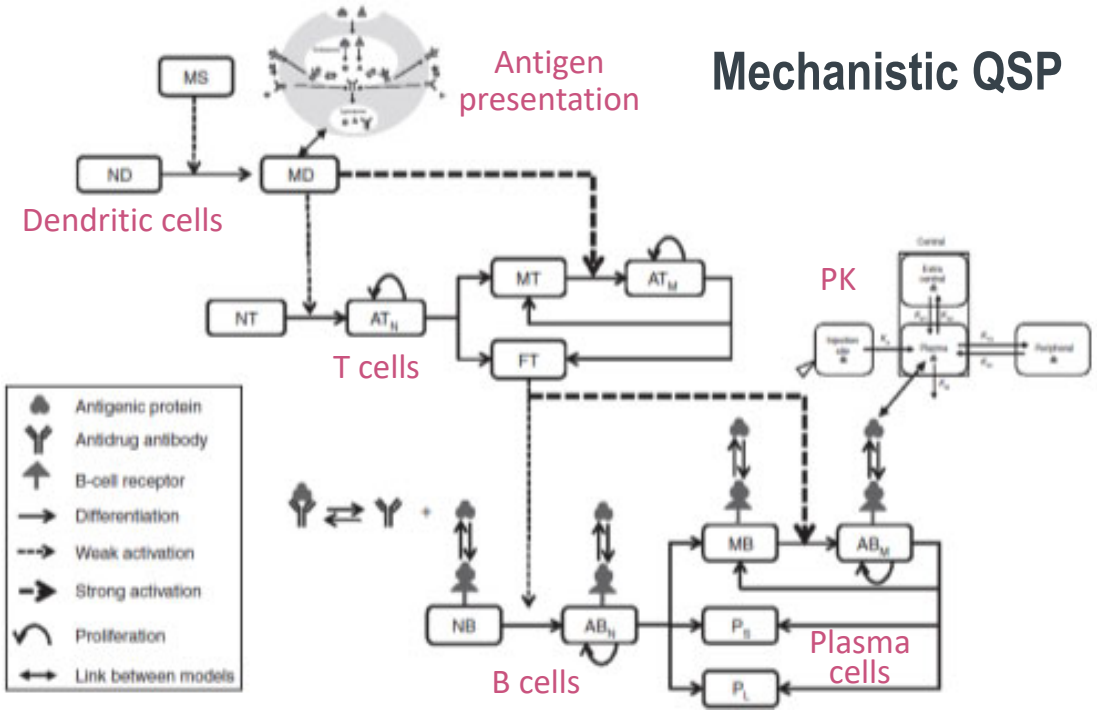
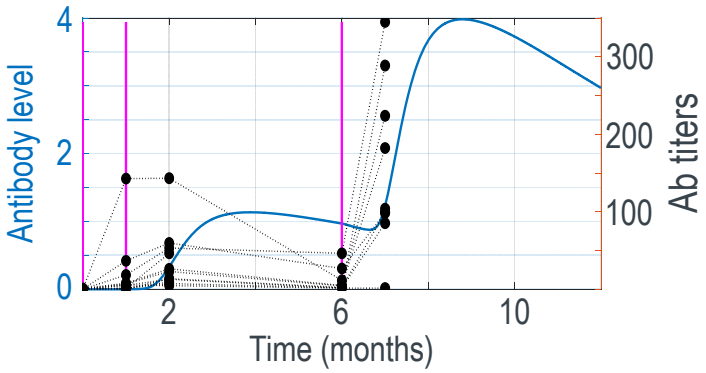
Basic Model of Some Immune System Components





Chen et al., CPT PSP 2014

Thanks: Jeff Perley, Josiah Ryman

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Basic Model of Some Immune System Components

Impact: Capability Development

Chen et al., CPT PSP 2014

Thanks: Jeff Perley, Josiah Ryman

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Phase	Key Question	Method(s)	Decision(s) / Impact
4	**How many doses of vaccine are needed to confer lasting protection?**	**QSP**	Suggests single dose could provide protective immune memory Mechanistic insight

Can we leverage mechanistic information to help inform regimen?

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Hepatitis B: Models for Antigen, Anti-viral Titer and Immune Memory

$$\frac{dV_i(t)}{dt} = -\sigma V_i(t)$$ Antigen

$$\frac{dM_i(t)}{dt} = (\gamma V_i(t) + \beta M_i(t))\left(1 - \frac{M_i(t)}{N}\right)$$ Immune memory

$$\frac{dA_i(t)}{dt} = \delta M_i(t) V_i(t)\left(1 - \frac{A_i(t)}{N}\right) - \frac{\mu A_i(t)}{T_i}$$ Anti-viral titer

- 10,815 anti-viral titres in 1,923 patients
- 2-4 vaccinations in 6-48 month period
- No Immune memory (Mi) or antigen (Vi) measurements

Wilson JN, Nokes DJ, Medley GF, Shouval D. Mathematical model of the antibody response to hepatitis B vaccines: implications for reduced schedules. Vaccine. 25(18):3705-12. 2007

