Introduction to Statistical Methods and Challenges in Vaccine Development

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Statistics, Vaccine Development, and the COVID-19 Crisis
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Outline of Presentation

- Introduction to Vaccines
- Safety Evaluation – Rotavirus Vaccine
- Efficacy Evaluation – HPV Vaccine
- Correlate of Risk and Correlate of Protection
  —Varicella and Herpes Zoster Vaccines
- Accelerating Vaccine Development Against Pandemic – COVID-19 Vaccines
- Opportunities for Continuous Improvement

What are vaccines?

- A product that stimulates a person's immune system to produce immunity for disease protection
- Administered as a single series with a potential booster dose
- Typically for prophylaxis, not treatment

- Vaccine is one of the greatest public health achievements
  - Eradication of smallpox from the world in 1980
  - Elimination of Polio in the US in 1979 (As of 2020, Afghanistan and Pakistan are the only two countries where the disease still occurs)
  - Control of Ebola outbreaks in West Africa, 2013-2016
  - Fight against COVID-19 pandemic

Examples of Vaccines

Pediatric vaccines

- Polio
- Chickenpox (varicella)
- Measles, mumps, rubella (MMR)
- Hepatitis B
- Diphtheria, tetanus, pertussis
- Rotavirus (infant gastroenteritis)
- Invasive pneumococcal disease

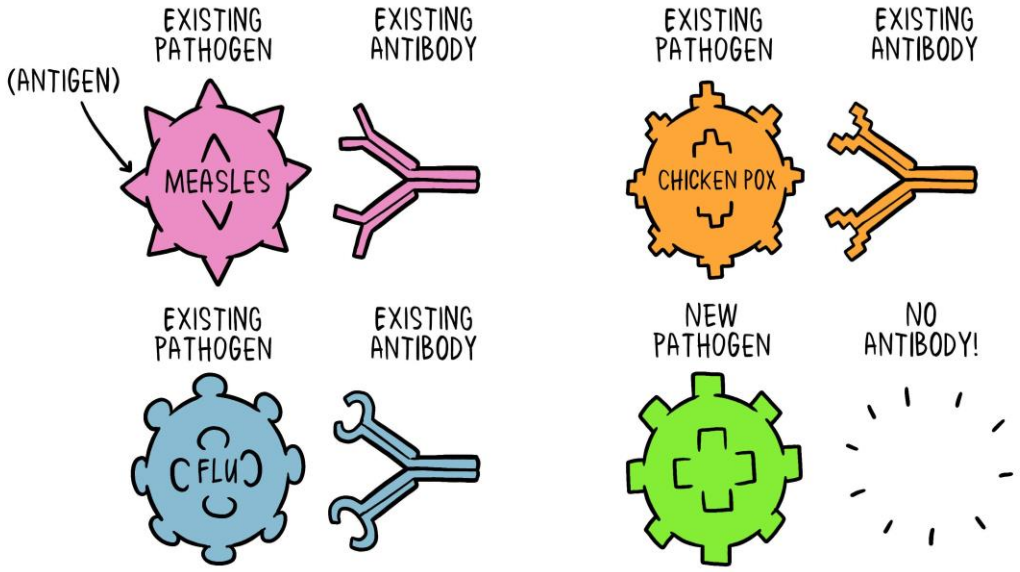
Adolescents and Adult vaccines

- HPV (cervical cancer)
- Meningitis
- Influenza
- Herpes zoster (shingles)

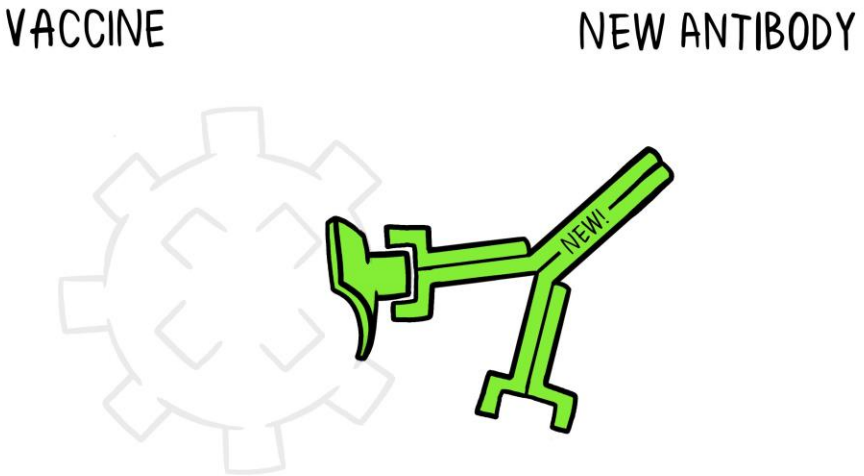
Vaccines for Disease Epidemics and Pandemics

- Ebola
- COVID-19

How Vaccine Works



When a new pathogen or disease enters our body, it introduces a new antigen. For every new antigen, our body needs to build a specific antibody that can grab onto the antigen and defeat the pathogen.



A VACCINE is a tiny weakened non-dangerous fragment of the organism and includes parts of the antigen. It's enough that our body can learn to build the specific antibody. Then if the body encounters the real antigen later, as part of the real organism, it already knows how to defeat it.

World Health Organization (who.int)

Type of Vaccines

Type of Vaccine	Mechanism of Stimulation	Example
Live attenuated	Attenuated live virus	Chickenpox, MMR, Ebola
Inactivated/Killed	Killed version of whole virus	Polio, flu, COVID-19 (China)
Toxoid (inactivated toxin)	Inactivated toxin	Diphtheria, tetanus
Viral vector	Uses adenoviruses to carry the genetic codes into human cells	COVID-19 (J&J, AZ, Russia)
Protein Subunit	Uses tiny pieces of virus-like particles	HPV, COVID-19 (Novavax)
mRNA	Uses messenger RNA	COVID-19 (Moderna, Pfizer/BioNTech)

Types of Immunity

Humoral (antibody-mediated) immunity

- B lymphocytes
- Plasma cells
- Immunoglobulins (IgG, IgM, IgA, IgD, IgE)
- Antibody titers increase to a plateau and then decline

Functions of Antibodies

- Neutralize viruses and bacterial toxins
- Bind antigen
- Prevent or clear first infection

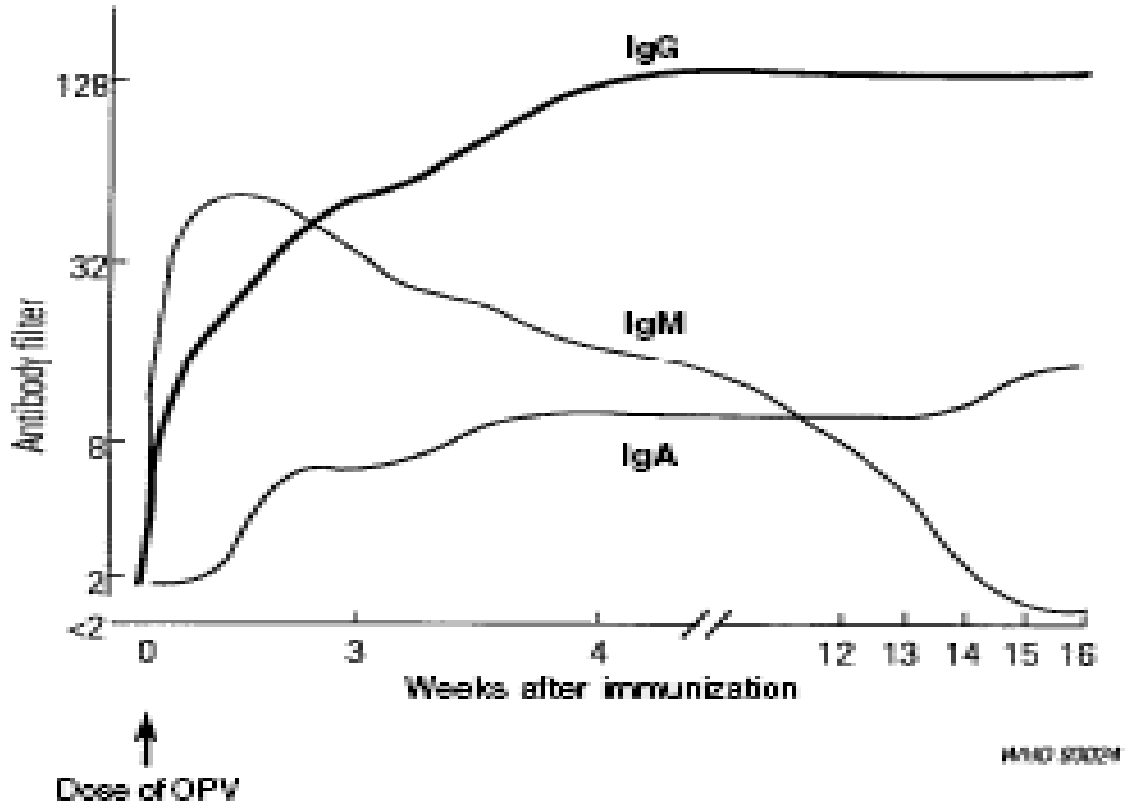
Cell-mediated or T-cell immunity

- T lymphocytes
- Cytokines/interleukins

Functions of Cell-mediated immunity

- T lymphocytes (helper cells) stimulate B cells to produce antibodies
- T suppressor (regulatory) cells play an inhibitory role and control the level and quality of the immune response (CD4)
- Cytotoxic T-cells recognize and destroy infected cells (CD8)

