Module 8:
Evaluating Immune Correlates of Protection

Instructors: **Ivan Chan, Peter Gilbert, Paul T. Edlefsen, Ying Huang**

Session 2: Introduction to Immune Correlates of Protection

Summer Institute in Statistics and Modeling in Infectious Diseases
University of Washington, Department of Biostatistics

Some course materials at:
http://faculty.washington.edu/peterg/SISMID2013.html

July 15-17, 2013

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Impact of Vaccines on Disease

Disease	Baseline 20th Century Annual Cases	2003 Cases	Percent Decrease
Measles	503,282	56	99.9%
Diphtheria	175,885	1	99.9%
Mumps	152,209	231	99.9%
Pertussis	147,271	11,647	92.1%
Smallpox	48,164	0	100%
Rubella	47,745	8	99.9%
Haemophilus influenzae type b, invasive	20,000	32	99.9%
Polio, paralytic	16,316	0	100%
Tetanus	1,314	20	98.5%

Source: MMWR 04/02/1999, 04/22/2005

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Impact of Vaccines on Disease

Disease	Years to Develop Vaccine
Typhoid	105
Haemophilus influenzae B	92
Pertussis	89
Measles	42
Polio	30
Hepatitis B	15
HIV	31 and counting

Source: Modified from H. Markel, NEJM, August 25, 2005

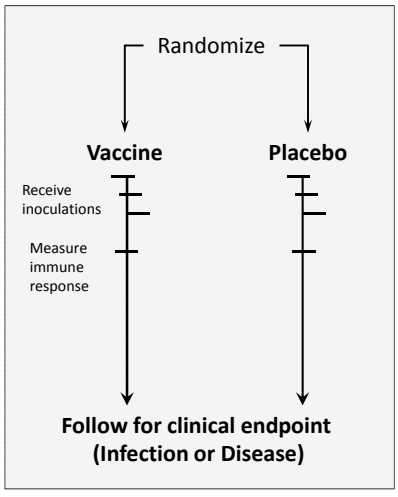
Outline of Module 8

Session 1 (Chan)	Introduction to Vaccines and Basic Concepts
Session 2 (Gilbert)	Introduction to Immune Correlates of Protection
Session 3 (Chan)	Evaluating Correlates of Protection using Individual, Population, and Titer-Specific Approaches
Session 4 (Gilbert)	Continuation of Session 2; plus Evaluating a Correlate of Risk (CoR)
Session 5 (Chan)	Use of Statistical Models in Assessing Correlates of Protection
Session 6 (Edlefsen)	Introduction to Sieve Analysis
Session 7 (Gilbert)	Thai Trial Case Study (Including Sieve Analysis)
Session 8 (Chan)	Validation using Prentice Criteria, Design Considerations
Session 9 (Gilbert)	Evaluating a Specific Surrogate of Protection Part I (Gilbert and Hudgens, 2008)
Session 10 (Huang)	Evaluating a Specific Surrogate of Protection Part II (Huang and Gilbert, 2011; Huang, Gilbert and Wolfson, 2013)

Outline Session 2

1. **Introduction: Concepts and definitions of immune correlates/surrogate endpoints**
   - Two paradigms: Predictive surrogates vs. mechanistic surrogates
2. Predictive surrogates Tier 1: Correlate of Risk (CoR)
3. Predictive surrogates Tier 2: Specific Surrogate of Protection (Specific SoP)
   - Statistical Surrogate (Prentice, 1989)
   - Principal Surrogate (Frangakis and Rubin, 2002)
4. Predictive surrogates Tier 3: General Surrogate of Protection (Bridging SoP)
5. Reconciling Immune Correlates Nomenclature
6. Conclusions and Discussion

Preventive Vaccine Efficacy Trial



- **Primary Objective**
  - Assess **VE**: Vaccine Efficacy to prevent infection or disease with a pathogen
- **Secondary Objective**
  - Assess vaccine-induced immune responses as "immune correlates of protection" against infection or disease

Importance of an Immune Correlate

- Finding an immune correlate is a central goal of vaccine research
  - One of the 14 'Grand Challenges of Global Health' of the NIH & Gates Foundation (for HIV, TB, Malaria)
- Immune correlates useful for:
  - Shortening trials and reducing costs
  - Guiding iterative development of vaccines between basic and clinical research
  - Guiding regulatory decisions
  - Guiding immunization policy
  - **Bridging efficacy of a vaccine observed in a trial to a new setting**
    - ✓ Pearl (2011, *International Journal of Biostatistics*) suggests that bridging is *the* reason for a surrogate endpoint

Regulatory Agencies Typically set Thresholds of Protection for Guiding Vaccine Licensure (this slide from Former FDA CBER Director, Dr. Norman Baylor)

Vaccine	Test	Correlate of Protection
Diphtheria	Toxin Neutralization	0.01-0.1 IU/mL
Hepatitis A	ELISA	10 mIU/mL
Hepatitis B	ELISA	10 mIU/mL
Hib Polysaccharides	ELISA	1 mcg/mL
Hib Conjugate	ELISA	0.15 mcg/mL
Influenza	HAI	1/40 dilution
Lyme	ELISA	1100 EIA U/mL
Measles	Microneutralization	120 mIU/mL
Pneumococcus	ELISA (Opsonophagocytosis)	0.20-0.35 mcg/mL (for children); 1/8 dilution
Polio	Serum Neutralization	1/4 - 1/8 dilution
Rabies	Serum Neutralization	0.5 IU/mL
Rubella	Immunoprecipitation	10-15 mIU/mL
Tetanus	Toxin Neutralization	0.1 IU/mL
Varicella	Serum Neutralization; gb ELISA	≥ 1/64 dilution ≥ 5 IU/mL

Adapted from Plotkin S. Correlates of Vaccine Induced Immunity (Vaccines 2008:47)

Hard to Rigorously Identify Immune Correlates: Knowledge Level about Correlates for Licensed Vaccines

None/Low	Intermediate	High
1. Acellular Pertussis	1. Anthrax	1. Diphtheria & Tetanus Toxoids
2. BCG Live	2. Hepatitis B Recombinant	2. Haemophilus b Conjugate
3. Hepatitis A	3. Influenza Live	3. Meningococcal Polysaccharide Diphtheria
4. Japanese Encephalitis Invactivated	4. Measles Live	4. Rabies
5. Poliovirus Inactivated	5. Mumps Live	5. Tetanus & Diphtheria Toxoids
6. Rotavirus	6. MMR	6. Varicella Live
7. Rubella Live	7. Pneumococcal Polyvalent	7. Yellow Fever
8. Typhoid Live	8. Smallpox	

But What Exactly is an Immune Correlate?

- Confusion in the meaning of the terms: "Immune correlate," "Correlate of protection," "Correlate of protective immunity"
- Clear definitions are surprisingly elusive and not widely understood
- Generally "immune correlate" is connected to the concept of a surrogate endpoint, e.g. with definition:

> *"A validated surrogate endpoint is an endpoint which allows prediction of a clinically important outcome."*
> - International Conference on Harmonization, document E8

- What exactly does this mean?
- Moreover, statistical methods for assessing the validity of surrogate endpoints are surprisingly subtle and not widely understood
- Many pitfalls for scientists to be misled about surrogate endpoints

But What Exactly is an Immune Correlate?

- This introductory talk will:
  - Clarify distinct concepts of "immune correlate"
    - ✓ Two paradigms: Prediction vs. causal mechanism
  - Focus on the prediction paradigm:
    - ✓ Define three types of immune correlates
    - ✓ For each type, summarize statistical frameworks for their assessment
  - Suggest how vaccine trials can be designed to improve the evaluation and development of immune correlates

Take Home Points

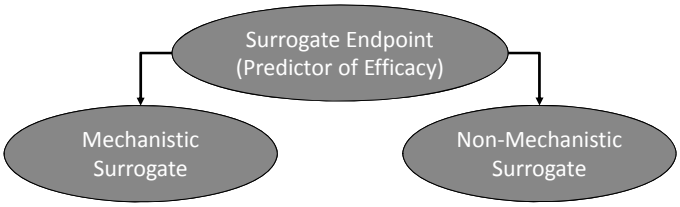
- Important for the vaccine field to use a common nomenclature on immune correlates
  - This talk will describe much of the existing nomenclature, and propose a reconciliation
- Participant characteristics that predict the immune responses of interest are helpful for assessing immune correlates
  - Suggests expanding research to develop predictors of vaccine-immunogenicity
  - Implications for study design (e.g., on sample collection and storage) to ensure rigorous assessment of immune correlates
- In efficacy trials, vaccinating placebo recipients at the end of follow-up and measuring their immune responses can be helpful for assessing immune correlates

Two Major Concepts/Paradigms for Surrogacy

- Causal agent paradigm (e.g., Plotkin, 2008, *Clin Infect Dis*)
  - **Causal agent of protection** = marker that **mechanistically causes** vaccine efficacy against the clinical endpoint
- Prediction paradigm (e.g., Qin et al., 2007, *J Infect Dis*)
  - **Predictor of protection** = marker that **reliably predicts** the level of vaccine efficacy against the clinical endpoint
- Both are extremely useful for vaccine development, but are assessed using different approaches
- For the goal of statistical assessment of surrogate endpoint validity in an efficacy trial, the prediction paradigm is used

A Predictive Surrogate May or May Not be a Mechanism of Protection*

- **Informal Definition of a Surrogate:** An endpoint that can be used to reliably predict the vaccine effect on the clinical endpoint



- **Example:** Meningococcal vaccine**
  - Mechanistic surrogate: Bactericidal antibodies
  - Non-mechanistic surrogate: Binding antibodies (ELISA)

* Plotkin and Gilbert (2012 *Clin Inf Dis*)
** Borrow et al. (2005, *Vaccine*)

Prediction Paradigm: Nested Hierarchy of Immune Correlates Definitions (Qin et al., 2007, *J Infect Dis*)

	Definition	Framework for Empiracal Assessment
Correlate of Risk: Tier 1	The biomarker correlates with the clinical endpoint measuring vaccine efficacy	Vaccine efficacy trials/ epidemiological studies
Specific Surrogate Protection: Tier 2	Vaccine effects on the biomarker predict vaccine efficacy, for the **same setting** as the efficacy trial	Single large efficacy trial or multiple similar trials
General Surrogate of Protection: Tier 3	A specific SoP that reliably predicts vaccine efficacy in **different settings** (e.g., across vaccine lots, vaccine formulations, human populations, viral populations)	Multiple diverse efficacy and/or post-licensure trials