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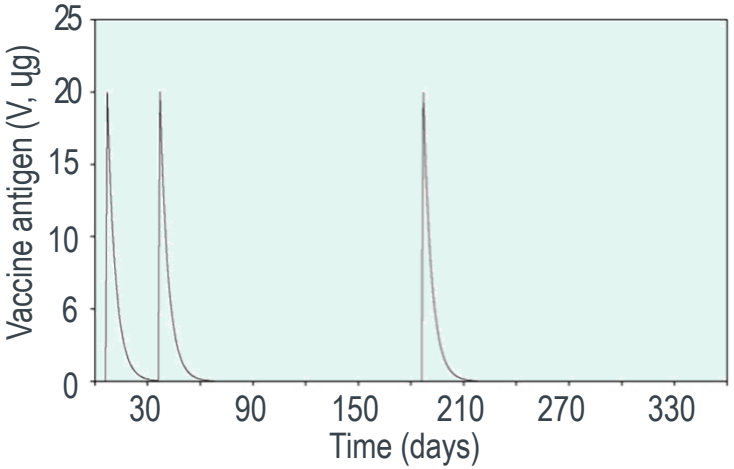
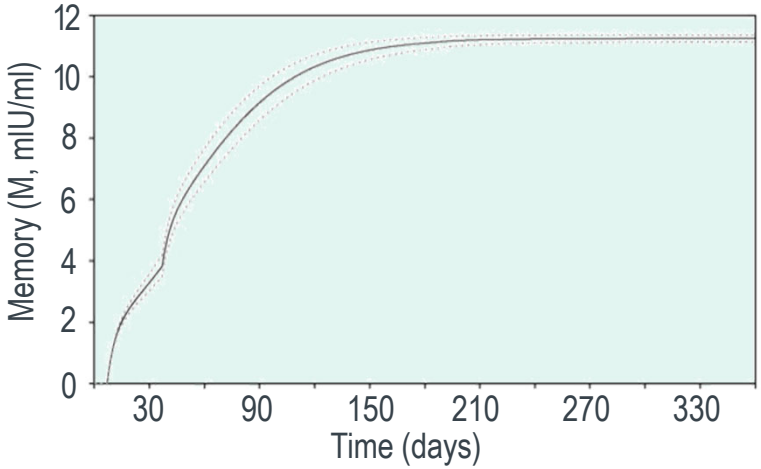
Simulation Results





Authors' Conclusions

- The model demonstrates **significant differences between different vaccines in** both the **time** taken to generate immune memory **and** the **amount of memory** generated.
- The model provides theoretical support for the hypothesis that a **single vaccine dose** can generate protective immune memory.

Wilson JN, Nokes DJ, Medley GF, Shouval D. Mathematical model of the antibody response to hepatitis B vaccines: implications for reduced schedules. Vaccine. 25(18):3705-12. 2007

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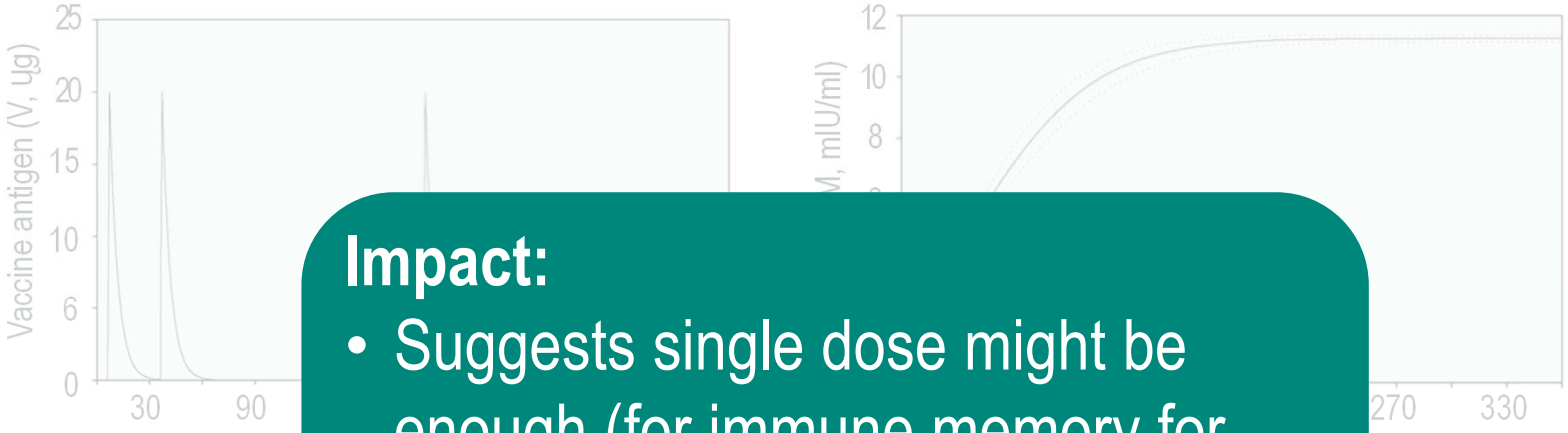
Simulation Results



Impact:

- Suggests single dose might be enough (for immune memory for this pathogen and vaccine mechanism)
- Mechanistic insight

Authors' Conclusions

- The model demo… …ines in both the **time** taken … …ted.
- The model provides theoretical support for the hypothesis that a **single vaccine dose** can generate protective immune memory.

Wilson JN, Nokes DJ, Medley GF, Shouval D. Mathematical model of the antibody response to hepatitis B vaccines: implications for reduced schedules. Vaccine. 25(18):3705-12. 2007

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Phase	Key Question	Method(s)	Decision(s) / Impact
2	**Which regimens should be tested in Ph. 2 Trial?** (Regimen: dose-level, # doses, timing)	QSP	Ph. 2 Trial Design: add new dose level and different regimen

Can we leverage mechanistic information to help inform regimen in Ph. 2 trial?

