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Statistical Methods for Assessing Differential Vaccine Protection Against Human Immunodeficiency Virus Types

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SUMMARY

The human immunodeficiency virus type 1 (HIV-1) is extremely diverse. In assessing the utility of an HIV-1 vaccine, an important issue is the possibility of differential protection. We discuss statistical methods of inferring how the vaccine efficacy may vary with viral type from data that would be collected from a randomized, double-blind, placebo-controlled preventive vaccine efficacy trial. Detailed characterization of virus isolated from individuals infected during the trial will be available. We focus on the highly simplified case in which the viral characteristics are summarized by a single feature, which may be nominal, or a scalar quantity that represents distance between the isolate and the prototype virus or viruses used in the vaccine preparation. We consider discrete categorical and continuous response models for this quantity and identify models whose parameters can be interpreted as log ratios of strain-specific relative risks of infection in a prospective model for HIV-1 exposure and transmission. Methods of inference are described for the multinomial logistic regression (MLR) model for discrete categorical response, and a new semiparametric model which can be viewed as a continuous analog of the MLR model is introduced. The methods are illustrated by application to HIV-1 and hepatitis B vaccine trial data.

1. Introduction

The high level of genotypic, phenotypic, and serotypic variation in human immunodeficiency virus type 1 (HIV-1) between and within infected individuals may present an important problem in the development of broadly protective vaccines. Safe vaccine candidates furthest along in development and evaluation, such as recombinant subunit vaccines and genetically engineered poxvirus vaccines, deliver antigens that are homologous to those from one or a few prototype viruses. This raises the important research question: How broadly do these vaccines protect? These vaccines may protect against challenge by strains similar to the prototype but, in the absence of cross-reactivity, may fail against divergent strains. This belief is founded on the observation that HIV-1 infected animals and humans produce virus type-specific antibody responses (Arendrup et al., 1993; Nkengasong et al., 1994; Zwart et al., 1992) and that neutralization is usually more effective against homologous than heterologous challenge virus (Mascola et al., 1996). More importantly, most vaccines based on a single prototype virus have failed to protect chimpanzees challenged with a different isolate (Warren and Dolatshahi, 1993).

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Key words: Cumulative logit model; Generalized logistic regression model; HIV vaccine efficacy trial; Human immunodeficiency virus; Multinomial logistic regression model; Sieve analysis; Stereotype model.
Overall, much is unknown about type-specific protection against HIV-1. Some observations suggest that broad protection may be possible. For example, two groups have demonstrated neutralization of a diverse set of laboratory and clinical isolates by antibodies to an MN rgp120 vaccine (Berman et al., 1992; Lasky et al., 1986), and recent studies show extensive cytotoxic T-lymphocyte cross-reactivity among different HIV-1 clades (Cao et al., 1997). Further, two groups (Berman et al., 1996a; Girard et al., 1995) have demonstrated protection of MN-vaccinated chimpanzees against SF-2 challenge, which is approximately 18% at variance with MN in amino acid envelope sequence (Myers et al., 1992).

Data from animal vaccine challenge studies or in vitro measures such as breadth of neutralizing activity are insufficient for reliably assessing how the degree of protection conferred by an HIV-1 vaccine in humans may depend on characteristics of the virus. To make a definitive evaluation, it is necessary to conduct a randomized vaccine efficacy trial in humans. Therefore, in our development of statistical methods to assess differential protection, we assume to have data from a randomized, double-blind, placebo-controlled preventive vaccine efficacy trial. Several such trials are being planned (Cohen, 1995). In these trials, uninfected high-risk volunteers will be randomly allocated to receive vaccine or placebo and will be monitored for infection. Genotypical, phenotypical, and serotypical viral characteristics will be measured on virus isolated from individuals infected during the trial.