- Hierarchy in scientific importance and degree of data requirements for statistical assessment
- Bridging surrogates are for a particular new setting
  - E.g., new vaccine formulation, vaccine delivery, human population, viral population
  - Reliable prediction to one new setting may fail for a different new setting

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Importance of Causal Agency for Credibility of Bridging Predictions of Vaccine Efficacy

	Prediction Concepts	Causal Agency Concepts
A single efficacy trial can provide empirical support	Correlate of Risk (CoR)	
	Specific Surrogate	Specific Mechanistic Surrogate
The efficacy trial provides limited or no data	Bridging Surrogate	Bridging Mechanistic Surrogate

- A single efficacy trial can provide direct data for assessing CoRs and specific surrogates, and perhaps supportive data for assessing causal agency, but typically provides few or no direct data for assessing bridging surrogates
- But, reliable bridging predictions is a central need for guiding research and deployment
- **Knowledge of the causal mechanism(s) of protection is core for building the rationale basis for bridging**

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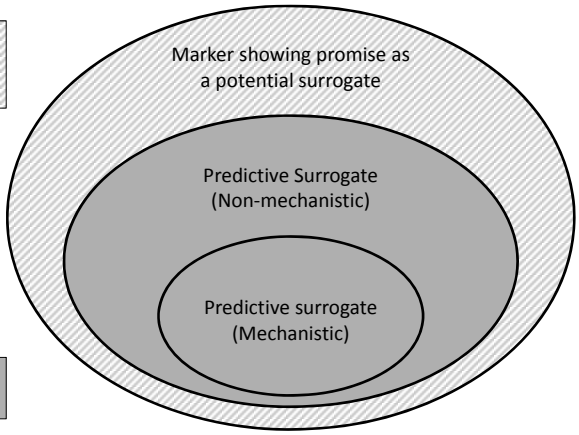
Assessing a Surrogate as a Mechanism of Protection

- Many approaches outside of vaccine efficacy trials are needed
- Basic science
  - Understand specificity/functionality of biomarkers
  - Understand all the effects of vaccination (intended and unintended)
  - Understand the disease process
- Laboratory validation studies
  - Understand measurement/variability characteristics of immune biomarkers
- Causal manipulation studies in animal trials
  - Challenge efficacy trials comparing animals with and without induction of the immune biomarker(s)
  - E.g., passive antibody transfer repeated low-dose challenge studies in macaques

Nesting of Correlate and Surrogate Definitions/Concepts

Misleading for vaccine development: Does not predict clinical vaccine efficacy



Useful for vaccine development: Predicts clinical vaccine efficacy

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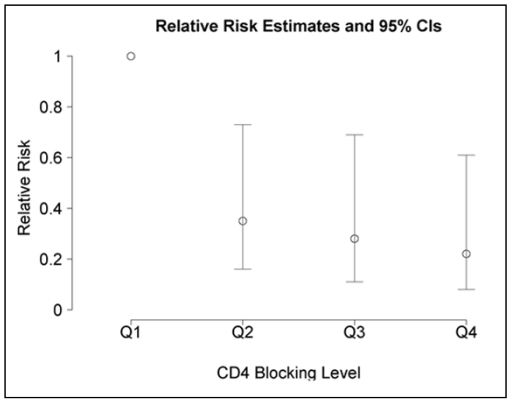
Tier 1: "Correlate of Risk" (CoR)

- **Definition:** A *correlate of risk (CoR)* is an immunologic measurement that predicts the rate of the clinical endpoint used to measure vaccine efficacy in some population
- **Example:** Individuals with higher antibody titers have a lower rate of pathogen-specific disease
  - In an observational study
  - In the vaccine group of a Phase III trial
  - In the placebo group of a Phase III trial

Example 1. VaxGen 004 Phase III Trial: Assess Antibody Response Readouts as CoRs for HIV Infection in the Vaccine Group*

In vaccine group assess several antibody response readouts including MN neutralization and MN/GNE8 CD4 blocking levels as predictors of HIV infection (Cox model)



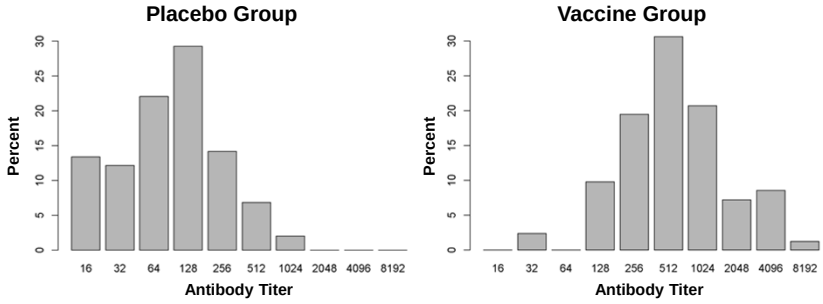
Case-cohort design: Antibody data measured on 239 infected/163 uninfected

*Gilbert et al., 2005,JID

Example 2. 1943 Influenza Vaccine Field Trial (Salk, Menke, and Francis, 1945)

- N = 1,776 men in an Army Service Unit at the University of Michigan
- Evaluated a trivalent vaccine containing Weiss Strain A and PR8 Strain A
- Men assigned vaccine or placebo based on alphabetical ordering of names
  - Inoculations completed in 7 days
- Strain-specific Ab titers to Weiss Strain A and to PR8 Strain A measured 2 weeks post-inoculation
  - Every 10^{th} vaccinee and 5^{th} placebo
- Clinical endpoint = Hospitalization due to respiratory illness with a specific influenza strain found in throat culture
- Follow-up: Oct 25 1943 to Jan 1 1944

Example 2. 1943 Influenza Vaccine Field Trial Distributions of Weiss Strain A Log Ab Titer



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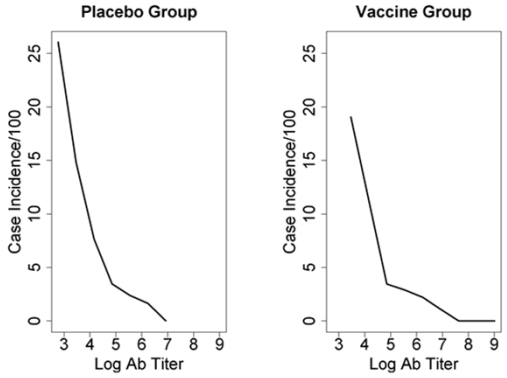
Example 2. Ab Titer a CoR for Weiss Strain A- Specific Hospitalization

- **CoR Estimation**
  - Estimate relationship between log Weiss strain A Ab titer and clinical risk in the placebo group and in the vaccine group



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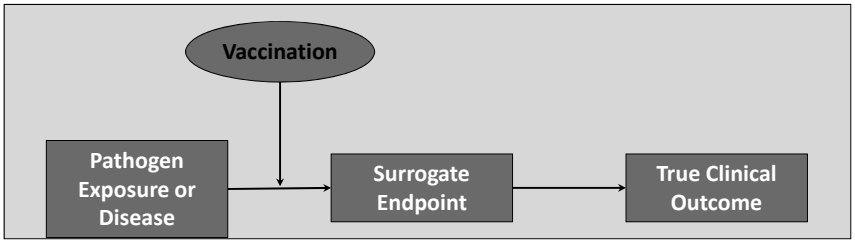
"A Correlate Does not a Surrogate Make"
– Tom Fleming

Reasons Why CoRs Fail to be Surrogates

A Perfect Surrogate is Mechanistic and Highly Predictive of the Vaccine Effect on the Clinical Endpoint



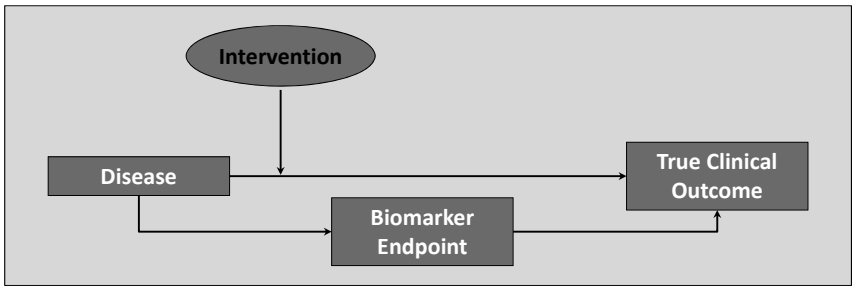
- Assurance about surrogate validity requires a comprehensive understanding of:
  - the biological processes leading to the clinical endpoint
  - the effects of vaccine on the surrogate and on the clinical endpoint
- Understanding causal mechanism often leads to more predictive surrogates, but not necessarily

Surrogate Failure Can Happen in Many Ways

1. The biomarker is not in the pathway of the intervention's effect, or is insensitive to its effect
2. The biomarker is not in the causal pathway of the disease process
3. The intervention has mechanisms of action independent of the disease process

Reason for Surrogate Failure

1. The biomarker is not in the pathway of the intervention's effect, or is insensitive to its effect



Surrogate Failure Due to Measurement Error

- If the tool for measuring the mechanism of protection has significant measurement error, then the biomarker may fail to be a predictive surrogate
- A basic issue for developing surrogates is precision of estimation of the biological function
- **Example 1:** Seminal VL vs Plasma VL as surrogates for secondary transmission
  - Seminal VL may be a mechanistic surrogate
  - However, the seminal VL assay [qt-HIV assay (Gen-Probe)] has greater intra-subject variability than the plasma VL assay
  - Plasma VL is a stronger predictor of transmission than seminal VL (Butler, Little, et al., 2007, *2nd International Workshop on HIV Transmission*)

Surrogate Failure Due to Measurement Error

- **Example 2:** iPrEX trial of oral PrEP (Grant et al., 2009, *NEJM*)
  - Trial showed that oral PrEP prevented HIV-1 infection (Estimated risk reduction vs. placebo = 44%)
  - Secondary analysis supported that the protection was strongest in or restricted to those adherent to oral PrEP
  - Self-reported adherence fails as a surrogate because of the high degree of measurement error
  - Plasma drug levels may be a valid surrogate because they provide a much more accurate indication of adherence
- Defining marker variability (both biological and measurement error) is a basic part of developing surrogates