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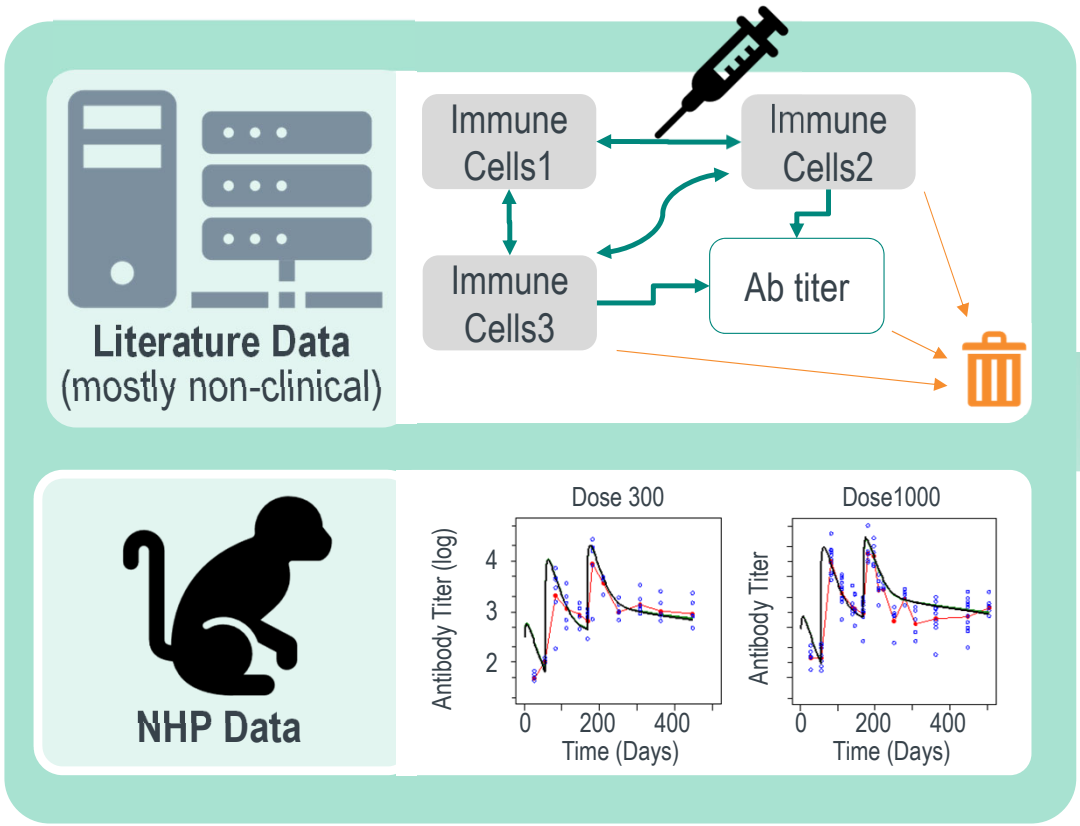
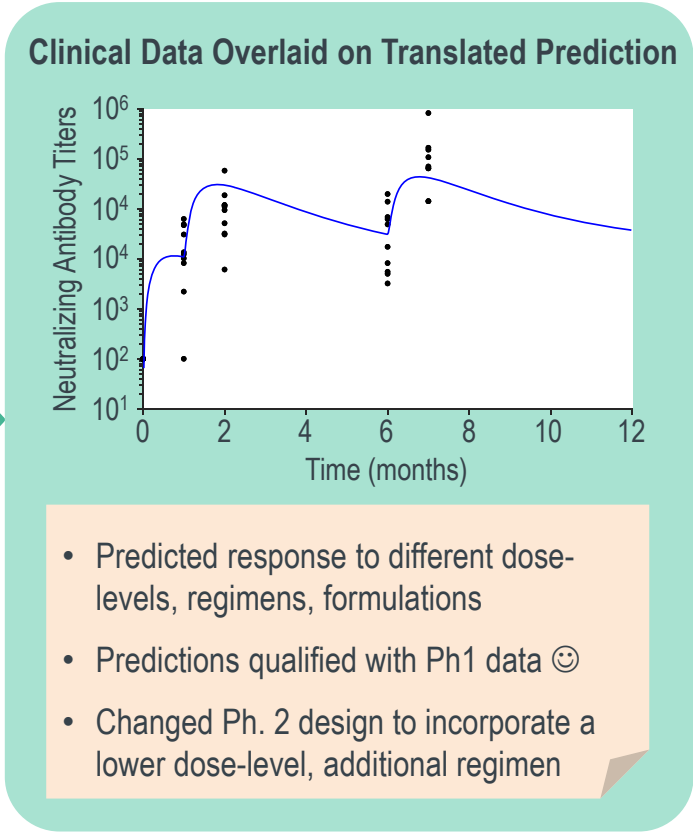
Trial Design by QSP