In the geographic setting of a vaccine trial, there will be a vast array of distinct HIV viruses in circulation. The data for sieve analysis consist of frequency distributions of infecting strains in the placebo and vaccine groups, as depicted in Figure 1. The challenge of this problem is that only those types that lead to an infection can be observed, so that data are only available from an improper subset of trial participants. This lends the name sieve analysis to this problem, where the sieve is a barrier to HIV-1 infection (Berman et al., 1996b), which separates the observable from the unobservable exposure virus types. Because of the sieve, it is not possible to directly measure strain-specific attack rates in the placebo and vaccine groups. Thus, since vaccine efficacy is measured by the ability of the vaccine to reduce the attack rate of the pathogen, strain-specific vaccine efficacies cannot be calculated directly. This is analogous to case–control studies in which

![Figure 1: Sieve analysis of breakthrough infections.](image-url)
relative risks cannot be directly estimated—rather, odds ratios are estimated and assumptions are
needed in order that the odds ratios approximate relative risks. Similarly, in sieve analysis, strain-
specific odds ratios can be estimated and assumptions are needed to relate these to parameters
that describe strain-specific vaccine efficacy.

Parametric models from which strain-specific vaccine efficacies can be estimated are identified
in Section 3, with inference procedures developed in Section 4. We begin in Section 2 by discussing
nonparametric sieve analysis and identifiability issues. Section 5 illustrates the methodology by
applying it to data from an HIV-1 vaccine trial and from a hepatitis B vaccine trial. Section 6
addresses power for detecting type-specific protection.

2. Sieve Analysis of Strain-Specific Vaccine Efficacy

2.1 Factoring Likelihoods

From vaccine trial outcome data, the analysis of vaccine efficacy can be decomposed into a primary
analysis of the overall vaccine effect and a secondary sieve analysis of strain-specific differences.
Suppose there are \( K \) distinct strains in circulation, labeled 0, 1, \ldots, \( K - 1 \). Let the time interval
\([0, \tau]\) be the follow-up period of the vaccine trial. Let \( N_v \) and \( N_p \) be the number of trial participants
on the vaccine and placebo arms and \( N_{vI} = \sum_{s=0}^{K-1} n_{vs} \) and \( N_{pI} = \sum_{s=0}^{K-1} n_{ps} \) be the number of
infections on the vaccine and placebo arms, respectively. Here \( n_{vs} \) \((n_{ps})\) is the number of trial participants
in the vaccine (placebo) group observed to be infected with HIV strain \( s \) during \([0, \tau]\).

The data can be described as the cell counts of a \( 2 \times (K + 1) \) contingency table, as shown in Table
1.

Under the assumption that infection can occur from at most one strain during follow-up, it
follows from the formula for conditional probability that the likelihood of observing the counts of
the \( 2 \times (K + 1) \) contingency table factorizes as

\[
L_{\text{full}} = \left\{ \pi_v^{N_v} (1 - \pi_v)^{N_v - N_vI} \pi_p^{N_p} (1 - \pi_p)^{N_p - N_pI} \right\} \times \prod_{s=0}^{K-1} \frac{P_{us}^{n_{us}} P_{ps}^{n_{ps}}}{P_{us} P_{ps}}.
\]

\[L_{\text{primary}} \times L_{\text{sieve}}, \quad (2.1)\]

where \( \pi_v \) \((\pi_p)\) is the probability that a vaccinated (nonvaccinated) trial participant is infected
during \([0, \tau]\) and \( P_{us} \) \((P_{ps})\) is the probability that a vaccinated (nonvaccinated) participant’s
infection was caused by strain \( s \). Here we assume that the effect of the vaccine against each strain \( s \) is
homogeneous in that it reduces the probability of transmission resulting from a single exposure to a
type \( s \) strain by a fixed fraction for all individuals. This proportional hazards modeling assumption
for the vaccine’s protective effect is known as Smith’s model 1 (Smith, Rodrigues, and Fine, 1984).

Corresponding to the factorization of likelihoods is a partitioning of likelihood ratio chi-squared
statistics: the likelihood ratio statistic for the full \( 2 \times (K + 1) \) contingency table is equal to the
sum of the likelihood ratio statistic, which tests the null hypothesis of no overall vaccine effect
\((H_0: \pi_v = \pi_p)\), and the sieve likelihood ratio statistic, which tests the null hypothesis of uniform
vaccine protection \((H_{0S}: P_{us} = P_{ps}, 0 \leq s \leq K - 1)\). Therefore, the analysis of vaccine efficacy
can be orthogonally decomposed into a primary analysis of vaccine efficacy and a secondary sieve
analysis of strain-specific differences.