Reason for Surrogate Failure

2. The biomarker is not in the causal pathway of the disease process.

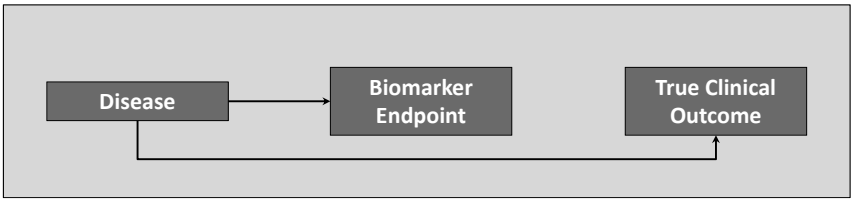


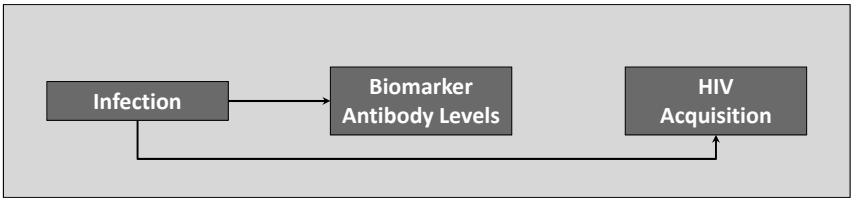
Illustration: VaxGen 004 Trial 1998-2003

The immune response is not in the causal pathway of HIV acquisition (antibodies only neutralize specific lab strains)

- **AIDSVAX:**

VE	95% CI
6%	(-24%, 17%)

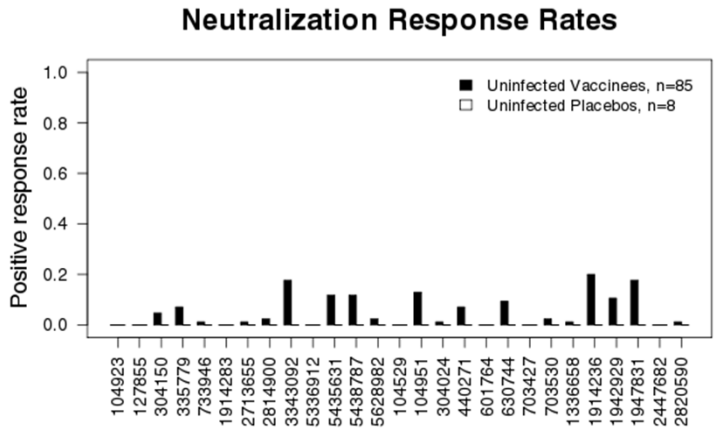
- **Biomarkers:** MN neutralization titers, CD4 blocking levels, binding antibodies, ADCVI antibodies



VaxGen 004 Trial: Antibody Readouts are Inverse CoRs But Do Not Predict VE

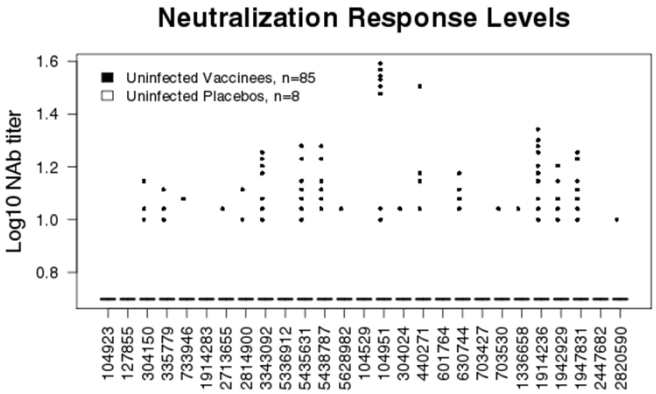
- Antibody readouts are "mere markers" of infection risk- no ability to predict **VE**
  - Vaccine recipients with lowest (highest) antibody titers had immune systems less (more) able to naturally ward of infection
  - A third unmeasured factor (e.g., based on innate immunity/host genetics) confounds the association between the potential surrogate and the clinical endpoint
- Support for this explanation comes from a follow-up study of the ability of vaccine recipient sera to neutralize 27 primary HIV-1 isolates sampled from VaxGen infected subjects

VaxGen 004 Trial Example: Validation Study (Gilbert et al., 2010, JID)



HIV isolates from infected trial participants

VaxGen 004 Trial Example: Validation Study (Gilbert et al., 2010, JID)

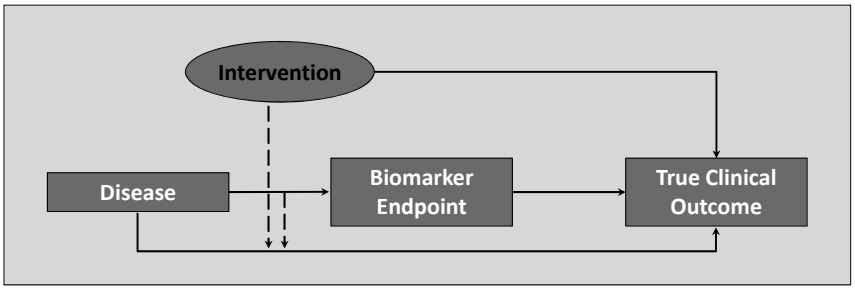


HIV isolates from infected trial participants

Conclusion: Absent or at best weak neutralization of circulating/exposing viruses supports that MN Neutralization is not a surrogate

Reason for Surrogate Failure

3. The intervention has mechanisms of action independent of the disease process



Dotted lines = mechanisms of action that might exist

Example 1: Acellular Pertussis Vaccines with Mechanisms of Action Independent of the Disease Process*

(Sweden I Trial with DT control: 10,000 subjects)

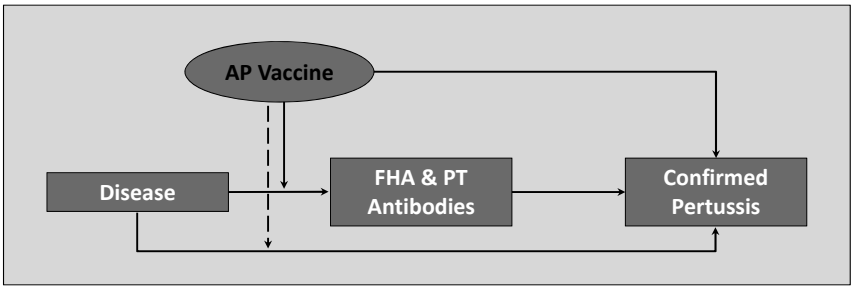
- Other relevant immune responses not captured by the assay (incomplete measurement of Ab responses)

Vaccine	VE	95%
SKB	58%	(51%, 66%)
Aventis Pasteur	85%	(81%, 89%)

- Biomarkers: *Filamentous Haemagglutinin (FHA) and Pertussis Toxoid (PT)* antibody responses were superior with the SKB vaccine

*Example from Tom Fleming

Example 1: Acellular Pertussis Vaccines with Mechanisms of Action Independent of the Disease Process



- Other immune responses, including those resulting from additional antigens in the vaccines:
  - Pertactin
  - Fimbriae (types 2 and 3)

Example 2: CAST Trial*

- Encainide and flecainide in partients after a heart attack had a promising effect on the putative surrogate Arrhythmia suppression
- However, these drugs increased the rate of mortality compared to placebo
- Classic example of surrogate failure

*Echt et al., 1991, *New Engl J Med*

Example 3: AIDS Patients With MAI Bacteremia

	Clarithromycin Dose (mg bid)		
	500	1000	2000
Bacterial Load	145	34	25

Chaisson et al., 1994

Example 3: AIDS Patients With MAI Bacteremia

	Clarithromycin Dose (mg bid)		
	500	1000	2000
Bacterial Load	145	34	25
12 week Mortality	5.7%	25.5%	28.0%

Chaisson et al., 1994

CAST and MAI Bacteremia Studies Illustrate the 'Surrogate Paradox'

- **Surrogate Paradox:** Positive treatment effect on the surrogate, positive association of the surrogate and clinical endpoints, but a negative overall clinical effect
  - For a vaccine trial, would mean that the vaccine induces an immune response, vaccinees with higher responses have a lower infection rate (inverse CoR), but nonetheless VE < 0%
- **Causes of the Surrogate Paradox***

1. Confounding of the association between the potential surrogate and the clinical endpoint (failure reason 1)
2. The vaccine positively affects both the surrogate and the clinical endpoint, but for different sets of subjects (failure reason 2)
3. The vaccine may have a negative clinical effect in ways not involving the potential surrogate (failure reason 3)

*From Tyler Van der Weele

"There is a plague on Man, the opinion that he knows something."

Michel de Montaigne (1580, *Essays*)

"Medicine is something a doctor prescribes while waiting for nature to cure the disease."

Voltaire (mid-18th Century)

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Tier 2: Specific SoP

- **Consider evaluation of a candidate surrogate based on a single efficacy trial**
- **Definition: A *specific surrogate of protection (specific SoP)* is an immunologic measurement such that vaccine effects on the marker reliably predict VE, for the same setting as the trial**
  - E.g., subgroups with no vaccine-induced Ab response have no efficacy, and subgroups with large vaccine-induced Ab response have large **VE**
  - 2 detailed definitions of a **specific SoP-** next slides
  - A **specific SoP** can reliably predict **VE** for identical or similar settings as the vaccine trial

Tier 2: Specific SoP

- Connect the definition to the general definition of a valid surrogate endpoint
- International Conference on Harmonization's statement in document E8:

> *"A validated surrogate endpoint is an endpoint which allows prediction of a clinically important outcome"*

*[More precisely, allows prediction of a **treatment effect** on a clinically important outcome/study endpoint]*

Two Definitions of a Specific SoP

- Statistical SoP
  - Prentice (1989, *Stats Med*) definition of a surrogate endpoint
  - Based on observed associations

1. Principal SoP
   - Builds on Frangakis and Rubin's (2002) definition of a surrogate endpoint
   - Based on potential outcomes framework for causal inference

Prentice (1989, Statistics in Medicine) Criteria for a Statistical SoP

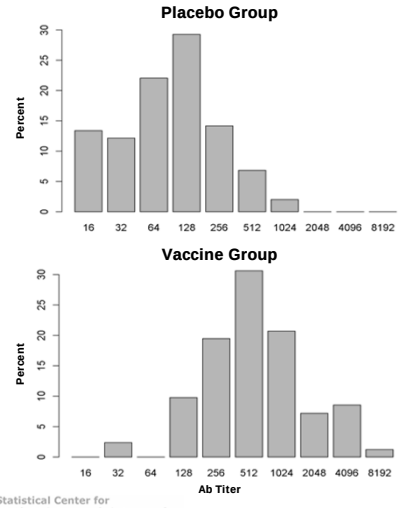
- **Definition:** A *statistical SoP* is an immunologic measurement satisfying:
  1. Vaccination impacts the immunological marker
  2. The immunological marker is a CoR in each of the vaccine and placebo groups
  3. The relationship between the immunological marker and the clinical endpoint rate is the same in the vaccine and placebo groups
     - I.e., after accounting for the marker, vaccine/placebo assignment contains no information about clinical risk
     - **Interpretation:** All of the vaccine effect on the clinical endpoint is mediated through the marker