Thanks: Jeff Perley, Guido Jajamovich, Jos Lommerse (Certara), April Barbour

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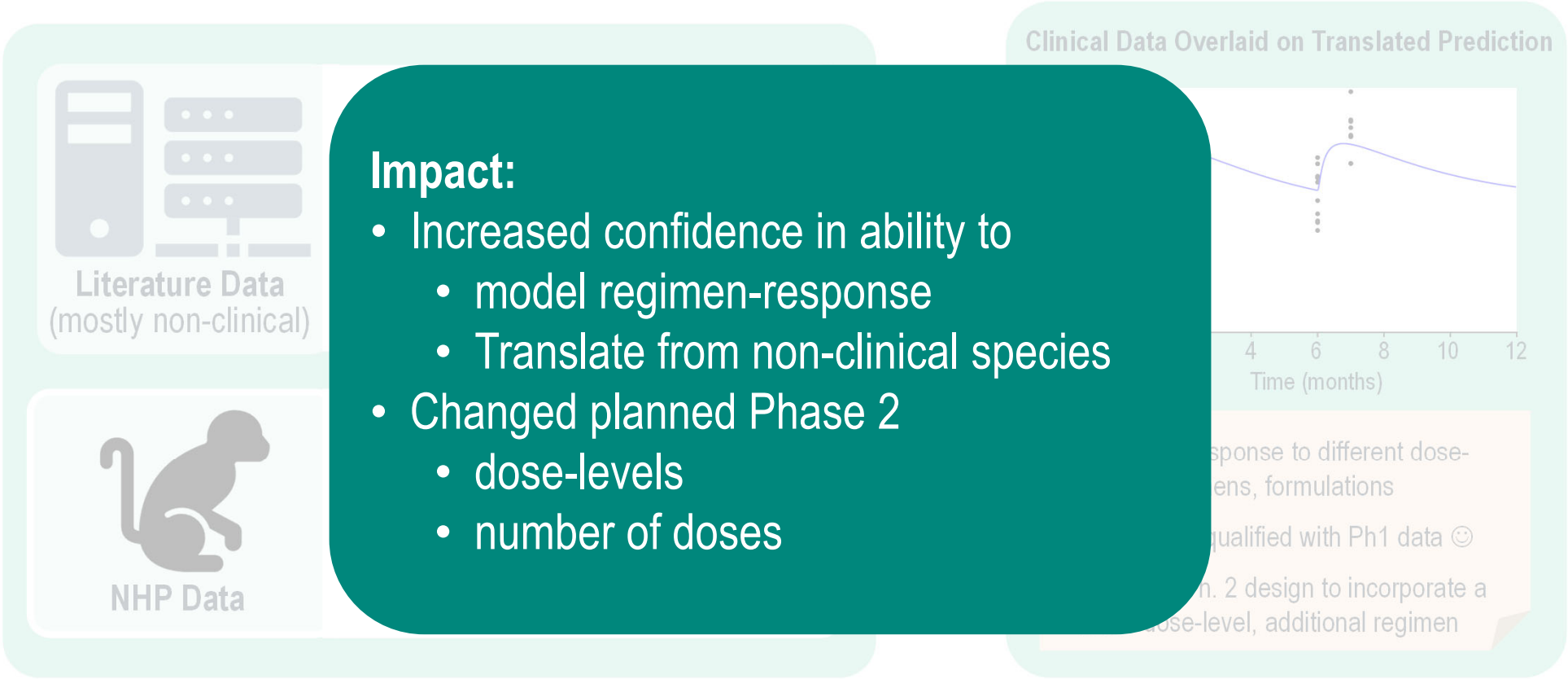
Trial Design by QSP



Impact:

- Increased confidence in ability to
  - model regimen-response
  - Translate from non-clinical species
- Changed planned Phase 2
  - dose-levels
  - number of doses

Thanks: Jeff Perley, Guido Jajamovich, Jos Lommerse (Certara), April Barbour

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Phase	Key Question	Method(s)	Decision(s) / Impact
2,3	**Do we have adequate evidence of efficacy if some pathogens have too few cases?**	PoDBA (= Probability of Disease Bayesian Analysis)	Novel Ph. 3 endpoint GNG test criteria

Can we increase POS by mitigating risk of a season with low incidence rate?

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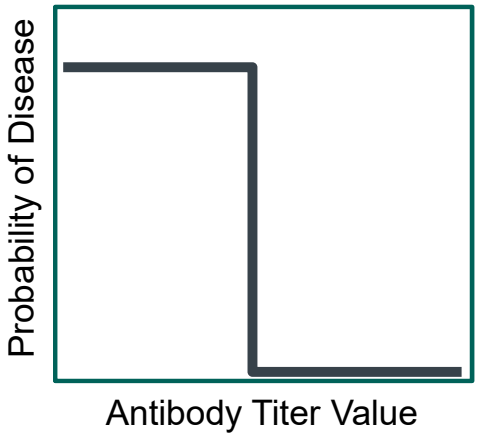
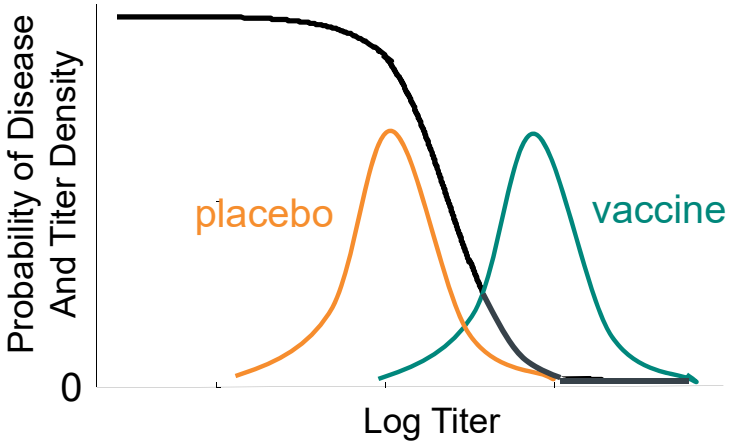
PoDBA Method

- Estimate relationship between probability of disease and antibody titer values based on titer values of subjects with and without disease



- Use this relationship and titer values of control and vaccine groups to estimate vaccine efficacy and its confidence interval



$$\textbf{Efficacy} = 1 - \frac{\textbf{Expected PoD(vaccinated)}}{\textbf{Expected PoD(placebo)}}$$

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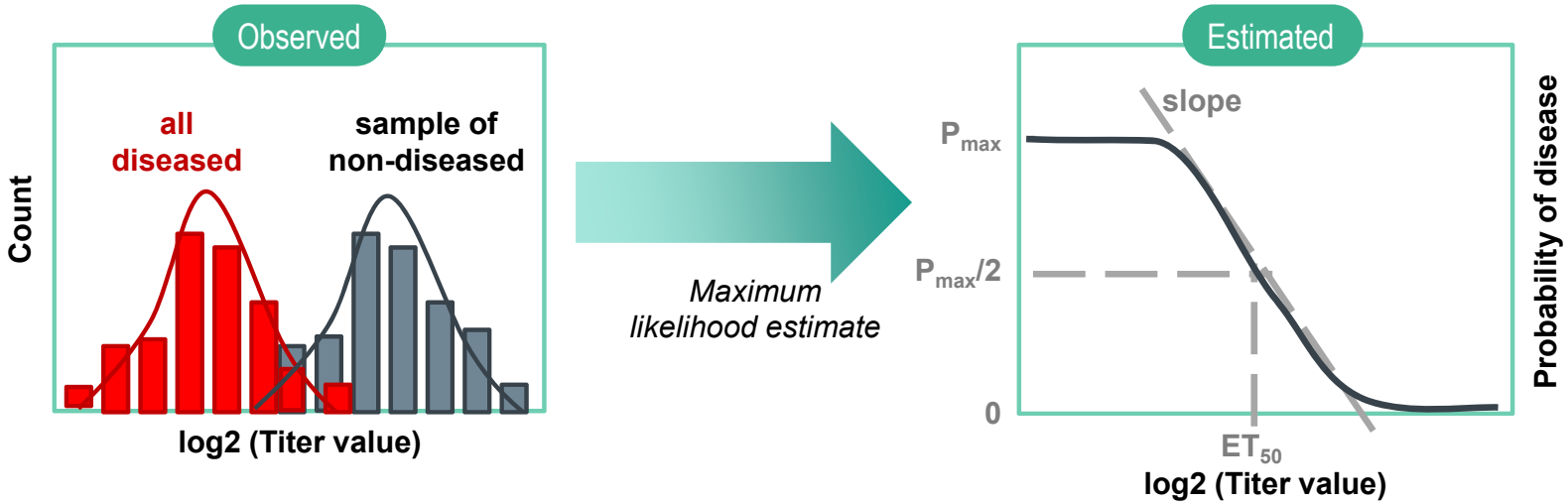
Method: Estimating the “Probability of Disease” Curve