Temporal Antibody Responses Following Primary Immunization

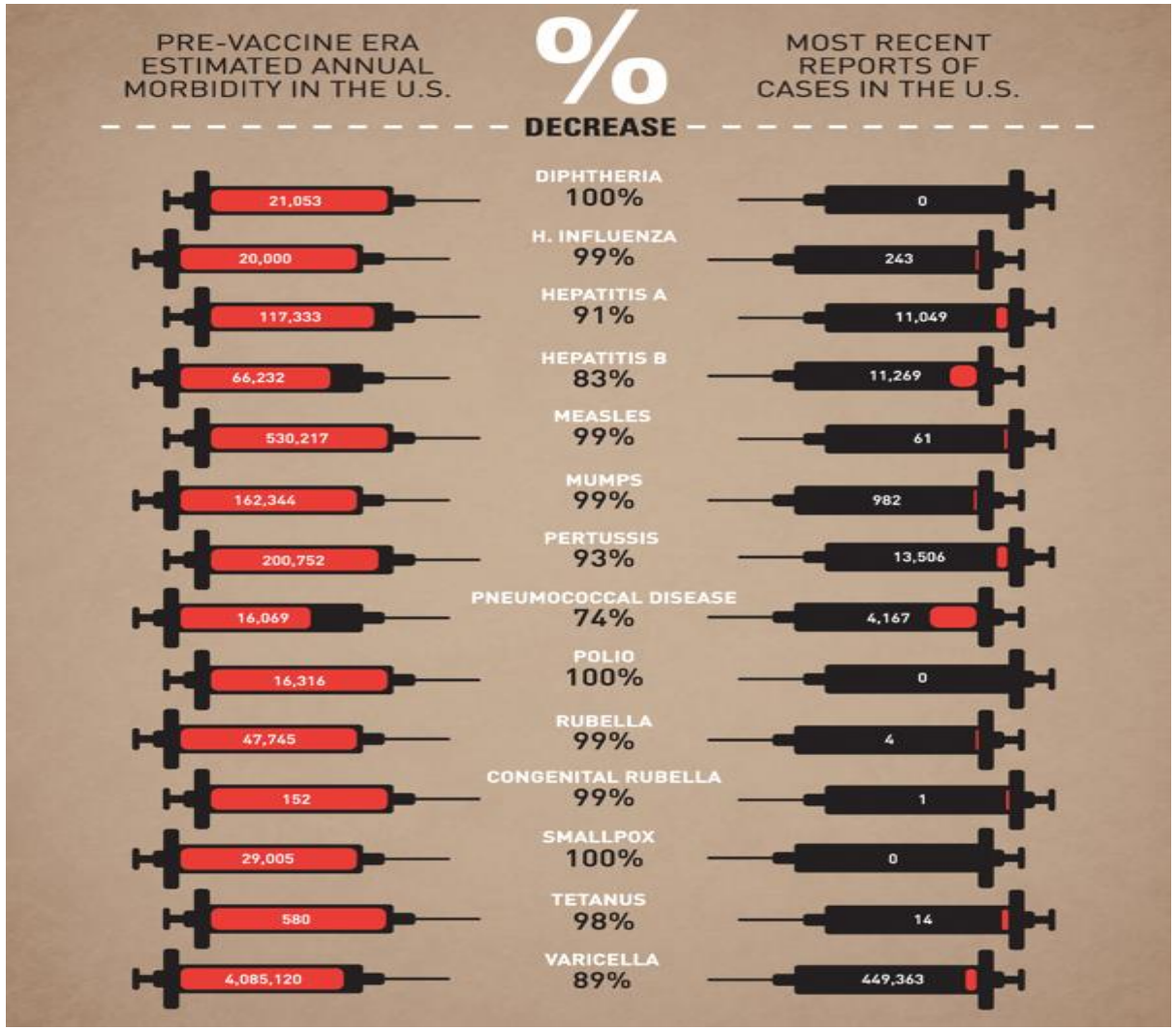


WHO Immunological Basis for Immunization Series, Module 1, General Immunology.

Impact of Vaccines

- Direct benefit
  - Protection to vaccinated individuals
  - Usually measured in clinical trials
  - Risk benefit at individual level

- Indirect benefit
  - Herd immunity (protection of non-immune individuals) by reducing exposure and transmission in the community
  - Public health impact



Data by CDC

The Salk Polio Vaccine Experiment - Involved >1.8 million children
(Brownlee 1955; Meier 1972)

Initial Design

- Used observed controls:
  - Vaccinated 2nd graders
  - Followed 1st and 3rd graders
- Criticized for bias with non-randomized controls

Revised Design

- Dr. Paul Meier introduced randomization and placebo-control concept to the study
- 41% study population was placebo controlled, 59% in the observed control cohort

Trial Outcome

- Both populations showed vaccine efficacy
- Interpretation complicated because
  - Case rate is 21% lower in the observed control cohort
  - Differences in demographics and case ascertainment procedures in unvaccinated controls

Key Learning

- Meier's leadership and passionate scientific arguments introduced several key principles:
- Foundational practice of randomization and double-blinded evaluation
- Case ascertainment
- Independent scientific oversight
- Ongoing monitoring of safety

Evaluation of New Vaccines - Safety

- Assess local (injection-site) and systemic adverse experiences
- Choice of safety parameters depend on type of disease, population, and route of administration
- Need a large database, particularly because of giving vaccines to healthy subjects
  - E.g., Rotavirus vaccines (RotaTeq and Rotarix), studied for intussusception with 60-75K subjects
- Need large-scale post licensure study for additional safety monitoring

Evaluation of New Vaccines - Efficacy

- Measure the relative reduction (RR) of disease incidence after vaccination compared with placebos (Chan, Wang and Heyse 2003)

$$VE = 1 - RR = 1 - P_V/P_C$$

- Require a high level of evidence and precision
  - Success typically requires showing efficacy greater than a non-zero (e.g. 20% - 50%) lower bound
  - For COVID-19 vaccine, lower bound requirement is 30%

- May need a very large study for diseases with low incidence rates
  - Event-driven design often used to guard against uncertain event rate (Chan and Bohidar 1998)

- Need long-term data to assess duration of efficacy
  - When is a booster dose needed?
  - Crossover placebo vaccination (Follmann et al 2021)
  - Real world data (RWD) may be used if concurrent controls are not available (Vessey et al 2001)

Impact of VE Lower Bound Requirement on Sample Size

- Rapid increase of sample size when VE lower bound increases
- Examples assumes
  - 5/1000 incidence
  - 90% power
  - 60% true VE
  - One-sided 2.5% test
  - 1:1 randomization
- Real example: Herpes zoster vaccine efficacy trial (Oxman et al 2005) used a lower bound of .25 (N = ~38,500).

VE Lower Bound	Total Number of Events	Total Sample Size
0	56	16,300
.10	74	20,800
.20	100	28,500
.30	154	43,900

Evaluation of New Vaccines - Immunogenicity

- Important for vaccine development
  - —understanding biological responses – T-cell responses to prevent virus reactivation and kill infected cells
  - —valuable measure for early phase clinical studies and dose selection
  - —useful for bridging studies (e.g., new vs. old formulations, process change) and assessing combination vaccines
  - —key endpoint for assessing consistency of vaccine manufacturing process and correlates of protection

Variability/Stability of Vaccines

- Vaccines are biological products that have more variability than chemical compound
  - Need to demonstrate consistency of manufacturing
  - May require lot consistency clinical study

Study Arm	Immune Response	Statistical Criteria for Consistency
Vaccine Lot 1	Demonstrate consistent responses among the 3 lots	• Response rate (margin: 5 – 10 pct points) • Geometric mean titers (margin 1.5 or 2-fold difference)
Vaccine Lot 2		
Vaccine Lot 3		
Control	Compare Vaccine vs Control	

- Many vaccines contains attenuated live viruses and will lose potency over time
- Need to establish a range of potency for manufacturing and product shelf-life
  - Study safety at the high potency
  - Establish efficacy at near-expiry potencies

Some Examples of Statistical Innovation in Vaccine Development (Heyse and Chan 2016)

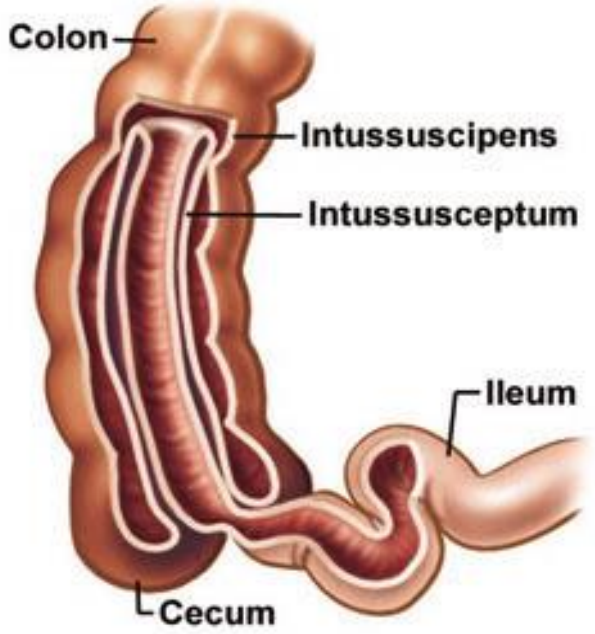
- Safety monitoring using sequential likelihood test
- Efficacy evaluation using adaptive designs
- Use of immune marker and correlate of protection to guide smart R&D

Rotavirus Safety Study

- Sequential likelihood test for safety monitoring

Evaluation of Intussusception in Rotavirus Vaccine Development

- In 1998, a tetravalent rhesus-human reassortant rotavirus vaccine (RRV-TV; Rotashield, Wyeth) was licensed and recommended by the ACIP for routine immunization.
- Post-Marketing surveillance studies detected a temporal association with intussusception.
- Risk was primarily during the exposure window 3-14 days post dose 1 and the first week post dose 2 —(OR = 21.7: 95% CI [9.6 to 48.9] post dose 1)
- Manufacturer withdrew the product from the US and the ACIP withdrew the recommendation in 1999.