Example 2. 1943 Influenza Vaccine Field Trial (Salk, Menke, and Francis, 1945)

- 98% retention of study participants
- Incidence of Hospitalization with Weiss Strain A
  - **Placebos:** 75 of 888 (8.45%)
  - **Vaccinees:** 20 of 888 (2.25%)

  Estimated **VE** = (1 – 2.25/8.45)×100% = 73%
- **Goal:** Assess Weiss Strain A antibody titer as a statistical SoP (check the 3 Prentice criteria)

Criterion 1 Holds



- Criterion 1: Weiss strain A Ab titers are higher in the vaccine than placebo group
- Criterion 1 holds ✓

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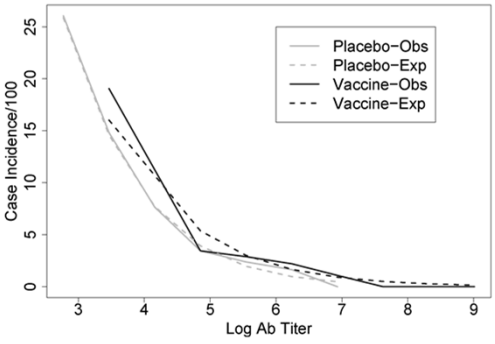
Criterion 2 Holds*



- Criterion 2: Weiss Strain A Ab titers are inversely correlated with case rate in each study group
- Criterion 2 holds ✓

*Based on logistic regression and on empirical fits

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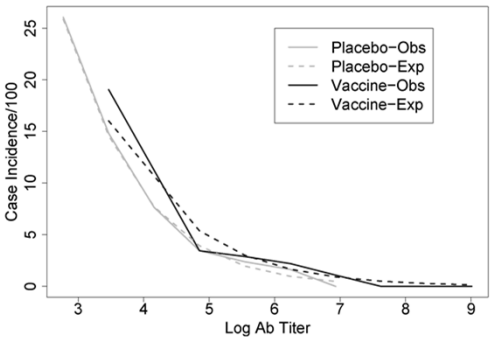
Criterion 3 Holds*



*Based on logistic regression and on empirical fits

- Criterion 3: Check for consistency between CoR models in the vaccine and placebo groups
- Same relationship of antibody levels with the disease rate in the two groups
- Criterion 3 holds ✓

Criterion 3 Holds

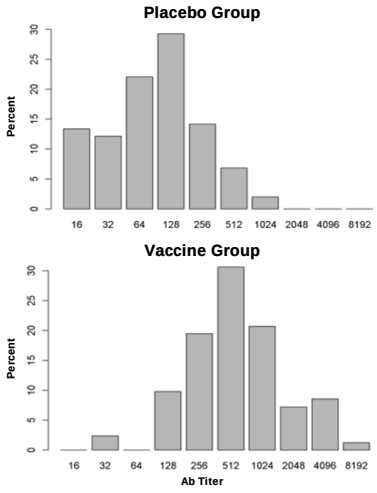
Logistic Regression Models: Estimated Coefficients (SE)

Weiss Strain A

	Control Group Only		**Control and Vaccine Groups**					
	Model 1		Model 2		Model 3		Model 4	
Intercept	1.80	(0.54)	-2.38	(0.12)	1.62	(0.45)	1.80	(0.54)
Log (Titer)	**-1.30**	**(0.14)**	-		**-0.98**	**(0.12)**	-1.03	(0.14)
Trt	-		**-1.39**	**(0.25)**	**0.33**	**(0.32)**	-0.43	(1.28)
Trt x log Titer	-		-		-		0.16	(0.25)

- As suggested by Model 3, vaccine assignment does not affect influenza risk after controlling for log Ab titer
  - Criterion 3 holds ✓

Further Validation of a Statistical SoP: Estimated VE ≅ Predicted VE



- **Direct estimate of VE (ignoring Ab titer)**
  - Estimated **VE** = 73%
- **Predicted VE**
  - Based on the CoR model for the placebo group and the distribution of Ab titers in the vaccinated
  - Predicted **VE** = 82%
- **Conclusion: Log Weiss strain A Ab titer satisfies the Prentice criteria for a statistical SoP**

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What about PR8 Strain A Ab titers?

Evaluate them as a CoR and a SoP for hospitalization with PR8 Strain A-specific influenza infection

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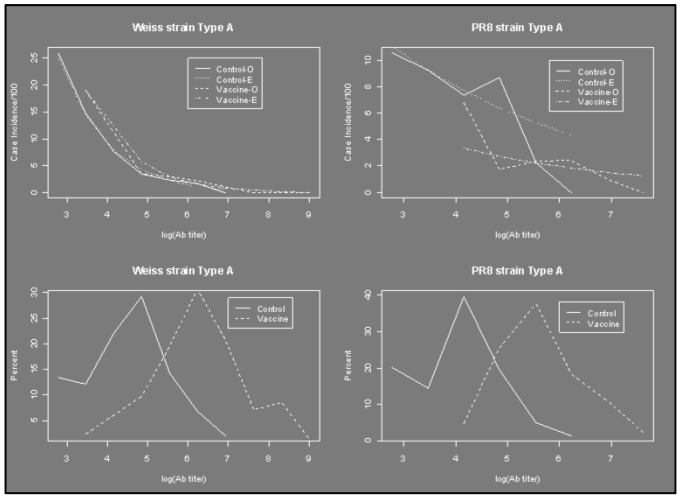
VE for PR8 Strain A

- **Incidence of Hospitalization with PR8 Strain A**
  - **Placebos:** 73 of 888 (8.22%)
  - **Vaccinees:** 20 of 888 (2.25%)

  Estimated **VE** = (1 – 2.25/8.22)×100% = 73%

(incidentally the same Estimated VE as for Weiss Strain A)

Estimated Case Incidence as a Function of Log Ab Titer for Weiss and PR8 Strain A



Logistic Regression Models: Estimated Coefficients (SE)

PR8 Strain A

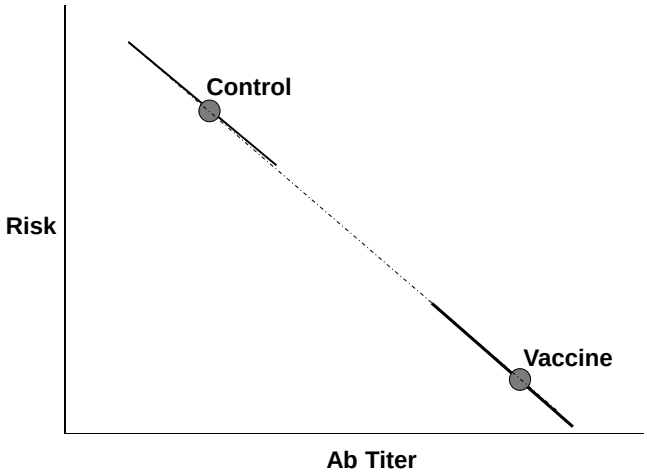
	Control Group		Control and Vaccine Groups					
	Model 1		Model 2		Model 3		Model 4	
Intercept	-1.37	(0.59)	-2.41	(0.12)	1.27	(0.53)	-1.37	(0.59)
Log (Titer)	-0.27	(0.15)	-		-0.29	(0.14)	-0.27	(0.15)
Trt	-		-1.36	(0.26)	-0.89	(0.34)*	-0.22	(1.79)
Trt*log Titer	-		-		-		0.13	(0.34)

Evidence that vaccination impacts PR8 Strain A hospitalization after accounting for Ab titer

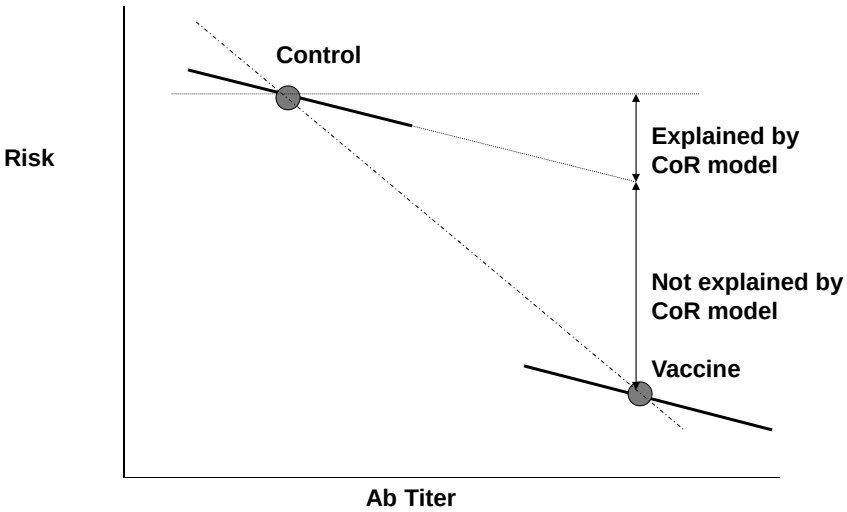
Estimated and Predicted VE: PR8 Strain A

- **Direct estimate of VE (ignoring Ab titer)**
  - Estimated **VE** = 73%
- **Predicted VE**
  - Based on the CoR model for the placebo group and the distribution of Ab titers in the vaccinated
  - Predicted **VE** = 33%
- **Full mediation condition for a statistical surrogate:**
  - Log(Ab titer) does *not* satisfy criterion
  - Only ~½ of overall protective effect is predicted from effect on Ab titer

Weiss Strain A



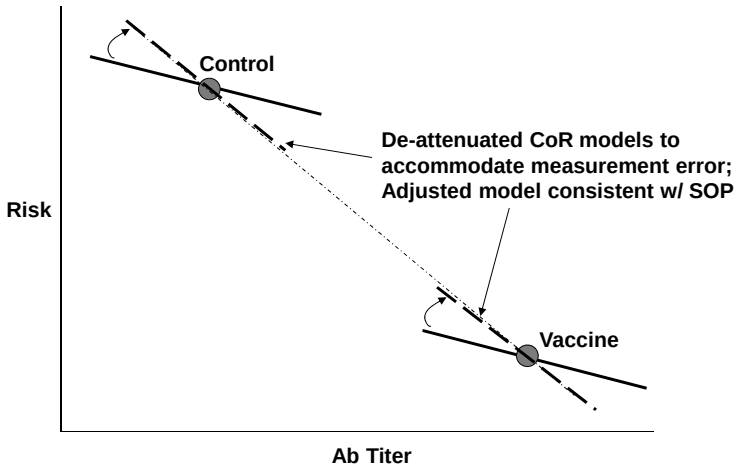
PR8 Strain A



Why Are PR8 Strain A Titers an Imperfect SoP?

