Module 8
Evaluating Immunological
Correlates of Protection

# Session 5
# Use of Statistical Models in Assessing Correlates of Protection

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## Modeling the Correlation

- Link the whole antibody titer distribution to disease protection using statistical models
  - Extends the titer-specific method beyond the step-function model
  - Measures the strength of correlation
  - Allows adjustment for important covariates, such as age
  - Models can be used for prediction of efficacy

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## Some Statistical Models Considered

- Logistic regression
- Accelerated failure time (AFT) models
- Piecewise exponential model
- Scaled logit model (Dunning, SIM 2006)

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"All models are wrong, some are useful."

George Box

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## Specificity of Correlate Models

- Correlates of protection model are developed specific to
  - Population (children or adults)
  - Assay type and timing
  - Follow-up (long-term or short-term exposure)
- Important to check consistency (or predictive value) of model across different situations

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## Varicella Vaccine Example

VARIVAX®

Chan et al, SIM 2002

Li, Parnes, Chan JBS 2013

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## Varicella (Chickenpox) Vaccine

- A live attenuated Oka/Merck varicella vaccine (VARIVAX®) was shown to be highly (95-100%) efficacious in a placebo-controlled trial during 1982-3
- Long-term efficacy is evaluated by
  - Following vaccinees for varicella breakthroughs
  - Comparison to varicella rate in unvaccinated subjects (historical controls)
- Antibody responses measured by glycoprotein enzyme-linked immunosorbent assay (gpELISA)

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## Is Antibody Titer (by gpELISA) a Correlate of Protection for Varicella?

- Glycoprotein enzyme-linked immunosorbent assay (gpELISA) was developed in the 1980s
  - More sensitive than commercial antibody assays
- VZV antibody responses by gpELISA have been shown to correlate with
  - neutralizing antibody: 96-97% concordance
  - cell mediated immunity: 95% concordance

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## Comparison of gpELISA and Neutralization Titers of 6-Week Postvaccination Sera



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## Objectives of Investigation

- Evaluate VZV antibody response as a correlate of protection against varicella
  - Show that levels of antibody response correlate with long-term protection
- Model the correlation between gpELISA titers and long-term protection
  - Allows adjustment for covariates, such as age
  - Can be used for prediction of efficacy
  - Helps interpretation of bridging trials using gpELISA as a immune marker

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## Varivax® Long-Term Follow-up Study

- 1000+ healthy children 1-12 years old received 1 dose of varicella vaccine in 2 studies during 1991-1992
- 1000+ children received 2 doses of vaccine
- Follow-up for varicella breakthrough cases among these children conducted through
  - Persistence blood samples
  - Contact by telephone or mail
  - Survey of exposure and varicella
  - Spontaneous reporting of varicella

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## Estimation of Vaccine Efficacy

- The vaccine efficacy can be estimated by

$$\hat{E}_O(t) = 1 - \frac{\hat{A}_O(t)}{A_E(t)}$$

$\hat{A}_O(t)$ = Total number of cases observed / total number of person-years at risk observed during the study

$A_E(t)$ = Age-adjusted expected event rate in unvaccinated susceptible subjects (reference population)

- Confidence interval (CI) can be calculated based on Poisson assumption for the # of cases

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## Exact CI for Poisson Rate

If X ~ Poisson (θT), then an exact (1 - 2α)100% CI for θ is ($\theta_L$, $\theta_U$):

$$\theta_L = 0.5\chi^2_{2x,\alpha}$$

$$\theta_U = 0.5\chi^2_{2(x+1),1-\alpha}$$

Based on the relationship between the Poisson and $\chi^2$ distributions.