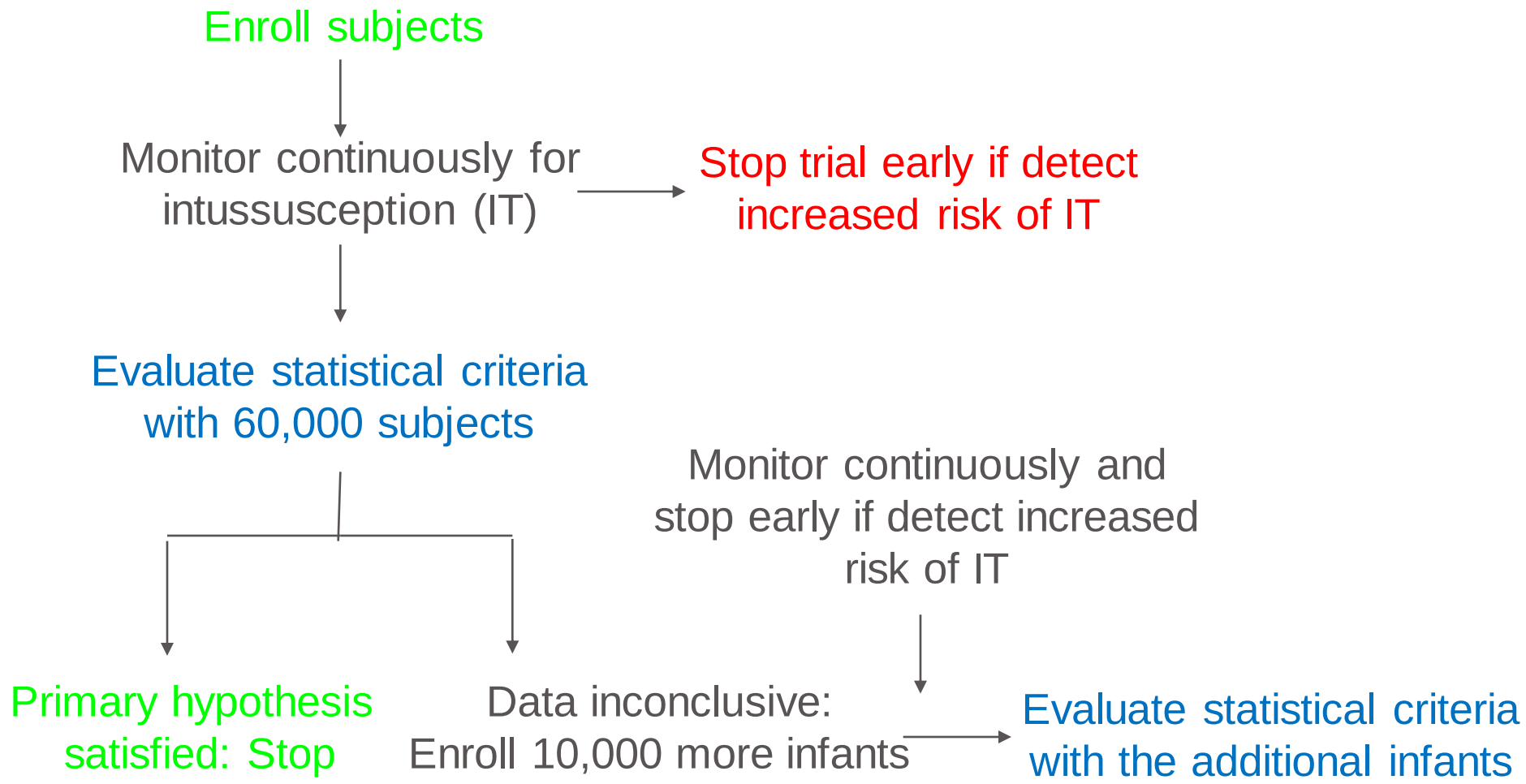
- Invagination of intestine (telescoping)
- Uncommon: Incidence ~1/2000 infant-years
- Peak incidence is between 5 and 9 months of age

Rotavirus Efficacy and Safety Trial (REST) on Intussusception

(Vesikari et al NEJM 2006; Heyse et al Clinical Trials 2008)

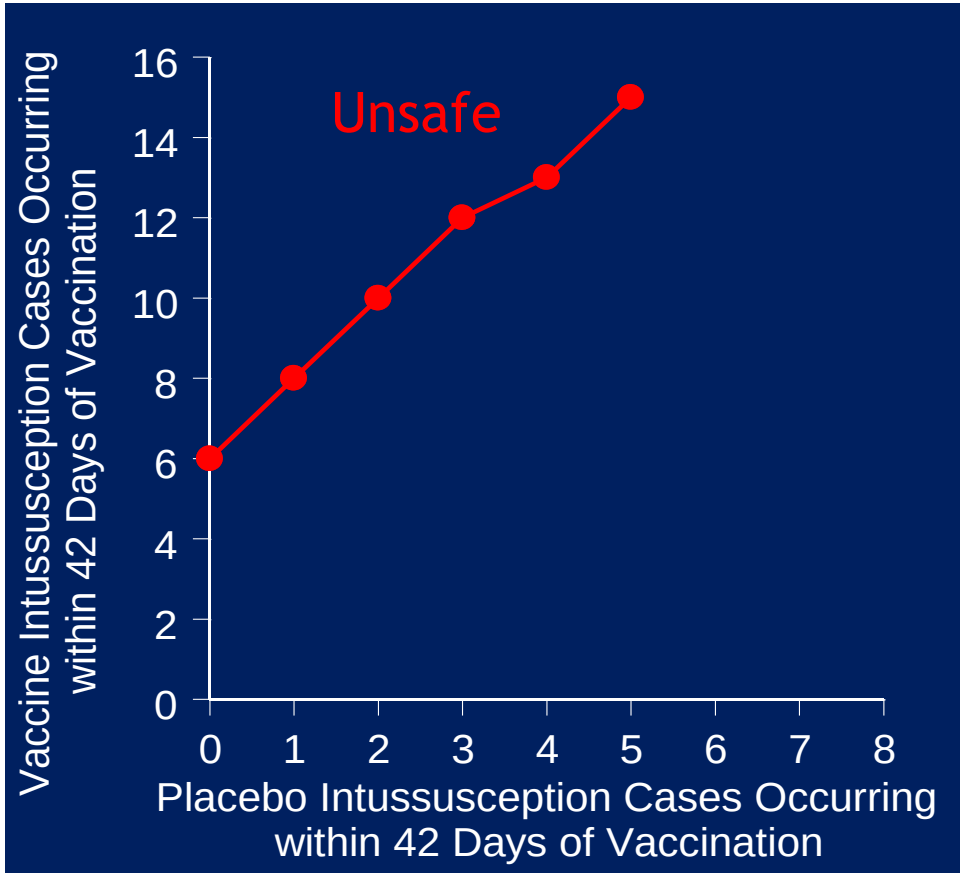
- REST was a placebo-controlled study of RotaTeq™ to evaluate the risk of intussusception
  - —~70,000 infants 6-12 weeks of age
  - —3 oral doses: 1 dose every 4 to 10 weeks
  - —1 to 1 randomization
- Study conducted at ~500 sites in 11 countries from 2001 to 2005
- Primary hypothesis:
  - Oral RotaTeq™ will not increase the risk of intussusception relative to placebo within 42 days after any dose
- Interim safety monitored by an independent DSMB

REST Group Sequential Study Design

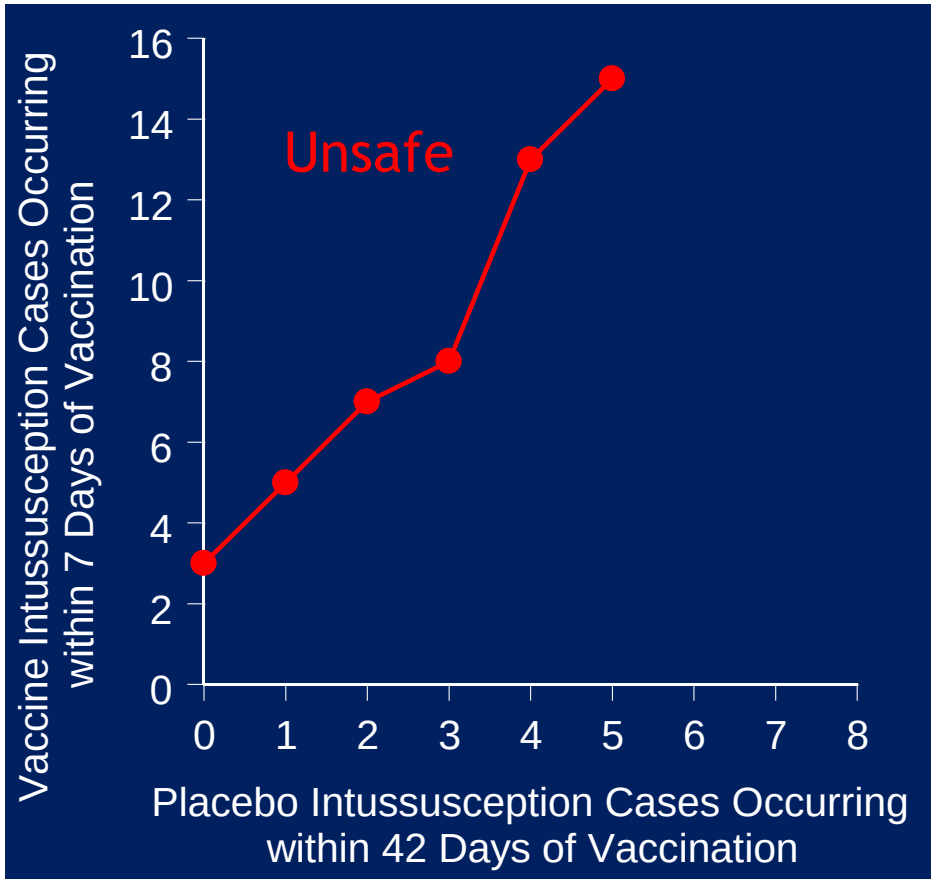


REST Safety Monitoring Boundaries Based on Repeated Likelihood Test - Safety reviewed by an independent DSMB