- Protection from PR8 Strain A only partly explained by PR8 Ab titer
  - A possible explanation is that antibodies are protective, but the measurements reflect something else besides protective responses (i.e., measurement error)
    - Measurement error distorts (possibly attenuating) within-group association
    - Q: How to accommodate measurement errors in assessment of CoR as a SoP?

PR8 Strain A



Why Are PR8 Strain A Titers an Imperfect SoP?

- Protection from PR8 Strain A only partly explained by PR8 Ab titer
  - Another possible explanation is that there are other protective immune responses that were not measured
    - E.g., cell-mediated immune responses
  - Another is that PR8 Strain A has different protective determinants than Weiss Strain A
  - Yet another is that PR8 Ab titer **is** a valid SoP, but there was residual confounding in the regression assessment (more later)

Challenges with the Statistical SoP Approach*

- The immunologic measurement is a response to a pathogen-specific protein or proteins
  - If trial participants have never been infected with the pathogen, the immune response will be "non-response"/zero for (almost) all placebo recipients
- No variation of the marker in the placebo arm implies:
  - **CoR** model in placebo group cannot be evaluated (Criterion 2)
  - Conceptually difficult to check Criterion 3 of "full mediation"

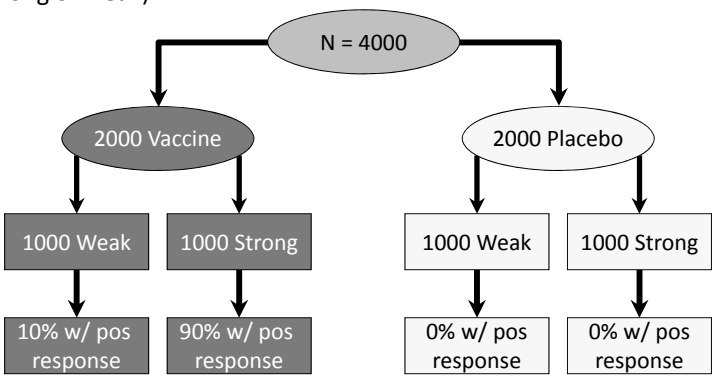
*This challenge discussed by Chan et al. (2002, *Stats Med*)

Another Challenge with the Statistical SoP Approach

- Checking "full mediation" entails checking, for each immune response level s, equal clinical risk between the groups
  - {Vaccinees w/ marker level s} vs {Placebos w/ marker level s}
- However, S is measured after randomization
  - Therefore this comparison may reflect **selection bias, potentially misleading about the markers' value as a SoP**
  - This limitation pointed out by Frangakis and Rubin (2002, *Biometrics*)

Illustration of Post-randomization Selection Bias

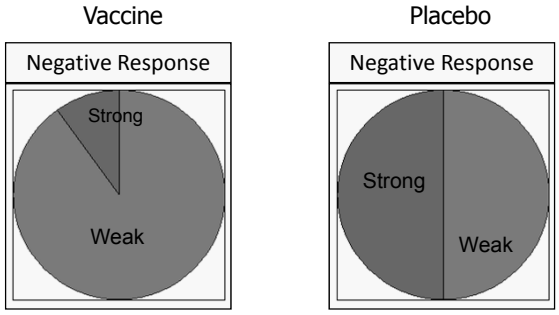
- Binary immunologic measurement (positive or negative)
- Consider an unmeasured covariate reflecting strength of immune system (strong or weak)



Criterion for a Statistical SoP: Compares Apples and Oranges

{Vaccinees w/ neg response} vs {Placebos w/ neg response}

compares clinical endpoint rates between the groups



Compares a group with 90% weak immune systems to one with 50% weak immune systems: Incomparable

Implicit Assumptions for the Validity of the Statistical SoP Approach

- Assumes that **all common causes*** of the biomarker and the clinical endpoint are included in the regression model†
  - A strong unverifiable assumption
  - Need biological understanding to make the assumption plausible
- Assumes that **all common causes** of the clinical endpoint prior to and after the measurement of the biomarker are included in the regression model
  - I.e., need to adjust for all prognostic factors

*a common cause is a predictor of both endpoints
† Discussed in Joffe and Greene (2009, Biometrics)

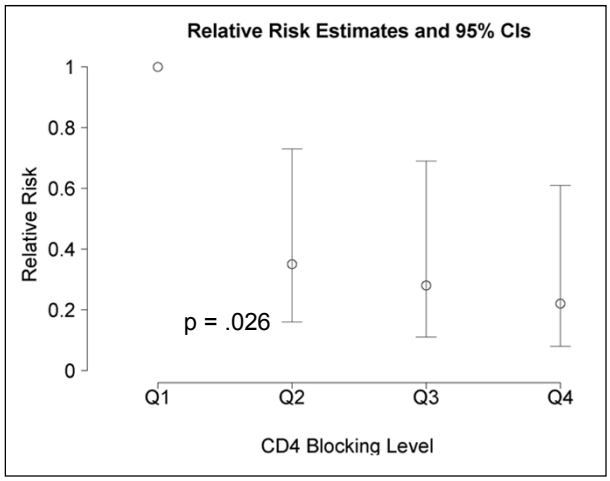
Alternative Approach to Evaluating a Specific SoP

- These limitations motivate research into an alternative approach to surrogate endpoint evaluation
  - **Principal surrogate framework** which leverages augmented data collection from vaccine efficacy trials

Outline Session 2

1. Introduction: Concepts and definitions of immune correlates/surrogate endpoints
   - Two paradigms: Predictive surrogates vs. mechanistic surrogates
2. Predictive surrogates Tier 1: Correlate of Risk (CoR)
3. Predictive surrogates Tier 2: Specific Surrogate of Protection (Specific SoP)
   - Statistical Surrogate (Prentice, 1989)
   - **Principal Surrogate (Frangakis and Rubin, 2002)**
4. Predictive surrogates Tier 3: General Surrogate of Protection (Bridging SoP)
5. Reconciling Immune Correlates Nomenclature
6. Conclusions and Discussion

Motivation for Principal SoP Definition: CD4 Blocking Level a CoR in the Vaccine Group [VaxGen 004 Trial]



Case-cohort design:
Antibody data measured on 239 infected/163 uninfected

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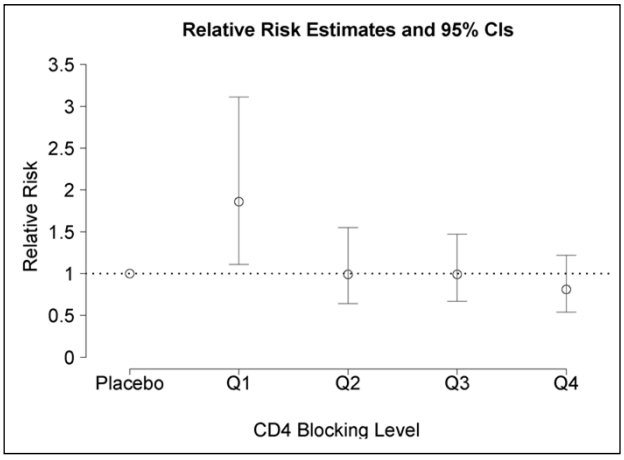
Motivation for Principal SoP Definition: Re-Analysis with Placebo Group as Reference



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How Assess Immune Response as a Principal SoP?

Infection Rate by Quartile of Immune Response to Vaccine

GROUP	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Placebo	?	?	?	?	.11
Vaccine	.18	.10	.10	.08	.11
VE	1 – .18/? 	1 – .10/? 	1 - .10/? 	1 - .08/? 	

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Hypothetical Example 1: The CoR is Not a Principal SoP (VE flat)

Infection Rate by Quartile of Immune Response to Vaccine

GROUP	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Placebo	.18	.10	.10	.08	.11
Vaccine	.18	.10	.10	.08	.11
VE	0.0	0.0	0.0	0.0	

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Hypothetical Example 2: The CoR is a Principal SoP (VE Increases with Ab Titer)

Infection Rate by Quartile of Immune Response to Vaccine

GROUP	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Placebo	.11	.11	.11	.11	.11
Vaccine	.18	.10	.10	.08	.11
VE	-.64	.09	.09	.27	

Definition of a Principal SoP (Heuristic- Precise Mathematics in Talk 2+)

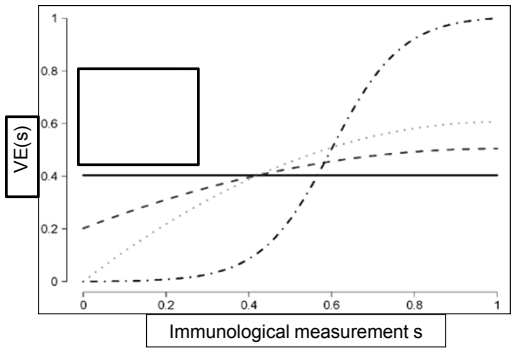
- Consider the case where all placebo recipients have S = 0
- Define

$$VE(s) = 1 - \frac{\text{Risk of infection for Vaccinees with Ab titer s to Vaccine}}{\text{Risk of infection for Placebos with Ab titer s to Vaccine}}$$

- Interpretation: Percent reduction in clinical risk for groups of vaccinees with Ab titer compared to if they had not been vaccinated
- Definition: A Principal SoP is an immunologic measurement satisfying

1. **VE**(negative response s = 0) = 0 [Average Causal Necessity]
2. Large variability of **VE**(s) in s

The Principal SoP Framework Provides a Way to Compare the Ability of Different Markers to Predict VE



- Black marker: Worthless as surrogate
- Green and blue markers satisfy average causal necessity
- Blue marker: Very good surrogate

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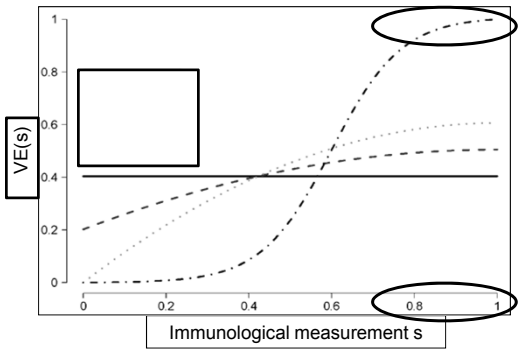
Excellent Surrogate: Sets the Target for Improving the Vaccine