(Johnson, Kotz, Kemp, Univariate Discrete Distributions, 2nd Ed., Wiley, 1992)

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## Age-adjusted Expected Event Rate

- Calculated using the standardization method based on age-specific incidence rates among unvaccinated susceptible subjects
  - derived from a national population survey

Expected # of events = $I_1 \times T_1 + I_2 \times T_2 + \ldots + I_s \times T_s$

$I_k$ = Age-specific incidence rate

$T_k$ = Duration of time a subject is at risk in the $k^{th}$ age interval

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# Expected Number of Events Example

Subject is 8 years old with 6.88 follow-up time

| Age Interval (yr) | Incidence Rate | Person-years at risk | # Expected Events |
|---|---|---|---|
| <1 | 3.4% | 0 | 0 |
| 1 to 4 | 9.7% | 0 | 0 |
| 5 to 9 | 19.7% | 1.47 | 0.29 |
| 10 to 14 | 11.6% | 5.0 | 0.58 |
| 15 to 19 | 3.1% | 0.41 | 0.01 |
| ≥20 | 0.4% | 0 | 0 |
| Total | | 6.88 | 0.88 |

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# VZV Antibody Titer by gpELISA in Children 1 to 12 Years of Age Receiving 1 Dose of Varicella Vaccine

| | |
|---|---|
| **At Baseline (N=1087)** | |
| Seronegative (<0.6 gpELISA units/mL) | 86% |
| ≥0.6 and <5 gpELISA units/mL | 9% |
| ≥5 gpELISA units/mL | 3% |
| Status unknown | 2% |
| **At 6 Weeks Postvaccination** | |
| Seronegative (<0.6 gpELISA units/mL) | 1% |
| ≥0.6 gpELISA units/mL | 99% |
| Geometric Mean Titer (95% CI) | 12.9 (12.1, 13.8) |

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## VZV Antibody Response 6 Weeks Postvaccination (1 Dose) by Varicella Breakthrough Status

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## Life-Table Estimates of Varicella Event Rates Through 7 Years Postvaccination (1 Dose)

| Time Interval Postvaccination | Person-Years at Risk (N=1087) | Event Rate During Interval | Cumulative Event Rate | 95% Confidence Interval on Cumulative Event Rate |
|---|---|---|---|---|
| Year 1 | 956.4 | 0.2% | 0.2% | (0.0%, 0.5%) |
| Year 2 | 1074.4 | 1.0% | 1.2% | (0.6%, 1.9%) |
| Year 3 | 1062.5 | 1.2% | 2.4% | (1.5%, 3.4%) |
| Year 4 | 1043.9 | 2.2% | 4.6% | (3.4%, 5.8%) |
| Year 5 | 1027.1 | 1.1% | 5.6% | (4.2%, 7.0%) |
| Year 6 | 1019.0 | 0.3% | 5.9% | (4.5%, 7.3%) |
| Year 7 | 967.2 | 0.3% | 6.2% | (4.7%, 7.6%) |

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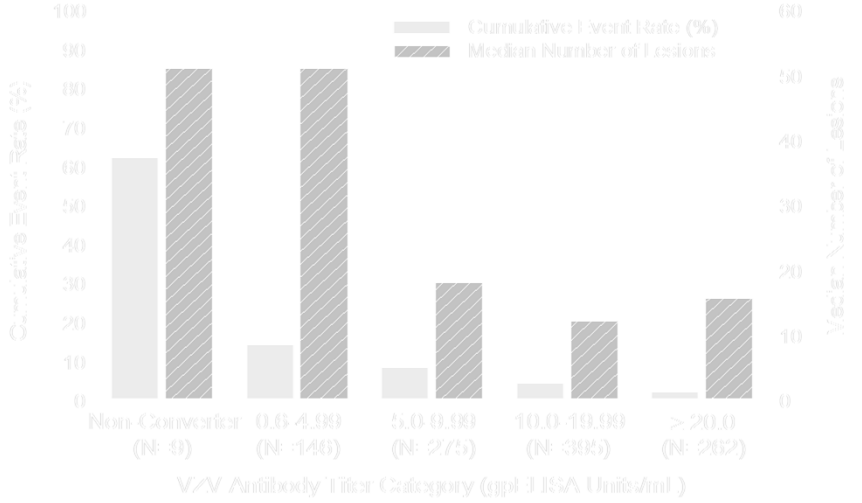
## Life-table Estimates of 7-Year Cumulative Varicella Event Rates by 6-Week Antibody Titer (1 Dose)

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## First Analysis: Approximate Protective Level

### Estimated Vaccine Efficacy by Antibody Titer Level after 1 Dose

| 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 |

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## 5 gpELISA units/mL: An Approximate Protective Level

