

Correlates of Protection – Advances and Challenges

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Correlates of Protection

- Immunological assays measure characteristics of the immune system, such as antibody concentrations, that are believed to be associated with protection from disease
- Statistical question of interest: How to model and validate the relationship between assay values and protection?

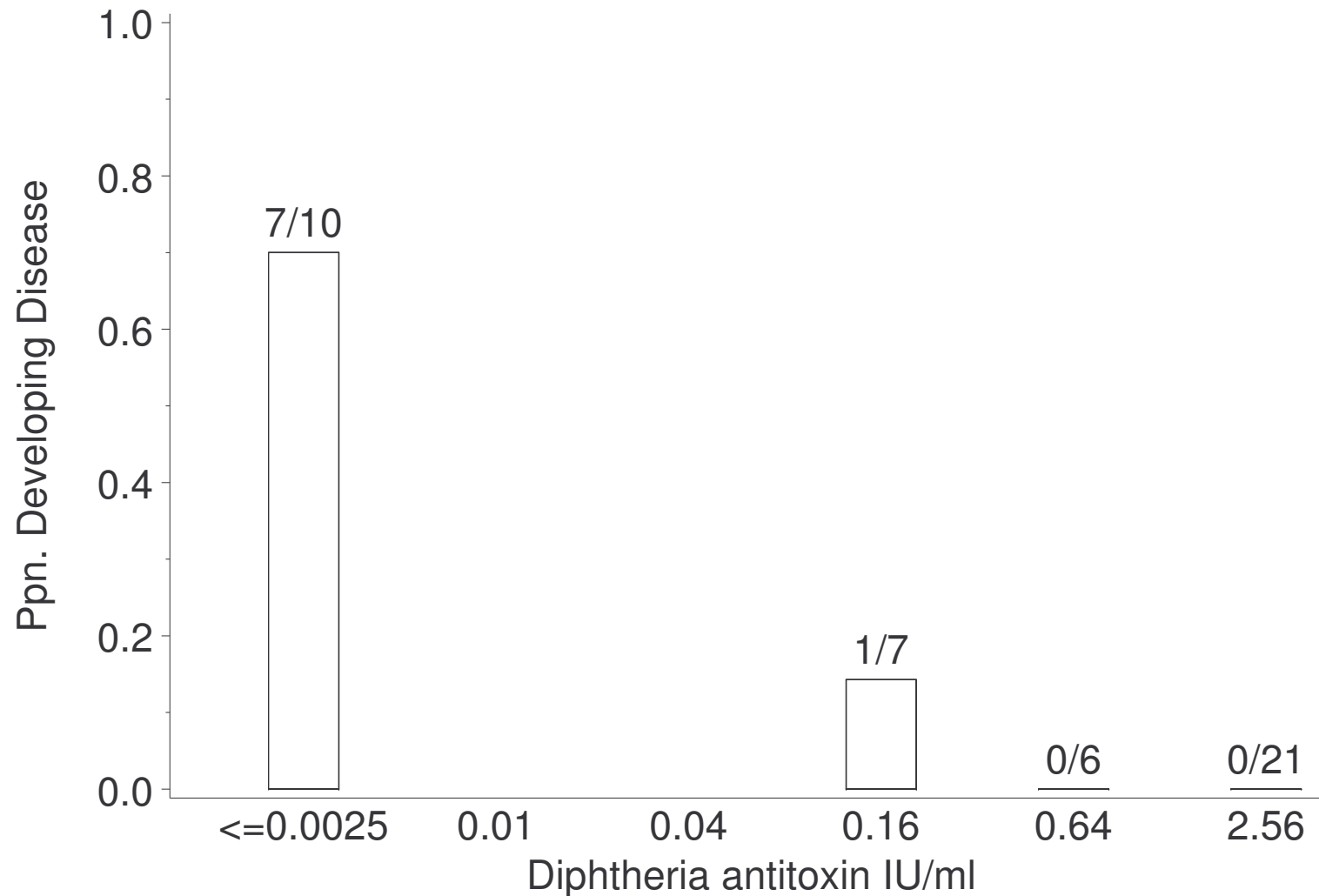
Early Methods: Titer-specific Protection

- Rates of disease at different levels of immunological titer calculated
- A level distinguishing those with disease from those without identified
- Protection inferred from absence of disease

Example: Björkholm/diphtheria

- Measured diphtheria antitoxin titers in 44 individuals admitted to hospital during a diphtheria epidemic among alcoholics in Sweden, 1984
 - 7/10 patients with antitoxin titers <0.01 IU/ml died or had neurological complications
 - 1/34 patients with antitoxin titers ≥ 0.16 IU/ml died or had neurological complications
- 0.01 IU/ml and 0.01 IU/ml accepted correlates of protection for diphtheria

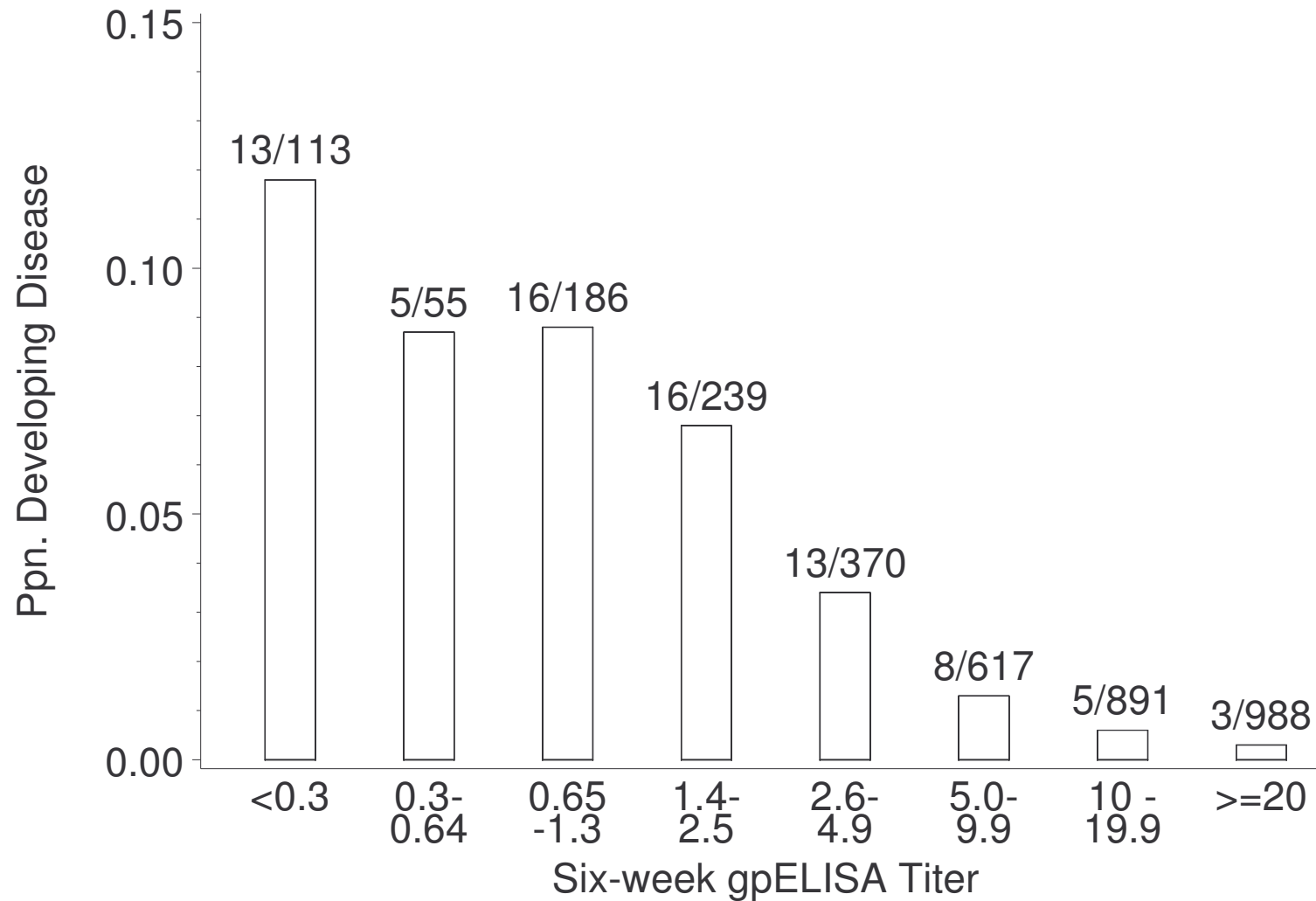
Titer-specific Protection – Björkholm/diphtheria data