Target: Improve the vaccine regimen by increasing the percentage of vaccinees with high immune responses



- Black marker: worthless as surrogate
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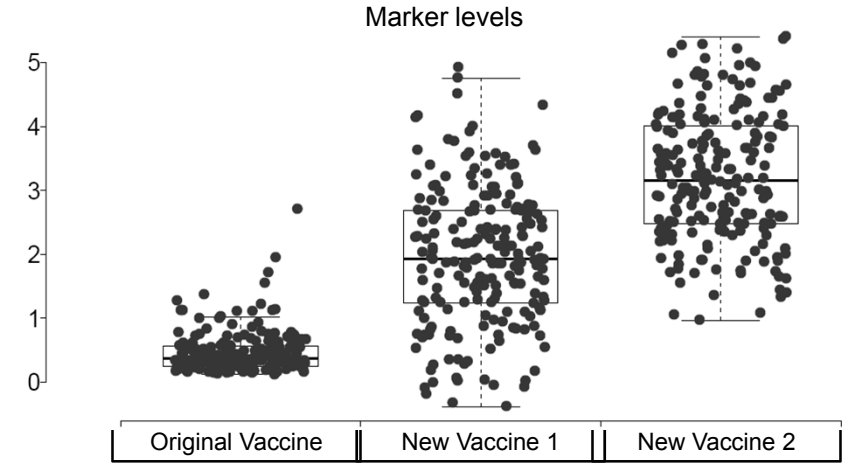
Simplest Way to Think About Principal Surrogacy

- Conceptually it's the same as evaluating vaccine efficacy in subgroups
  - Evaluate if and how VE varies with 'baseline' subgroups defined by S
  - Principal stratification makes S equivalent to a baseline covariate
  - A good surrogate will have strong effect modification / VE(s) varies greatly in s
  - It would be even more valuable to identify actual baseline covariates that well-predict VE(s), but it's often more likely that a response to vaccination well-predicts VE

Knowledge of the Potential Surrogate May Guide Future Research to Develop Improved Vaccines

- Identification of a good surrogate in an efficacy trial is the ideal primary endpoint in follow-up Phase I/II trials of refined vaccines
- It also generates a **bridging hypothesis:** If a future vaccine is identified that generates higher marker levels in more treated subjects, then it will have improved overall clinical efficacy

Using the Surrogate for Improving the Vaccine Regimen



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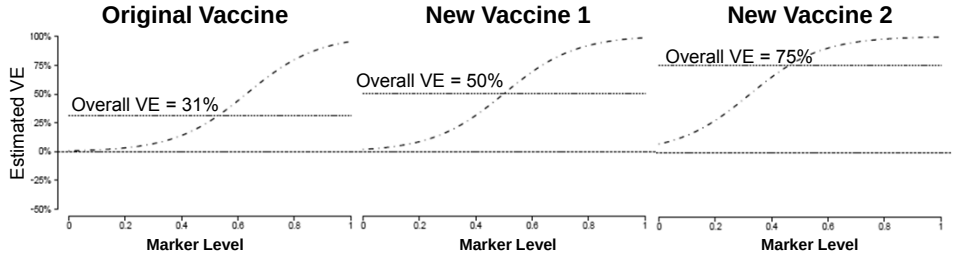
Using the Surrogate for Improving the Vaccine Regimen

- Suppose each new vaccine is tested in an efficacy trial
- Under the bridging hypothesis we expect the following efficacy results:



- This is the idealized model for using a surrogate to iteratively improve a vaccine regimen

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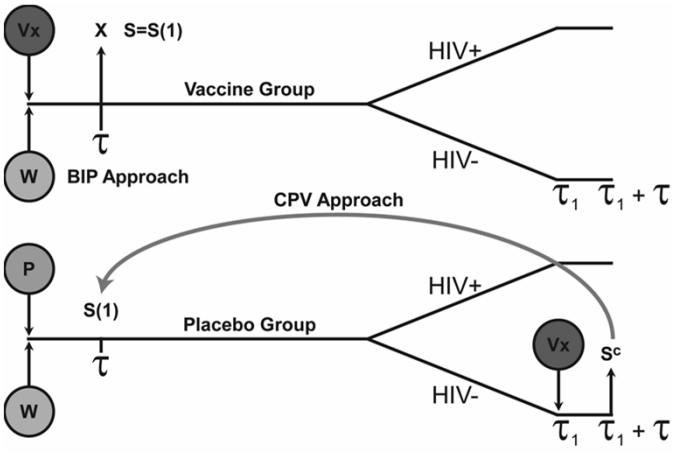
Challenge to Evaluating a Principal SoP: The Immune Responses to Vaccine are Missing for Placebos

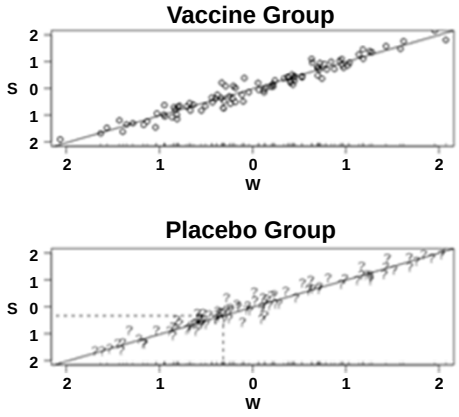
- Accurately filling in the unknown immune responses is needed to precisely evaluate a principal SoP
- Approaches to fill in the missing data:
  - At baseline, measure a predictor(s) of the immune response in both vaccinees and placebos (Follmann, 2006, Biometrics)
  - Close-out placebo vaccination (Follmann, 2006, Biometrics)
- Methods for evaluating a principal SoP
  - Gilbert and Hudgens (2008, Biometrics)
  - Gilbert, Qin, Self (2009a, 2009b, Statistics in Medicine)
  - Joffe and Greene (2009, Biometrics)
  - Gallop, Small, Lin, Elliott, Joffe, Ten Have (2009, Statistics in Medicine)
  - Wolfson and Gilbert (2010, Biometrics)
  - Huang and Gilbert (2011, Biometrics)
  - Zigler and Belin (2012, Biometrics)
  - Miao, Li, Gilbert, Chan (2013, In: Risk Assessment and Evaluation of Predictions)
  - Huang, Gilbert, and Wolfson (2013, Biometrics)

Schematic of Baseline Predictor and Closeout Placebo Vaccination Trial Designs*



*Proposed by Follmann (2006, Biometrics)

Baseline Predictor Trial Design



Evaluate correlation of W and S in vaccine group

Predict S from vaccine group model and W in placebos

Closeout Placebo Vaccination

- At the end of the trial, inoculate a random sample of uninfected placebo recipients with HIV vaccine
- Measure the immune response on the same schedule as it was measured for vaccinees
- Assume the measurement is what we would have seen, had we inoculated during the trial

Illustration with 1943 Influenza Trial

- S = log Ab titer to Weiss strain A if vaccinated
- Inverse ranking approach to filling in S for placebos
  - Assume any two placebos with log Ab titers $s1^{Plac} < s2^{Plac}$ have s1 > s2
  - This assumption allows construction of a complete dataset of **S'**s for all subjects for whom the Ab titer was measured

Assume Inverse Ranking*

Ab titer observed in placebos	Imputed S (Ab titer to vaccine)
16	8192
32	4096
64	2048
128	1024
256	512
512	256
1024	32 or 128 (coin flip)

*Supported by studies including Gorse et al. (2004, JID)

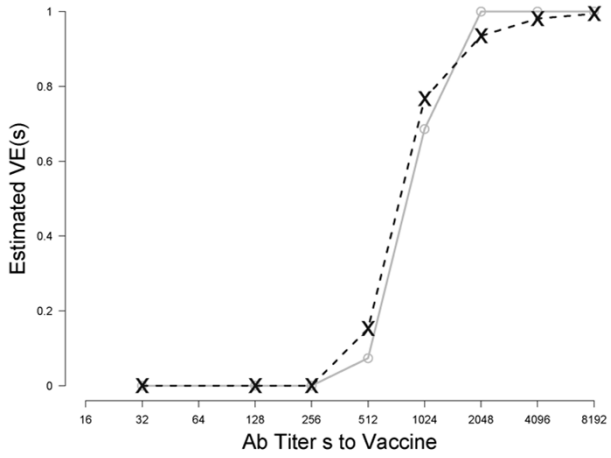
Estimate of VE(s)

- For each observed Ab level s = {32, 128, 256, 512, 1024, 2048, 4096, 8192} estimate VE(s) by

$$\text{Est. VE(s)} = 1 - \frac{\text{Case rate for Vaccinees with Ab titer s}}{\text{Case Rate for Placebos with Imputed Ab titer s}}$$

- Can also estimate the case rates by fitted values from regression models

Influenza Trial: Estimated VE(s) Under Inverse Rank-Preserving Assumption



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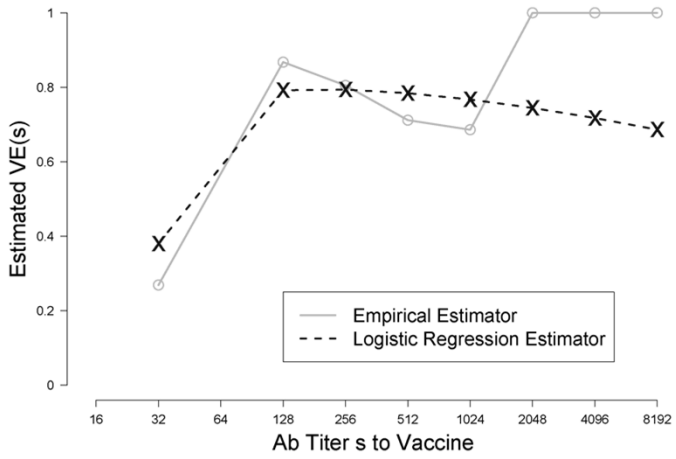
Sensitivity Analysis: Estimated VE(s) Under Rank-Preservation



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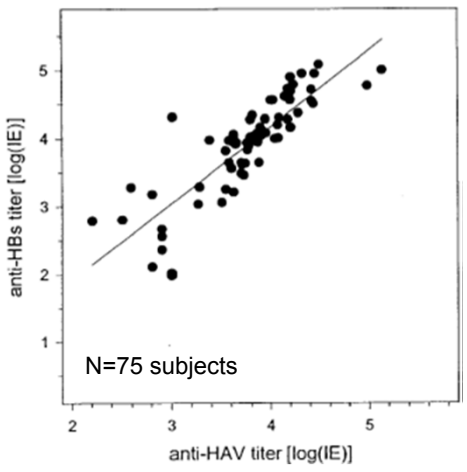
Vaccine Development May Be Improved by Prospective Research to Discover / Measure Baseline Predictors

