Module 10: Evaluating Immune Correlates of Protection

Instructors: Peter Gilbert, Paul T. Edlefsen, Ying Huang

Talk 2: Introduction to Sieve Analysis of Pathogen Sequences

Summer Institute in Statistics and Modeling in Infectious Diseases

University of Washington, Department of Biostatistics

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Statistical Center for HIV/AIDS Research & Prevention
SCHARP

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Outline Talk 2

1. Introduction: Concepts and definitions of sieve effects / sieve analysis
   - Vaccine efficacy versus particular pathogen strains
   - Sieve effects and other effects
   - Some immunological considerations
   - Some sieve analysis results from HIV-1 vaccine efficacy trials

2. Some statistical approaches to sieve analysis
   - Binary endpoint (Infected yes/no)
     - Discrete pathogen types: Categorical data analysis
     - Continuous types: Distance-to-insert comparisons

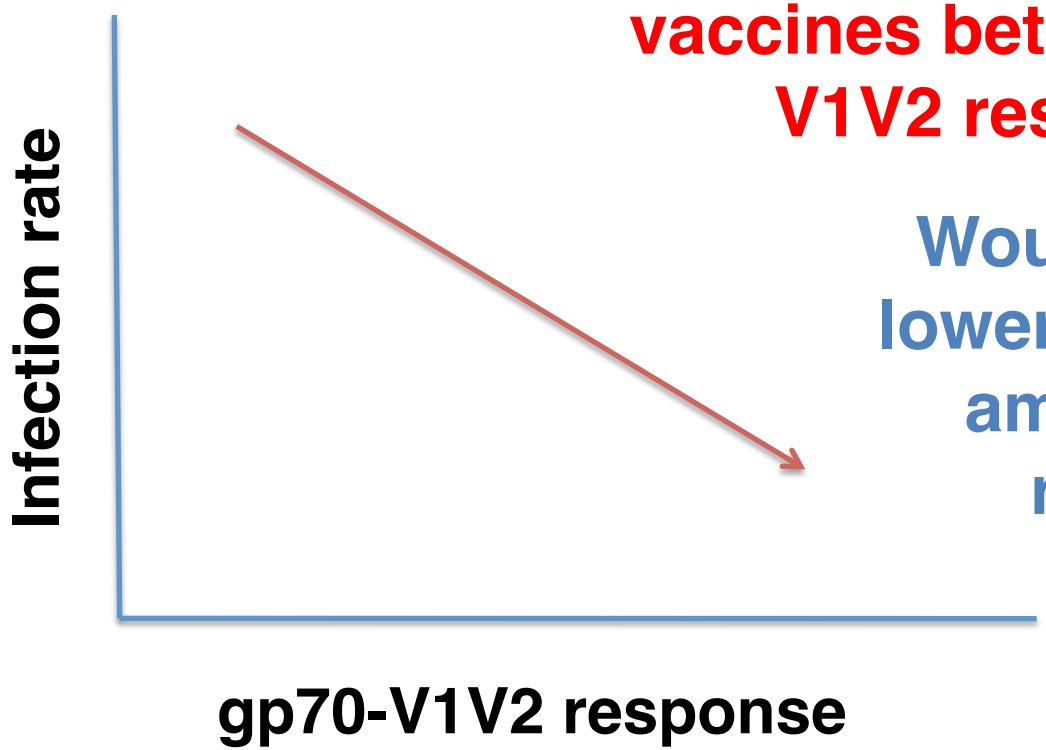
3. Assumptions required for interpretation as per-exposure vaccine efficacy

RV144 Correlates Result

- Vaccine recipients with higher gp70-V1V2 responses tended to have lower rates of infection.

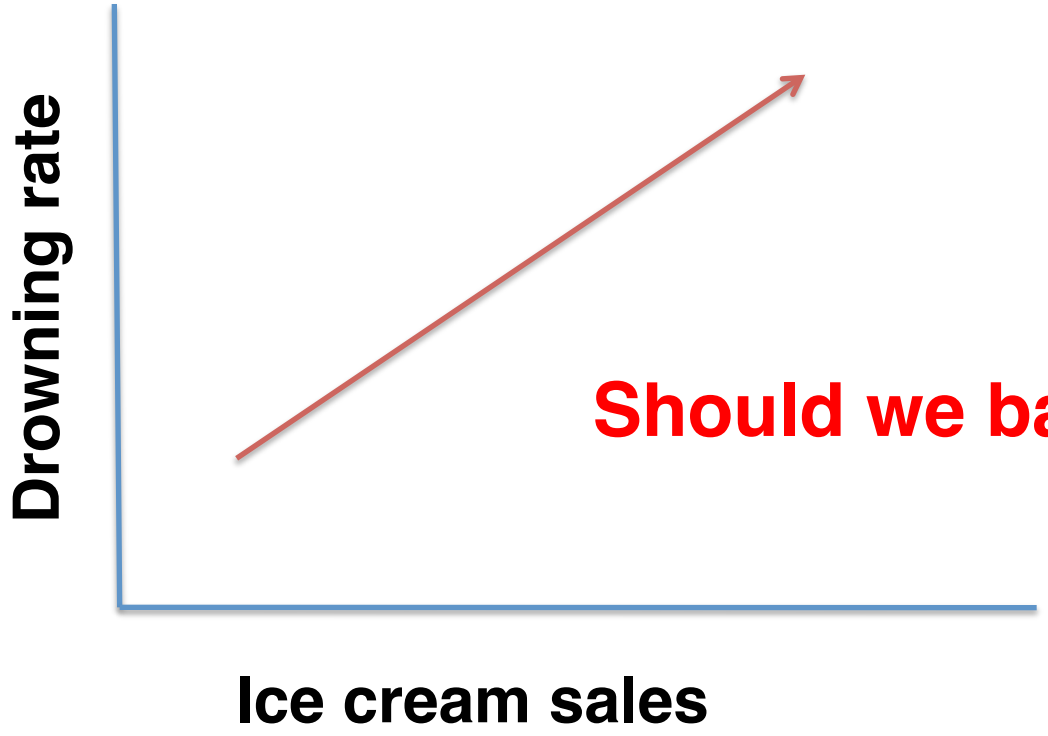
Should we make our vaccines better at eliciting V1V2 responses?

Would that lead to lower infection rates among vaccine recipients?



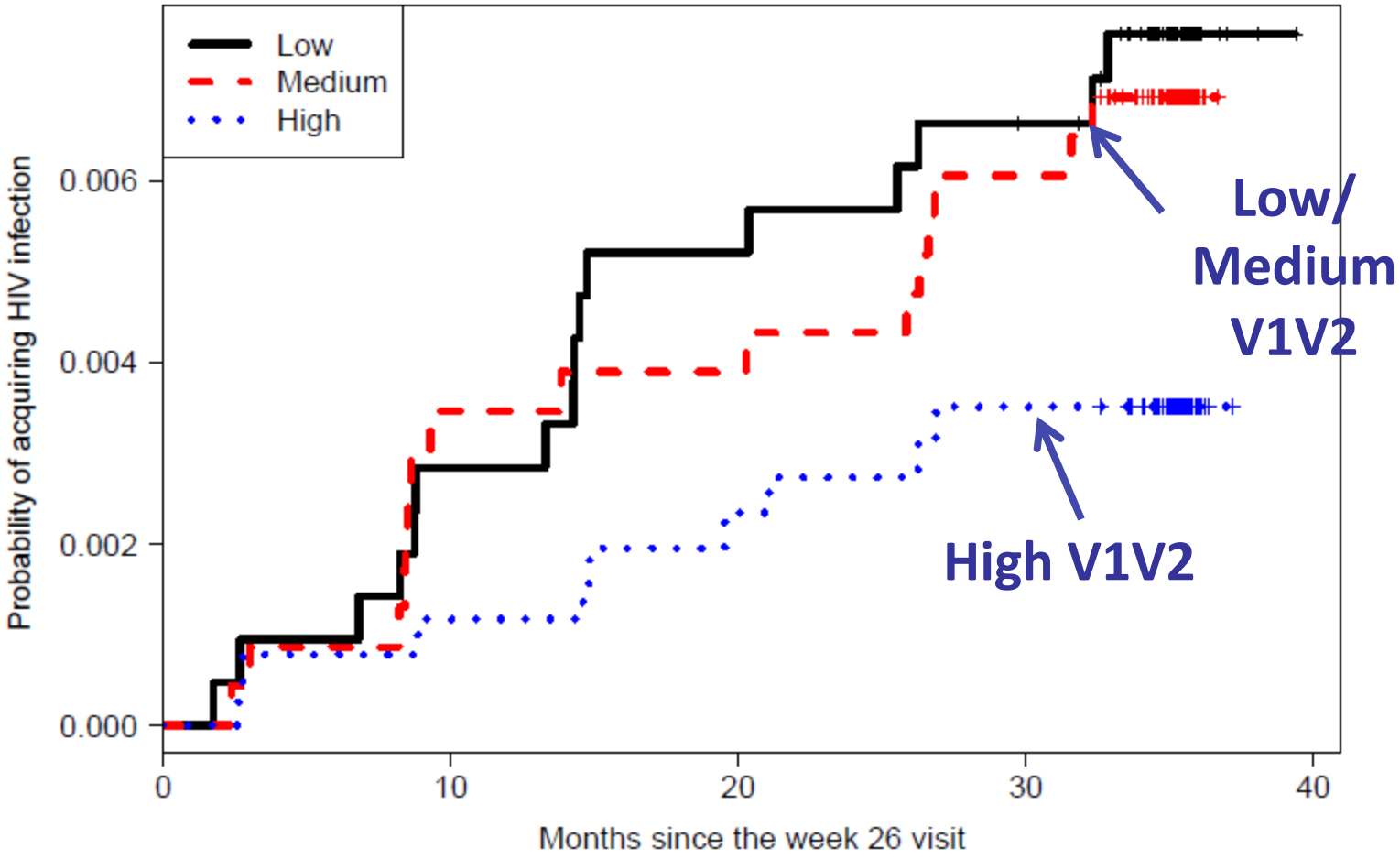
Correlation ≠ Causation

- Locations with higher sales of ice cream tend to have higher rates of drowning.



Should we ban ice cream?

Cumulative Infection Rates With V1V2-gp70 Scaffold Assay



Should we make our vaccines better at eliciting V1V2 responses?

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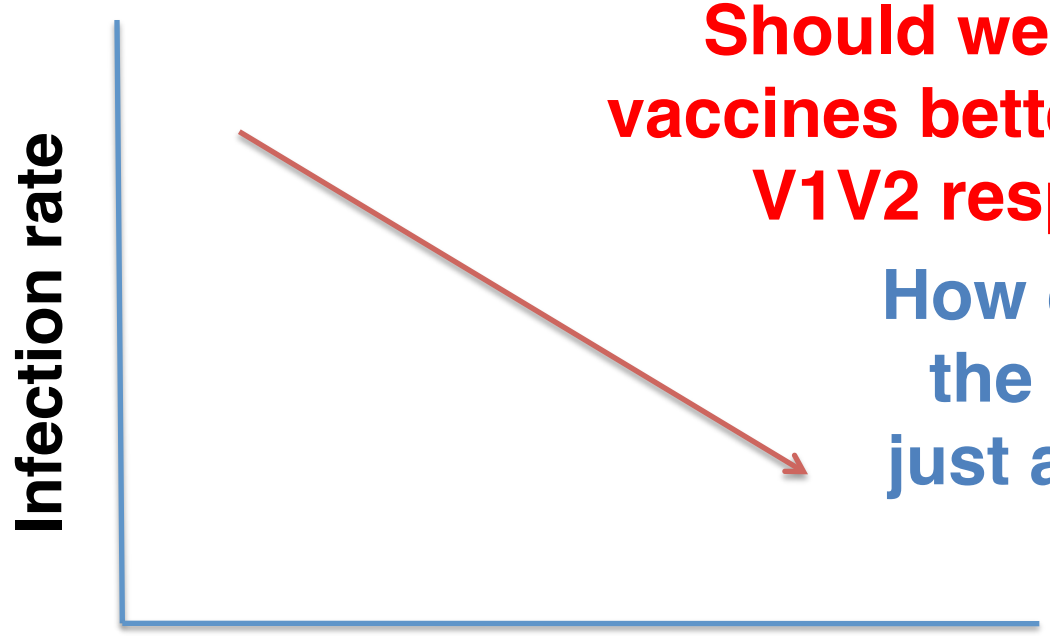
Randomized Controlled Trials (RCTs)

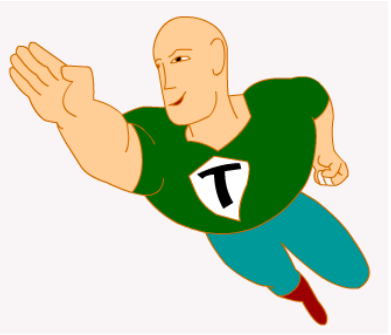


Should we make our vaccines better at eliciting V1V2 responses?