The form of the sieve likelihood ratio statistic is the usual one for testing the homogeneity of
\( K - 1 \) proportions, as given by Armitage (1971). This omnibus test of \( H_{0S} \) may have low power.
If the strain categories are ordered, power may be gained by testing for a trend in odds ratio with
increasing strain category. Breslow and Day (1980, p. 148) give an appropriate statistic, which is
asymptotically chi-squared with one degree of freedom.

### Table 1

<table>
<thead>
<tr>
<th>Vaccine trial contingency table</th>
</tr>
</thead>
</table>
| \( \begin{array}{ccc|c|c}
| \text{Infected strains} & 0 & 1 & K - 1 & \text{Not infected} & K \\
| \hline
| \text{Placebo} & n_{p0} & n_{p1} & \cdots & n_{pK-1} & N_p - N_pI & N_p \\
| \text{Vaccine} & n_{v0} & n_{v1} & \cdots & n_{vK-1} & N_v - N_vI & N_v \\
| \hline
| \text{n0} & n_1 & n_{K-1} & N - N_I & N \\
| \hline
| \end{array} \) |


For nominal response, a suitable exact test of $H_{0S}$ is the Fisher–Freeman–Halton test, which utilizes the multiple hypergeometric distribution. For ordinal response, a suitable exact test is based on the Kruskal–Wallis nonparametric rank statistic. For ordinal response and multiple vaccine dose groups, the linear-by-linear association test (Agresti, 1990, p. 284) is appropriate, as it accounts for the ordering in vaccine dose. An advantage of this test is its flexibility—the user specifies scores to weight the relative importance of successive rows or columns of the contingency table. Exact $p$-values for these tests can be computed using StatXact software (Mehta and Patel, 1995).

2.2 Structuring Viral Variation for Sieve Analysis

The enormous genotypic diversity of HIV-1, coupled with the capability of laboratories to sequence genes, means that each isolate of infecting virus will be genetically unique upon close enough examination. Thus, the number of strain categories $K$ will be of the same order as the number infected, so that the $2 \times K$ sieve table will be too sparse and unstructured for meaningful analysis.

Our proposed solution is to add structure to the table by comparing strains on the basis of some summary viral feature that is putatively correlated with vaccine efficacy. For instance, this feature could be based on a specific gene or region of a gene or on a specific phenotype. Examples of important phenotypes are serotype, cellular or tissue tropisms (which may reflect route of transmission and are the strongest known determinants of transmission (Weiss, 1993)), and surrogates for severity of HIV disease, such as capacity of virus to replicate or to induce synctia.

The viral feature may be nominal categorical, ordered categorical, or a continuous distance, where the ordering is by some measure of similarity to the prototype virus or viruses. A simple example of a viral distance is the Hamming distance based on the amino acid sequence of some coding region. Viral variation can also be structured by a multidimensional viral feature, incorporating various categorical and/or continuous features. As there is no consensus on how to structure viral variation for sieve analysis, a chief goal of sieve analysis is identification of viral characteristics that are associated with differential vaccine efficacy.

2.3 Identifiability and Reinterpretation of Infection Probabilities

The data for sieve analysis follow a retrospective sampling probability model in that the strain-specific probabilities $\{P_{ps}\}$ and $\{P_{vs}\}$ condition on infection. The probability ratios $P_{vs}/P_{ps}$, $s \in \{0, \ldots, K - 1\}$, are identifiable from the cell counts of the $2 \times K$ contingency table of infecting strains. These strain-specific retrospective relative risks $RR_v(s) \equiv P_{vs}/P_{ps}$ do not give a direct interpretation of strain-specific protection. In this paper, we characterize simple assumptions on the exposure and infection dynamics of the circulating HIV-1 strains in the trial population, which allows the estimation of quantities interpretable as log ratios of strain-specific relative per-contact transmission rates in a prospective model for HIV-1 exposure and transmission. The concept of estimating parameters based on a prospective model from retrospectively sampled data has been advanced for general infectious disease modeling of vaccine effects by Rhodes, Halloran, and Longini (1996).