- In efficacy trials where participants have prior exposure to the pathogen, measure the potential surrogate at baseline and use it as the baseline predictor
  - **Example:** influenza vaccine trials
- Investigate immune responses to licensed vaccines as baseline predictors
  - **Example:** In preparation for HIV vaccine efficacy trials in South Africa, the HIV Vaccine Trials Network is assessing hepatitis B vaccination and tetanus vaccination in a preparatory Phase I HIV vaccine trial in South Africa
  - An objective of the Phase I trial is assessment of Hepatitis B surface antigen antibody levels and tetanus toxoid antibody levels as predictors of a set of immune responses to the HIV vaccine

Precedent for Antibody Levels to a Vaccine Predicting Response to Another Vaccine: Hepatitis A and B Vaccines*



- r = .85
- No cross-reactivity

*Czeschinski et al. (2000, *Vaccine*) 18:1074-1080

Outline Session 2

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   - Statistical Surrogate (Prentice, 1989)
   - Principal Surrogate (Frangakis and Rubin, 2002)
4. **Predictive surrogates Tier 3: General Surrogate of Protection (Bridging SoP)**
5. Reconciling Immune Correlates Nomenclature
6. Conclusions and Discussion

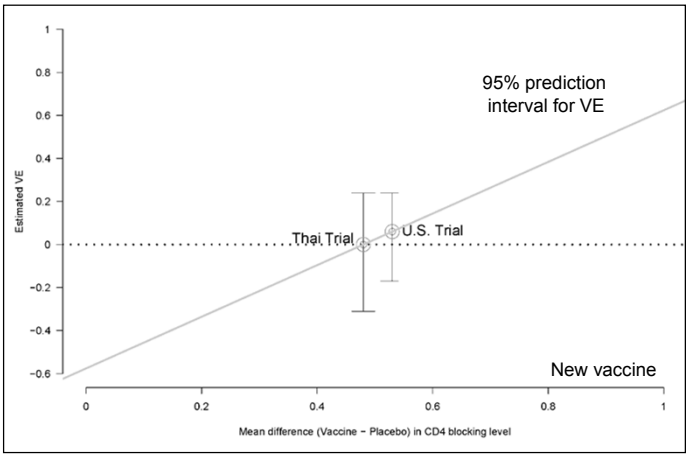
Challenge in Evaluating a Surrogate from a Single Trial

- There is less precision for validating a surrogate than there is for directly assessing the vaccine effect on the clinical endpoint!
- Suggests the necessity of meta-analysis of multiple studies

Tier 3: General SoP

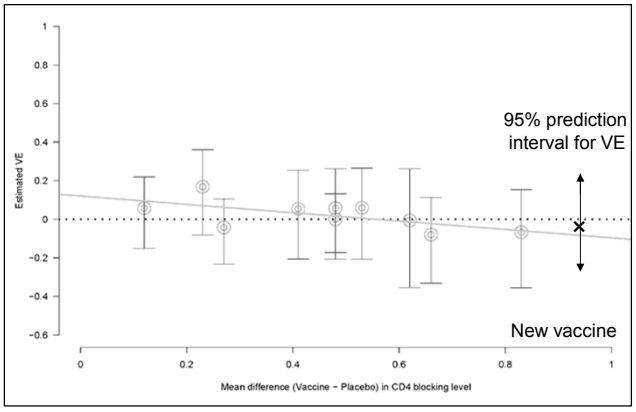
- Definition: An immunologic measurement that is a specific SoP in an efficacy trial(s) and is predictive of VE in different settings (e.g., across vaccine lots, vaccine formulations, human populations, viral populations)
- Approach to Evaluation: Meta-Analysis
  - N pairs of immunologic and clinical endpoint assessments among vaccinees and placebos
  - Pairs chosen to reflect specific target of prediction
    - Example: Predict efficacy of new vaccine formulation: N vaccine efficacy trials of comparable vaccines but with different formulations
  - ➡ **Evaluation:** Study the relationship between the estimated **VE** and the estimated vaccine effect on the immune response

Meta-Analysis Example: VaxGen Trials (003, 004) of rgp120 Immunogens with Different HIV Strains in the Vaccine and Different Study Populations



2 Real Trials:
- **U.S. trial** of MN/GNE8 gp120 in MSM
- **Thai trial** of MN/A244 gp120 in IDU

Meta-Analysis Hypothetical Example: 10 Efficacy Trials of rgp120 Immunogens with Different HIV Strains in the Vaccine and Different Study Populations



2 Real Trials + 8 new hypothetical trials

Demonstrates that CD4 blocking level is not useful as a SoP for HIV infection

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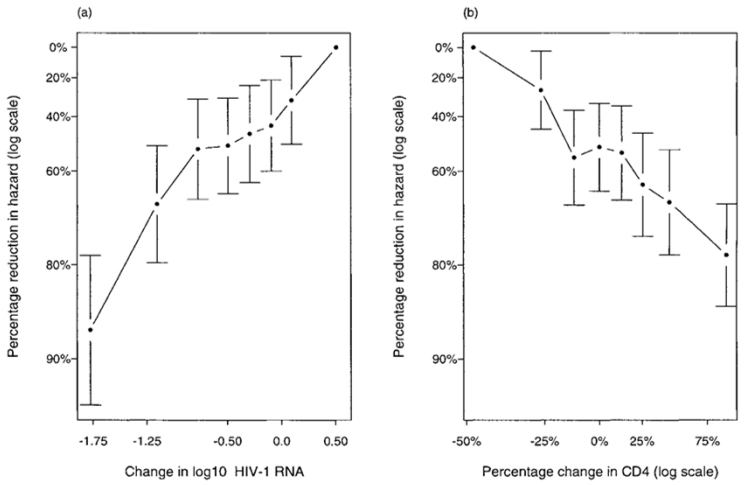
HIV-1 RNA and CD4 as CoRs for AIDS [HIV Surrogate Marker Collaboration Group, 2000, AIDS Res Hum Retroviruses]



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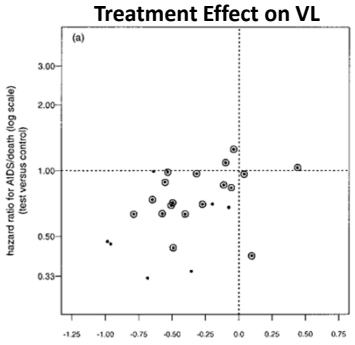
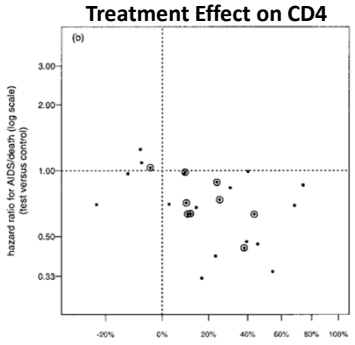
Surrogate Evaluation from Multiple Trials: Meta-Analysis (N = 25)*

Treatment Effect on AIDs vs Treatment Effect on VL



Treatment Effect on AIDs vs Treatment Effect on CD4

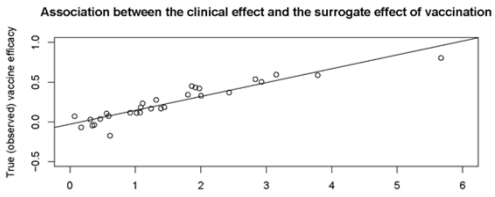


*HIV Surrogate Marker Collaborative Group, 2000, AIDS Res Hum Retroviruses

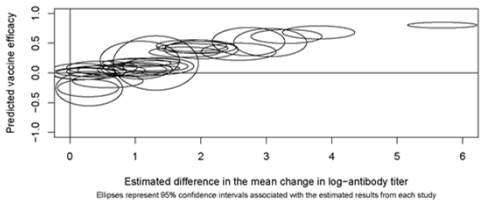
Simulated Meta-Analysis Based on 29 Influenza Vaccine Trials (Villari et al., 2004, Vaccine)

Estimated VE vs Average difference in log Ab titer (Vaccine - Placebo)

Est. VE in trial

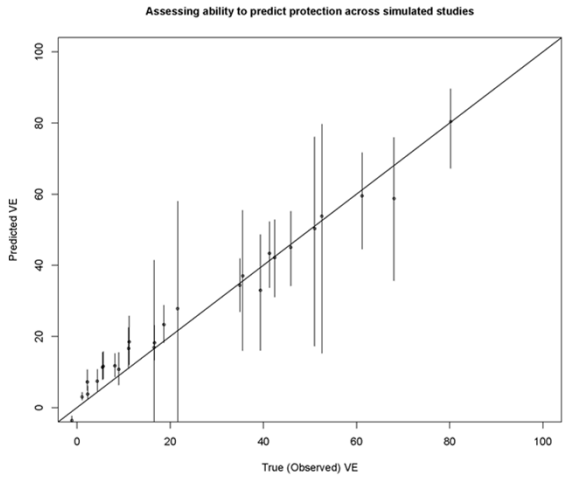


Est. VE



- Selected all placebo-controlled influenza vaccine trials of PIV vaccines with ≥ 5 placebo cases
- The N = 29 studies span different flu seasons over 30-40 years
- Objective: Predict VE for next year's flu season
- Clinical endpoint = clinically Confirmed influenza infection
- Marker endpoint = log Ab titer to the dominant strain circulating in the trial region

Simulated Meta-Analysis Based on 29 Influenza Vaccine Trials (Villari et al., 2004, Vaccine)



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Predicting VE in a New Trial

- **Building on Daniels and Hughes (1997, Stats Med), Gail et al. (2000, Biostatistics) developed methods for predicting VE with a bootstrap confidence interval in a new trial from**
  - A series of N trials with estimated vaccine effects on the biomarker and on the clinical endpoint
  - A new trial with data on the biomarker only
- **Summary of Gail et al. conclusions:**
  - The strength of correlation of vaccine effects has a large effect on the precision for predicting VE
  - Need at least N=10 studies that have reasonably precise estimates of VE
    - Even with this, prediction of VE is quite imprecise
  - **Fundamental Challenge:** Do the N studies constitute an appropriate basis for extrapolating results to the setting of the new trial?