Titer-specific Protection

- See also ...
 - Goulon/tetanus, Neumann/measles, Chen/measles, White varicella, others
 - discussion in Siber 1997

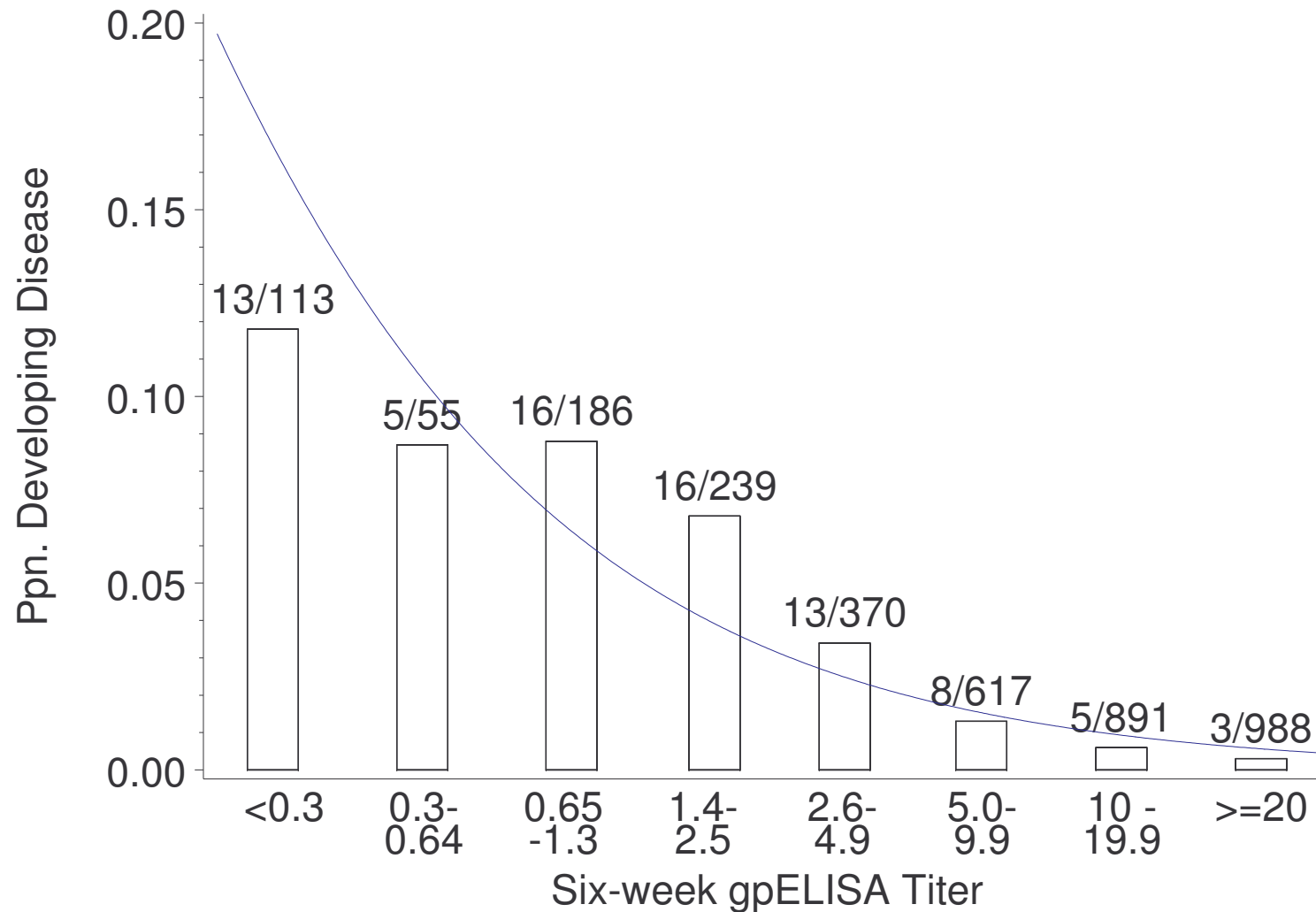
White/varicella data – Titer-specific Protection



White/varicella

- No clear threshold distinguishing those who develop disease from those who do not
- Rate of disease among those with low titers less than 100%
- \Rightarrow Protection cannot be inferred from absence of disease
- many similar examples

Logistic regression – White/varicella data



Logistic regression

- Modeling disease, not protection

$$P(\text{Disease}) = \frac{1}{1 + \exp(\alpha + \beta s)}$$

- c.f. Björkholm, Goulon, Chen

$$P(\text{Protection}) = 1(s \geq s_p)$$

- where s = assay value; s_p = protective level

- Interpretability of conclusion

- “for every 1 log₂ increase in titer of neutralizing antibody to RSV-A there was a significant increase in the likelihood of not having an RSV-associated hospitalization of 22.3%”

Logistic regression

- See also ...
 - Piedra/RSV, Cherry/pertussis, Storsaeter/pertussis, Dagan/pneumococcal (nasopharyngeal carriage), Rapola/pneumococcal (acute otitis media), others
- Other linear models
 - Proportional hazards (Rapola), applied Bayesian generalized linear models (Jokinen), Weibull, log-normal, log-logistic and piecewise exponential (Chan)
- Preference for single-valued threshold among vaccine research community, practitioners
 - see e.g. vaccine package inserts
 - c.f. cholesterol < 200 mg/dL, other reference levels

Disease & protection; exposure

- Possible solutions
 - Ensure 100% exposure
 - Challenge studies (e.g. Influenza/Belshe, malaria)
 - Household transmission studies (e.g. Storsaetter/pertussis)
 - Explicitly model protection