How can we know if the correlation is just a coincidence?

- In an RCT, treatments (vaccine or placebo) are randomly assigned.
- If you compare across treatment groups, the only explanation for a difference is the vaccine.

Towards a CoP and/or a Mechanistic CoP

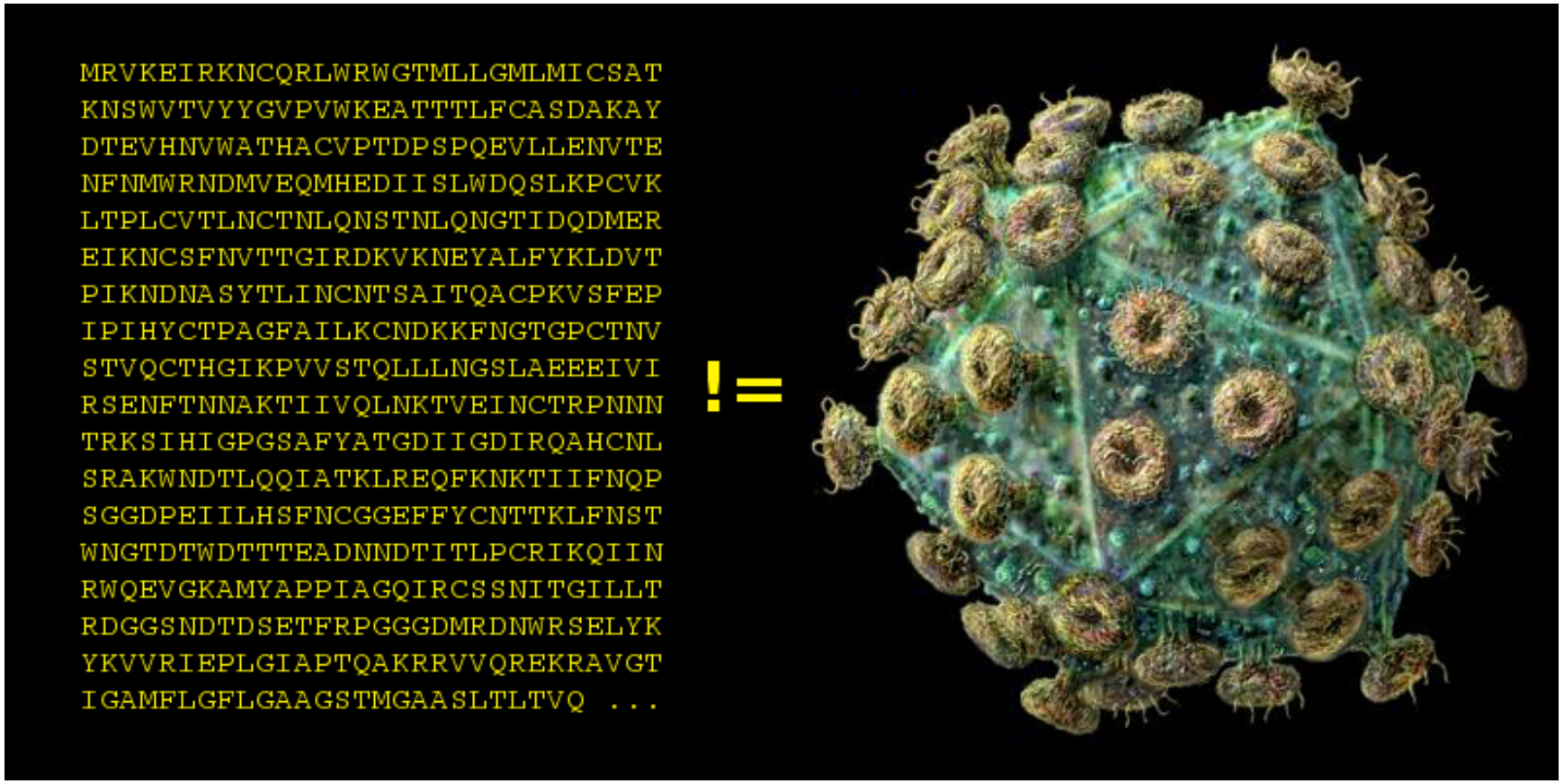


- The correlates so far are not CoPs.
  - The comparison is among vaccine recipients, not across randomized treatment arms.
- Could we randomly assign anti-V1V2 antibodies?
  - Maybe. There's other statistical ways, too.
  - We'll need to wait until future RCTs.
- Idea: use RV144 placebo vs. vaccine recipients
  - to address hypotheses implied by a causal correlate. Like: "Anti-V1V2 antibodies in vaccine recipients (partially) protected them."

Sieve Analysis

- Vaccination should induce an immune response
  - that targets circulating HIV
    - (at least the HIV that's similar to the vaccine HIV)
- Idea: investigate the sequence data
- If we see evidence for a difference in the sequences of viruses infecting vaccinees versus placebo recipients,
  - it must be due to the vaccine.
    - (It's a randomized trial!)
- If we see a difference in the sequences of V1V2,
  - then it supports the hypothesis of anti-V1V2 antibodies selectively filtering HIV.

Sequence data is an abstraction



… but a useful one …

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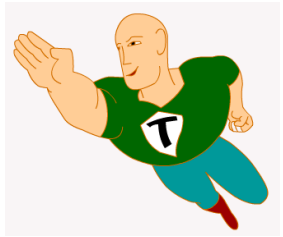
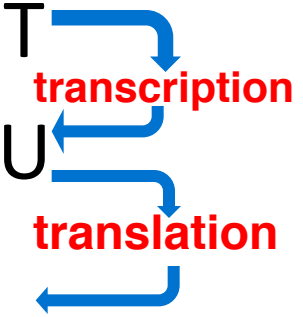
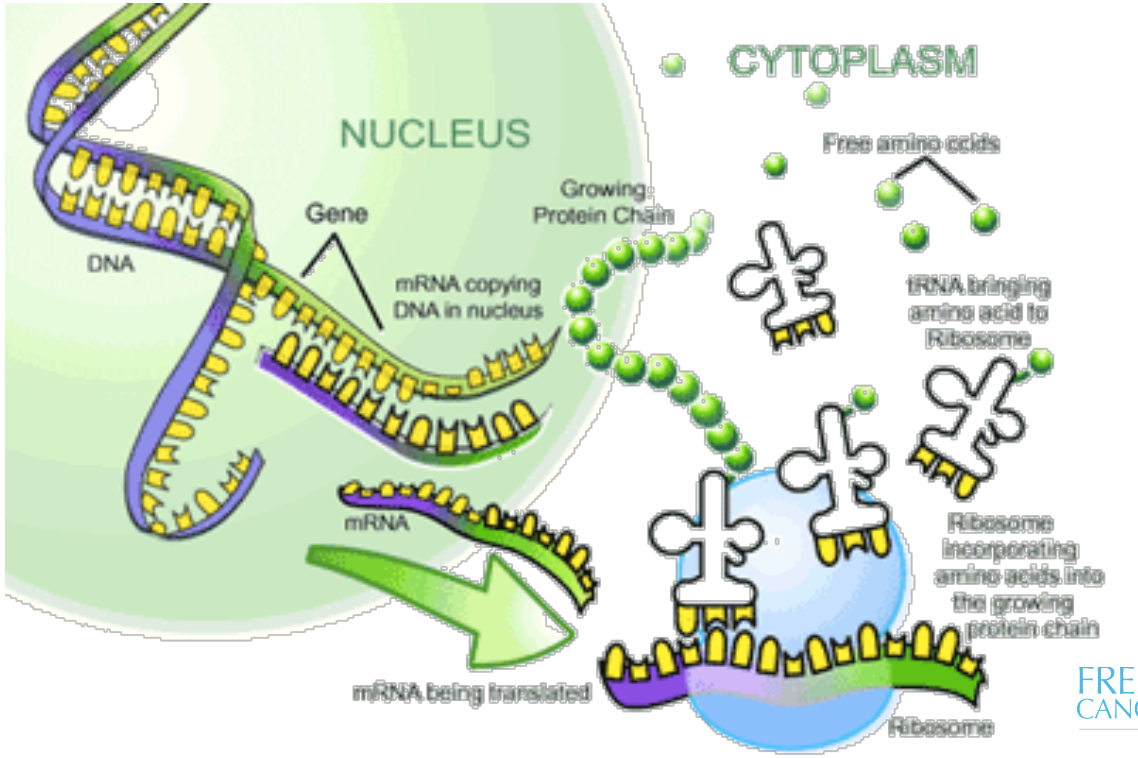
Three kinds of biosequences



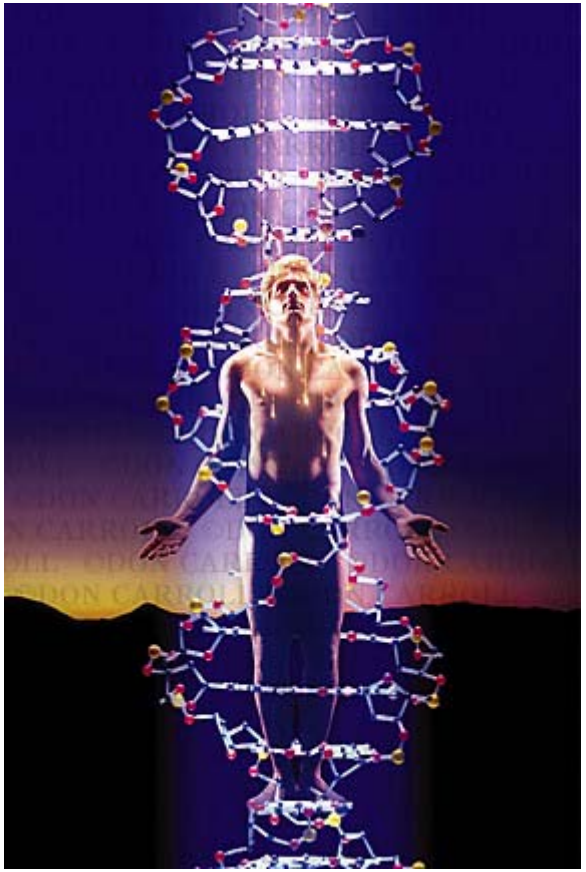
- DNA: sequences of 4 nucleic acids: ACGT
- RNA: sequences of 4 nucleic acids: ACGU
- Protein: sequences of 20 amino acids