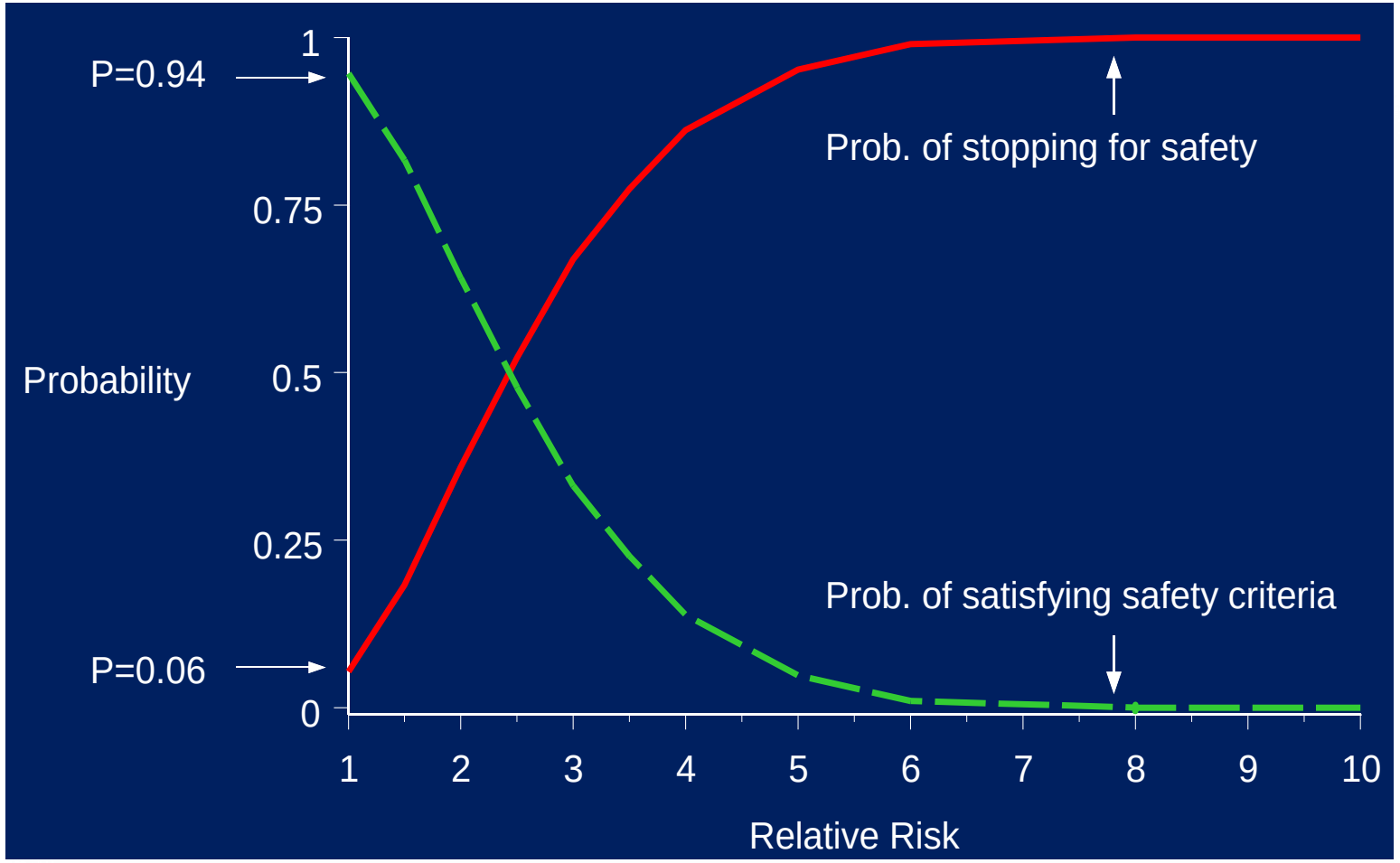
Day 1 - 42



Day 1 - 7



Statistical Operating Characteristics for REST
(Heyse et al 2008 Clinical Trials; Heyse and Chan 2016 SBR)

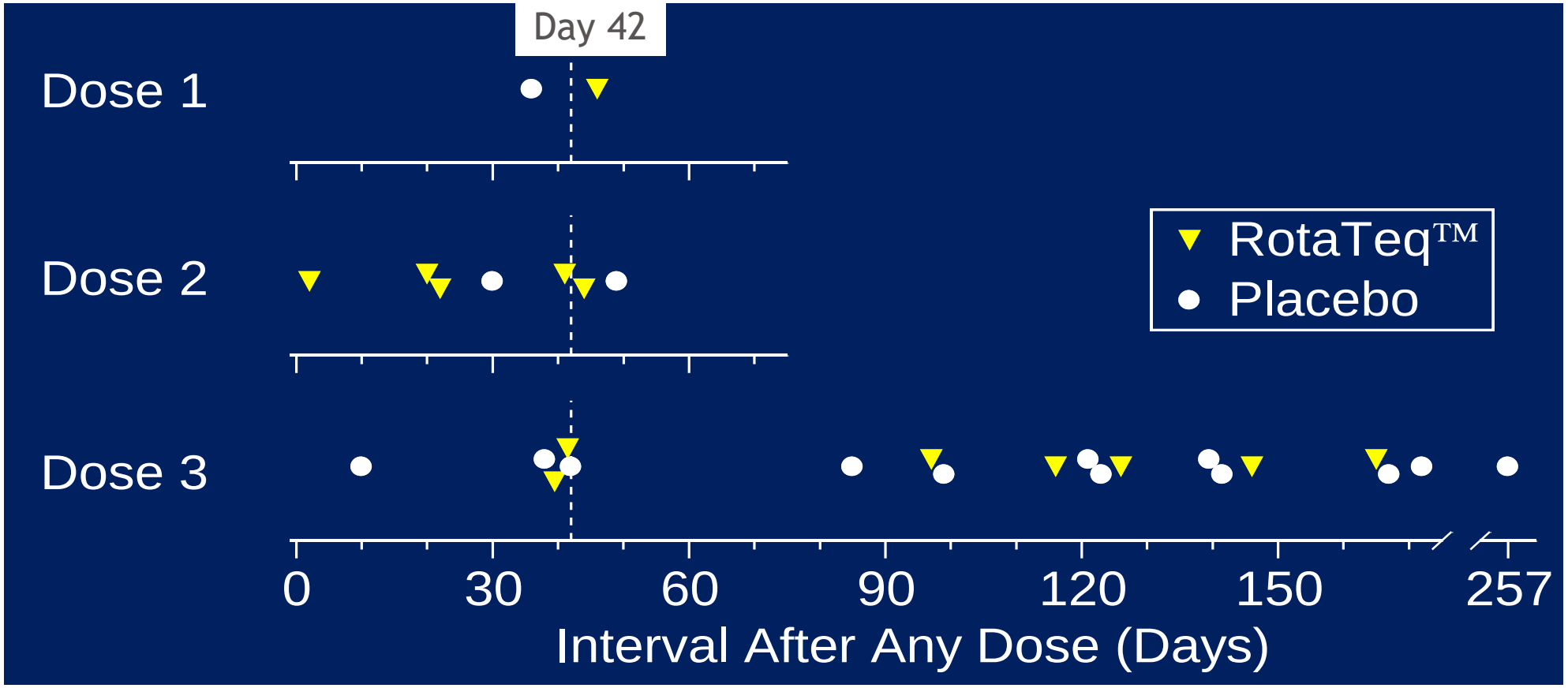


- Method further developed into Generalized Likelihood Ratio test (Shih et al 2010 SIM), adapted for post market surveillance

Confirmed Intussusception Cases in REST Within 42 Days of Each Dose

6 Vaccine : 5 Placebo

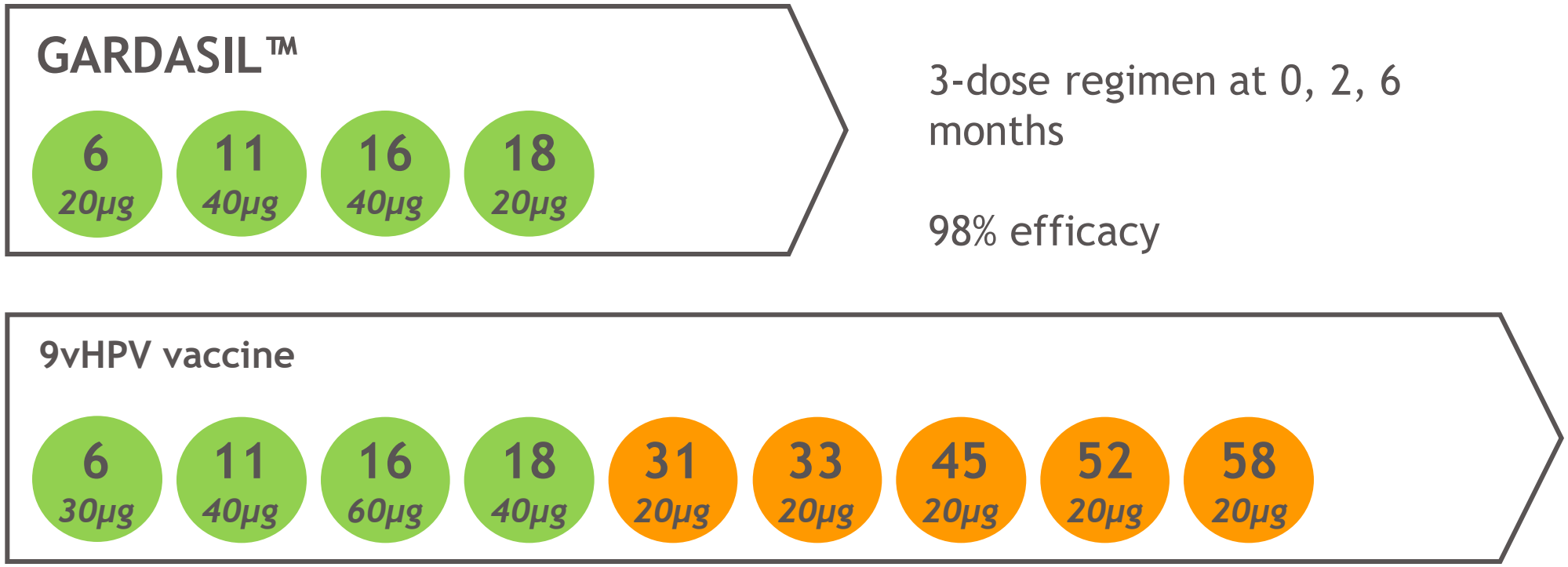
RR=1.2; 95% CI (0.3, 5.0)