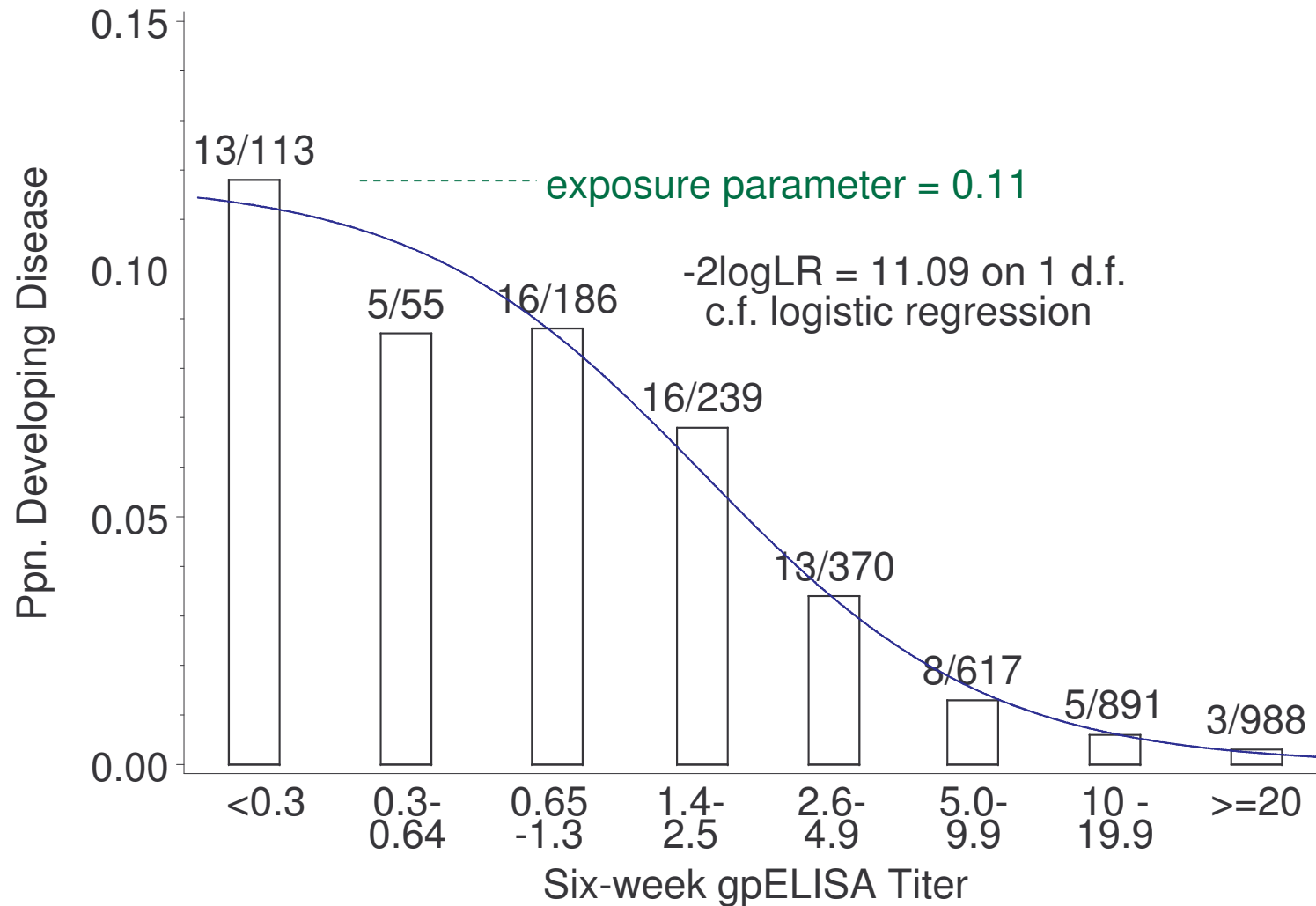
$$\begin{aligned}P(\text{Disease}) &= P(\text{Susceptible}) \times P(\text{Exposed}) \\ &= [1 - P(\text{Protected})] \times P(\text{Exposed})\end{aligned}$$

- e.g. scaled logit model

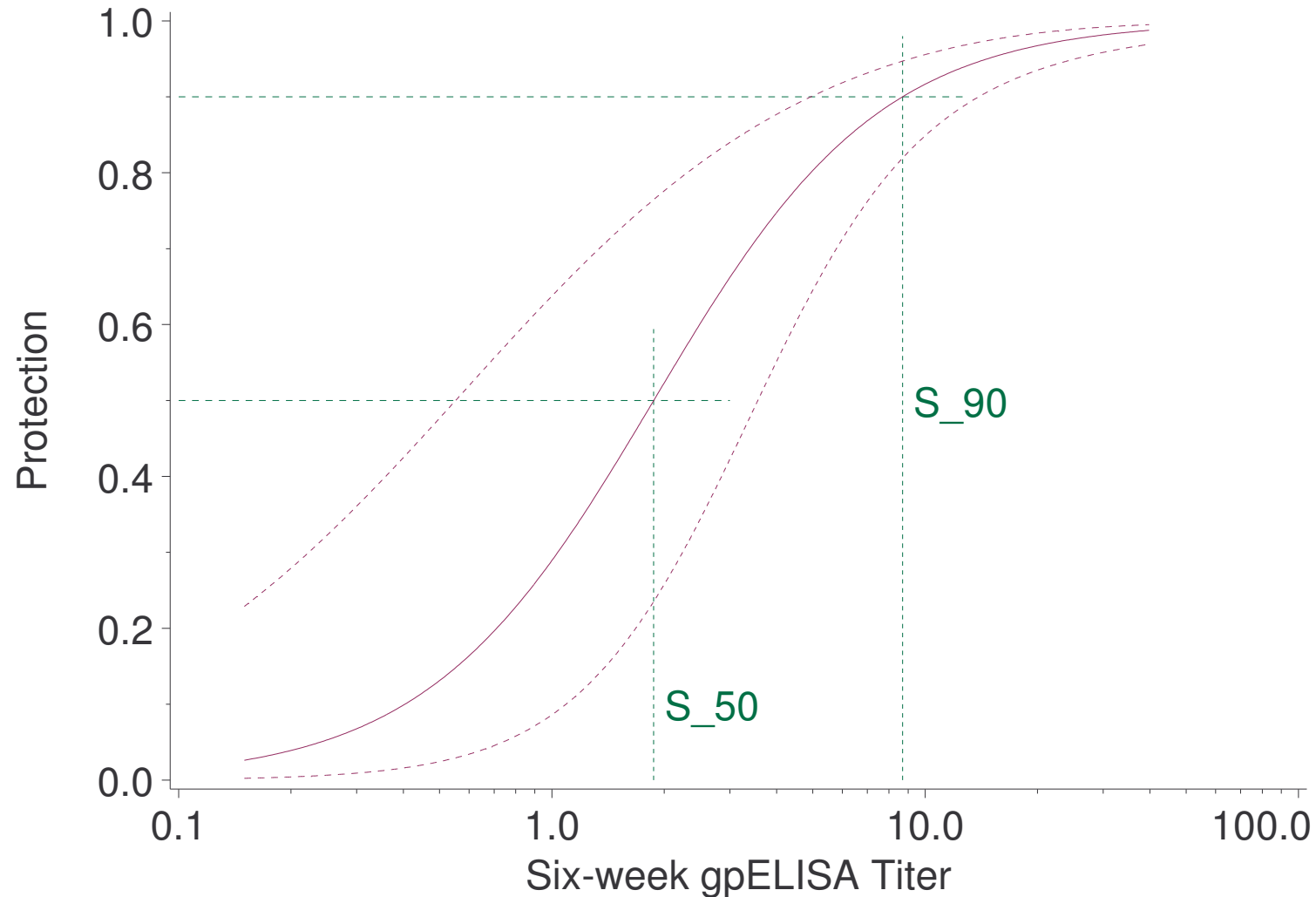
$$P(\text{Disease}) = \frac{1}{1 + \exp(\alpha + \beta s)} \times \lambda$$

where α , β = location, scale parameters of logit function; s = assay value or log(assay value); λ = exposure parameter;

Scaled logit – White/varicella data



Scaled logit protection curve with 95% C.I. – White/varicella data



Protection and Vaccine Efficacy

- Clearly vaccines with higher VE protect more people
 - How quantify the relationship between VE and protection?
- Note: different data structure
 - Now have $\{d, s, z\}$
 - Previously $\{d, s\}$
 - where d = disease outcome
 s = assay value
 z = vaccination status