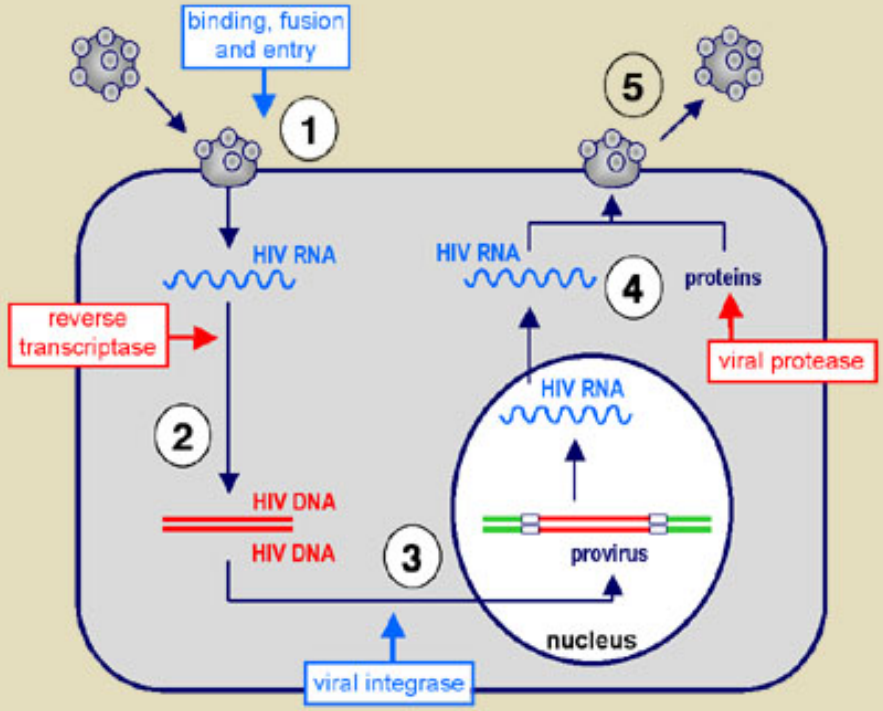


The human genome

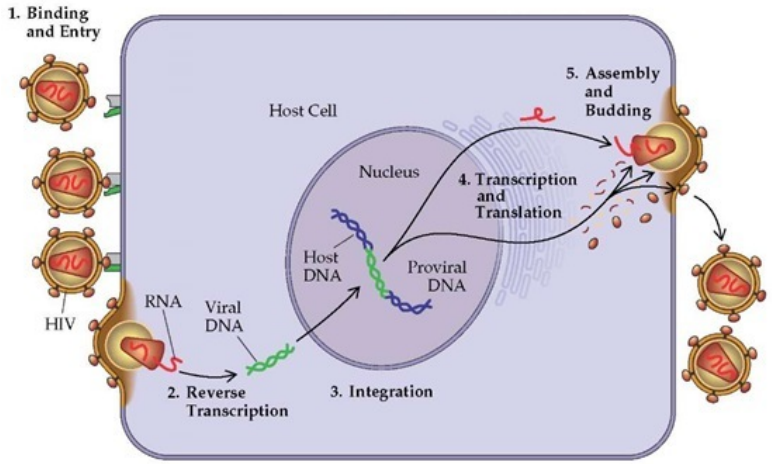
- DNA: 23 chromosomes, ~3 billion pairs of nucleic acids
- RNA: ~135,000 unique transcripts
- Protein: ~25,000 different protein products



HIV: a selfish genome

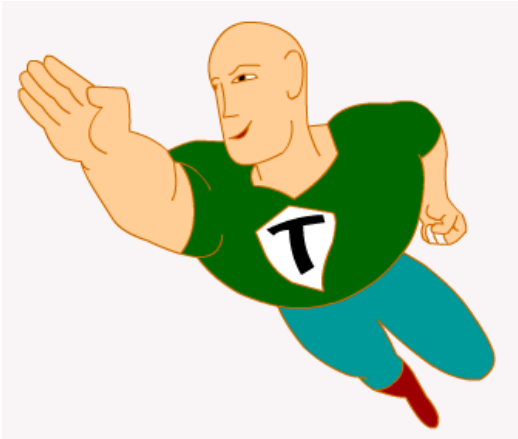


1. HIV binds, fuses to immune system cells, releases its RNA
2. HIV RNA converted to HIV DNA during reverse transcription
3. Viral DNA enters host cell nucleus and is integrated into host cell chromosomal DNA
4. HIV RNA is made and viral protease processes proteins for viral assembly
5. Newly made HIV buds from the cell and is ready to infect other cells



Biosequences and adaptive immunity

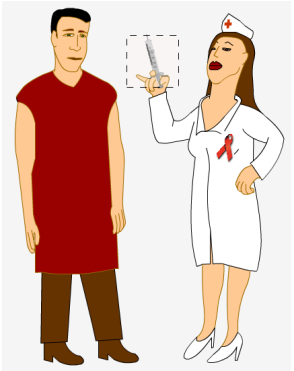
- Two major components: B cells and T cells
- Cells constantly report status: T cells monitor.
  - Fragments of protein sequences are brought to cell surface
  - Cells are destroyed when they report "bad" fragments
  - T cells adapt to learn what "bad" looks like



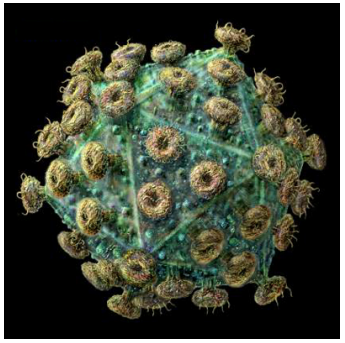
- B cells create antibodies,
  - which recognize proteins & flag them for destruction.
  - B cells also adapt to recognize "bad" proteins.

- Vaccines can train an immune system to recognize HIV earlier
  - and more effectively.

HIV Vaccines



- Contain fragments of the HIV genome
  - Either proteins or DNA that will be expressed as proteins
- Recipients produce HIV-targeting T&B cells
  - No need to wait: destroy HIV before it destroys the immune system
  - Like when you become immune to a flu after infection or vax.
- What sequence(s) to include in the vaccine?
  - Want to create immune responses that protect people



Variation in the HIV genome

- The HIV genome is highly variable
  - due in part to a sloppy reverse-transcriptase.
- HIV evolves rapidly to evade immune systems
  - Variation and selection: Darwin's essentials for evolution
- Some adaptations hinder HIV
- Ideal vaccine: immune system targets Achilles' heel

Back to Sieve Analysis

- Vaccination should induce an immune response
  - that targets circulating HIV
    - (at least the HIV that's similar to the vaccine HIV)
- Idea: investigate the sequence data
- If we see evidence for a difference in the sequences of viruses infecting vaccinees versus placebo recipients,
  - it must be due to the vaccine.
    - (It's a randomized trial!)
- If we see a difference in the sequences of V1V2,
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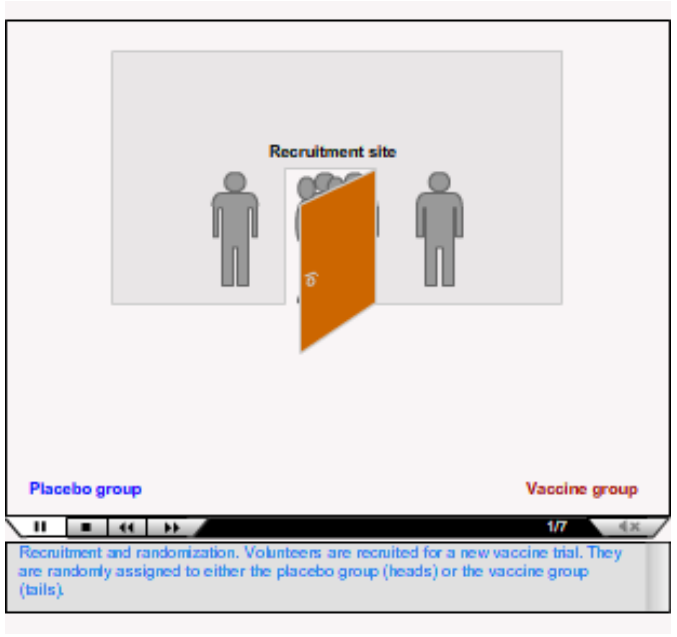
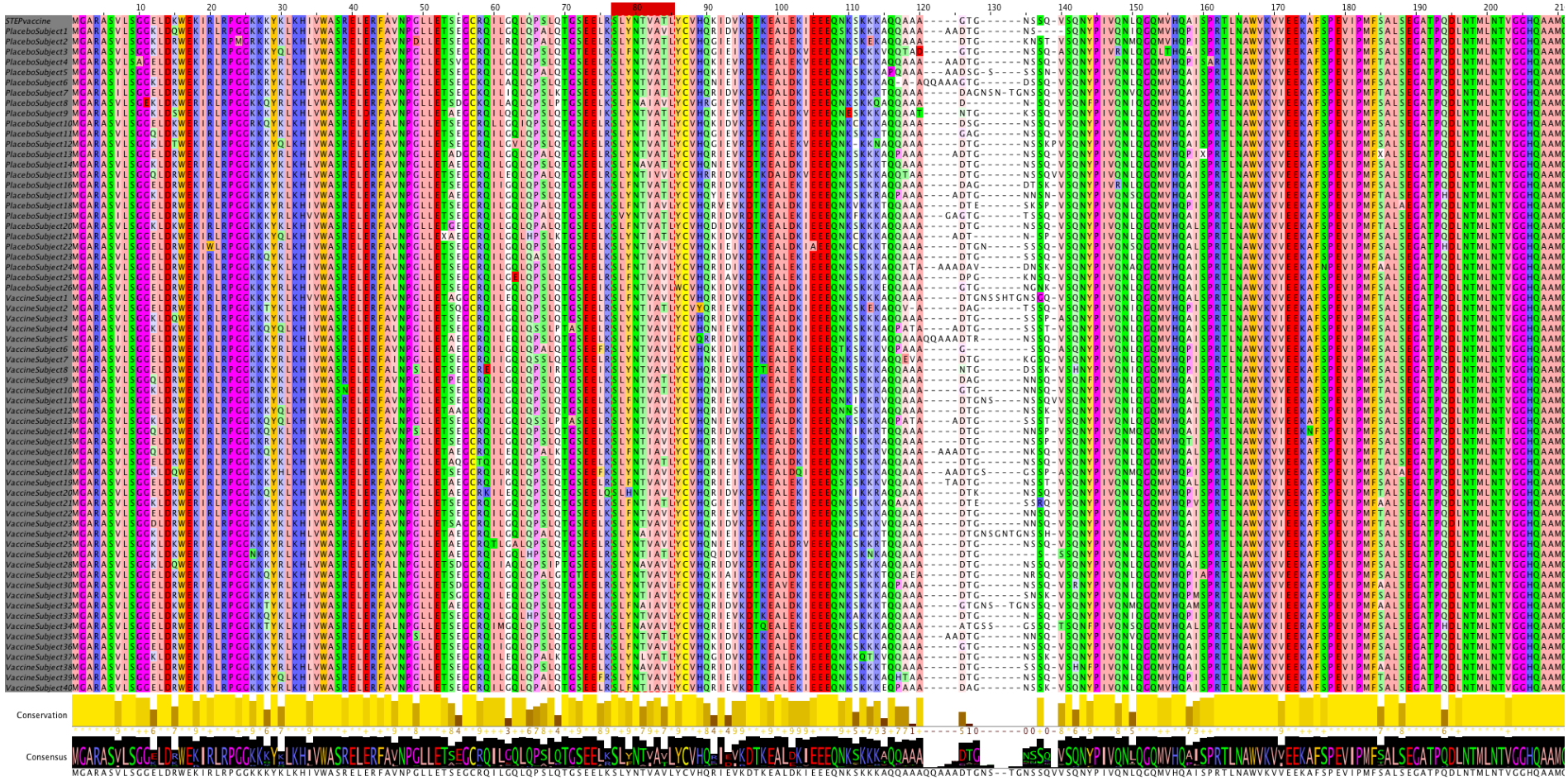
The sieve effect