For $s \in \{0, \ldots, K - 1\}$, define $P_{Vs}^p$ to be the prospective probability that a trial participant with vaccination status $V$ ($V = 0$ or $p$, placebo; $V = 1$ or $v$, vaccine) is infected by a type $s$ strain during $[0, \tau]$. Thus, the retrospective probabilities $\{P_{Vs}\}$ and prospective probabilities $\{P_{Vs}^p\}$ are defined by

$$P_{Vs} \equiv \Pr(\text{strain } s \mid \text{infected in } [0, \tau], V)$$

and

$$P_{Vs}^p \equiv \Pr(\text{infected by a type } s \text{ strain in } [0, \tau] \mid V).$$

(2.2)

Denote the prospective relative risk of infection by a type $s$ strain during $[0, \tau]$ by $RR_{p}(s) \equiv P_{vs}^p/P_{ps}$. The prospective and retrospective relative risks are related. Under the assumption that infection can occur from at most one strain during follow-up, it follows that

$$P_{Vs}^p = \pi_v \times P_{Vs},$$

(2.3)

which implies $RR_{v}(s) = RR_{p} \times RR_{v}(s)$, where $RR_{p} \equiv \pi_v/\pi_p$ is the relative probability of infection occurring during follow-up. Thus, $RR_{v}(s)$ is proportional to $RR_{p}(s)$ under the assumption.

The $\{RR_{p}(s)\}$ are informative of strain-specific protection but do not account for the amount of exposure. For $s \in \{0, \ldots, K - 1\}$, define

$$RR(s) \equiv \frac{\Pr(\text{infected by strain } s \mid \text{one exposure to strain } s, \text{vaccinated})}{\Pr(\text{infected by strain } s \mid \text{one exposure to strain } s, \text{placebo})}$$

(2.4)
to be the relative risk of transmission resulting from a single exposure to strain $s$. Under Smith’s model 1 that the vaccine effect is homogeneous in trial participants against each strain, these relative risks are equal to one minus the strain-specific vaccine efficacy. We now introduce categorical models of the identifiable retrospective probabilities \{$P_{rs}$\} from which ratios of strain-specific relative risks as in (2.4) can be estimated under simple assumptions.

3. Categorical Models for Sieve Analysis

3.1 Introduction of Categorical Models

Suppose viral variation is structured by a single categorical feature. A natural method of relating the strain categories to one another is through parametric functions. We introduce three parametric categorical models for sieve analysis, the multinomial logistic regression (MLR) model (Anderson, 1972; Cox, 1970) for a nominal viral feature and the related stereotype model (Anderson, 1984) and a cumulative logit model (cf., Agresti, 1984, 113–114) for an ordinal viral feature. We argue that they are appropriate for sieve analysis because, under simple assumptions, they are equivalent to a prospective model for HIV-1 exposure and transmission.

Let $Y$ be a discrete categorical response variable, representing the infecting strain category, with possible values $0, \ldots, K-1$. The categories should be defined exhaustively in that every infection is by one of the $K$ strains. Let $x = (x_1, \ldots, x_p)^t$ be a vector of predictors. The MLR model specifies

$$
Pr(Y = s \mid x) = \frac{\exp \left\{ \beta_{0s} + \beta_s^T x \right\}}{1 + \sum_{t=1}^{K-1} \exp \left\{ \beta_{0t} + \beta_t^T x \right\}}
$$

$(0 \leq s < K), \quad (3.1)$

where $\beta_{00} = \beta_0 = 0$ for identifiability. This is a generalized linear logit model. Anderson (1972, 1983, 1984) has found this model to be useful in many distributional contexts for discrete and continuous predictors. It provides a flexible, general approach to discrete regression modeling. The MLR model is appropriate for a nominal categorical response but can be easily modified to model an ordered categorical response variable. To do this, restrict the parameters $\beta_s$ of the model (3.1) to be parallel,

$$
\beta_s \equiv \phi_s \beta \quad (1 \leq s < K), \quad \phi_0 \equiv 0, \quad \phi_{K-1} \equiv 1, \quad (3.2)
$$

where $\beta = (\beta_1, \ldots, \beta_p)^T$ and the $\{\phi_s\}$ are now the parameters to estimate. The constraint of an ordered regression relationship is expressed by requiring the parameters $\{\phi_s\}$ to be monotone, e.g., monotone nondecreasing, i.e.,

$$
0 = \phi_0 \leq \phi_1 \leq \cdots \leq \phi_{K-1} = 1. \quad (3.3)
$$

Changing the sign of $\beta$ specifies monotone nonincreasing $\{\phi_s\}$. Substituting (3.2) and (3.3) into (3.1) gives Anderson’s (1984) ordered stereotype model.