Chang and Kohberger

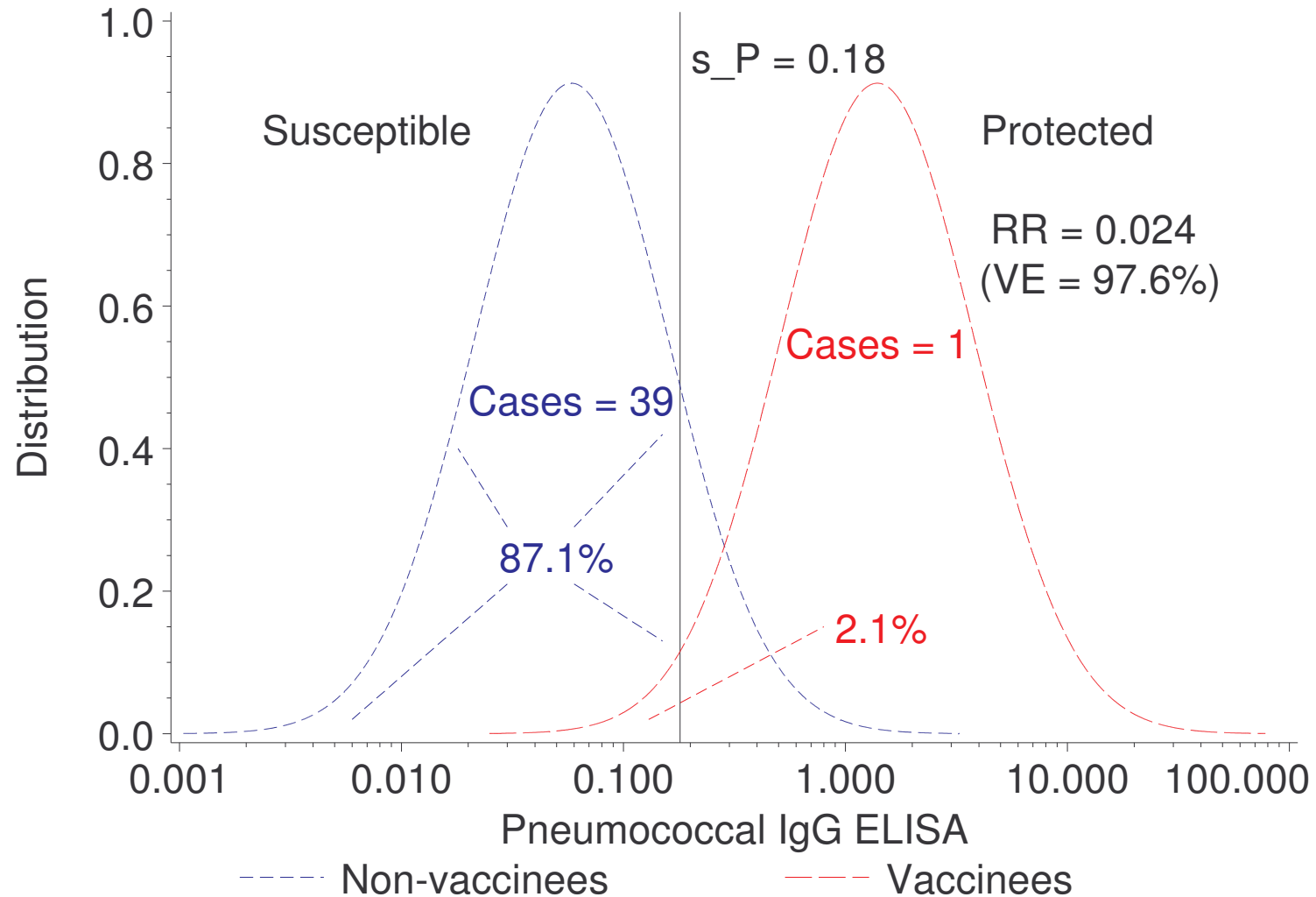
- Pneumococcal conjugate vaccine efficacy trial

$$s_p : \frac{P(s < s_p \mid \text{vaccinated})}{P(s < s_p \mid \text{not vaccinated})} = \frac{P(\text{Disease} \mid \text{vaccinated})}{P(\text{Disease} \mid \text{not vaccinated})}$$

where s_p = threshold level of assay value, i.e. correlate of protection

- see also Andrews/meningococcal C

Chang and Kohberger



Consistency of Relationship

- Chang & Kohberger assume same threshold s_p for vaccinees and non-vaccinees
- Efficacy prediction generally

$$VE_{\text{Predicted}} = 1 - \frac{\frac{1}{N_V} \sum_{i \in V} f_V(s_i)}{\frac{1}{N_P} \sum_{i \in P} f_P(s_i)}$$

- where $f(\cdot)$ is susceptibility function
- need $f_V(\cdot) = f_P(\cdot)$ (or estimate separately)

Consistency of Relationship

- $f_V(\cdot)$ may not equal $f_P(\cdot)$ because...
 - Assay values peak shortly after vaccination or infection, then decline; protection may last longer
 - Immune response to vaccination can be qualitatively different from response to natural infection
 - Mechanism whereby antibodies develop in individuals never diseased or vaccinated poorly understood

Testing Consistency

- a.k.a. testing ‘common threshold’ or ‘common curve’ assumption, or ‘validating’
- Does $P(\text{Susceptible}) = f(s)$ or $f_z(s)$?
- Examples of testing:
 - Gilbert/influenza & HIV: logistic regression – Prentice criteria, potential outcomes
 - Coudeville/influenza: scaled logit – bootstrap
 - Forrest/influenza: scaled logit – Wald-type F test
- Alternative: examine robustness to ‘common threshold/curve’ assumption

Surrogate endpoints

- Since Prentice, almost all statistical research on surrogate endpoints has been in context of effects of treatment vs. non-treatment
 - $P(\text{disease}) = f(s,z)$
 - not applicable to Björkholm/Goulon/Chen-type non-comparative data
- Specific to particular treatment
 - “ ... universal surrogate not practical”
- “...captures the full effect...”
 - proportion of treatment explained (Lin, Fleming et al)
 - recent publications moved away, towards consistency of relationship
- May be used in different senses in vaccines context

Causal inference

- Regression with assay value and vaccination status as predictors provides no information whether the characteristic measured by the assay is in the causal chain

- Causal estimands (Gilbert, Qin et al)

$$P(\text{disease} \mid s_{\text{vaccinated}}, s_{\text{not vaccinated}})$$

- or if no assay value if not vaccinated

$$P(\text{disease} \mid s_{\text{vaccinated}}, 0) \equiv P(\text{disease} \mid s_{\text{vaccinated}})$$

- Identifiability

- innovative designs (Follmann)

Difficulties with testing

- Absence of cases among vaccinees
 - cannot fit $P(\text{Disease}) = f(s \mid \text{vaccinee})$
- Lack of measurable immune response in non-vaccinees
 - cannot fit $P(\text{Disease}) = f(s \mid \text{non-vaccinee})$
- s measured post-vaccination
 - post-randomization selection bias?
- No generally accepted criteria for clinically significant difference
 - inconclusive inference if null not rejected

Non-statistical Validation

- Association between assay values and protection often inferred from
 - understanding of the immune system
 - between-group comparisons of assay values and disease rates (GMTs, ppns exceeding defined levels, VE)

‘Establishment’ vs. ‘validation’

- Correlates of protection become ‘established’, i.e. generally accepted, by occurrences such as
 - statements in FDA package inserts
 - acknowledgement by WHO
 - references in respected scientific literature, e.g. Plotkin/Vaccines