Click here to view SieveAnimation.swf

Looking for sequence differences



… a needle in a haystack …

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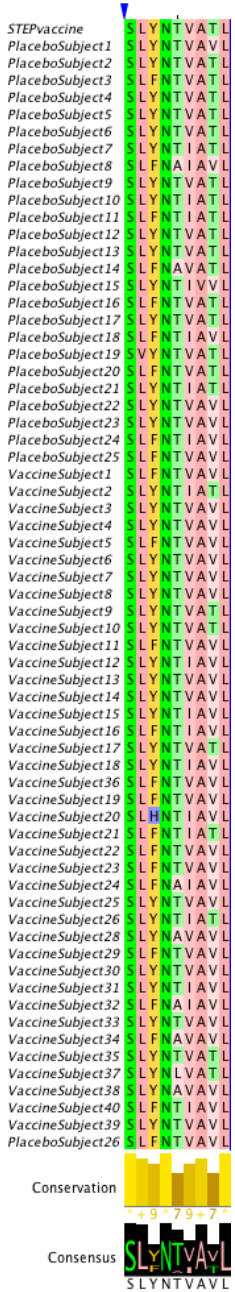
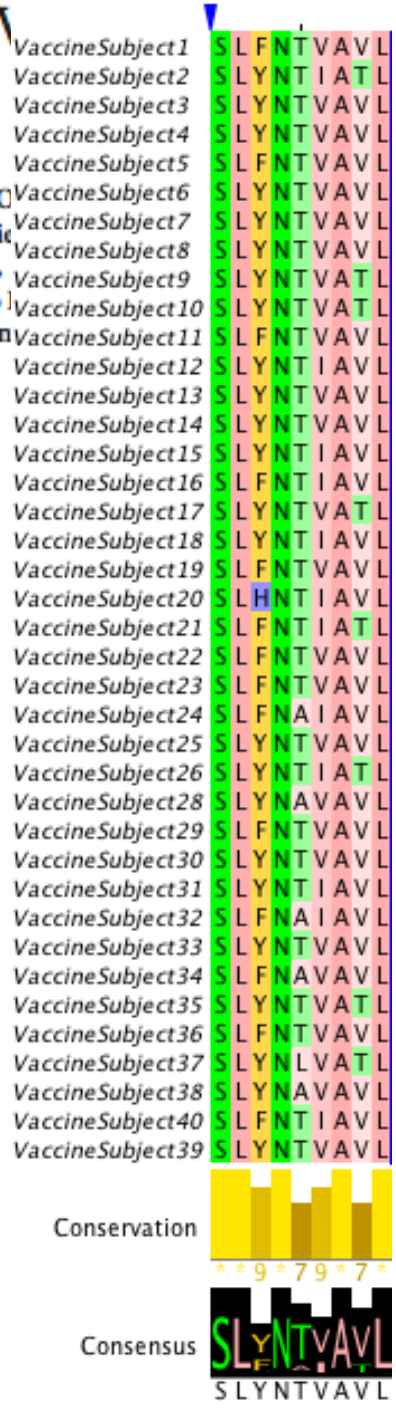
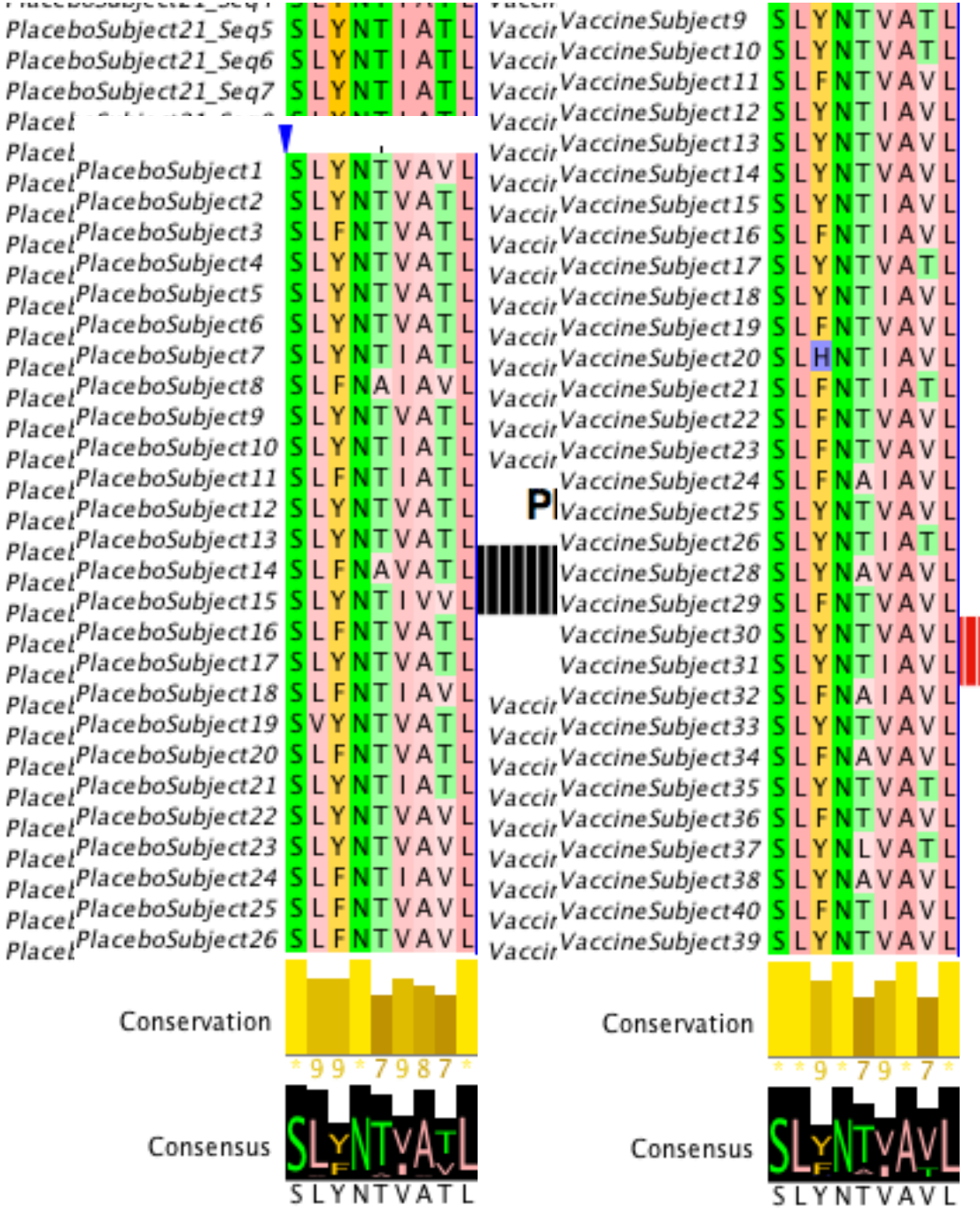
Genetic impact of vaccination on breakthrough HIV sequences from the STEP trial

Morgane Rolland[1,7], Sodsai Tovanabutra[2,7], Allan C deCamp[3,7], Nicole Frahm[3,7], Peter B Gilbert[3], Eric Sanders-Buell[2], Laura Heath[1], Craig A Magaret[3], Meera Bose[2], Andrea Bradfield[2], Annemarie C Jacqueline Crossler[2], Teresa Jones[2], Marty Nau[2], Kim Wong[1], Hong Zhao[1], Dana N Raugi[1], Stephanie Julia N Stoddard[1], Brandon S Maust[1], Wenjie Deng[1], John Hural[3], Sheri Dubey[4], Nelson L Michael[2], John Shiver[4], Lawrence Corey[3], Fusheng Li[3], Steve G Self[3], Je ilo Michael N Robertson[4], Ann Duerr[3], M Juliana McElrath[3], Fr llin

Signature site Gag84 showed the greatest distinction between vaccine and placebo recipients ($q = 0.012$): it is encompassed by several known CTL epitopes, including the well-characterized HLA-A*02 epitope SLYNTVATL (amino acids 77–85; italicized T is the site showing the distinction between vaccine and placebo recipients). Thirty-six of 64 subjects had an HLA class I allele restricting epitopes that spanned Gag84 (ref. 6). The signature at Gag84 was more pronounced among individuals with an HLA allele matching an 'A-list' epitope (epitopes fulfilling criteria intended to ensuring reliable description of the optimal length epitope and correct assignment of the restricting HLA class I alleles)[7] (79%:17% mismatch vaccine:placebo compared to 80%:46% mismatch in the 28 subjects without an A-list restricting allele), supporting that vaccine-induced T cell pressure







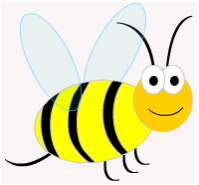
We begin with Sanger sequences, usually multiple per subject.

We align and translate the DNA sequences to AAs.

Some analysis methods use all of the subjects' sequences.

Others use one per subject: a representative sequence.

Two Types of Potential Selective Effects



1. Acquisition Sieve Effect

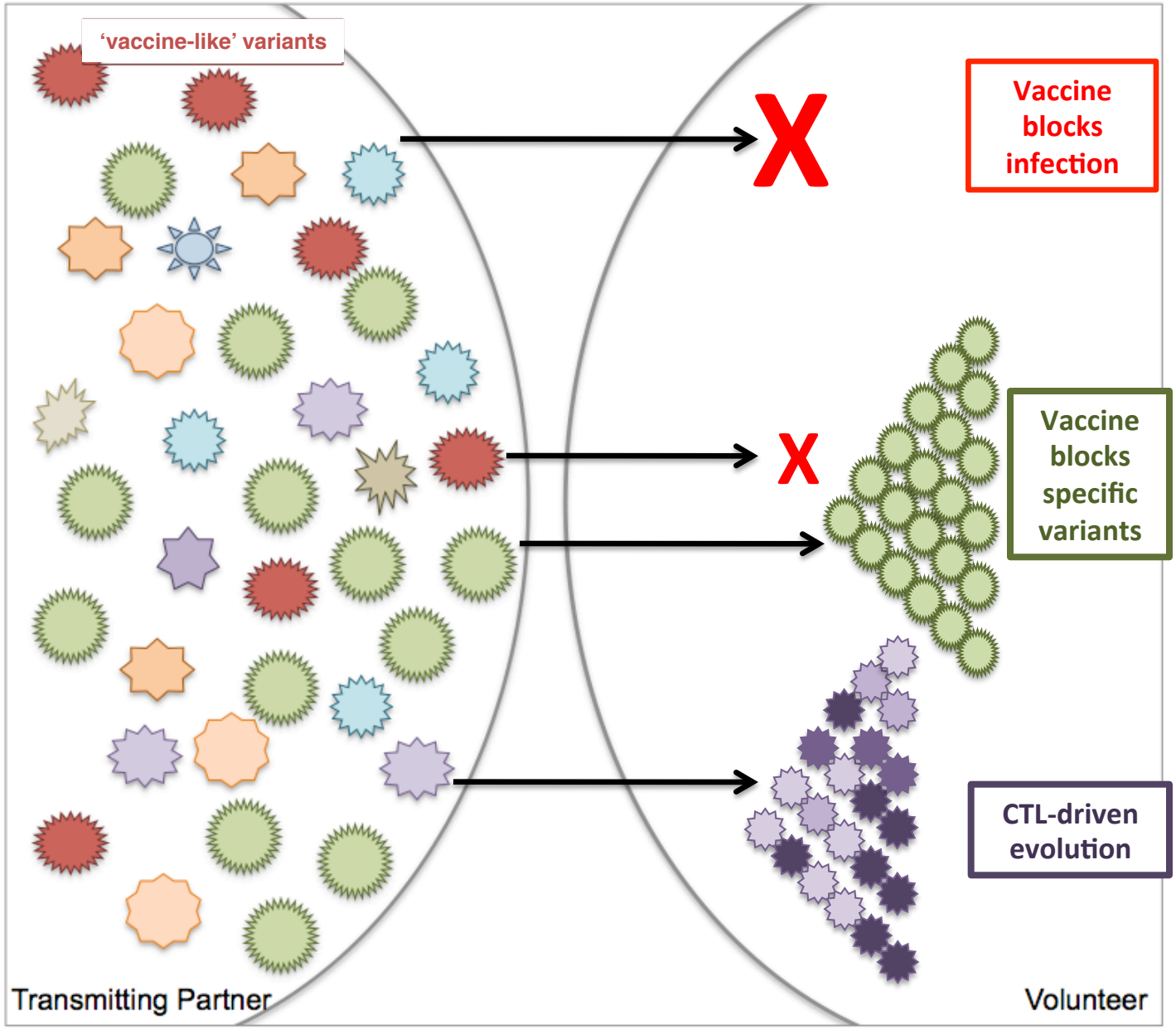
The vaccine selectively blocks (or enhances) acquisition with specific HIV variants

2. Post-Infection Selective Effect

The vaccine drives HIV sequence evolution

- **Longitudinal HIV sequences (and some acute-phase sequences) are needed to distinguish these two types of effects**
- **But at the moment we only have one time-point per subject**