HPV Vaccine Study

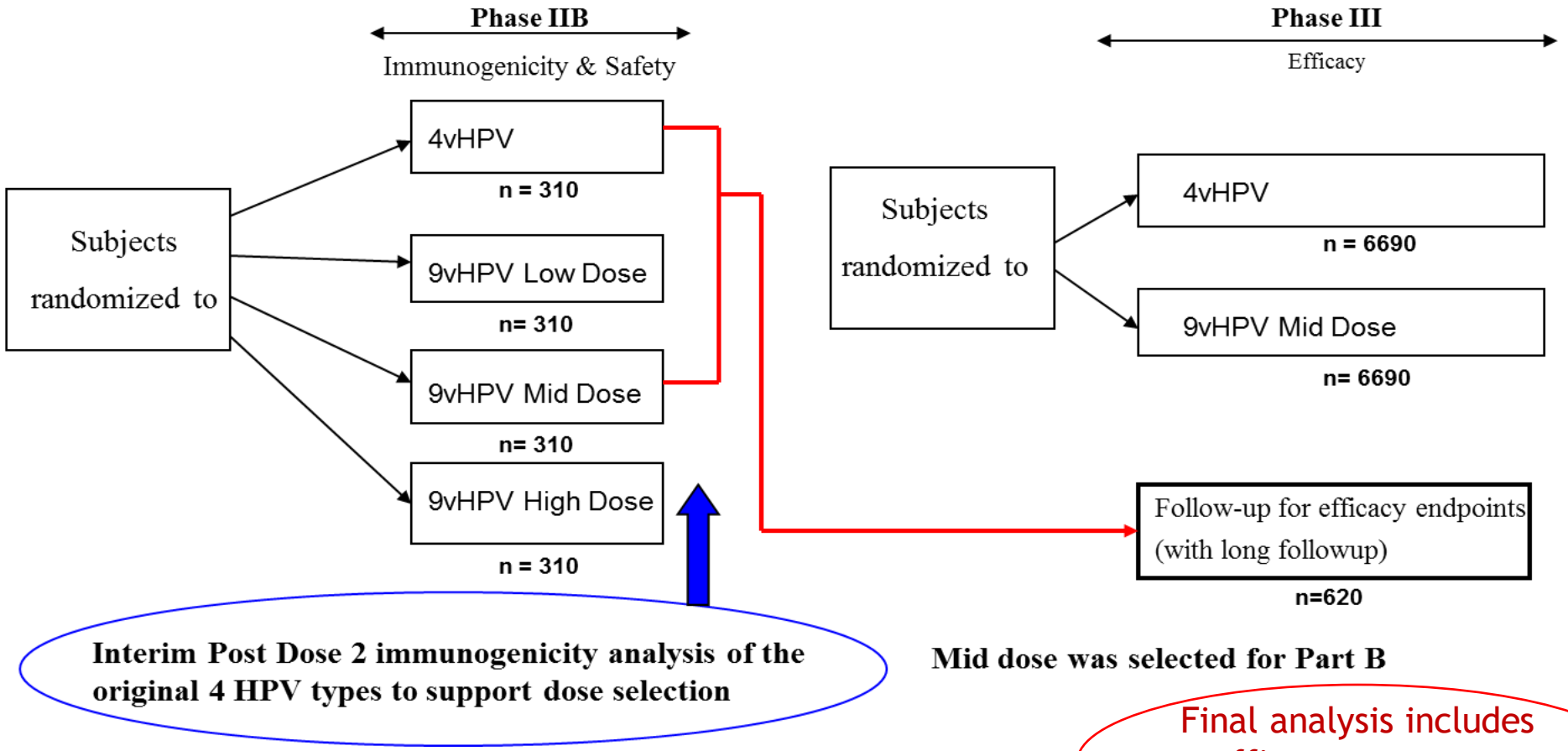
- Adaptive design with dose selection

Development of the 9-Valent HPV Vaccine



Increase cancer coverage from 70% to 90%

Seamless Phase II/III Design with Dose Selection Based on Immune Marker for Human Papillomavirus (HPV) Vaccine



Chen, Gesser, and Luxembourg 2015 Clinical Trials;
Li, Zhao, Sun and Chan 2015 SIB

Type I Error Control Considerations

- Usually, seamless design with data-driven dose selection may require multiplicity adjustment to ensure control of type I error rate
  - Some useful approaches are, e.g.
    Posch, Maurer, and Bretz. (2011)
    Li, Zhao, Sun and Chan (2015)
- Depending on the alpha level adjustment (or statistical 'penalty'), a seamless design may or may not be statistically efficient
  - Statistical penalty can lead to potential power loss
  - Inclusion of Part IIB subjects can lead to power gain
  - Statistical efficiency determined by the above factors

Empirical Type I Error Rate Not Increased for the Dose-Selection Phase II/III Trial (Li, Zhao, Sun and Chan 2015)

Simulation Setup

- Continuous immune marker
- Binary disease outcome
- Exact test for efficacy at 0.025 Level

Summary

- Adequate control of overall type I error rate across different sample sizes, disease incidence rates, and correlations

Sample Size	Correlation (marker and disease)	Disease Incidence Rate			
		p=0.2	*p=0.1*	*p=0.01*	*p=0.004*
N_1=300 N_2=6000	ρ =0.8	0.017	0.023	0.025	0.022
	ρ =0.5	0.016	0.022	0.023	0.021
	ρ =0.1	0.014	0.019	0.023	0.019
N_1=300 N_2=9000	ρ =0.8	0.016	0.023	0.025	0.023
	ρ =0.5	0.016	0.021	0.023	0.021
	ρ =0.1	0.014	0.019	0.021	0.018

N_1- Phase II sample size per arm; N_2 – Phase III sample size per arm
Dose Selection: maximum effective based on 100,000 simulations

Efficacy Results for the 5 New HPV Types

Endpoint	No. of Cases/Total Evaluable		Vaccine Efficacy % (95% CI)
	9vHPV Vaccine	qHPV Vaccine	
Cervical, vulvar, vaginal disease (any grade)	3 / 6016	103 / 6017	97.1% (91.8, 99.2)
CIN 2/3, VIN 2/3, VaIN 2/3, or worse	1 / 6016	30 / 6017	96.7% (80.9, 99.8)

Joura et al 2014 NEJM

Impact of Adaptive Design

- Improved efficiency by including data from both phases (10% increase in information)
- Increased statistical power
- Reduced time to licensure
- Cited as a successful example in FDA Guidance on Adaptive Design (2019)

Immune Markers as Correlates of Risk and Correlates of Protection

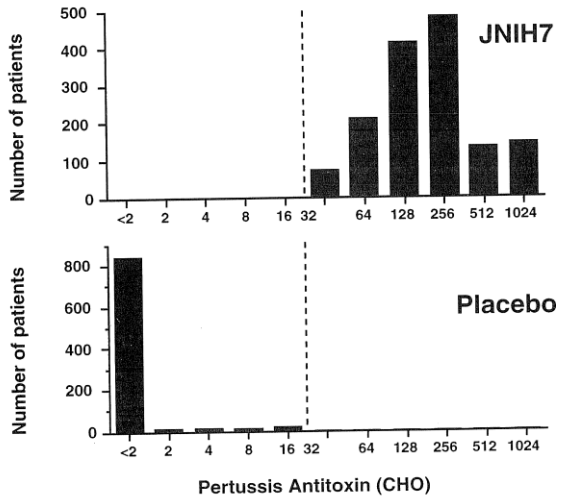
Assessing Immune Responses and Correlates of Protection

- Assess correlates of risk (CoR) and correlates of protection (CoP, “surrogate” endpoints)
  - CoR is an immune marker that is correlated with the risk of disease
  - CoP is an immune marker statistically correlated with vaccine efficacy (predictive of vaccine efficacy) (Plotkin and Gilbert, CID 2012)
    - CoP is *mechanistic* if immune response is a causal agent to protection
    - CoP is *non-mechanistic* if immune response predicts vaccine efficacy but is not a causal agent to protection
  - Useful for bridging studies (new vs. old formulations) and combination vaccine studies
  - Key endpoint for assessing consistency of vaccine manufacturing process
  - May also support approval of second-generation vaccines or follow-on vaccines

General Challenges in CoP Evaluation

- A small number of vaccine failures due to high efficacy
- Most individuals do not have immunity before vaccination (constant biomarker), making it difficult to apply the Prentice Criteria (Prentice 1989)
  - Prob of contracting disease is independent of vaccination status given the level of immune responses