Established correlates of protection

- against diphtheria:
 - 0.01 IU/mL lowest serum antitoxin level giving some degree of protection
 - 0.1 IU/mL protective level
 - 1.0 IU/mL and above associated with long-term protection
- against invasive pneumococcal disease: 0.35 IU/mL of IgG antibody in serum ~30 days after completion of vaccination (infants vaccinated with polysaccharide conjugate CRM₁₉₇? vaccine)

Established correlates of protection

- Also for tetanus; measles; mumps; rubella; polio types 1, 2 & 3; meningococcal disease; influenza ; hepatitis A ; hepatitis B; and others
- Some of above are tentative or specific to particular populations, vaccines or disease definitions
- No correlates established for pertussis
 - see however Kohberger & Jemiolo

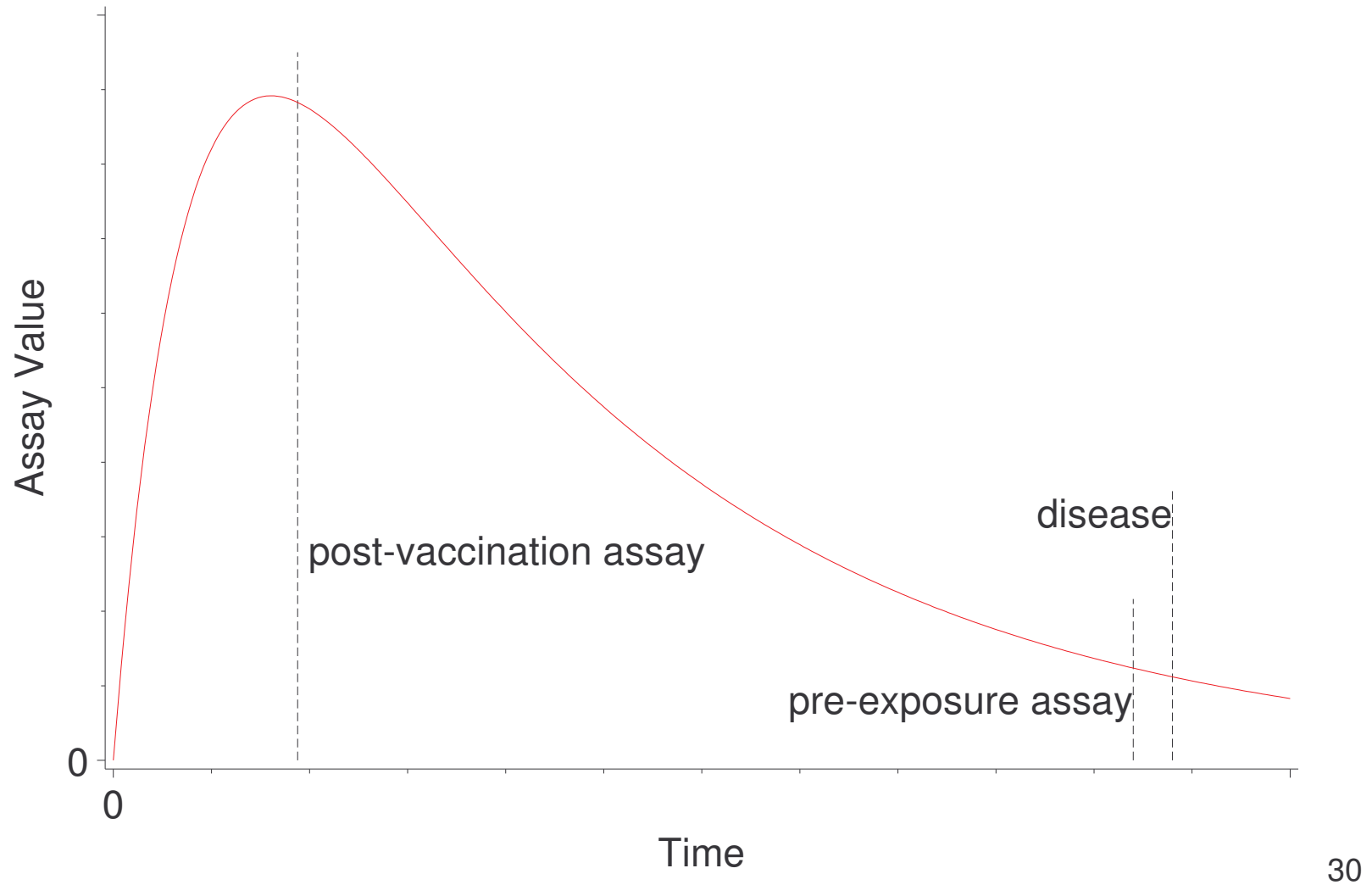
Diagnostic testing

- Application of diagnostic testing methods – sensitivity and specificity – to non-comparative data (Björkholm/Goulon/Chen) $\{d,s\}$
 - Exposure is nuisance parameter
 - Establish lower bound for exposure parameter
 - for given loss function, estimate of protective threshold robust to choice of exposure parameter within allowable range
 - Susan Chen, unpublished work

Timing of Assay

- Note Björkholm, Goulon, Chen, Piedra, Storsaeter assayed pre-exposure or at first symptoms
- White, Black, influenza examples assayed post-vaccination
 - correlate is specific to timing of assay
 - post-vaccination correlate is specific to surveillance period

Timing of assay



Numerous Mechanisms of Action

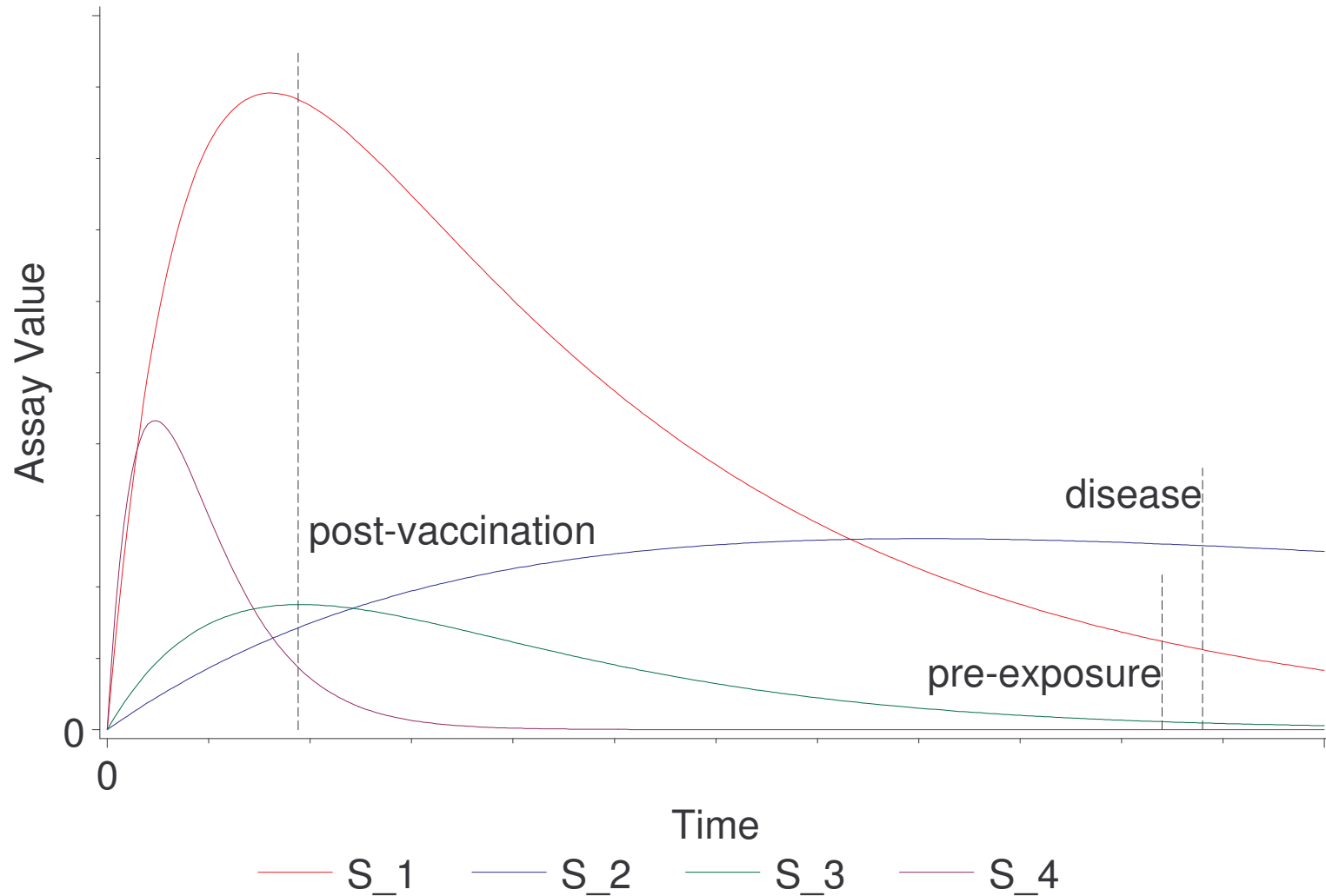
- The immune system operates through numerous mechanism of action, responding to multiple characteristics of the antigen
 - non-specific immune responses
 - specific immune responses
 - humoral immunity
 - plasma B-cells
 - memory B-cells
 - antibodies – IgG, IgA, IgM
 - cell-mediated immunity
 - CD4, CD8 T-cells
 - helper T-cells
 - cytotoxic T-cells
 - cytokines – interleukins, interferons, TNF