Potential selective effects of vaccines



Challenged Statistical Power

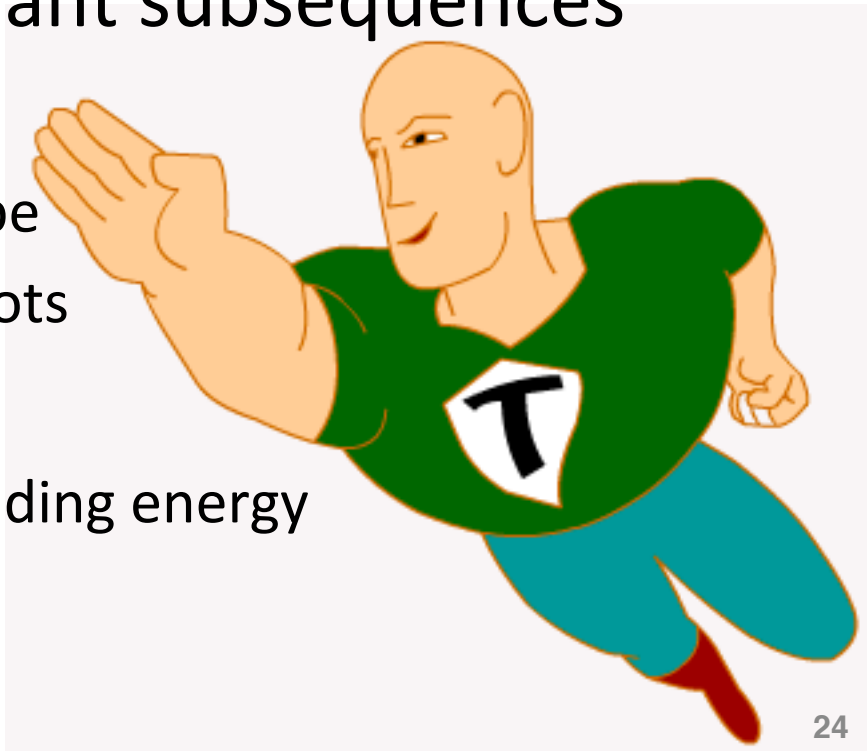
- Achieving high statistical power requires:
  - Large n of infected subjects with sequence data
  - A vaccine that induces immune responses that 'react strongly' with the infecting viruses.

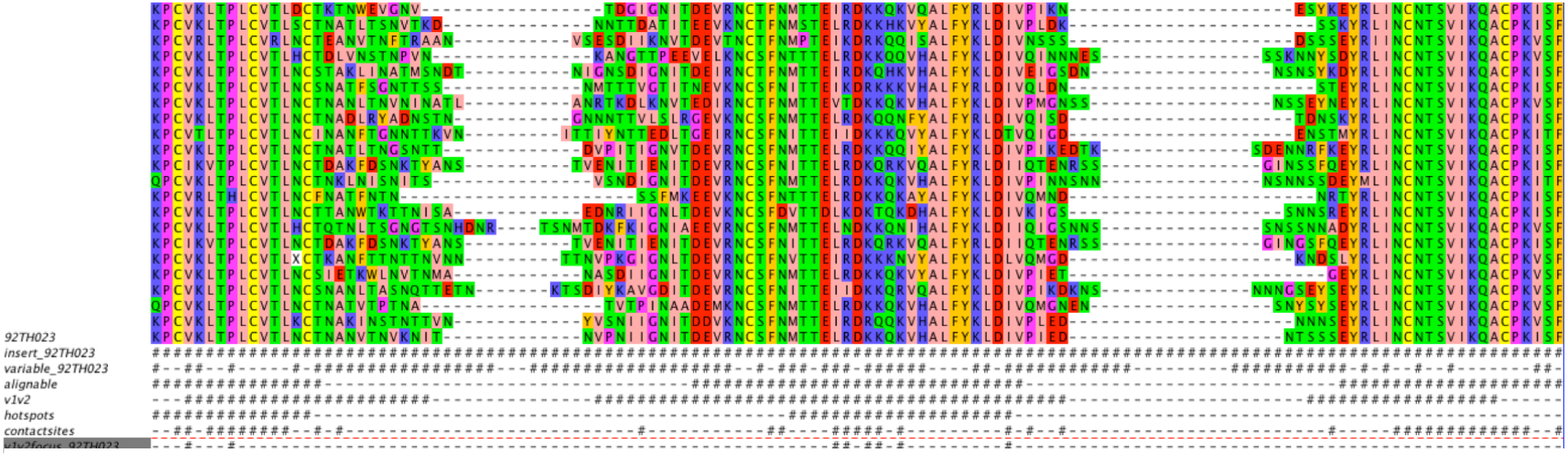
- For most HIV trials, the sieve analyses have low power
  - rv144: n = 121
    - **But for analysis, only n = 110**
      - **(44 vaccine recipients, 66 placebo)**
  - Phambili: n = 82
    - **But for analysis, only n = 43**
      - **(23 vaccine recipients, 20 placebo)**
  - STEP: n = 66
  - VaxGen: n = 336

- Can only detect relatively large sieve effects

Maximizing power

- Compare sequences to the vaccine insert
- Pre-filter based on treatment-blinded data
  - Fewer analyses ➡ greater power
- Focus analysis on relevant subsequences
  - Epitopes
    - CTL epitopes by HLA type
    - Antibody binding hotspots
  - Escape routes
    - Consider changes to binding energy
- **Plan ahead**





Screening to Maximize Statistical Power

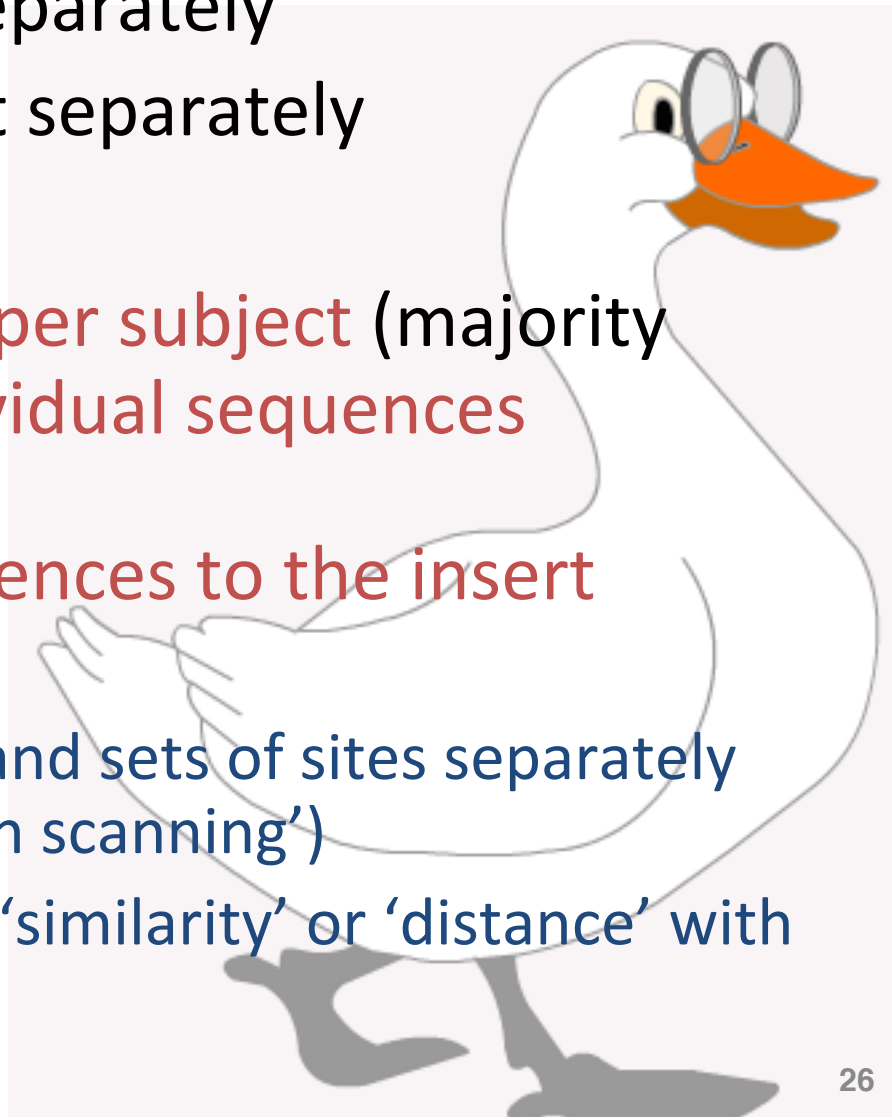
- Only include sites contained in every one of these sets:
  - The 85 sites in the V1V2 region
  - Sites with sufficient variability
  - Sites for which we have confidence in the alignment
  - Sites in antibody-relevant sites
    - (we asked our expert colleagues for sites)
- All of this screening is done **before unblinding**

Methods for RV144 Sieve Analysis

- Assess each HIV-1 gene separately
- Assess each vaccine insert separately

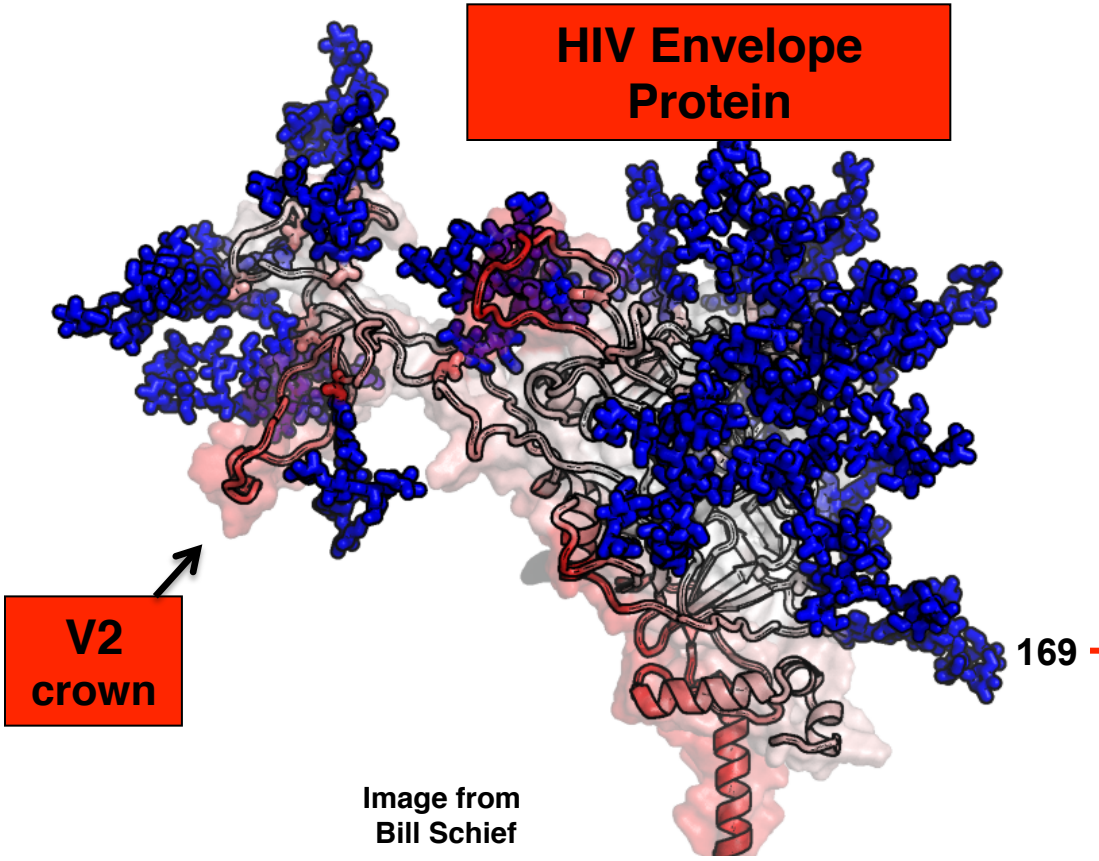
- Assess either 1 sequence per subject (majority consensus) or use all individual sequences

- Compare a subject's sequences to the insert sequence in 2 ways:
  - Local: Evaluate each site and sets of sites separately (eg. 'site scanning', 'antigen scanning')
  - Global: Summarize overall 'similarity' or 'distance' with a single number

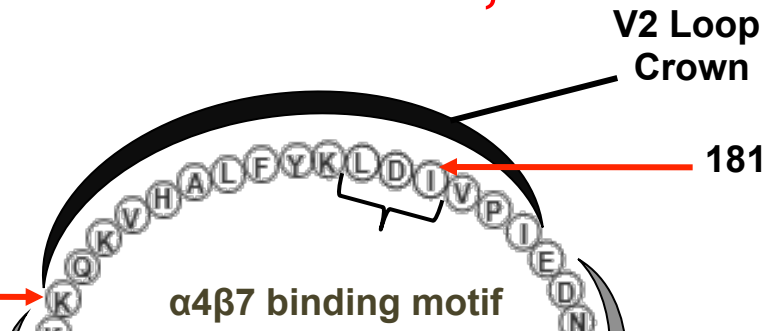


Summary of RV144 V1V2 Results

- V1V2 focused analysis.
- Analyzed only 9 sites!
- Used multiplicity correction to protect against false discoveries.