Suppose vaccination status is the lone covariate, i.e. $x = V$, and the retrospective response probabilities $\{P_{V,s}\}$ of (2.2) are assumed to satisfy the MLR model (3.1) or the stereotype model. It is natural to take category 0 to represent the prototype strain. The parameters $\{\beta_{0s}\}$ are not of principle interest but are interpretable as log relative probabilities in the general infected population that infection was initiated by a type $s$ strain compared to a prototype strain, i.e., $\beta_{0s} = \log \{P_{ps}/P_{p0}\}$. The regression parameters $\{\beta_s\}$ have interpretation as strain-specific log odds ratios

$$
\beta_s = \log \left\{ \frac{P_{0s}}{P_{00}} \bigg/ \frac{P_{ps}}{P_{p0}} \right\} \equiv \log \{OR(s)\}.
$$

Rearranging the quotients expresses $\beta_s$ as a log ratio of retrospective relative risks defined in Section 2.2,

$$
\beta_s = \log \left\{ \frac{RR_t(s)}{RR_t(0)} \right\} \quad (1 \leq s < K). \quad (3.4)
$$

Thus, for any two strain categories $s$ and $t$, $\exp(\beta_s - \beta_t)$ gives the ratio of retrospective relative risks specific to categories $s$ and $t$.

The interpretation of the ordered stereotype model is identical, with $\beta_s$ replaced by $\phi_s \beta$. The maximum likelihood parameter estimates will differ because the likelihood is maximized under the
ordering constraint (3.3). For sieve analysis, the ordering hypothesis is met if and only if the \{\text{OR}(s)\}, or equivalently the \{\text{RR}_r(s)\}, are monotone with strain category. Biologically, the ordering hypothesis is that the vaccine works best against the prototype strain and increasingly worse against more divergent strains. This hypothesis is intuitive and is supported by HIV-1 and SIV vaccine challenge studies of chimpanzees and rhesus macaques, which indicate greater efficacy against the prototype strain (AIDS Vaccine Evaluation Group, 1992).

A cumulative logit model is also appropriate for an ordinal viral feature. It specifies
\[
\frac{\Pr(Y > s \mid x)}{\Pr(Y \leq s \mid x)} = \exp \left\{ \beta_{0s} + \beta_s^T x \right\} \quad (0 \leq s < K - 1).
\]
When vaccination status is the lone covariate, the regression parameter \(\beta_s\) is the log odds ratio that infection was caused by a strain \(Y > s\) in a vaccinee relative to a nonvaccinee, i.e., \(\beta_s = \log(\text{OR}(> s)), s = 0, \ldots, K - 2\).

We now show that, under three assumptions, the regression parameters \(\beta_s\) of the sieve MLR model, or the \(\phi, \beta\) of the sieve stereotype model, can be reinterpreted as log ratios of prospective exposure–transmission relative risks defined in (2.4) and that the \(\beta_s\)'s of the sieve cumulative logit model enjoy a parallel reinterpretation.

### 3.2 Identifying the Sieve Models with Prospective Models for HIV-1 Exposure and Transmission
Let \(T \in [0, \tau]\) be the infection time of a trial participant and \(Y\) be the category of the virus causing infection, as above. Let \(\lambda(t, s \mid V)\) be the hazard of infection by strain \(s\) at time \(t \in [0, \tau]\) for an individual with vaccination status \(V\) such that
\[
\lambda(t, s \mid V) = \lim_{\Delta t \searrow 0} \Pr(t \leq T < t + \Delta t, Y = s \mid T \geq t, V)/\Delta t.
\]
Let \(N_{Es}\) be the counting process counting exposures to strain \(s\), with Markov intensity \(\lambda_{Es}\) defined by
\[
\lambda_{Es}(t) = \lim_{\Delta t \searrow 0} \Pr(\text{exposed to strain } s \text{ in } [t, t + \Delta t))/\Delta t.
\]
Assume the proportional hazards assumption for strain-specific vaccine effect introduced in Section 2.1. This is expressed mathematically as follows: The probability of transmission resulting from a single exposure to strain \(s\) is parametrized by
\[
\Pr(\text{infected by strain } s \mid \text{one exposure to strain } s, V) = e^{\alpha_s + \gamma_s V} \quad (V \in \{0, 1\}, s \in \{0, \ldots, K - 1\}).
\]
This implies that the parameter \(\gamma_s\) has interpretation as the log strain-specific relative risk defined in (2.4), i.e.,
\[
\gamma_s = \log\{\text{RR}(s)\}.
\]

The following three assumptions are necessary.