Numerous Mechanisms of Action

- A single assay can only capture one aspect of the immune response
- To capture the full protective effect of the immune system, a number of assays would be needed

$$P(\text{Protection}) = f(s_1, s_2, s_3, s_4, \dots)$$

Mechanisms of Action



Immune response specific to stimulus

- The immune response (the aggregate of the mechanism of action) is specific to the stimulus
 - natural infection
 - vaccination
 - type of vaccine
 - e.g. influenza
 - » intra-muscular inactivated influenza vaccine
 - » intra-dermal inactivated influenza vaccine
 - » live attenuated influenza vaccine
 - » cold adapted live attenuated influenza vaccine
 - killed vaccine
 - component vaccine (e.g. pertussis)
 - asymptomatic carriage

Response Specific to Population

- Defined by immunological history
 - immunologically naïve
 - previous vaccination
 - previous natural infection/asymptomatic carriage
 - immunologically competent/compromised
- Defined by Age
 - Infants
 - Children
 - Adults
 - Elderly
 - immunosenescence
- possibly $P(\text{Protection}) = f_{\text{population}}(s_1, s_2, s_3, s_4, \dots)$

Specificity of Correlates

- Unless all 'sufficient' immune characteristics are measured, correlate must be specific to
 - assay timing
 - stimulus
 - population
- and
 - case definition
 - surveillance period (for post-vaccination assays)
- as well as the assay itself

Ethics and Data Availability

- Both disease and immunogenicity data necessary to estimate correlate
- Both not typically available until pivotal efficacy trial
- If no efficacy, correlate cannot be estimated
- If efficacious, may be unethical to use placebo in future
 - also insufficient cases to estimate correlate
- ⇒ Limited (one?) opportunities to generate correlate data
 - Sample size limited to sample size for efficacy estimation

Assay consistency

- Assay measurement error
- Inter-laboratory assay consistency
 - assays standardized; however
 - recent influenza example: pre-vaccination HAI – GMT=75; 65% HAI>40
 - pneumococcal 6B IgG post-infant series vaccination in ten studies, GMT in IU/mL: 0.30, 0.61, 0.72, 0.91, 1.22, 1.82, 2.18, 2.50, 2.97, 4.70.
- Avidity maturation
 - antibodies created by B-cells become more specific to the antigen over time

Uses of Correlates

- Non-inferiority studies
 - comparison of two vaccines
- Non-interference studies
 - non-interference with response to other vaccine
- To predict efficacy
 - (in theory)
- To indicate individual protection
 - occasionally

Possible opportunities

- Direct methods for thresholds from non-comparative data (e.g. Björkholm)
 - a:b model (Siber, Chang et al)
 - derive from exposure-susceptibility
 - ‘steepest point of curve’
- Local estimation
 - direct estimation of C_{50} and C_{90}
 - little interest in C_{20} or C_{99}
 - polynomial regression? polynomial scaled logit?
- Case-control design

Greater challenges

- General, non-specific, correlates
 - across populations
 - across stimuli
- Meta-analysis
- Combinations of two or more assays
- Duration of immunity
 - Kinetic curves

Questions?

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References & further reading

- General reading
 - Gerard J. Tortora GJ, Funke BR, Case CL. Microbiology: An Introduction (9th Edition)
 - Plotkin SA, Orenstein WA, Offit PA. Vaccines (5th edition)
 - Package inserts for vaccines (available online)
 - WHO. Immunological Basis for Immunization Series
- Methods
 - Jódar L, Butler J, Carlone G, Dagan R, Goldblatt D, Käyhty H, Klugman K, Plikaytis B, Siber G, Kohberger R, Chang I, Cherian T. Serological criteria for evaluation and licensure of new pneumococcal conjugate vaccine formulations for use in infants. *Vaccine* 2003; 21(23):3265-72.

References & further reading

- Methods, contd.
 - Andrews N, Borrow R, Miller E. Validation of serological correlate of protection for meningococcal C conjugate vaccine by using efficacy estimates from postlicensure surveillance in England. *Clinical & Diagnostic Laboratory Immunology* 2003; 10(5):780-6.
 - Hudgens MG, Hoering A, Self SG. On the analysis of viral load endpoints in HIV vaccine trials. *Statistics in Medicine* 2003; **22**(14):2281-2298.
 - Dunning AJ. A model for immunological correlates of protection. *Statistics in Medicine* 2006; 25:1485-97.
 - Chan IS, Li S, Matthews H, Chan C, Vessey R, Sadoff J, Heyse J. Use of statistical models for evaluating antibody response as a correlate of protection against varicella. *Statistics in Medicine* 2002; **21**(22):3411-30.

References & further reading

- Methods, contd.
 - Dagan R, Givon-Lavi N, Fraser D, Lipsitch M, Siber GR, Kohberger R. Serum serotype-specific pneumococcal anticapsular immunoglobulin g concentrations after immunization with a 9-valent conjugate pneumococcal vaccine correlate with nasopharyngeal acquisition of pneumococcus. *Journal of Infectious Diseases* 2005; 192(3):367-76.
 - Rapola S, Jääntti V, Eerola M, Mäkelä PH, Käyhty H, Kilpi T. Anti-PsaA and the risk of pneumococcal AOM and carriage. *Vaccine* 2003; 21:3608-3613.
 - Jokinen JT, Ähman H, Kilpi TM, Mäkelä PH, Käyhty H. Concentration of antipneumococcal antibodies as a serological correlate of protection: An application to acute otitis media. *Journal of Infectious Diseases* 2004; 190:545-550.