- **2 sites with evidence of a sieve effect:**
  - **Sites 169, 181**



Vaccine Efficacy by HIV-1 Genotype
(Defined by Site 169, 181)

HIV-1 Genotype	Number Infections	Estimated VE*	95% CI	P-value
169 match	87	48%	18% to 66%	0.0036
169 mismatch	23	-55%	-258% to 33%	0.30
181 match	88	17%	-26% to 45%	0.38
181 mismatch	22	78%	35% to 93%	0.0028

- VE greater against 169-matched than mismatched HIV-1: p = 0.034**
- VE greater against 181-mismatched than matched HIV-1: p = 0.024

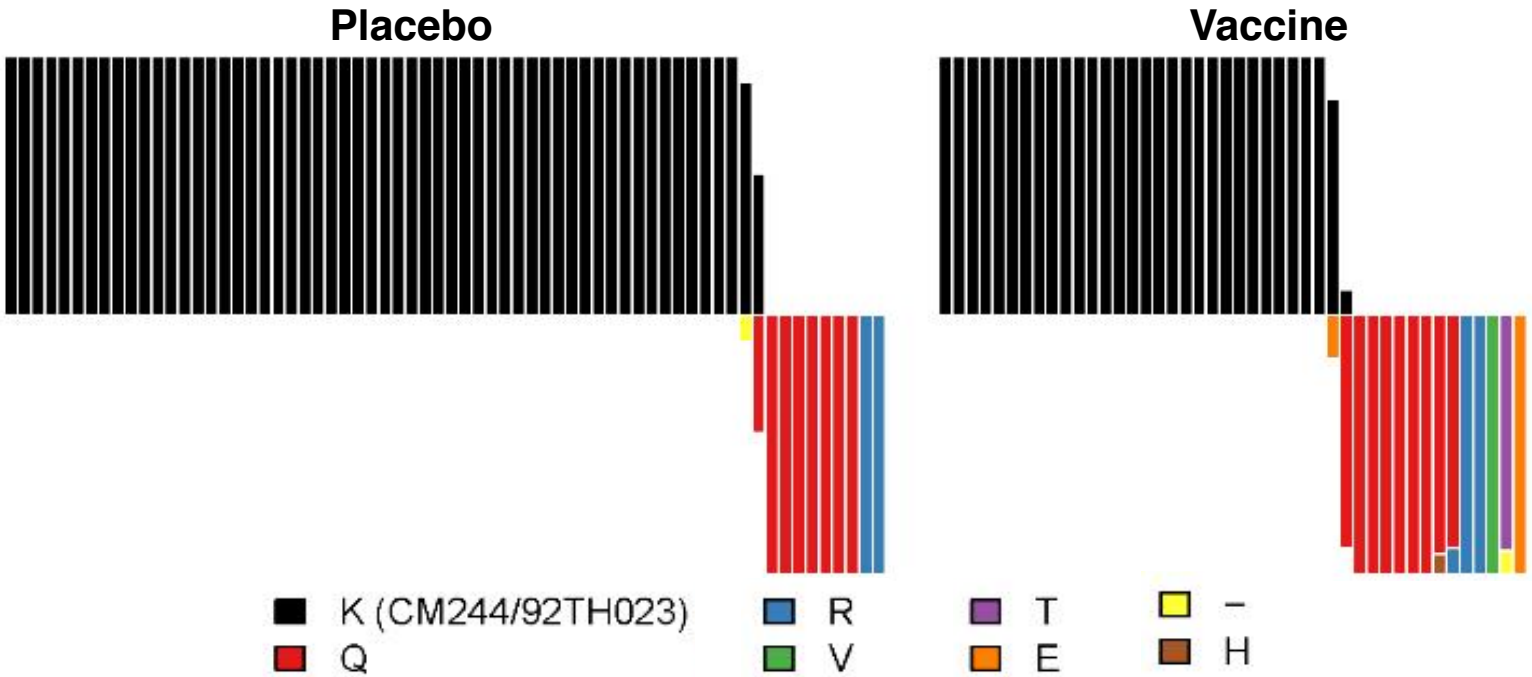
*** Estimated with a Cox model (Prentice et al., Biometrics, 1978)**

**** Estimated with a Cox model (Lunn and McNeil, Biometrics, 1995)**

Position 169

Gilbert, Wu, Jobes:
p =.018, q =.077

Model-Based Sieve:
P(sieveldata) = .334, p =.050, q = .202



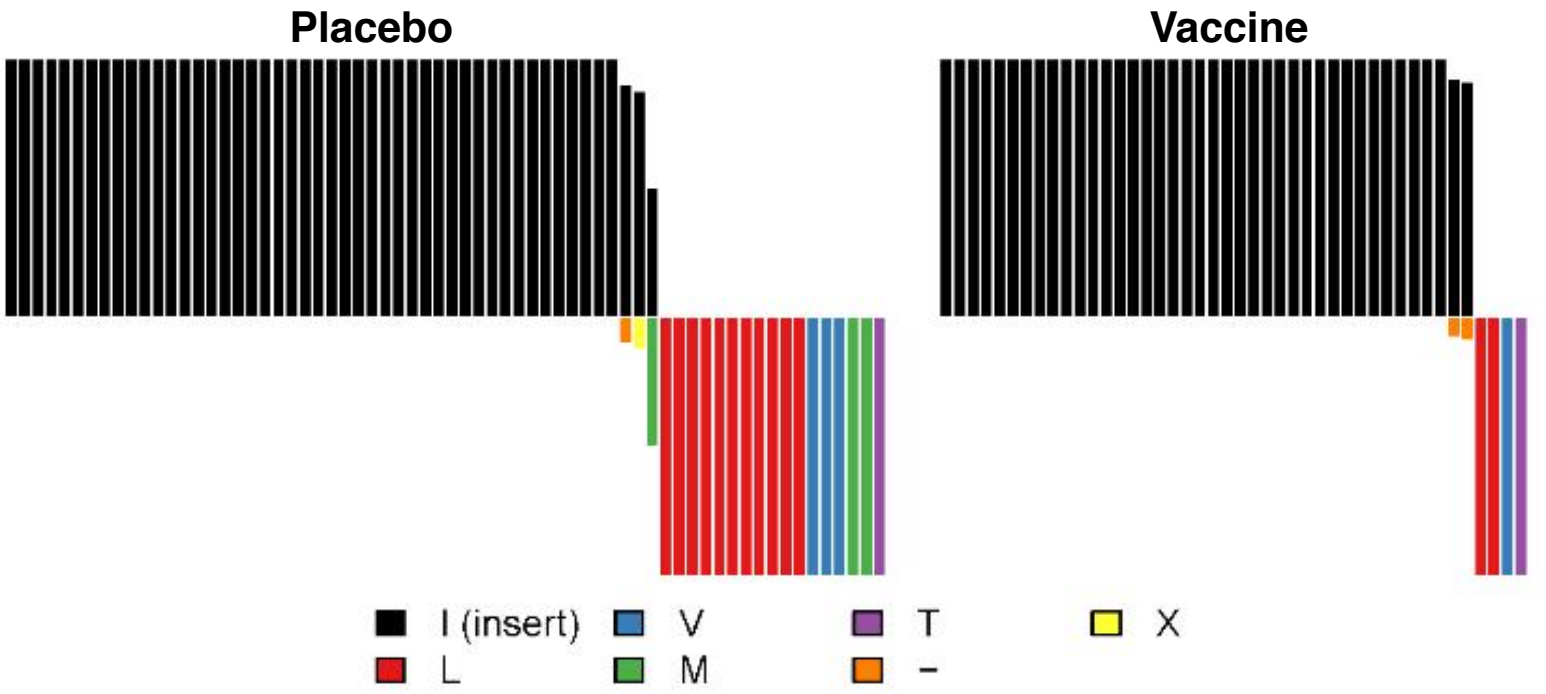
Met (MN) not observed

Key:
Each subject is represented by a bar
Bars all have equal height. Insert AA residue, in black, is shown above the midline
Within a bar, colors depict the fraction of the subject's sequences with that AA residue

Position 181

Gilbert, Wu, Jobes:
p=.019, q =.077

Model-Based Sieve:
P(sieve|data) = .002, p =.021, q = .065



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Outline Talk 2

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   - Vaccine efficacy versus particular pathogen strains
   - Sieve effects and other effects
   - Some immunological considerations
   - Some sieve analysis results from HIV-1 vaccine efficacy trials

2. **Some statistical approaches to sieve analysis**
   - Binary endpoint (Infected yes/no)
     - Discrete pathogen types: Categorical data analysis
     - Continuous types: Distance-to-insert comparisons

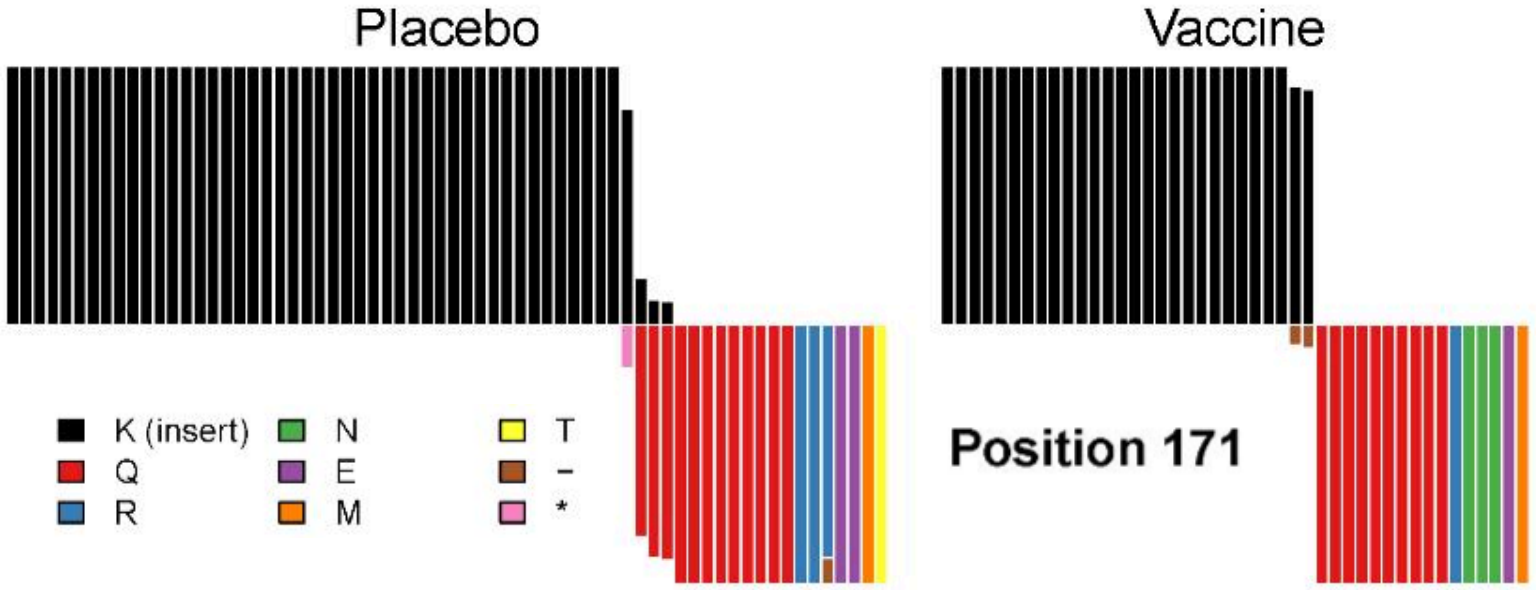
3. Assumptions required for interpretation as per-exposure vaccine efficacy