- Use **titer values** measured in infected and non-infected subjects
- Assume that the relationship between titer values and probability of disease follows a **sigmoidal curve**
- **Estimate** the **parameters** of the curve and their **confidence intervals** using standard statistical method (*Maximum likelihood)*



Qualified PoDBA method & Efficacy CI (demonstrated predictive power) with published data and simulation

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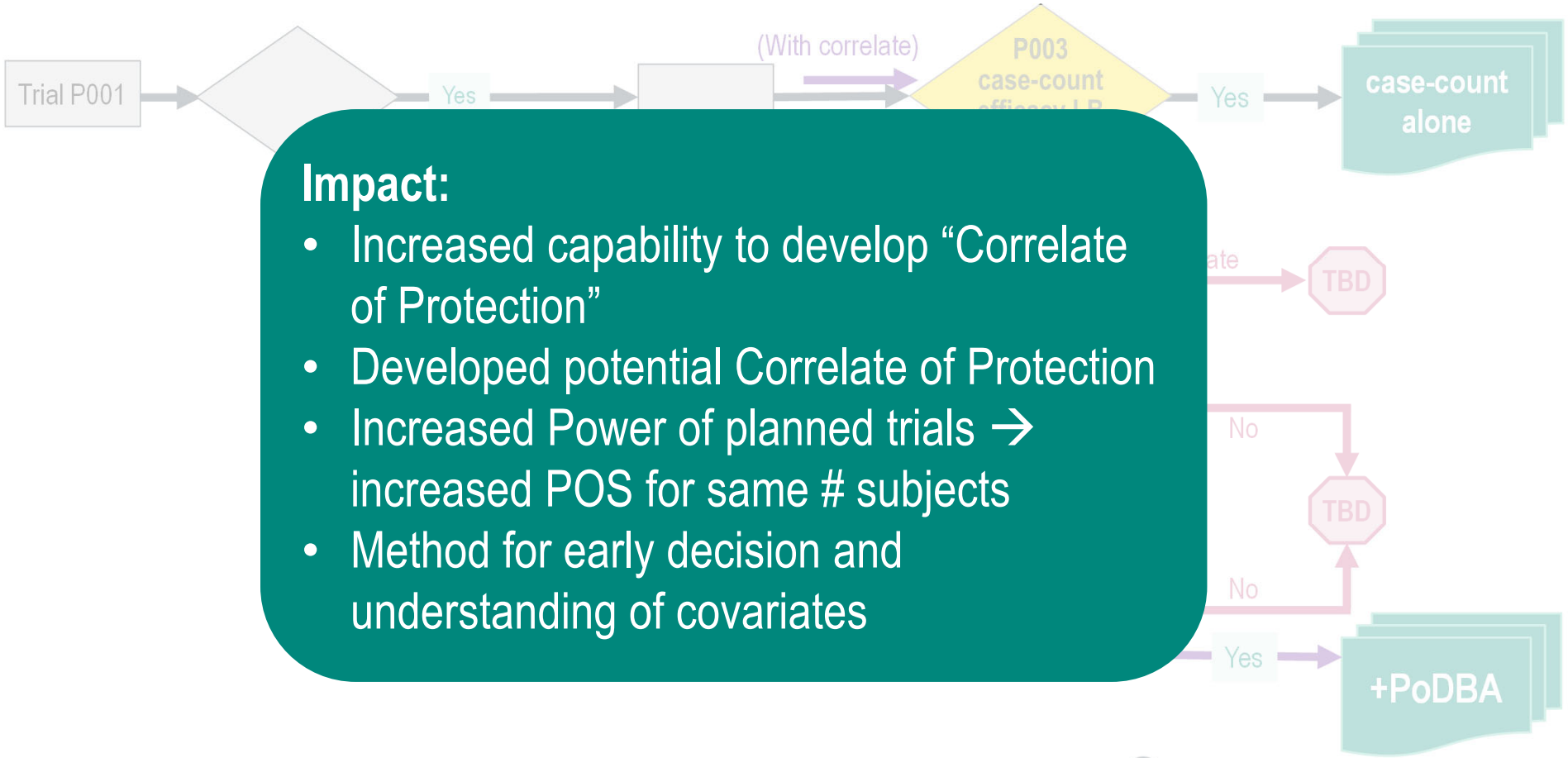
PoDBA → Novel Endpoint (example from a program plan, not agency guidance on different approaches to basis of licensure)



Impact:

- Increased capability to develop "Correlate of Protection"
- Developed potential Correlate of Protection
- Increased Power of planned trials → increased POS for same # subjects
- Method for early decision and understanding of covariates

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Phase	Key Question	Method(s)	Decision(s) / Impact
2	**Is our immunogenicity likely to provide the necessary protection, and at what dose-level?**	NLME+ MBMA + PoDBA (Comparator modeling + PoDBA)	No-go, GO, Dose-selection

Can we leverage literature data and early immunogenicity data to drive early, objective, risk-based decisions?