References & further reading

- Methods, contd.
 - Forrest BD, Pride MW, Dunning AJ, Capeding MRZ, Chotpitayasunondh T, Tam JS, Rappaport R, Eldridge J, and Gruber WC. Correlation of Cellular Immune Responses with Protection Against Culture-Confirmed Influenza in Young Children. *Clinical and Vaccine Immunology*, published online ahead of print 30 April 2008.
 - Siber GR. Methods for estimating serological correlates of protection. *Developments in Biological Standardization* 1997; **89**:283-296.
 - Siber GR, Chang I, Baker S, Fernsten P, O'Brien KL, Santosham M, Klugman KP, Madhi SA, Paradiso P, Kohberger R. Estimating the protective concentration of anti-pneumococcal capsular polysaccharide antibodies. *Vaccine* 2007; 25:3816-3826.

References & further reading

- Methods, contd.
 - Gilbert PB, Qin L, Self SG. Evaluating a surrogate endpoint at three levels, with application to vaccine development. *Statistics in Medicine*, published online ahead of print September 2007.
 - Qin L, et. al. A framework for assessing immunological correlates of protection in vaccine trials, *JID* 196, p1304-1312 (2007)
 - Follmann D. Augmented designs to assess immune response in vaccine trials. *Biometrics* 62, p1161-1169 (2006)
 - Kohberger RC, Jemiolo D, Noriega F. Prediction of pertussis vaccine efficacy using a correlates of protection model. *Vaccine* 2008; 26(27-28):3516-21

References & further reading

- Studies (datasets)
 - Björkholm B, Böttiger M, Christenson B, Hagberg L. Antitoxin antibody levels and the outcome of illness during an outbreak of diphtheria among alcoholics. *Scandinavian Journal of Infectious Diseases* 1986; **18**(3):235-9.
 - Chen RT, Markowitz LE, Albrecht P, Stewart JA, Mofenson LM, Preblud SR, Orenstein WA. Measles antibody: reevaluation of protective titers. *Journal of Infectious Diseases* 1990; **162**(5):1036-42.
 - Goulon M, Girard O, Grosbuis S, Desormeau JP, Capponi MF. Antitetanus antibodies: Assay before anatoxinotherapy in 64 tetanus patients. *Nouveau Presse Medicin* 1972; **1**(45):3049-50.

References & further reading

- Studies (datasets)
 - Neumann PW, Weber JM, Jessamine AG, O'Shaughnessy MV. Comparison of measles antihemolysin test, enzyme-linked immunosorbent assay, and hemagglutination inhibition test with neutralization test for determination of immune status. *Journal of Clinical Microbiology* 1985; 22(2):296-8
 - Piedra PA, Jewell AM, Cron SG, Atmar RL, Glezen WP. Correlates of immunity to respiratory syncytial virus (RSV) associated-hospitalization: establishment of minimum protective threshold levels of serum neutralizing antibodies. *Vaccine* 2003; **21**(24):3479–3482.
 - White CJ, Kuter BJ, Ngai A, Hildebrand CS, Isganitis KL, Patterson CM, Capra A, Miller WJ, Krah DL, Provost PJ, Ellis RW, Calandra GB. Modified cases of chickenpox after varicella vaccination: correlation of protection with antibody response. *Pediatric Infectious Disease Journal* 1992; **11**:19-23.

References & further reading

- Studies (datasets)
 - Storsaeter J, Hallander HO, Gustafsson L, Olin P. Levels of anti-pertussis antibodies related to protection after household exposure to *Bordetella pertussis*. *Vaccine* 1998; 16:1907–1916.
 - Stehr K, Cherry JD, Heininger U, Schmitt-Grohe S, Uberall M, Laussucq S, Eckhardt T, Meyer M, Engelhardt R, Christenson P, the Pertussis Vaccine Study Group. A comparative efficacy trial in Germany in infants who received either the Lederle/Takeda acellular pertussis component DTP (DTaP) vaccine, the Lederle whole-cell component DTP vaccine, or DT vaccine. *Pediatrics* 1998; **101**(1):1–11.

Fragments

Exposure

- For infectious diseases, both susceptibility and exposure are necessary for the development of disease

	Protected	Susceptible
Exposed	No	Disease
Not exposed	No	No

Goodness of fit – logistic vs. scaled logit models

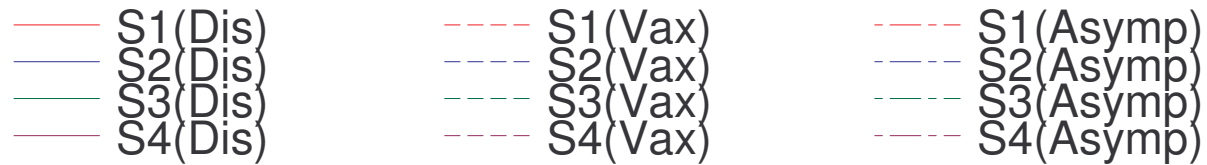
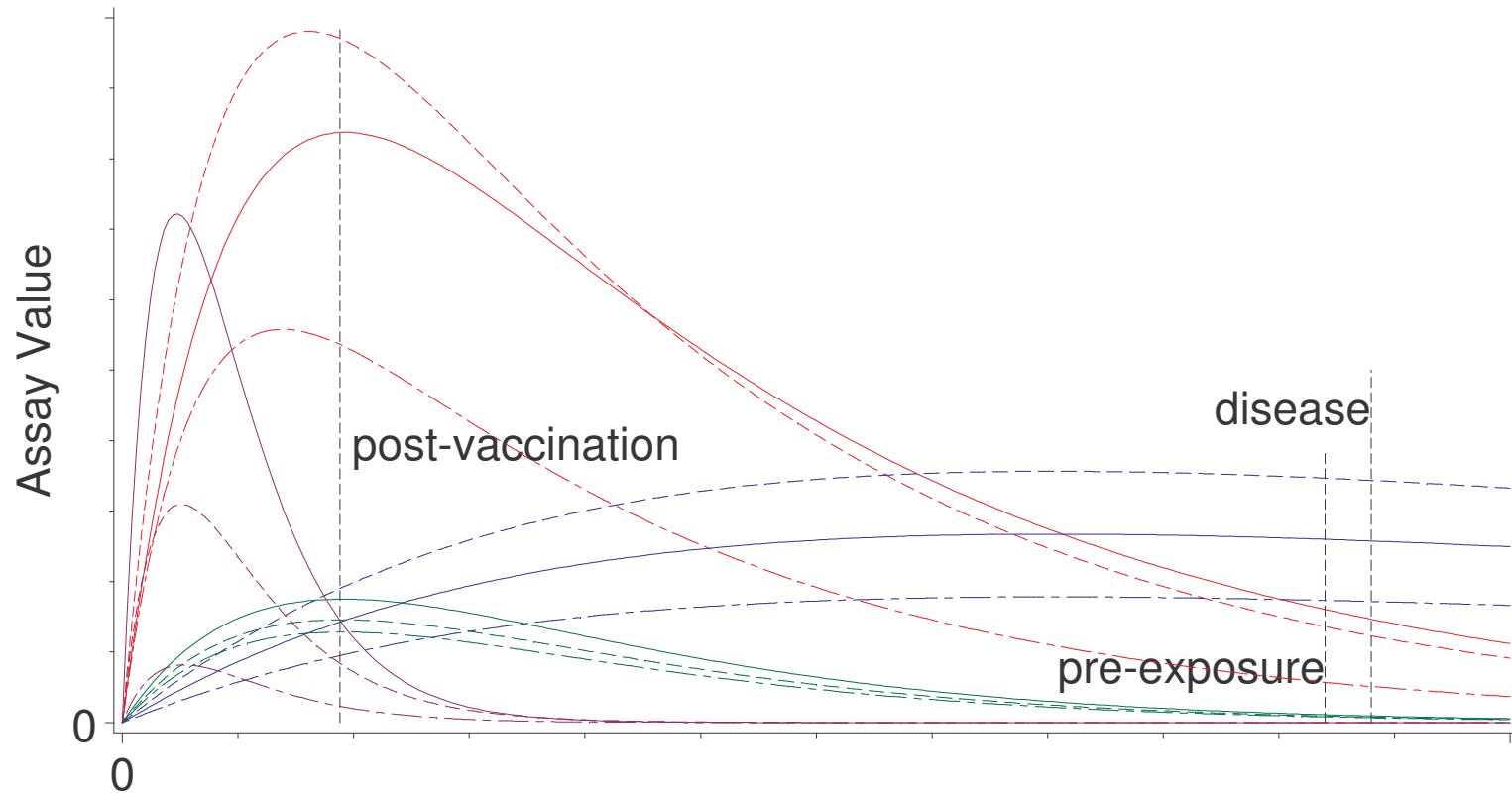
	-2 Log Likelihood		-2 Log LR	df	χ^2 p-value
	Logistic Regression	Scaled logit model			
Storsaeter/Gustafsson household pertussis study					
Anti-PT IgG	271.676	270.205	1.472	1	0.225
Anti-PRN IgG	259.417	247.621	11.796	1	0.001
Anti-FIM IgG	251.346	250.822	0.524	1	0.469
Piedra/RSV					
RSV/A	159.798	159.270	0.528	1	0.468
RSV/B	154.923	154.449	0.474	1	0.491
White/varicella					
Disease in first year	655.647	641.765	13.882	1	0.000
Disease in second year	834.685	817.678	17.006	1	0.000
Disease in either year	1244.694	1219.101	25.593	1	0.000
Random kinetics subset of German acellular pertussis study					
Anti-FHA IgG	378.556	375.247	3.309	1	0.069
Anti-PT IgG	380.081	378.741	1.340	1	0.247
Anti-PRN IgG	383.406	381.081	2.325	1	0.127
Anti-FIM IgG	379.429	376.683	2.746	1	0.098