- Subjects with antibody titers ≥5 gpELISA units/mL have (as compared with those with titers <5 gpELISA units/mL)
  - Fewer breakthroughs (3.5-fold reduction, $p<0.001$)
  - Fewer lesions in the event of breakthrough (15.5 vs 51, $p<0.001$)
  - >95% protection at the population level
- Subjects with titers <5 gpELISA units/mL still had reasonable protection (83.5%)

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## Further Analysis: Modeling the Correlation

- Link the whole antibody titer distribution to disease protection using statistical models
  - Adjusting for age
  - Use models to predict efficacy
- Statistical models considered
  - Accelerated failure time (AFT) models
  - Piecewise exponential model
  - Use Cox's regression model to check consistency of regression parameters

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## Accelerated Failure Time (AFT) Models

$$\log T_i = \beta_0 + \beta_1 X_{i1} + \cdots + \beta_k X_{ik} + \sigma\varepsilon_i$$

where $i$ = 1, …, $n$ subjects

$Ti$ = time to varicella breakthrough following vaccination

($X_{i1}$, …, $X_{ik}$) = covariates with parameters

$\sigma$ = scale parameter

$\varepsilon_i$ = random error term

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## Three AFT Models Considered

- Weibull Model
  - Constant, increasing, or decreasing hazards
  - Proportional hazards
- Log-Normal Model
  - Hazard rises from 0 to a peak and then declines
- Log-Logistic Model
  - Longer tail than log-normal hazard
  - Proportional odds model

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# Piecewise Exponential Model

- Allows flexible estimation of hazards (constant) in different time intervals:

- Similar to Cox proportional hazards model for estimating covariate effects with many small time intervals
- Allows prediction based on a simple functional form of hazard

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# Model-Based Event Rates

$$\text{Cumulative Event Rate} \quad \hat{C}_M(t) = \frac{1}{n}\sum_{i=1}^{n} \hat{C}_i(t)$$

$$\text{Average Event Rate} \quad \hat{\lambda}_M(t) = \frac{1}{n}\sum_{i=1}^{n} \hat{\lambda}_i(t)$$

$$\text{where} \quad \hat{\lambda}_i(t) = 1 - \left(1 - \hat{C}_i(t)\right)^{1/t}$$

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## Parameter Estimates of the Statistical Models for Varicella Event After Vaccination

| Model | Regression Parameter ($\beta$) Estimates (Standard Error) | |
|---|---|---|
| | Log Antibody Titer | Age |
| Weibull | 0.67 (0.11) | 0.36 (0.08) |
| Log-normal | 0.73 (0.13 ) | 0.37 (0.08) |
| Log-logistic | 0.70 (0.12) | 0.36 (0.08) |
| Piecewise Exponential | -0.79 (0.11) | -0.42 (0.08) |

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## Estimated Cumulative Varicella Event Rates of 1 Dose Vaccine

| Time Interval | Observed Life-Table Estimate | Model-Based Estimate | | | |
|---|---|---|---|---|---|
| | | Weibull | Log-normal | Log-logistic | Piecewise Exponential |
| Year 1 | 0.2% | 0.7% | 0.6% | 0.7% | 0.2% |
| Year 2 | 1.2% | 1.5% | 1.5% | 1.5% | 1.2% |
| Year 3 | 2.4% | 2.4% | 2.4% | 2.5% | 2.4% |
| Year 4 | 4.6% | 3.4% | 3.4% | 3.4% | 4.6% |
| Year 5 | 5.6% | 4.3% | 4.4% | 4.4% | 5.6% |
| Year 6 | 5.9% | 5.3% | 5.3% | 5.3% | 5.9% |
| Year 7 | 6.2% | 6.2% | 6.3% | 6.3% | 6.2% |