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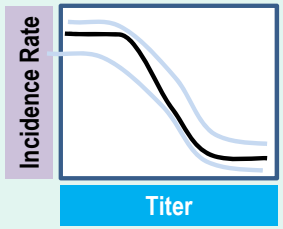
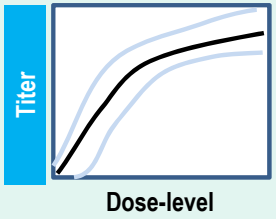
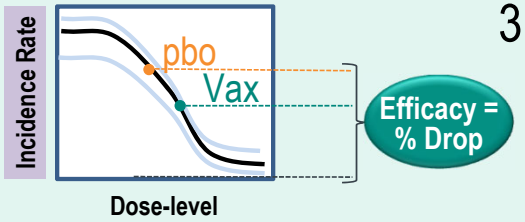
Modeling Overview for Supporting Both Go and No-Go Decisions



1. Titer → Incidence Rate ("IR")
   - Published clinical data
   - Incidence rate for different disease levels
   - Data cover various populations



2. Dose-level → Titer
   - Relate dose-level to serum neutralization titer response
   - FIH Data



3. Combine 1 & 2 ➔ "integrated" modeling:

Dose-level → Titer → Incidence Rate
Predicted change in incidence rate → efficacy

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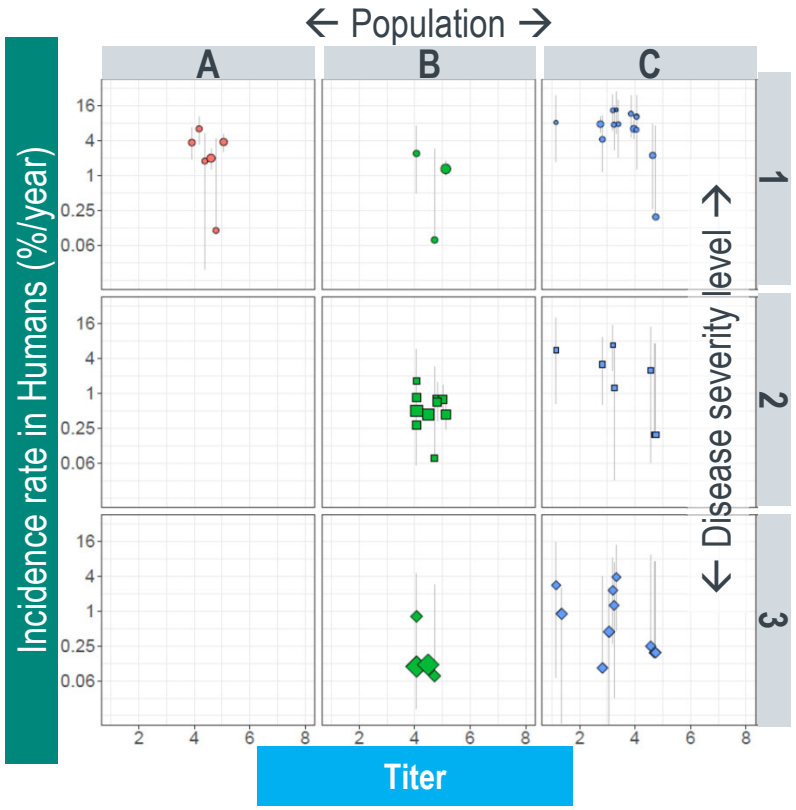
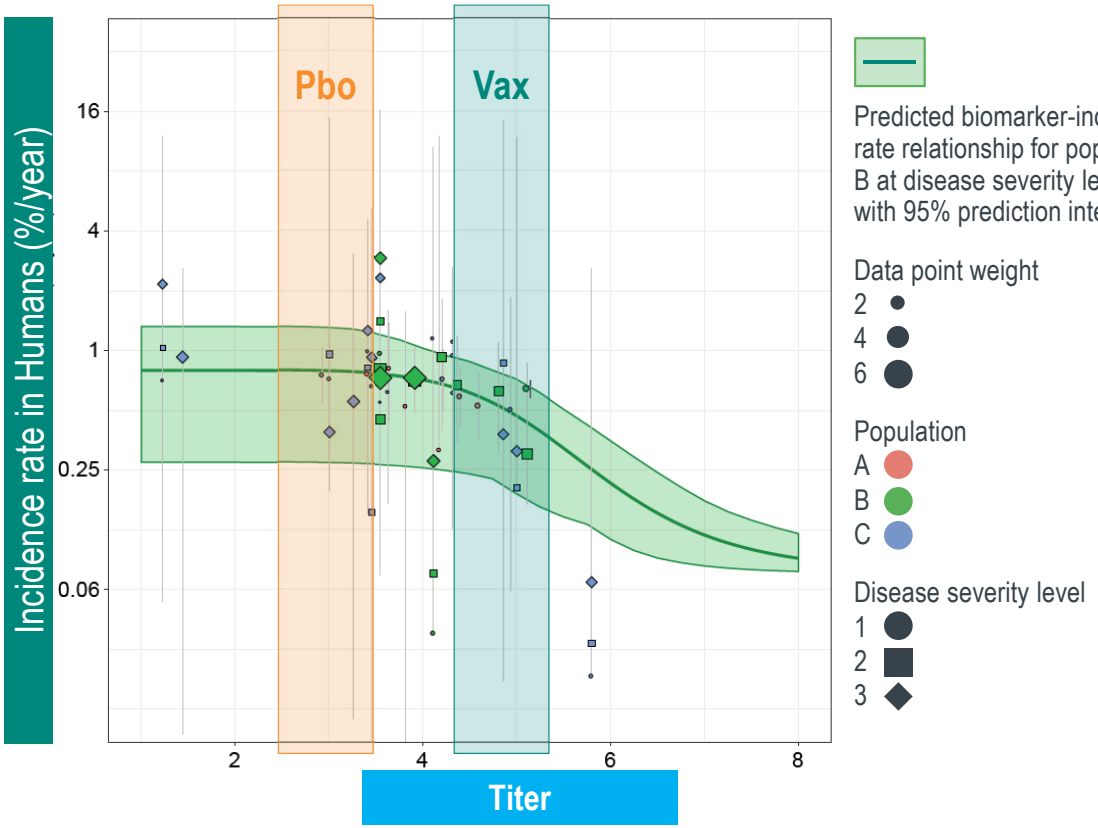
Visualization Has to Tie Together Data for Different Disease Levels and Populations