Scaled logit: Testing “common curve” assumption, contd.

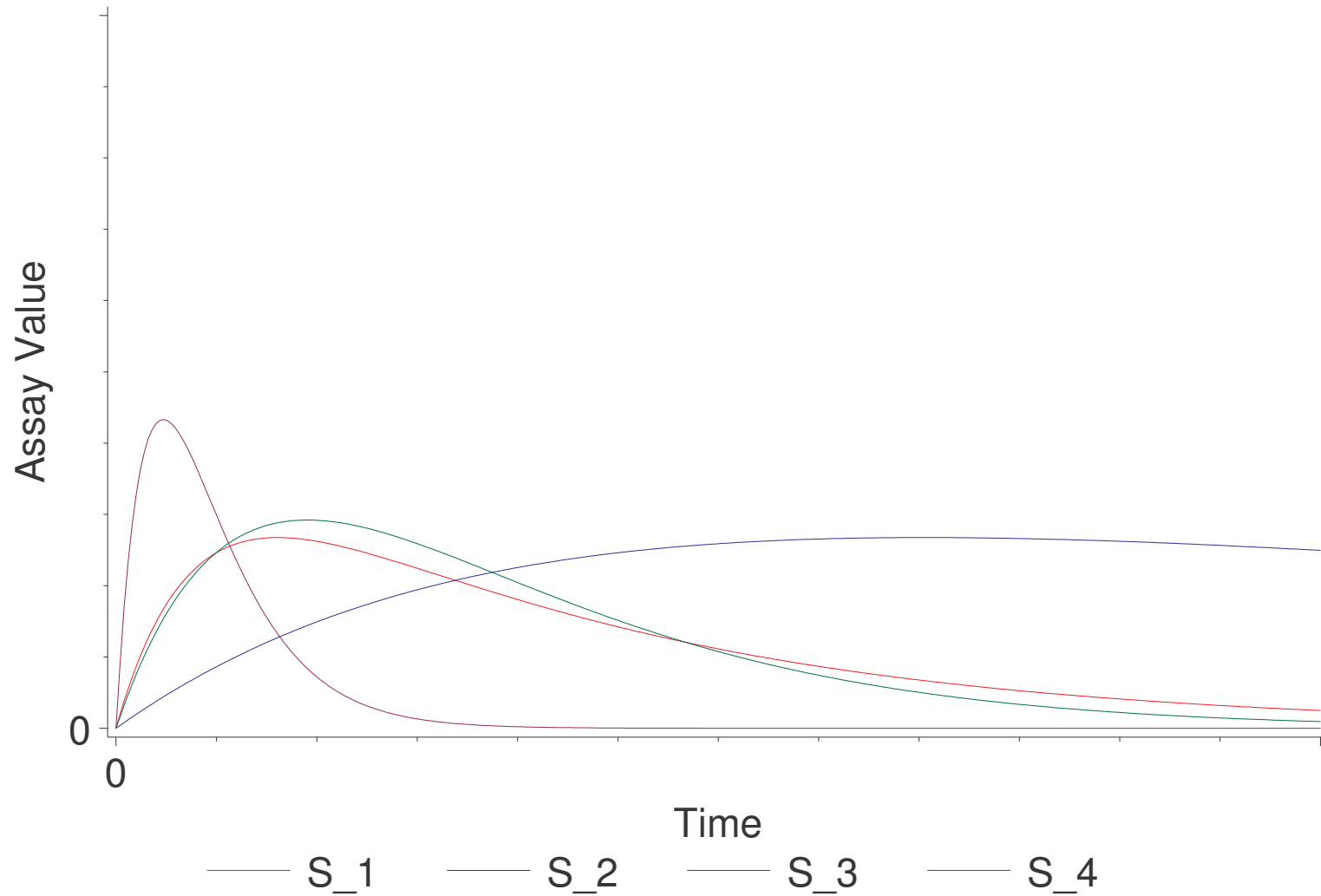
Scaled logit: Test of common curve assumption

	Estimate of exposure parameter		p-value
	Vaccinees	Non-vaccinees	
Storsaeter/Gustafsson household pertussis study			
Anti-PT IgG	43.0%	69.1%	0.002
Anti-PRN IgG	48.5%	67.1%	0.024
Anti-FIM IgG	58.1%	78.2%	0.051
Random kinetics subset of German acellular pertussis study			
Anti-FHA IgG	0.2%	7.2%	<0.001
Anti-PT IgG	0.2%	6.8%	<0.001
Anti-PRN IgG	0.2%	6.9%	<0.001
Anti-FIM IgG	0.3%	6.9%	<0.001

Different stimuli



e.g. Elderly response is diminished



Specificity – e.g. Pneumococcal

- Polysaccharide vaccine
 - significant increase in IgG antibody to capsular polysaccharide in adults
 - poorly immunogenic in children
- Conjugate vaccine
 - immunogenic in children (anti-capsular polysaccharide IgG; also immunologic memory)
 - also quantifiable opsonophagocytic response
- Protein vaccine
 - ??? (antibody to cell surface proteins)
- Nasopharyngeal carriage
 - may induce broad-based immunity in mid-childhood via IgA/cell-mediated immunity

Specificity – e.g. Influenza

- Inactivated vaccine (intramuscular)
 - HAI (principally IgG antibodies in serum) response in children and adults, little secretory IgA or T-cell stimulation
- Live attenuated vaccine
 - stronger HAI response and more efficacious in children,
 - lower HAI response but still highly protective in adults, nasal IgA may be more indicative of protection
- Natural infection
 - induces serum antibodies, antibodies at mucosal surface of respiratory tract, influenza-specific T-cells