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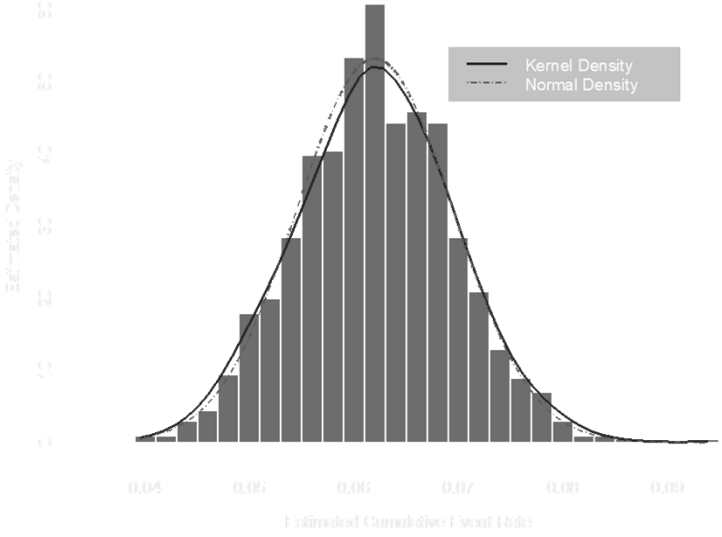
## Histogram of Model-Based Cumulative Event Rate Estimates from 1000 Bootstrap Samples

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## Results of Model Fitting

- Piecewise exponential model
  - Better fit to the data than AFT models
  - Gives same yearly hazards as Life-table method
  - Gives nearly identical covariate estimates as Cox model
- Shows that VZV antibody titer measured 6 weeks after 1 dose of vaccine strongly correlates with long-term disease protection

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## Cumulative Varicella Event Rate by VZV Antibody Titer (gpELISA)

| 6-week VZV Antibody Titer Categories (gpELISA units/mL) | Number of Participants | Number of Cases | Estimated Cumulative Varicella Event Rate | |
|---|---|---|---|---|
| | | | Life-Table Method | Piecewise Exponential Model |
| Seronegative | 9 | 3 | 62.1% | 50.6% |
| 0.6 to 4.99 | 146 | 20 | 14.1% | 12.8% |
| 5.0 to 9.99 | 275 | 22 | 8.1% | 7.6% |
| 10.0 to 19.99 | 395 | 16 | 4.1% | 4.5% |
| ≥20.0 | 262 | 5 | 1.9% | 2.1% |

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## Estimated 7-Year Varicella Event Rate After 1 Dose of Vaccine by Antibody Titer (Piecewise Exp. Model)

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## Model Prediction of Vaccine Efficacy

- The final model established can be used to predict the long-term breakthrough rate, $\hat{\lambda}_P(t)$, and hence vaccine efficacy for a new data set using 6-week VZV antibody data

$$\hat{E}_P(t) = 1 - \frac{\hat{\lambda}_P(t)}{\lambda_E(t)}$$

- CI can be calculated using 2-step Bootstrap sampling to account for 2 sources of variability:
  - Variability in the model parameter estimates (original data)
  - Variability in the new dataset

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## Observed vs. Model-Predicted Breakthrough Rates and Efficacy for 434 Vaccine Recipients in the Efficacy Trial (1982-3)

| | GMT of Antibody Response (gpELISA) at 6 weeks post-vaccination (95% CI) | Annualized Incidence of Varicella Postvaccination (%) | | Age-adjusted Expected Annualized Incidence of Varicella Among Unvaccinated Susceptible Subjects (%) | Vaccine Efficacy (%) | |
|---|---|---|---|---|---|---|
| Median Age (Years) | | Observed (95% CI) | Model-Predicted (95% CI) | | Estimated (95% CI) | Model-Predicted (95% CI) |
| 4.7 | 18.6 (17.4, 19.9) | 0.5 (0.2, 0.7) | 0.4 (0.3, 0.5) | 15.1 | 97.0 (95.4, 98.4) | 97.4 (96.5, 98.2) |

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## Predictive Value of Piecewise Exponential Model: Estimated vs. Model-Predicted Efficacy in 5 Cohorts

| Age Range (Potency, PFU) | N (Follow-up) | 6-Wk GMT (gpELISA units/mL) | % ≥5 gpELISA units/mL | Estimated Efficacy (%) | Model-Predicted Efficacy (%) |
|---|---|---|---|---|---|
| 1-12 Yr † (2900-9000) | 1087 (7 Yrs) | 12.9 | 85.7 | 94.0 | 93.9 |
| 1-14 Yr (17,000) | 434 (7 Yrs) | 18.5 | 87.3 | 97.0 | 97.4 |
| 1-12 Yr (1000-1600) | 3594 (9 Yrs) | 10.1 | 72.6 | 82.7 | 89.5 |
| 12-23 Mo † (2900-9000) | 233 (7 Yrs) | 14.9 | 91.0 | 90.5 | 88.1 |
| 12-23 Mo (1000-1600) | 1335 (9 Yrs) | 9.7 | 74.4 | 80.2 | 82.1 |