	Baseline Titer	Post Vaccination Titer
Vaccine	-	+
Placebo	-	-



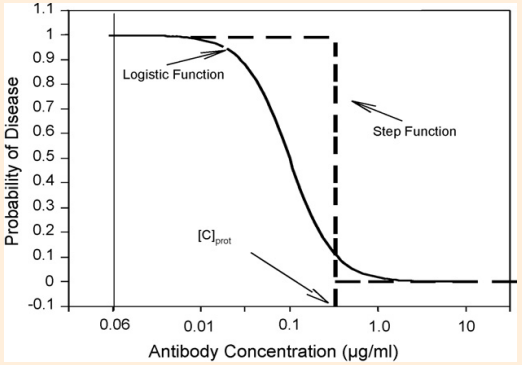
- Follmann (2006) proposed augmented designs to address this issue
  - Include baseline predictors
  - Include closeout placebo vaccination

Assessing Correlates of Risk and Correlates of Protection

Correlate of Risk

Titer-Specific Method (Siber et al, Vaccine 2007)

- Model risk of disease as a step function of immune responses
- Used to establish the immune correlate for licensure of Prevnar13



Statistical Modeling and Predictive Efficacy

- Assess relationship between immune response and long-term disease risk (Chan et al 2002)
- Determine protective level of immune responses based on maximizing correlation (Li, Parnes, Chan 2013)
- Used for bridging trials and for predicting vaccine durability at expiry-dose and its shell life

Correlate of Protection

Prentice criteria for surrogate endpoint validation (Prentice 1989)

- Proportion of treatment effect explained
- Prob of contracting disease is independent of vaccination status given the level of immune response

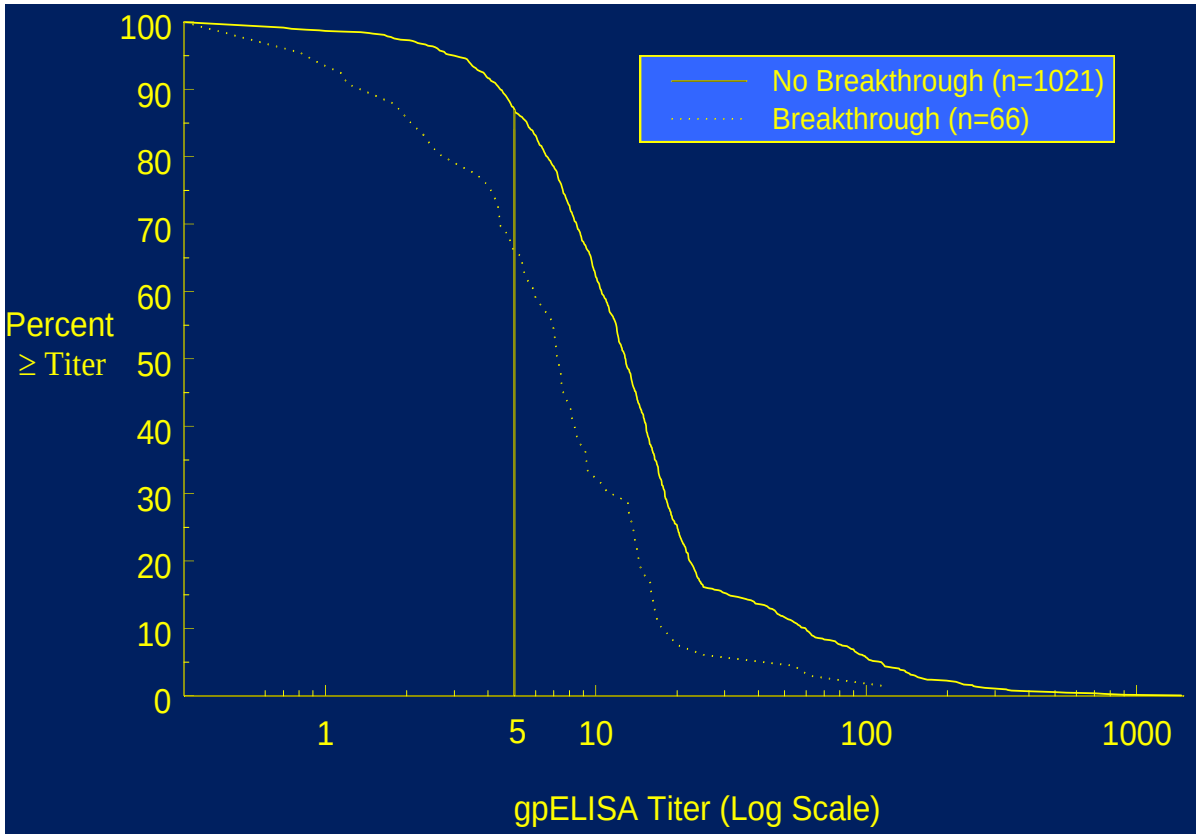
Causal inference (Gilbert and Hudgen 2008)

- Herpes zoster vaccine study - Miao et al 2013; Gilbert et al 2014
- Supported antibody responses as an immune correlate for bridging trials

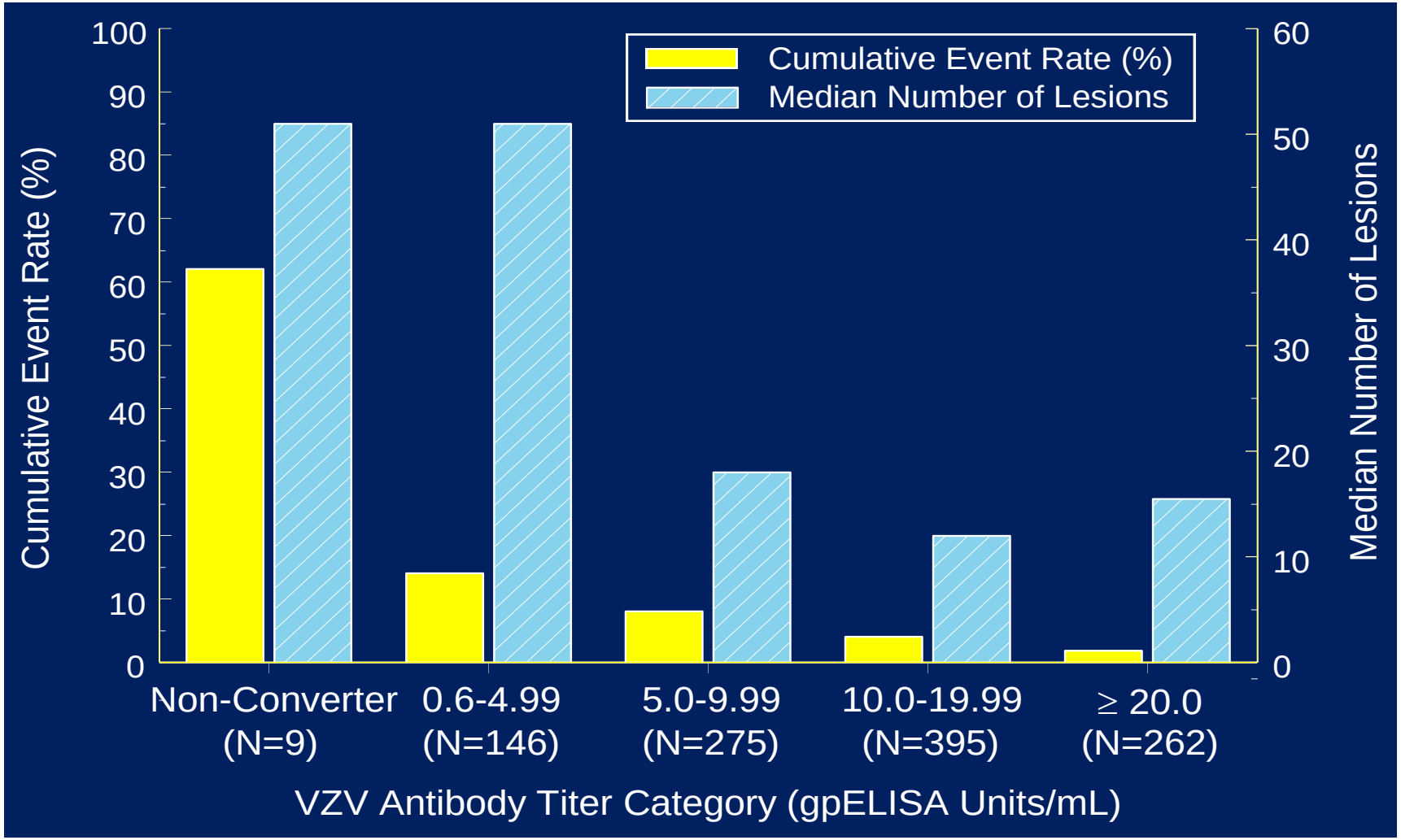
Varicella Vaccine Example
(Chan et al 2002)

- Evaluate VZV antibody response as a correlate of risk against varicella based on a long-term (7 years) follow-up of ~1000 vaccinated children
  - 66 breakthrough disease cases
- Real-world data (RWD) from a national population survey were used to derive the expected age-specific incidence rate among unvaccinated susceptible children
- Goal is to
  - Establish an immune response level that correlates with protection
  - Develop a predictive model for durability of vaccine protection
  - Support use of immune response as an endpoint for bridging trials

VZV Antibody Response 6 Weeks Postvaccination by Varicella Breakthrough Status



Life-table Estimates of 7-Year Cumulative Varicella Event Rates by 6-Week Antibody Titer After 1 Dose of Vaccine