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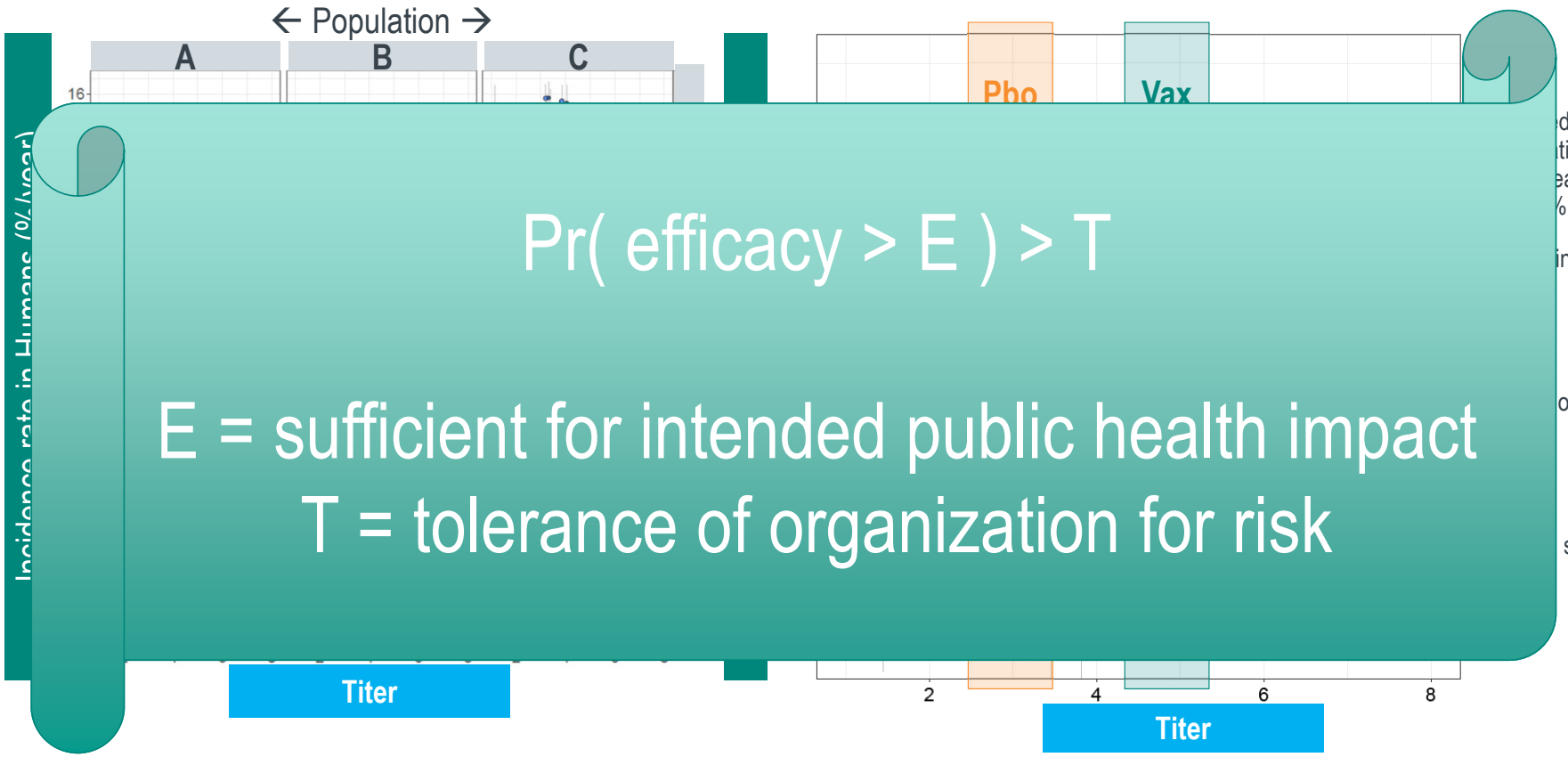
Visualization Has to Tie Together Data for Different Disease Levels and Populations



Visualization Has to Tie Together Data for Different Disease Levels and Populations

Phase	Key Question	Method(s)	Decision(s) / Impact
2	What N (# subjects) will let us tell if vaccines A and B are different?	Phenomenological model Clinical trial simulation	Trial design, program strategy for sequence of trials
2	What immunogenicity assay(s) should we use and how often?	QSP and Bayesian probabilistic	Saved $, increased POS Choice of assay, frequency
(na)	Can we model enough of the immune system to be predictive?	QSP	Capability development
4	How many doses of vaccine are needed to confer lasting protection?	QSP	Suggests 1 less dose Mechanistic insight
2	Which regimens should be tested in Ph. 2 Trial? (Regimen: dose-level, # doses, timing)	QSP	Ph. 2 Trial Design: add new dose level and different regimen
2,3	Do we have adequate evidence of efficacy if some pathogens have too few cases?	PoDBA (= Probability of Disease Bayesian Analysis)	Novel Ph. 3 endpoint GNG test criteria
2	Is our immunogenicity likely to provide the necessary protection, and at what dose-level?	NLME+ MBMA + PoDBA (Comparator modeling + PoDBA)	No-go, GO, Dose-selection