**Assumption 1**: Infection is possible from at most one strain during follow-up.

**Assumption 2**: The relative prevalence of circulating strains is constant over time \([0, t]\).

**Assumption 3**: The probability of being exposed with any strain \(s\) is equal for vaccinated and unvaccinated trial participants (equal mixing of exposures).

Assumption 1 is that no trial participants become infected by multiple strains. Assumption 2 implies that the strain-specific exposure intensities are proportional, i.e.,
\[
\lambda_{Es}(t) = \theta_s \lambda_{E0}(t) \quad (1 \leq s < K),
\]
where the parameter \(\theta_s\) represents the relative frequency of strain \(s\) compared to strain \(0\) among exposing strains. If Assumption 2 did not hold, it would be necessary to include time-dependent parameters describing the underlying strain prevalence distribution. Alternatively, the follow-up period could be broken into several intervals and time-stratified analyses conducted. Assumption 3 is justified by randomization and blinding.

We now derive the key result of this paper. Suppose the identifiable probabilities \(\{P_{Vs}\}\) of (2.2) satisfy the MLR model (3.1). Then under Assumptions 1–3, the regression parameters \(\beta_s = \log\{\text{OR}(s)\} = \log\{\text{RR}_r(s)/\text{RR}_r(0)\}\) also have interpretation \(\beta_s = \log\{\text{RR}(s)/\text{RR}(0)\}\).
Similarly, if the \( \{P_{Vs}\} \) satisfy the ordered stereotype model, then under Assumptions 1–3, the \( \phi, \beta \) also have interpretation \( \phi, \beta = \log\{RR(s)/RR(0)\} \). In the derivation, we show that Assumptions 1–3 imply \( RR_p(s) \) is proportional to \( RR(s) \), so that, by Assumption 1, as in (2.3), \( RR_r(s) \) is also proportional to \( RR(s) \).

To begin, it is straightforward to show that, for any \( t \in [0, \tau] \),

\[
\Pr(t \leq T < t + \Delta t, Y = s \mid T \geq t, V) = \Pr(\text{exposed to strain } s \text{ in } [t, t + \Delta t) \mid V, \text{exposure history}) \\
\times \Pr(t \leq T < t + \Delta t, Y = s \mid T \geq t, V, \text{exposed to } s \text{ in } [t, t + \Delta t), \text{exposure history}).
\]

Dividing both sides by \( \Delta t \) and taking the limit as \( \Delta t \to 0 \) gives

\[
\lambda(t, s \mid V) = \lambda_{Es}(t)e^{\alpha_s + \gamma_s V},
\]

where the parameterization (3.6) is used to ensure that the strain-specific infection intensities are constant over time and Assumption 3 is used to ensure that the probability of exposure by strain \( s \) is independent of vaccination status. Now, with prospective infection probabilities \( P_{Vs}^p \) defined as in (2.2),

\[
P_{Vs}^p = \int_0^\tau \lim_{\Delta t \to 0} \frac{\Pr(t \leq T < t + \Delta t, Y = s \mid V)}{\Delta t} dt = \int_0^\tau \lambda(t, s \mid V) \times \Pr(T \geq t \mid V) dt,
\]

using Assumption 1 to ensure that the probability of an individual being infected by a type \( s \) strain in the time interval \([t, t + \Delta t)\) and by another type of strain at time \( t \) is zero.