Estimated Vaccine Efficacy by Antibody Titer Level after 1 Dose

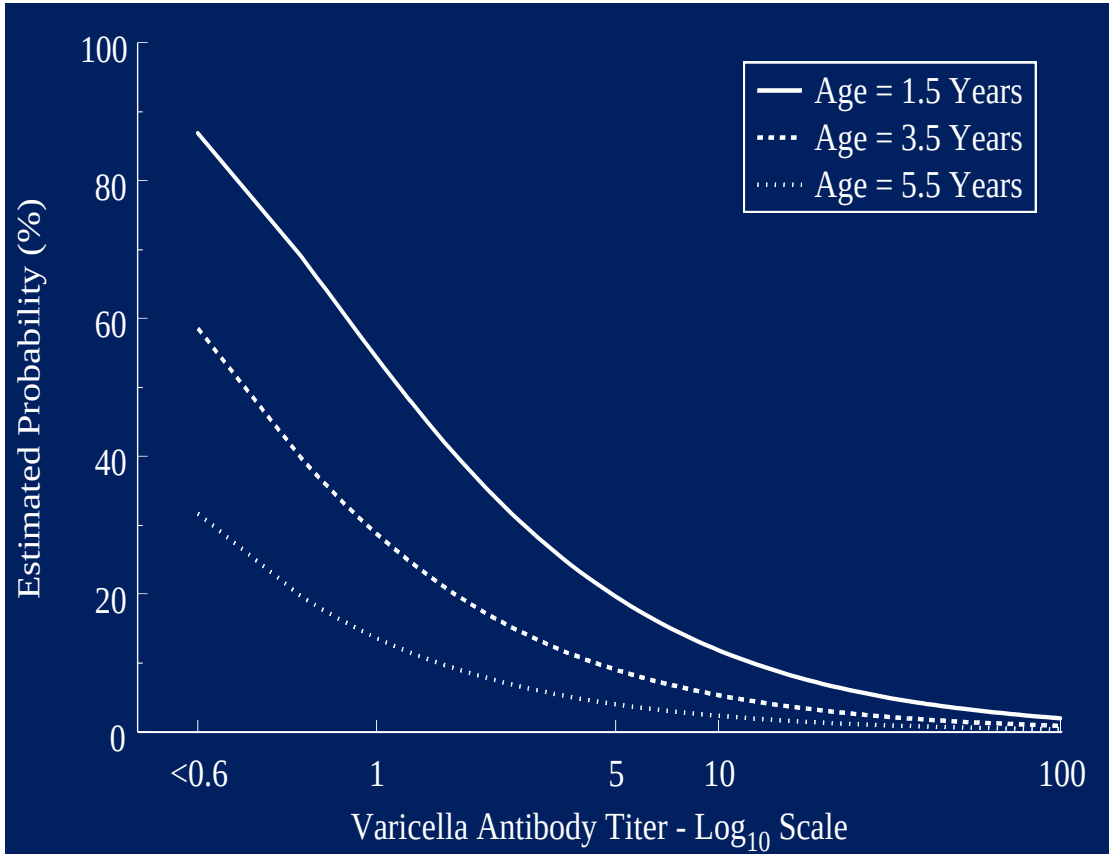
Results support VZV antibody titers ≥5 gpELISA/mL as an approximate protective level and can be used as an endpoint for bridging trials

VZV Antibody Titer Category	N	Number of Cases (Rate per 100 PY)	Estimated Efficacy (95% CI)	Median Lesion Count
<5 gpELISA/mL	155	23 (2.5)	83.5% (76.9%, 89.5%)	51
≥5 gpELISA/mL	932	43 (0.7)	95.5% (94.2%, 96.8%)	15.5
Overall	1087	66 (0.9)	94.0% (92.6%, 95.4%)	25

Statistical Modeling for Efficacy Prediction (Chan et al 2002)

- Piecewise exponential model performs best compared with other survival-time models
  - Allow adjustment for important covariates and varying baseline hazards
- Prediction variability (CI) used 2-step Bootstrap sampling to account for 2 sources of variability:
  - Model building
  - New dataset
- Predictive model validated against other long-term follow-up data
- Model used to predict durability of vaccines made by new manufacturing process

Estimated 7-Year Varicella Event Rate After 1 Dose of Vaccine by Antibody Titer



Herpes Zoster Vaccine Example

- Herpes zoster (HZ)
  - A viral disease characterized by a painful skin rash with blisters
  - Caused by reactivation of varicella-zoster virus (VZV)
- Clinical efficacy endpoint: HZ incidence
  - SPS: ~38,000 subjects 60+ years of age (Oxman et al 2005)
  - ZEST: ~22,000 subjects 50-59 years of age (Schmader et al 2012)
- Immune marker
  - VZV-specific antibody responses, as measured by glycoprotein enzyme-linked immunosorbent assay (gpELISA)
- Goal is to assess antibody response as a correlate of protection (non-mechanistic)

Correlate of Risk Analysis From Two Phase III Trials of ZOSTAVAX® (Antibody Responses by gpELISA)

Study Protocol	Population	Vaccine Effect on incidence of HZ	Vaccine effect on antibody response	Correlation between antibody and risk of HZ
SPS sub-study (N=38546, n=1328)	60+ years	51% (p <.0001)	1.7 fold (p <.0001)	38% risk reduction per one-log-unit increase (p <.0001)
ZEST case-cohort (N=22439,n =2269)	50-59 years	70% (p <.0001)	2.3 fold (p <.0001)	31% risk reduction per one-log-unit increase (p <.0001)

VZV antibody response measures (natural log scale):
(1) gpELISA titer at 6 weeks
(2) gpELISA fold rise at 6 weeks (6-week titer/baseline titer)

Correlate of Protection Analysis Based on the Prentice Criteria

Antibody responses by gpELISA: Titer + I[foldrise>cutoff]

Study	Proportion of Treatment Effect Explained (PTE)
SPS	0.783
ZEST	0.645

I[foldrise > cutoff] is a binary indicator of whether foldrise from baseline is > cutoff

Correlate of Protection Analysis Based on Principle Stratification
(Gilbert et al 2014 JID)

Fold Rise in Antibody Titers by Measured by Glycoprotein-Based Enzyme-Linked Immunosorbent Assay Is an Excellent Correlate of Protection for a Herpes Zoster Vaccine, Demonstrated via the Vaccine Efficacy Curve

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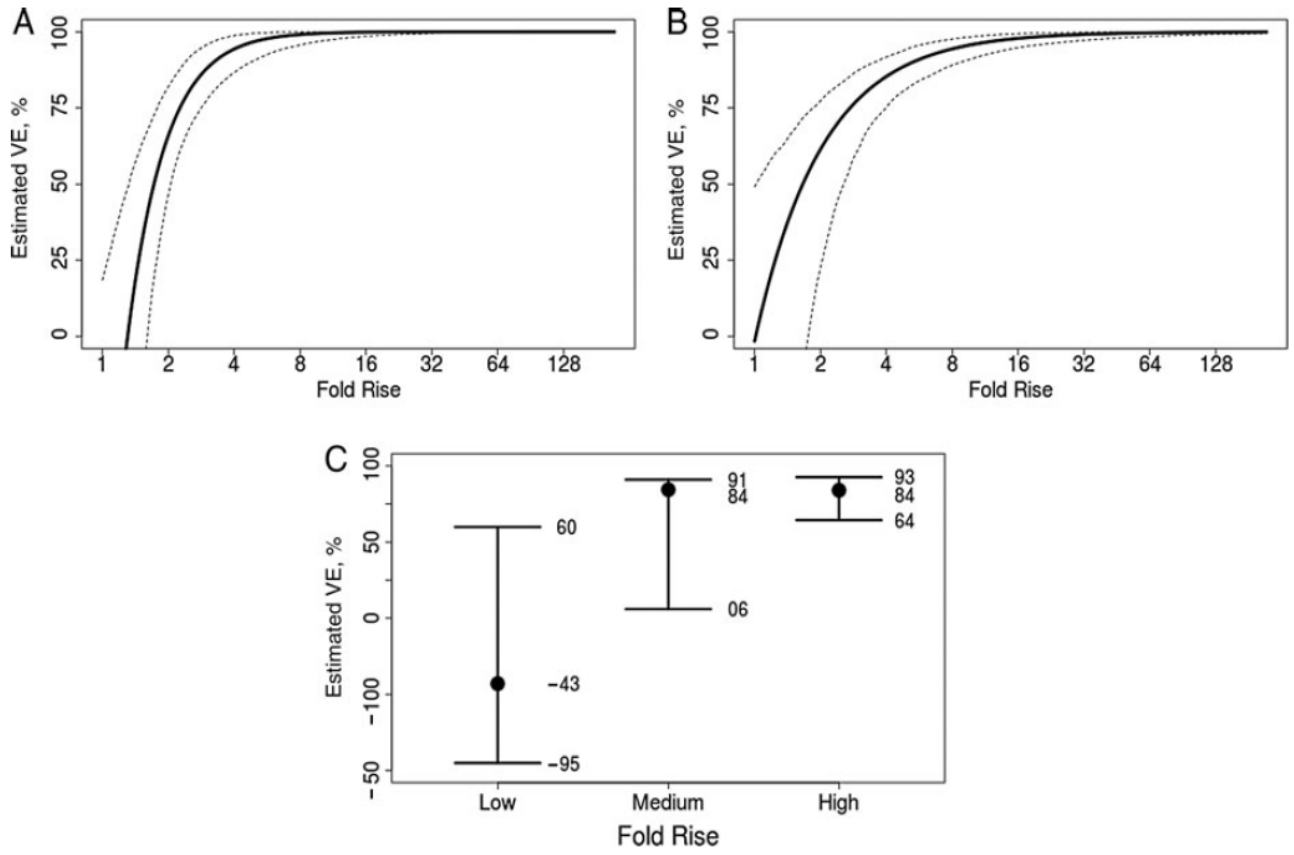
[1]Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center and Department of Biostatistics, University of Washington, and [2]Biostatistics, Gilead Sciences, Seattle, Washington; [3]National Institute of Allergy and Infectious Diseases, Biostatistics Research Branch, Bethesda, Maryland; [4]Department of Biometrics, Biogen Idec, Cambridge, Massachusetts; and [5]Merck, Whitehouse Station, New Jersey

(See the editorial commentary by Wittes on pages 1523–5.)