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Example of Bridging Surrogate Failure: HSV-2 Vaccine (From Tom Fleming)

- 2 Trial Meta-Analysis of HSV-1 Negative Subjects
  - **VE vs. HSV-2 Infection:** Females: 52% (25, 69); Males: -14% (-85, 29)
  - **VE vs. Disease:** Females: 75% (51, 87); Males: 9% (-76, 53)
  - **Putative surrogates:** No difference by gender in:
    - Glycoprotein-D-Alum-MPL vaccine elicited binding and neutralizing antibodies vs. HSV-2
    - Glycoprotein-D-specific responses in the form of lymphoproliferation and interferon-γ secretion

Because the Bridging Hypothesis Cannot be Tested Directly Until the Future Efficacy Trial, Thought Exercises and Additional Analyses are Needed to Evaluate Bridging Credibility

- **Example:** The RV144 Thai trial generated the hypothesis that V1V2 antibody responses are a specific SoP for protection against HIV infection, and follow-up trials are planned of modified prime-boost vaccine regimens in South Africa
  - Differences of new setting compared to RV144:
    - Ethnic population/host genetics
    - Frequency and pattern of HIV exposure
    - Distribution of characteristics of HIV exposure (route, HIV genotype, HIV viral load)
    - Vaccine regimen (new vectors, new protein boosts)
    - New vaccination schedule (add an extra boost)

Summary on Tier 3 Evaluation

- Meta-analysis is part of the statistical validation of SoPs
  - Directly assesses how well vaccine effects on the surrogate predict vaccine effects on the clinical endpoint
  - The specific principal SoP framework is similar conceptually to meta-analysis (more in sequel talks)
- Of course, large resource challenges to conducting several diverse efficacy trials
- Recent work is of interest: Pearl and Bareinboim (2011, Technical Report) developed a Directed Acyclic Graph (DAG)-based approach to evaluating a general surrogate

Outline Session 2

1. Introduction: Concepts and definitions of immune correlates/surrogate endpoints
   - Two paradigms: Predictive surrogates vs. mechanistic surrogates
2. Predictive surrogates Tier 1: Correlate of Risk (CoR)
3. Predictive surrogates Tier 2: Specific Surrogate of Protection (Specific SoP)
   - Statistical Surrogate (Prentice, 1989)
   - Principal Surrogate (Frangakis and Rubin, 2002)
4. Predictive surrogates Tier 3: General Surrogate of Protection (Bridging SoP)
5. **Reconciling Immune Correlates Nomenclature**
6. Conclusions and Discussion

Nomenclature Re-Visited

Qin et al. (2007)

- **Correlate (of risk)** = measured immune response that predicts infection in the vaccine group
- **Surrogate** = measured immune response that can be used to reliably predict VE (may or may not be a mechanism of protection)

Plotkin (2008)

- **Correlate (of protection)** = measured immune response that actually causes protection (mechanism of protection)
- **Surrogate** = measured immune response that can be used to reliably predict VE (is definitely not a mechanism of protection)

Qin et al. correlate $\neq$ Plotkin correlate [very different]

Qin et al. surrogate $\cong$ Plotkin surrogate

Reconciliation: Plotkin and Gilbert (2012, *Clin Inf Dis*)

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
mCoP	Mechanistic Correlate of Protection	Causal Agent of Protection; Protective Immune Function	A CoP that is mechanistically causally responsible for protection
nCoP	Non-Mechanistic 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 CoP can be used to accurately predict the level of vaccine efficacy conferred to vaccine recipients (individuals or subgroups defined by the immune marker level). Assessment may be based on the Prentice or principal surrogate approaches.

Nested Nomenclature [Figure 1 from Plotkin and Gilbert (2008)]

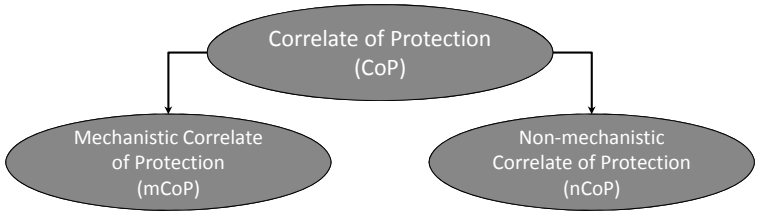

Figure 1. A correlate of protection (CoP) may either be a mechanism of protection, termed mCoP, or a non-mechanism of protection, termed nCoP, which predicts vaccine efficacy through its (partial) correlation with another immune response(s) that mechanistically protects

Mapping of New Nomenclature to Past Nomenclature

- CoP = SoP of Qin et al. (2007)
  - Thus 'correlate of protection' and 'surrogate of protection' mean the same thing, and are about statistical prediction of vaccine efficacy
  - Equalizing these terms may prevent confusion
- mCoP = CoP of Plotkin (2008)
  - Now the modifier 'mechanistic' is needed to denote that a predictive surrogate is also a mechanism of protection
- nCoP = surrogate of Plotkin (2008)
  - Now the modifier 'non-mechanistic' is needed to denote that a predictive surrogate is not a mechanism of protection
- mCoP and nCoP supplant Plotkin's (2008) CoP and surrogate

Remaining Nomenclature From Qin et al. (2007), Plotkin (2008), Plotkin and Gilbert (2012)

- Correlate of Risk (CoR)
  - Its assessment precedes assessment of a predictive surrogate
- Correlate of Protection (CoP) = Surrogate of Protection (SoP)
  - Specific CoP = Specific SoP
  - General CoP = General SoP
- Mechanistic Correlate of Protection (mCoP)
  - Specific mCoP
  - General mCoP
- Non-mechanistic Correlate of Protection (nCoP)
  - Specific nCoP
  - General nCoP

Examples of Mechanistic and Non-Mechanistic CoPs

- Meningococcal vaccine (Borrow et al., 2005, *Vaccine*)
  - mCoP = bactericidal antibodies
  - nCoP = binding antibodies (ELISA)
- Zoster vaccine (Weinberg et al., 2009, *J Infec Dis*)
  - mCoP = cellular response (IFN-γ ELISpot)
  - nCoP = binding antibodies to varicella-zoster virus (gpELISA)
- Rotavirus vaccines (Franco et al., 2006, *Vaccine*)
  - mCoP = none known
  - nCoP = total serum IgA antibody titers

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6. **Conclusions and Discussion**

Conclusions and Discussion (1)

- **What about 'modern data?'**
  1. Microarrays, proteomics, microbiomics, etc.
     - Many of the concepts and principles are the same
  2. Promise of modern data:
     - May yield more comprehensive understanding of vaccine effects and of the infection and disease process, yielding mechanistic surrogates that could not be uncovered with lower-dimensional techniques
     - May yield earlier predictive surrogates (closer to randomization), greatly aiding surrogate assessment methods and improving their practical utility
     - E.g., 2-4 subgroups may be defined based on high-dimensional expression array profiles, and the categorical subgroup variable may be assessed as a CoP

Conclusions and Discussion (2)

- **Some approaches to improving surrogate endpoint assessment**
  1. A basic issue is evaluation and optimization of biomarkers
     - Develop biomarkers that are biologically/functionally relevant and that have favorable variability characteristics, and consider pilot studies to down-select biomarkers to potentially assess as surrogates (e.g., RV144 HIV vaccine trial)
  2. Increase standardized and publicly available data-bases on efficacy trials and in some cases on post-licensure studies
     - Critical for meta-analysis
  3. Increase research into subject characteristics predictive of the potential surrogates
     - Critically important for principal surrogate assessment
     - If good baseline predictors available, important to store baseline samples from all subjects
  4. Vaccinating placebo recipients at the end of follow-up and measuring their immune responses aides the principal surrogate approach

Conclusions and Discussion (3)

- **Understanding surrogate validity is highly inter-disciplinary and requires synthesis of many experimental and data sources**
  - Basic science, pre-clinical research, clinical research work iteratively and in parallel to generate and test hypotheses
  - Knowledge of mechanism is particularly important for building credibility of surrogacy, especially for bridging efficacy to new settings

Conclusions and Discussion (4)

Predictive Surrogates Tier 1: Correlate of Risk (CoR)

1. Where immune correlates are of interest, efficacy trials should be powered to detect CoRs, taking into account factors such as error in the immunologic measurement that can attenuate power
2. A CoR may not be a SoP ["a correlate does not a surrogate make" (Tom Fleming)]
3. Identifying a CoR generates the hypothesis that it is also a specific SoP, and possibly also a general SoP for certain kinds of predictive bridges

Conclusions and Discussion (5)

Predictive Surrogates Tier 2: Specific Surrogate of Protection

1. **The statistical SoP approach has 2 challenges:**
   - Difficult to handle immunological measurements with no responses in placebos
   - For validity assumes no unmeasured common causes of the immune response and clinical risk, and no unmeasured common causes of early clinical risk and clinical risk
2. **The principal SoP approach may be more promising when can find a reasonable way to fill in placebos' immune responses to vaccine. Therefore evaluating a principal SoP presents an opportunity for innovative trial design and data collection.**
3. **A specific SoP can be used for predicting VE for the same or similar setting as the efficacy trial. It may mislead for predicting VE in a new setting.**

Conclusions and Discussion (6)

Predictive Surrogate Tier 3: General Surrogate of Protection

1. Predictions based on a general SoP apply to a particular type of predictive bridge
2. Meta-analysis can be used to empirically evaluate whether a specific SoP is a general SoP
3. Predicting VE for a new setting based on meta-analysis usually can only be done with low precision, and it may be difficult to know that the N selected trials form a reliable basis for prediction (Gail et al., 2000, Biostatistics)
4. Mechanistic/biological knowledge can form the basis for making the leap from a specific SoP to a general SoP

Conclusions and Discussion (7)

- **Important for the vaccine field to use a common nomenclature on immune correlates of protection**

Conclusions and Discussion (8)

- **Under all approaches surrogate endpoint assessment is hard***
  - Many ways for a promising correlate to turn out to mislead about predicting clinical vaccine efficacy
  - Surrogate assessment methods need assumptions whose validity may be difficult to verify
  - High data requirements for precise surrogate endpoint assessment

**"Surrogate endpoint assessment is one of the most important problems and one of the most difficult."*
− Tom Fleming

Descartes vs. Pascal: Complexity of the Surrogate Endpoint Problem

- Cartesian scientific method for discovering scientific truth:
  - Accepting as "truth" only clear, distinct ideas that could not be doubted
  - Breaking a problem down into parts
  - Deducing one conclusion from another
  - Conducting a systematic synthesis of all things
- Limited success, turned out to be overly-optimistic about what 'reductionist science' could deduce

- Pascal was skeptical about what Descartes' method could deliver:

  "But the parts of the world are all so related and linked together that I think it is impossible to know one without the other and without the whole"

  Blaise Pascal
  (1670, *The Pensees*, Lafuma Edition, No. 199)
- Correctly anticipated that complexity is too great to understand via reductionist methods