Using the equation \( \Pr(T \geq t \mid V) = e^{-\Lambda(t\mid V)} \) relating a survivor function to a cumulative hazard function and equation (3.9), it follows that

\[
\Pr(T \geq t \mid V) = e^{\int_0^t \lambda(u\mid V) du} = e^{\int_t^\tau \lambda(u\mid V) du} = e^{\int_0^t \lambda_{Ei}(u)e^{\alpha_i + \gamma_i V} du}.
\]

Thus, from (3.9) and (3.11), equation (3.10) becomes

\[
P_{Vs}^p = \int_0^\tau \lambda_{Es}(t)e^{\alpha_s + \gamma_s V} \times e^{\int_0^t \lambda_{Ei}(u)e^{\alpha_i + \gamma_i V} du} dt
\]

\[
= \int_0^\tau \lambda_{E0}(t)e^{\alpha_s + \gamma_s V} \times e^{-\Lambda(t\mid V) \sum_i e^{\alpha_i + \gamma_i V}} dt
\]

\[
= \left[ \sum_i e^{\alpha_i + \gamma_i V} e^{-\Lambda(t\mid V) \sum_i e^{\alpha_i + \gamma_i V}} \right]_0^\tau \times e^{\alpha_s + \gamma_s V}
\]

\[
= \left[ 1 - e^{-\Lambda(t\mid V) \sum_i e^{\alpha_i + \gamma_i V}} \right] \times \left[ e^{\alpha_s + \gamma_s V} \sum_i e^{\alpha_i + \gamma_i V} \right],
\]

with \( \alpha_s^* = \alpha_s + \log \theta_s \). It immediately follows from (3.12) that

\[
\gamma_s - \gamma_0 = \log \left( \frac{RR(p)(s)}{RR(p)(0)} \right).
\]

Since the regression parameters \( \{\beta_s\} \) of the sieve MLR model satisfy \( \beta_s = \log\{RR_r(s)/RR_r(0)\} \) as in (3.4), this implies, using (2.3), which follows from Assumption 1, that

\[
\beta_s = \gamma_s - \gamma_0 = \log \left( \frac{RR(s)}{RR(0)} \right).
\]

Moreover, since the \( \{\theta_{0s}\} \) of the sieve MLR model satisfy \( \theta_{0s} = \log\{P_{Vs}/P_{V0}\} \), straightforward calculation yields \( \beta_{0s} = \alpha_s^* - \alpha_0 \). Combining this with (3.13) and using (3.11), which implies \( \pi_V = 1 - e^{-\Lambda(t\mid V) \sum_i e^{\alpha_i + \gamma_i V}} \), expression (3.12) becomes

\[
P_{Vs}^p = \pi_V \times \frac{\exp\{\beta_{0s} + \beta_s V\}}{\sum_{t=1}^{K-1} \exp\{\beta_{0t} + \beta_t V\}} = \pi_V \times P_{Vs}.
\]

This is relation (2.3), so the sieve MLR model is equivalent to the prospective model for HIV-1 exposure and transmission under the three assumptions. In particular, we conclude from (3.13)
that the regression parameters $\{\beta_s\}$ of the sieve MLR model equal log ratios of strain-specific exposure–transmission relative risks of infection.

To illustrate the interpretation, we give a simple hypothetical example in the context of an HIV-1 vaccine trial among intravenous drug users (IVDUs) in Thailand. Let the type of infecting strain $Y$ be the cladie, equal to $B$ or $E$. Suppose the vaccine is 50% protective overall, with counts of infections as in Figure 2. The odds ratio resulting from the $2 \times 2$ table is four, which, under the assumptions, can be interpreted as “the vaccine is four times as protective against challenge with strain B as it is against challenge with strain E.”

As a brief aside, the derivation yielded that the sieve baseline strain prevalence parameters $\{\beta_{0s}\}$ satisfy $\beta_{0s} = \alpha_s - \alpha_0 + \log(\theta_s)$. Thus, $\beta_{0s}$ is the sum of the relative baseline infectiousness of the $s$th strain and the relative abundance of strain $s$ among circulating strains, and their relative contributions cannot be separated out. Therefore, the relative transmissibility of strains cannot be estimated from the data for sieve analysis.

The cumulative logit model (3.5) enjoys a similar connection with a prospective model. Let “$s$” denote the cumulative category of strains $0 - s$. Parameterize the probability of transmission resulting from a single exposure to a strain $\leq s$ by

$$\Pr(\text{infected} | \text{one exposure to strain} \leq s, V) = e^{\alpha_s + \gamma_s V} \quad (V \in \{0, 1\}, s \in \{0, \ldots, K - 2\}).$$