†Cohort used to develop the model

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## Predictive Value of PE Model

- The piecewise exponential model offers reasonable efficacy prediction in different cohorts
  - Important to use the whole distribution of antibody titers
- % ≥5 gpELISA units/mL generally underestimates the vaccine's efficacy
  - Provides a conservative VE estimate

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## Efficacy Prediction (Over 7 Years) for Process Upgrade Varicella Vaccine (1997) in 326 Children 12 to 23 Month Olds

| Median Age (Months) | GMT of Antibody Response (gpELISA) at 6 weeks post-vaccination (95% CI) | Model-Predicted Annualized Incidence of Varicella Postvaccination (%) (95% CI) | Expected Incidence of Varicella Among Unvaccinated Susceptible Subjects (%) | Piecewise Exponential Model-Predicted Vaccine Efficacy (%) (95% CI) |
|---|---|---|---|---|
| **13** | **15.6 (14.2, 17.2)** | **1.9 (1.3, 2.5)** | **14.2** | **87.0 (82.4, 90.8)** |

Efficacy consistent with that for 12-23 month olds from long-term followup study

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## Correlate of Protection for 2-Dose Varicella Vaccine

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## Correlate of Protection After 2 Doses of Vaccine

- So far the correlate of protection is established based on 6-week antibody response after 1 dose of vaccine
- A 2nd dose vaccine significantly boosts the antibody titer (>10 fold)
- Will the relationship between antibody response and long-term breakthrough still hold?

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## Antibody Responses (gpELISA) 6 Weeks Postvaccination 1 vs. 2 Doses of Varicella Vaccine

| Varicella Vaccine Regimen | 6 Weeks Post Dose 1 | | 6 Weeks Post Dose 2 | |
|---|---|---|---|---|
| | % ≥5 | GMT | % ≥5 | GMT |
| 1 Dose (0 Months) | 84.7% (755/891) | 12.0 | --- | --- |
| 2 Doses (0 & 3 Months) | 87.2% (733/841) | 12.7 | 99.5% (765/769) | 141.5 |

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## 6-Week Antibody Responses Post 1 and 2 Doses of Vaccine

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## Efficacy of Over 10 Years of Followup 1 vs. 2 Doses of Varicella Vaccine

| Vaccine Regimen | N | Number of Cases | Observed Annual Rate of Varicella | | 10-Year Efficacy* |
|---|---|---|---|---|---|
| | | | Vaccine Recipients | Population (Historical Survey) | |
| 1 Dose | 1104 | 60 | 0.8% (0.6%, 1.0%) | 14.2% | 94.3% (92.8%, 95.6%) |
| 2 Doses (0 & 3 months) | 1017 | 17 | 0.2% (0.1%, 0.4%) | 13.9% | 98.3% (97.3%, 99.0%) |

* P <0.001

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Antibody Response 6 Weeks Postvaccination by Varicella Breakthrough Status in 2-Dose Vaccine Recipients



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# Extending the Piecewise Exponential Model to 2 Doses

- Re-estimate the model using data from both 1 and 2 doses
  - 2-dose group provided high-titer range data for modeling

| Key Covariates in PE Model | Parameter Estimate | Standard Error | P-value |
|---|---|---|---|
| Treatment ( 2 vs. 1 doses) | -0.07 | 0.35 | 0.84 |
| Log Antibody titer | 0.64 | 0.09 | <0.001 |
| Age | 0.40 | 0.07 | <0.001 |

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## Extending the Piecewise Exponential Model to 2 Doses

- Results suggest that the strong inverse relationship still holds between antibody response (6 weeks post 1 or 2 doses) and long-term breakthrough

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## Summary of the Varivax® Example

- Antibody titers measured by gpELISA correlates with protection
- Statistical model help interpret the immunogenicity trial results
  - Allow adjustment of covariates and prediction
- Support the use the % ≥ 5 gpELISA units and as a primary endpoint in clinical trials
  - Provide somewhat conservative prediction of efficacy

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