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Vaccine Pharmacometrics

Today

- Simulation-based trial design to add/save trial arms or subjects
- QSP modeling of the immune system as a platform
- Using dose, regimen, formulation to predict immunogenicity/efficacy
- Translation between preclinical and clinical immunogenicity
- Leveraging literature data
- Establishing new trial endpoints
- Understanding covariate (age, genetics, geography,…) effects on immunogenicity & efficacy

Don’t forget also…

- Predicting most effective vaccine platform by mechanistic modeling
- Understanding or predicting safety/toxicity
- Predicting the best route of administration
- Leveraging results of real-world trials
- Prioritizing vaccine candidates
- Prioritizing pathogen candidates

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CONCLUSION

"An ounce of prevention is worth a pound of cure"

Benjamin Franklin

Source: https://www.ag.ndsu.edu/news/columns/beeftalk/beeftalk-an-ounce-of-prevention-is-worth-a-pound-of-cure/.

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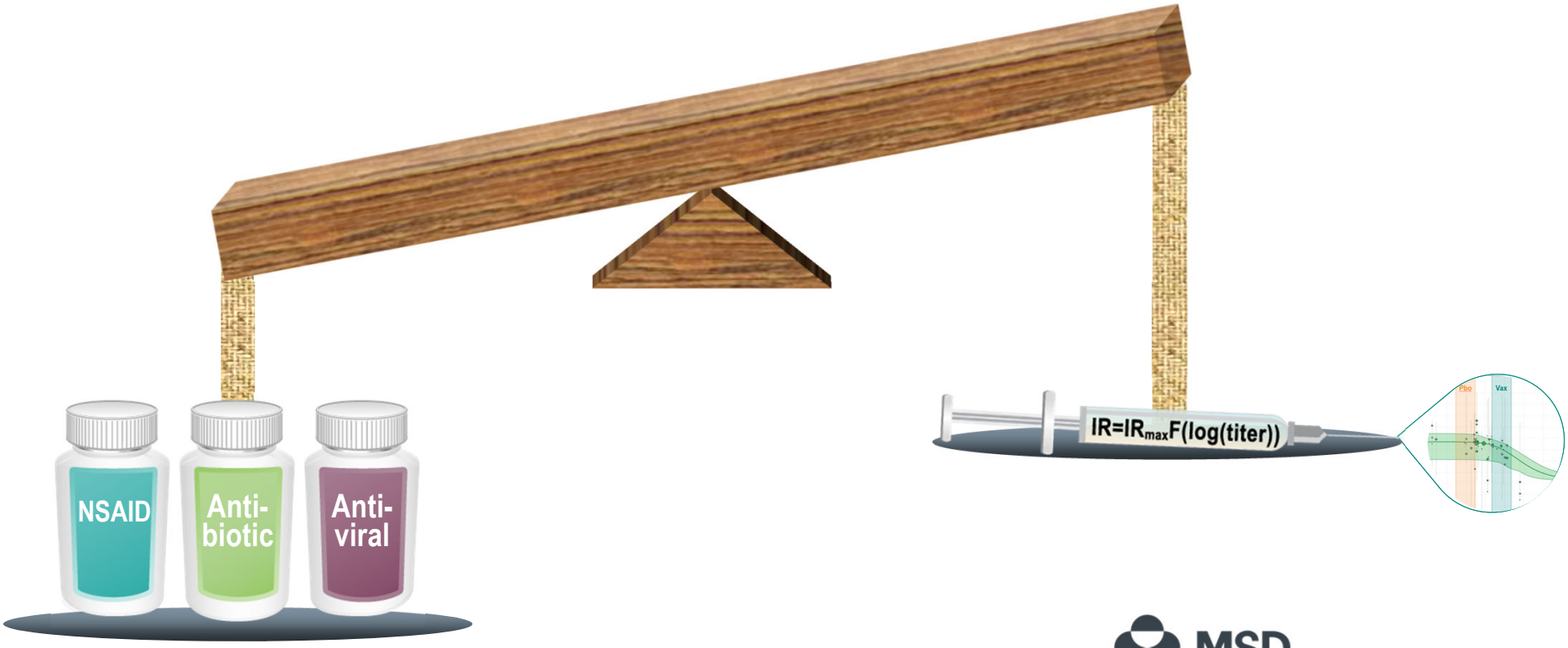
"An ounce of ~~prevention~~ Pharmacometrics is worth a pound of cure"

Benjamin Franklin



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"An ounce of ~~prevention~~ Pharmacometrics is worth a pound of cure"

Benjamin Franklin

- Vaccines are a key component of public health
- Pharmacometrics useful for vaccine discovery & development
  - QSP, PK/PD, Bayesian, comparator, translational,…
- These (and other) methods have impacted decisions
- Pharmacometrics (we) can impact human health by helping inform vaccine discovery & development ^ even more
  - Assumptions, study design & strategy, data interpretation

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Backup

Attributes of Vaccine Development

1. Stringent safety
2. Trial size and duration (event frequency)
3. Efficacy = proportional risk reduction
4. Surrogate marker (“Correlate of Protection,” a.k.a. “CoP”) challenges
5. Lack of translational models
6. Need arm with placebo or active comparator
7. Complex biologics, need to be transportable stable, usable

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CoP Challenges: Knowledge, Time, Resources, Variability…

Knowledge

- Which measurements?
- Which species?
- Predictive power?

Time

- Knowledge early enough
- Timely availability of clinical data

Resources

- Many samples
- Often multiple species
- Resource-intensive assays

Variability

- Assays often +/- 2-fold
- Large BSV in response
- Variability in CoP predictive power?

BSV: between-subject variability

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