- Use causal inference framework
- A biomarker is a principal surrogate if it satisfies:
  - Average causal necessity
  - Average causal sufficiency

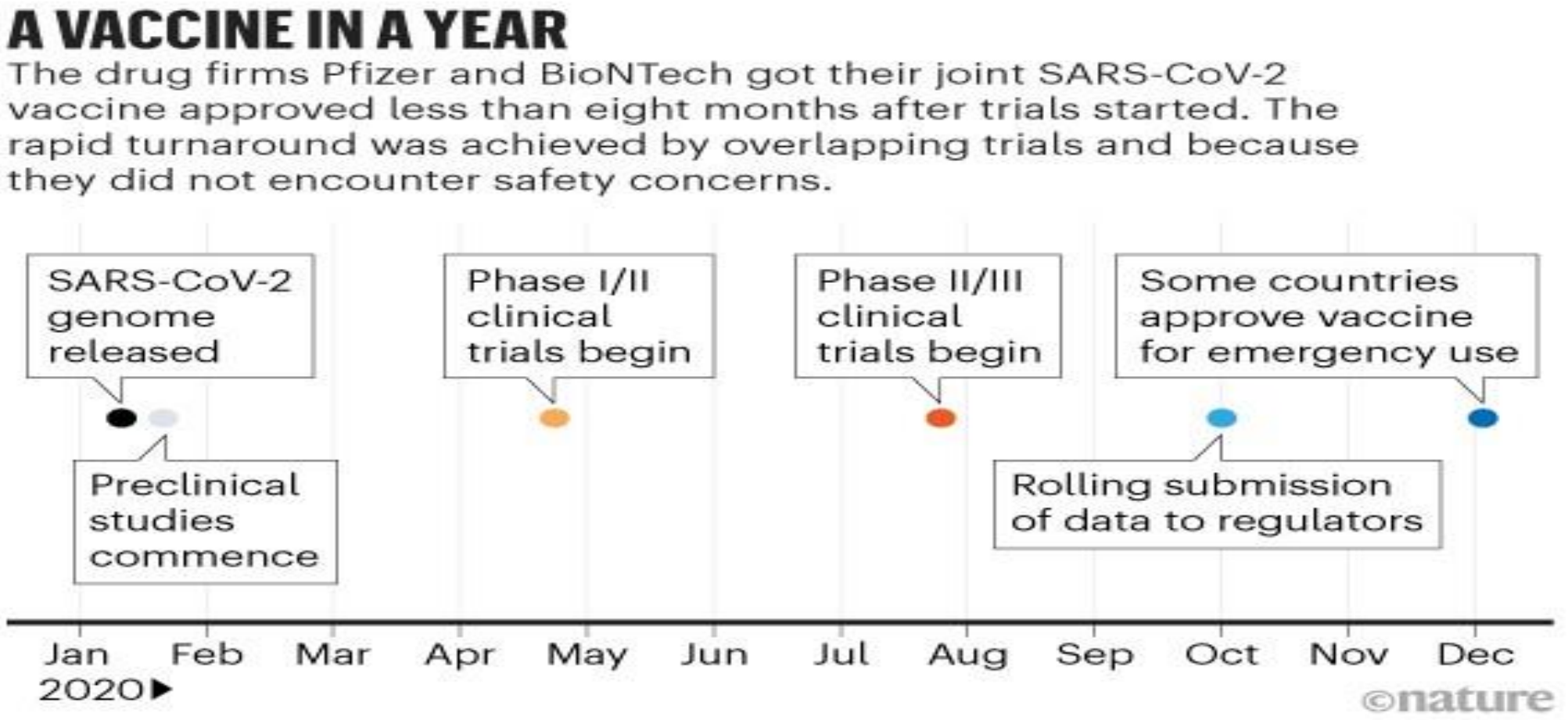
COVID-19 Vaccines

Accelerated development against pandemic

Acceleration of Vaccine Development Against Pandemic - COVID-19 Vaccine

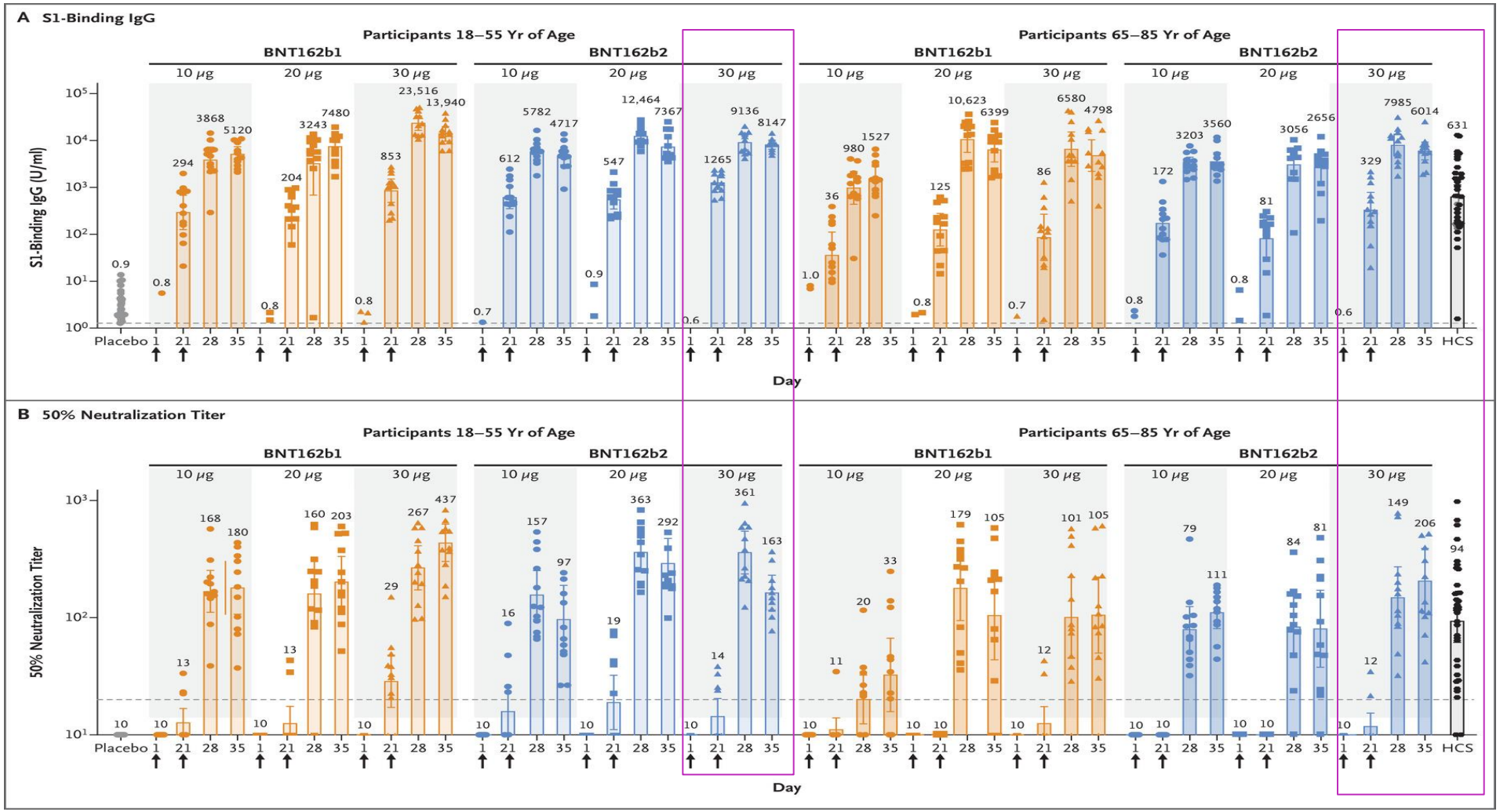
- Tremendous collaboration between industry and government to shorten the development timeline
- Leverage advancement of genomics to understand the coronavirus
- Conduct seamless phase I/II and II/III trials with interim analyses
- Rolling submission
- Develop manufacturing capabilities at risk
- Adapt Emergency Use Authorization (EUA) before full approval
  - —EUA requires demonstrating vaccine efficacy of at least 50% with a lower bound >30%, and at least 2 months of safety

Acceleration of Vaccine Development in Pandemics - COVID-19 Vaccine



Ball P. Nature V589, p16-18 (2021)

Immune responses of Pfizer/BioNTech COVID-19 Vaccine Candidates in Phase I Study (Walsh et al NEJM 2020)



- Two doses of 30μg BNT162b2 was selected for phase 3

Phase 3 Placebo-controlled Trials of COVID-19 Vaccines in the US

Vaccine Manufacturer	Vaccine Type	Dose Regimen	Phase 3 Trial (N)	Vaccine Efficacy against symptomatic COVID-19	Vaccine Efficacy Against Severe Disease
Pfizer/BioNTech	mRNA	2 doses	43,661	95.0%	90%
Moderna	mRNA	2 doses	30,000	94.5%	~100%
J&J	Viral vector	1 dose	43,783	67.0%	85.0%
Oxford/AZ	Viral vector	2 doses	32,449	76.0%	~100%
Novavax	Protein Subunit	2 doses	29,960	90.4%	~100%

- Real-world data have shown consistent vaccine effects due to the diversity of clinical trial participants

Opportunities for Continuous Improvement

- Innovative clinical trial designs, including Bayesian framework, platform trials, and trial optimization
- Use biomarkers for treatment stratification and population enrichment
- Leverage external data including real-world data in clinical development and regulatory submission
  —Historical clinical trial data, synthetic controls, digital twins
- Use digital technologies such as smart phones, wearables, telehealth
- Decentralized trials to improve the diversity of patient participation

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