Overview of statistical approaches to sieve analysis

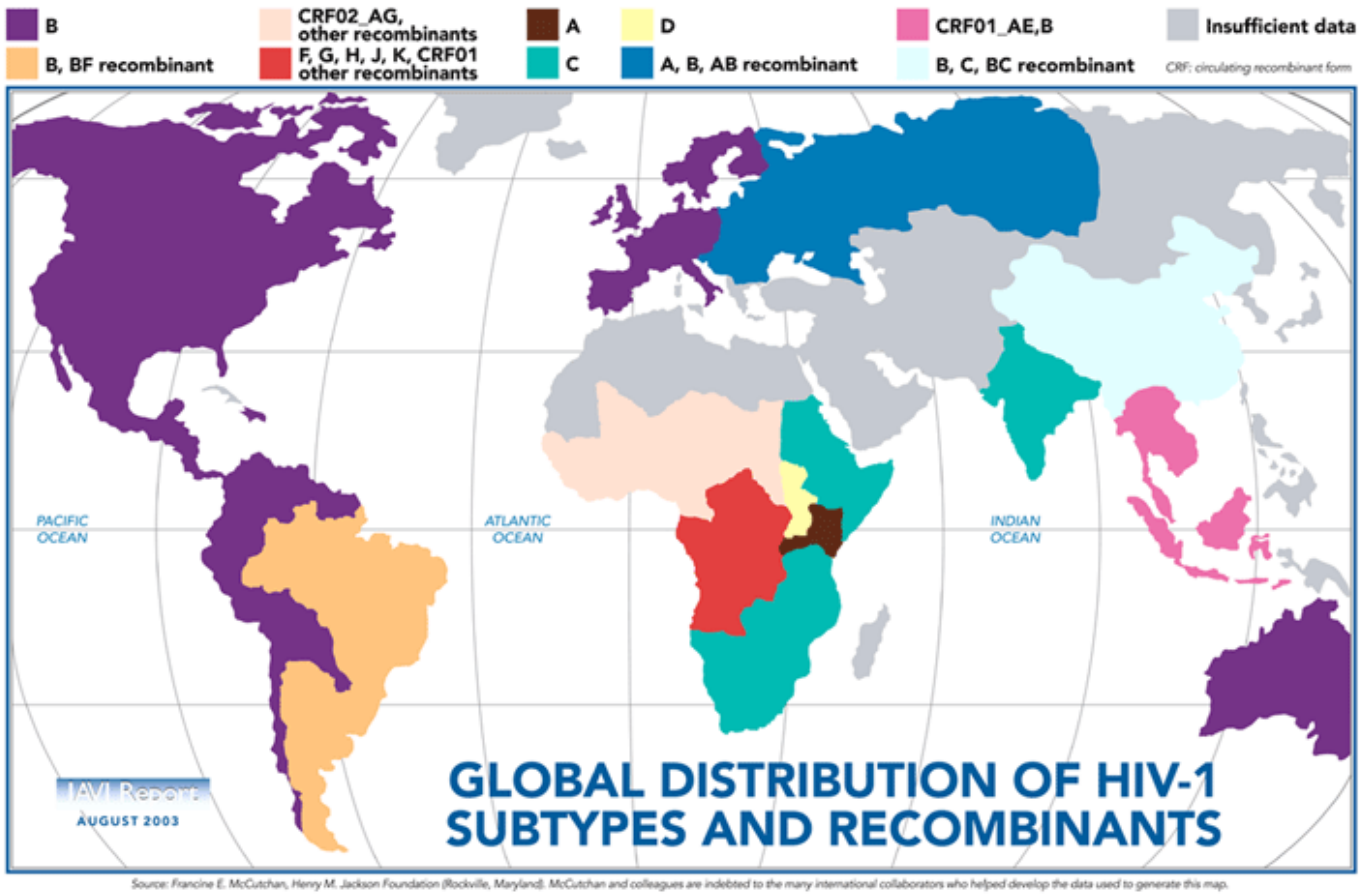
- Binary endpoint (Infected yes/no)
  - Discrete pathogen types: Categorical data analysis
  - Continuous types: Distance-to-insert comparisons
- Time-to-event endpoint (Survival analysis)
  - Discrete types: Competing risks
  - Continuous types: Mark-specific vaccine efficacy

Categorical Sieve Analysis

Fisher p = 0.3575	K	Q	R	N	E	M	T
Placebo	48	11	3	0	2	1	1
Vaccine	28	10	1	3	1	1	0

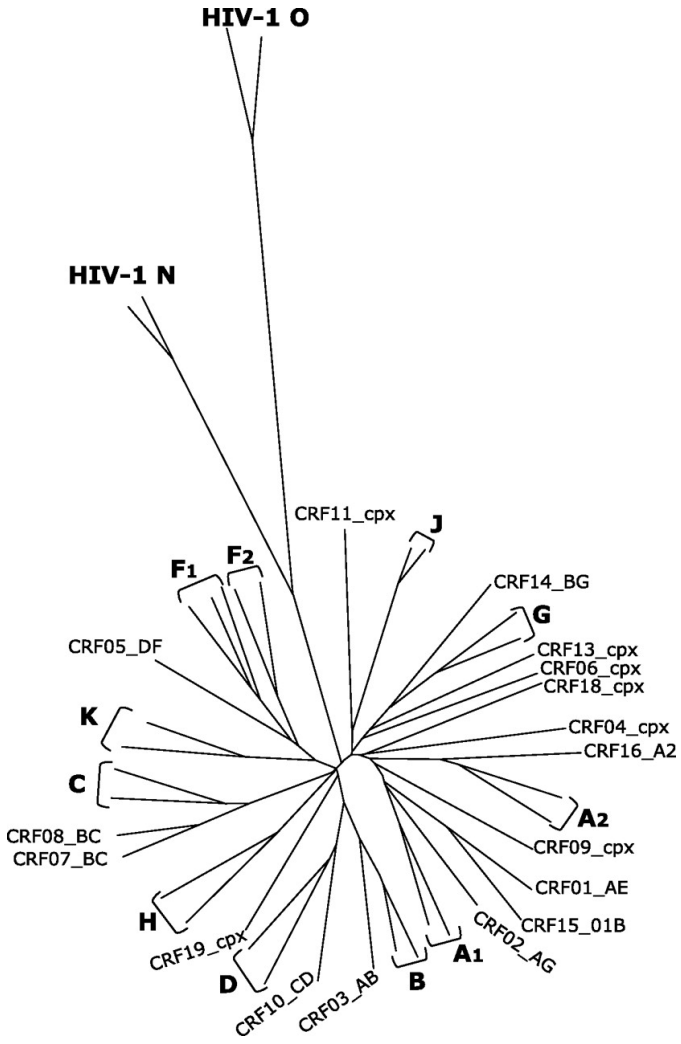


2003 Global Map of HIV-1 Subtypes



A vaccine might have different efficacy against different clades (subtypes) of HIV-1

Evolutionary relationships among nonrecombinant HIV-1 strains.



A vaccine might have different efficacy against different clades (subtypes) of HIV-1

Buonaguro L et al. J. Virol. 2007;81:10209-10219

Categories of pathogen types

- Human trials of preventative vaccines against heterogenous pathogens

Pathogen	Citation
Hepatitis	Szmuness et al. 1981
Cholera	Clemens et al. 1991 van Loon et al. 1993
Rotavirus	Lanata et al. 1989 Ward et al. 1992 Ukae et al. 1994 Jin et al. 1996 Rennels et al. 1996
Pneumococcus	Amman et al. 1977 Smit et al. 1977 John et al. 1984
Influenza	Govaert 1994
Malaria	Alonso et al. 1994

Some of these data are summarized in Gilbert et al. (2001, J Clin Epidem)

Vaccine efficacy vs pathogen type

- Human trials of preventative vaccines against heterogenous pathogens
  - Often there is no quantitative statistical assessment of differential VE across pathogen types
  - When there is, the interpretation and validity is often unclear
- Type-specific VE assessment
  - Can improve power to detect VE
  - Is often of interest
    - Multivalent vaccines: VE for each type
    - Partially protective vaccines: understanding and improving

Data setup

- Randomized vaccine trial
- K categories of infecting pathogens
  - (distinct strains, serotypes, amino acids, etc.)
  - Labeled 1 .. K
  - *wlog*, let category 1 be the "vaccine prototype strain"
    - eg the "insert" strain contained in the vaccine
- Nominal categorical: unordered strains
- Ordered categorical: eg ordered by distance to 1
- (We'll later consider continuous distances)

Meaningful classification

- Problem: sparsity of the 2xK table
  - in HIV, no clear serotypes
    - Star-like phylogeny within each clade
    - Each virus is unique (if you examine closely)
  - In general, for interpretation, want meaningful categories
- Solution: add structure to the table
  - Categorize infecting strains into nominal groups
    - Putatively related to strain-specific VE
    - eg: subtype/clade
    - eg: phenotype (in HIV, tropism: X4 vs R5)
  - (or) Order infecting strains
    - by putative correlate of strain-specifc VE
    - eg: order by measure of similarity to vaccine insert strain
      - Substitution matrix for nucleotide or amino acid sequence
  - Also possible: multidimensional features

Categorical data for sieve analysis

- Data: a 2xK table of counts

	1	2	3	4	5	…	K
Placebo						…	
Vaccine						…	

- Some analysis approaches
  - Fisher's exact test (or Fisher-Freeman-Halton for > 2x2)
  - Bayesian / Multinomial modeling
  - Recode as continuous values, use *eg* t-test
  - Multinomial logistic regression

Multinomial Logistic Regression (Cox, 1970; Anderson, 1972)

$$\Pr(Y = s|v) = \frac{\exp\{\alpha_s + \beta_s v\}}{1 + \sum_{k=2}^{K} \exp\{\alpha_k + \beta_k v\}}$$

- $s \in 1, \ldots, K$
- $\alpha_1 = \beta_1 \equiv 0$
- $v = 1$ indicates vaccine recipients

- A generalized linear logit model

$$\log\left\{\frac{\Pr(Y = s|v)}{\Pr(Y = 1|v)}\right\} = \alpha_s + \beta_s v$$

- Interpretation of the regression coefficients

$$\beta_s = \log\left\{\frac{\Pr(Y = s|\text{vacc})}{\Pr(Y = 1|\text{vacc})} \Big/ \frac{\Pr(Y = s|\text{plac})}{\Pr(Y = 1|\text{plac})}\right\}$$

$$= \log\{\,\text{OR}(s)\,\}$$

Multinomial Logistic Regression model properties

- Minimal assumptions
- Estimation by maximum likelihood
- Exact methods an option
  - Hirji, K. F. (1992). Computing exact distributions for polytomous response data. *Journal of the American Statistical Association* **87**, 487-492.
- Easily extended to ordered categories
  - Anderson's (1984) ordered stereotype model
  - Same model, but use $\beta_s = \phi_s \beta$ and set $\phi_1 \equiv 0$
  - For monotonicity, constrain the order, *eg*

$$0 = \phi_1 \leq \phi_2 \leq \cdots \leq \phi_K = 1$$

Multinomial Logistic Regression alternative ordered models

- Cumulative strain categories model
  - McCullagh 1980

$$\frac{\Pr(Y > s|v)}{\Pr(Y \leq s|v)} = \exp\{\alpha_s + \beta_s v\} \qquad s \in 1, \ldots, K-1$$

  - Interpretation of the regression coefficients

$$\exp\{\beta_s\} = \frac{\Pr(Y > s|\text{vacc})/\Pr(Y > s|\text{plac})}{\Pr(Y \leq s|\text{vacc})/\Pr(Y \leq s|\text{plac})}$$

$$= \text{OR}(> s)$$

- Scored ordinal models
  - Replace β_s with $(s-1)\beta$
  - Scored models have increased precision
    - But stronger modeling assumptions

Nonparametric Tests for Differential VE

- Null hypothesis: all $\mathrm{OR}(s) = 1$
- Nominal categorical:
  - Likelihood ratio chi-squared test (Armitage 1971)
- Ordinal categorical:
  - Test for trend in strain-specific odds ratios
  - Breslow and Day (1980)
- Multiple vaccine dose groups:
  - Kruskal-Wallis test
  - Linear-by-linear association test (Agresti, 1990, p. 284)

Parametric Tests for Differential VE

- MLR or cumulative categories
  - Null hypothesis: all $\beta_s = 0$
  - Likelihood ratio chi-squared test
  - Zelen's test (1991)
  - Note: could also test null that a subset of the $\beta_s = 0$
- Categorical scored models
  - Null hypothesis: $\beta = 0$
- Continuous Model
  - Null hypothesis: $\beta = 0$
  - Likelihood ratio, Wald, and score test

Hepatitis B example

- Hepatitis B vaccine trial in New York
  - Szmuness et al., 1981
- MLR test of differential VE
  - Sieve LRT: $\chi^2_2 = 28.3,\ p < 10^{-6}$
  - Zelen's: $\chi^2_2 = 26.1,\ p < 10^{-5}$
- MLR parameter estimates

	Hep B	Hep A	Hep other
Placebo	63	27	11
Vaccine	7	21	16

$$\exp(\hat{\beta}_2) = \frac{\mathrm{RR}(\text{hep A})}{\mathrm{RR}(\text{hep B})} = 7.0 \qquad 95\%\ \mathrm{CI}: (2.7, 18.4)$$

$$\exp(\hat{\beta}_3) = \frac{\mathrm{RR}(\text{hep other})}{\mathrm{RR}(\text{hep B})} = 13.1 \qquad 95\%\ \mathrm{CI}: (14.3, 39.3)$$

HIV-1 Ordinal Categorical Example
The 'GPGRAF' V3 loop tip sequence

- VaxGen's MN/GNE8 gp120 vax; early-phase trial
  - See Gilbert, Self, Ashby 1998
  - Not randomized
  - Low power, few endpoints
    - Breslow-Day: p=0.11
    - Kruskal-Wallis: p = **0.13**

# mismatches	0	1	>1
Historical	43	20	4
Vaccine	2	1	2

Fit of sieve models to breakthroughs in Genentech vaccine trial

Model	Category	$\hat{\beta}$	SE($\hat{\beta}$)	$\exp\{\hat{\beta}\} = \widehat{OR}$	95% CI[a] $\widehat{OR}$	p-value
MLR	1	.072	1.25	1.07	(0.09, 12.56)	0.95
	2	2.38	1.13	10.75	(1.18, 98.16)	0.035
Cumulative logit	>0	0.99	0.95	2.69	(0.42, 17.22)	0.30
	>1	2.35	1.05	10.50	(1.35, 81.96)	0.025
Adjacent categories	1	1.12	0.63	3.06	(0.90, 10.43)	0.074
linear logit	2	2.24	1.26	9.35	(0.80, 108.69)	0.074
Proportional odds	>0	1.18	0.52	3.27	(1.17, 9.11)	0.024
	>1	1.18	0.52	3.27	(1.17, 9.11)	0.024

[a] Ninety-five percent confidence intervals are derived from a normality approximation and the observed inverse information matrix.

Generalized Logistic Regression Model (Gilbert et al, 1999; Gilbert, 2000)

- Continuous analog of the MLR model
  - Parameterized $\beta_s = g(s)\theta \qquad s \in [0, \text{inf})$
    - For some deterministic function g

$$\Pr(Y = y|\text{vacc}) = \frac{\exp\{g(y)\theta\} f(y)}{\int_0^\infty \exp\{g(z)\theta\} dF(z)}$$

    - Where $f(y) \equiv \Pr(Y = y|\text{plac})$
  - Parametric component: regression coefficients
  - Nonparametric component:

    the placebo-recipient distribution F

Generalized Logistic Regression Model (continued)

- Interpretation of the regression coefficients

$$g(y)\theta = \log\{\mathrm{OR}(y)\} = \log\left\{\frac{\mathrm{RR}(y)}{\mathrm{RR}(0)}\right\}$$

  - Can also compute arbitrary log-odds ratios via:

$$\big(g(y_1) - g(y_2)\big)\theta = \log\left\{\frac{\mathrm{RR}(y_1)}{\mathrm{RR}(y_2)}\right\}$$

  - eg if $g(y) = y$,

$$\mathrm{RR}(y+1) = \exp\{\theta\}\mathrm{RR}(y)$$

Multidimensional pathogen variation

- The MLR and GLR models can accommodate pathogen variation described by multiple features
- Data examples:
  - Cholera: biotype, serotype, disease severity
  - Rotavirus: serotype, disease severity
  - HIV-1: vast possibilities
    - tropism
    - sequence distances to multiple vaccine inserts
    - presence (or affinity) of antibody binding targets
    - sequence distances in multiple regions

Multivariate GLR Model

- $\mathbf{Y} = (Y_1, \ldots, Y_d) \in [0, \infty)^d$
- *eg* for $d = 2$:

$$\Pr(\mathbf{Y} = (y_1, y_2) | \text{vacc}) = \frac{\exp\{g_1(y_1)\theta_1 + g_2(y_2)\theta_2 + g_1(y_1)g_2(y_2)\theta_3\} f(y)}{\int_0^\infty \int_0^\infty \exp\{g_1(z_1)\theta_1 + g_2(z_2)\theta_2 + g_1(z_1)g_2(z_2)\theta_3\} dF(z_1, z_2)}$$

- Can investigate dependence of VE on marginal distances, adjusting for other distances
  - *eg* $\frac{\text{RR}(y_1)}{\text{RR}(y_1')}$ adjusted for Y_2
- Can investigate interactions, *eg* does

$$\text{VE}(Y_1, Y_2) = \text{VE}(Y_1)\text{VE}(Y_2)?$$

HIV-1 Merck adenovirus-5 vector example

- Includes HIV-1 proteins coded by genes
  - *gag*, *pol*, and *nef*
- $\mathbf{Y} = (Y_{gag}, Y_{pol}, Y_{nef})$
  - Y_{gag} : a distance metric based on the *gag* gene
  - Y_{pol} : a distance metric based on the *pol* gene
  - Y_{nef} : a distance metric based on the *nef* gene
- Investigate how vaccine efficacy depends on heterogeneity in *gag*, *pol*, and *nef*

HIV-1 Merck adenovirus-5 vector example continued: introducing CDX metrics

- Question: What are the roles of CD4+ and CD8+ T-cell immune responses in vaccine protection?
  - Helper t cells (CD4+) vs Killer t cells (CD8+)
- $\mathbf{Y} = (Y_{\text{CD4+}}, Y_{\text{CD8+}})$ are **phenotypic marks**
  - $Y_{\text{CD4+}}$: strength of the CD4+ T cell response
    - **a T help metric**
  - $Y_{\text{CD8+}}$: strength of the CD8+ T cell response
    - **a CTL metric**
- Putting these together, get 3x2 = 6 dimensions:

$$\mathbf{Y} = (Y_{\text{CD4+},gag}, Y_{\text{CD4+},pol}, Y_{\text{CD4+},nef}, Y_{\text{CD8+},gag}, Y_{\text{CD8+},pol}, Y_{\text{CD8+},nef})$$

The *s*-sample GLR model

- *s* distinct covariate groups $x_1, \ldots, x_s$
  - *eg* for placebo & vaccine groups, $g_{\text{plac}}(y) \equiv 0$ in:

$$\Pr(Y = y|x_i) = \frac{\exp\{g_i(y)\theta\} f(y)}{\int_0^\infty \exp\{g_i(z)\theta\} dF(z)}$$

- For the *d*-dimensional case,
  the *s*-sample GLR model is

$$\Pr(Y = y|x_i) = \frac{\exp\{\sum_{k=1}^d g_{ik}(y)\theta_k\} f(y)}{\int_0^\infty \exp\{\sum_{k=1}^d g_{ik}(z)\theta_k\} dF(z)}$$

- *s* could also be multiple vaccine dose levels,
  stratification variable levels, etc.

Estimation for the GLR model

- The *s*-sample GLR model is a special case of a *semiparametric biased sampling model*:

$$\Pr(Y = y|i) = \frac{w_i(y,\theta)f(y)}{\int_0^\infty w_i(z,\theta)dF(z)} \qquad i \in 1,\ldots,s$$

- *eg* two-sample one-dimensional GLR model:

$$w_1(y,\theta) \equiv 1 \text{ and } w_2(y,\theta) \equiv g(y)\theta$$

- MLEs are obtained by maximizing a partial likelihood
  - see Gilbert et al, 1999 and Gilbert, 2000

Properties of the MLE in the GLR model

- GLR model is identifiable
- GLR model is uniquely estimable
  - Log profile partial likelihood is strictly concave
- MLEs are uniformly consistent, asymptotically Normal, asymptotically efficient
- Confidence intervals and variance estimation
  1. sample estimator of generalized Fisher information
  2. bootstrap
- Satisfactory finite-sample properties
- **Comparable to MLE in Cox model**

Outline Talk 2

1. Introduction: Concepts and definitions of sieve effects / sieve analysis
   - Vaccine efficacy versus particular pathogen strains
   - Sieve effects and other effects
   - Some immunological considerations
   - Some sieve analysis results from HIV-1 vaccine efficacy trials

2. Some statistical approaches to sieve analysis
   - Binary endpoint (Infected yes/no)
     - Discrete pathogen types: Categorical data analysis
     - Continuous types: Distance-to-insert comparisons

3. Assumptions required for interpretation as per-exposure vaccine efficacy

Model parameters and odds ratios

- Recall: for two-sample, one-dimensional MLR,

$$e^{\beta_s} = \frac{P_{vs}}{P_{v1}} \Big/ \frac{P_{ps}}{P_{p1}} = \frac{\mathrm{RR}(s)}{\mathrm{RR}(1)} = \log\{\ \mathrm{OR}(s)\ \}$$

$$P_{zs} \equiv \Pr\Big(\text{ infected by strain } s \,\Big|\, \text{infected in } [0,\tau],\ \text{vaccine treatment assignment is } z\ \Big)$$

  - MLR: $e^{\beta_2} = \mathrm{OR}(2), \cdots, e^{\beta_K} = \mathrm{OR}(K)$
  - Scored MLR: $e^{\beta} = \mathrm{OR}(2), \cdots, e^{(K-1)\beta} = \mathrm{OR}(K)$
  - Ordered stereotype:

$$e^{\phi_2\beta} = \mathrm{OR}(2), \cdots, e^{\phi_K\beta} = \mathrm{OR}(K)$$

  - Cumulative categories:

$$e^{\beta_2} = \mathrm{OR}(>1), \cdots, e^{\beta_K} = \mathrm{OR}(>K-1)$$

  - GLR: $e^{g(y)\beta} = \mathrm{OR}(y)$

Retrospective vs Prospective

- All of the methods (so far) condition on infection
  - A post-randomization subgroup
  - Potential for bias despite randomized design
- Gilbert, Self, Ashby (1998) define
  - (have) *retrospective* relative risk

$$\mathrm{RR}(s) = \frac{\Pr\left(\text{ infected by strain } s \,\middle|\, \text{infected, vaccine recipient }\right)}{\Pr\left(\text{ infected by strain } s \,\middle|\, \text{infected, placebo recipient }\right)}$$

  - (want) *per-contact* relative risk

$$\mathrm{RR}^{\mathrm{pc}}(s) = \frac{\Pr\left(\text{ infected by strain } s \,\middle|\, \text{one exposure to strain } s, \text{ vaccine recipient }\right)}{\Pr\left(\text{ infected by strain } s \,\middle|\, \text{one exposure to strain } s, \text{ placebo recipient }\right)}$$

The Sieve Conditions

- *per-contact* RR **is** *retrospective* RR **if**

  (during the trial follow-up period)

  1. Infection is possible from at most one strain
  2. The relative prevalence of strains is constant
  3. Exposure distributions are the same in both treatment groups, and homogeneous across subjects*

- Proof in Gilbert, Self, Ashby (1998)
  - Holds for all of the aforementioned models
  - * the homogeneity aspect of this assumption can be relaxed. See Gilbert, Statistics in Medicine 2000.
  - See Gilbert, et al (2001) for more discussion
- Allows for the interpretation of strain-specific VE as prospective, per-contact-by-*s* VE