This implies $RR(\leq s) = e^{\gamma_s}$ and $RR(> s) = (\theta_{K-1} e^{\alpha_K - 1 + \gamma_{K-1}} - \theta_0 e^{\alpha_s + \gamma_s}) / (\theta_{K-1} e^{\alpha_K - 1} - \theta_0 e^{\alpha_s})$, where $\theta_s$ represents the relative frequency of strains $\leq s$ compared to strain 0 among exposing strains. Through a derivation parallel to the above derivation, with infection and exposure processes for each cumulative strain category $\leq s$, it follows that, under Assumptions 1–3, $e^{\beta_s} = OR(> s)$ from the cumulative logit model equals $RR(> s) / RR(\leq s), s = 0, \ldots, K - 2$. Moreover, the derivation yields

$$P^B_{V \leq s} = \pi_V \times \theta_s e^{\alpha_s + \gamma_s V} / \theta_{K-1} e^{\alpha_K - 1 + \gamma_{K-1} V} \quad (V \in \{0, 1\}, s \in \{0, \ldots, K - 2\}),$$

where the second piece on the right-hand side can be shown to equal $P_{V \leq s}$, the identifiable cumulative probability satisfying (3.5). Therefore, the sieve cumulative logit model is equivalent to the prospective model under the three assumptions.

The identification of the regression parameters of the MLR model, the stereotype model, and the cumulative logit model with quantities that have direct interpretation as strain-specific vaccine protection in a prospective model for HIV-1 exposure and transmission shows that these models are appropriate for sieve analysis.

### 3.3 Scored Versions of the Sieve Models

In the sieve models, $K - 1$ strain-specific odds ratios are estimated. If the categories are ordered, an alternative is scoring the dependency of vaccine efficacy on virus type and estimating a single sieve parameter $\beta$. Since very few data have been available for sieve analysis by which to choose scores, the nonscored models are generally preferable. However, when scored models fit the data well, they offer a clean interpretation and increased precision. Two models in particular may be useful for sieve analysis. The first is the adjacent categories linear logit model, a special case of the stereotype model in which the parameters $\phi_s$ are replaced by scores, e.g., $\phi_s = s$. The second is McCullagh’s (1980) proportional odds model, the special case of the cumulative logit model in which the parameters $\beta_s$ are replaced by one parameter $\beta$. These models express a constant strain-specific odds ratio across adjacent categories and cumulative categories, respectively, and share the prospective interpretation of the nonscored models.
3.4 A Continuous Model for Sieve Analysis

To provide a comprehensive framework for modeling vaccine protection as a function of viral variation, we introduce a model for assessing how vaccine protection depends on a continuous viral distance from prototype. Let $Y$ denote a continuous viral distance, defined on $[0, \infty)$. Let $F$ be the distribution function of $Y$ in the baseline placebo group, and $f$ its density. Associate the parameters $\beta_0s$ and $\beta_s$ of the MLR model with their continuous analogs

$$\beta_0s \leftrightarrow \log \left\{ \frac{f(y)}{f(0)} \right\} \quad \text{and} \quad \beta_s^T x \leftrightarrow \beta^T g(y \mid x)$$

(3.15)

for some known function $g(y \mid x) = (g_1(y \mid x), \ldots, g_p(y \mid x))^T$, where each $g_k, k = 1, \ldots, p$, is real valued, and may be different for each distinct covariate value $x$, and satisfies $g_k(0 \mid x) = 0$. Substituting the expressions of (3.15) into the MLR model (3.1) and replacing summation by integration gives a continuous analog of the MLR model, which we name the generalized logistic regression model, as

$$\Pr(Y = y \mid x) = \frac{\exp \left\{ \beta^T g(y \mid x) \right\} f(y)}{\int_0^\infty \exp \left\{ \beta^T g(z \mid x) \right\} dF(z)}, \quad (y \in [0, \infty)).$$

(3.16)

For the two-sample problem of sieve analysis, in which $x = V$, $g(y \mid v)\beta$ is a log odds ratio of infection resulting from a strain with distance $y$. Under Assumptions 1–3 of Section 3.2, modified in the obvious way to fit this continuous case, a derivation essentially identical to that used for the MLR model shows that $g(y \mid v)\beta$ equals the log ratio of prospective exposure–transmission relative risks of infection $g(y \mid v)\beta = \log \{RR(y)/RR(0)\}$. Notice that $\beta = 0$ reflects a constant relative risk (uniform vaccine protection) and that $e^\beta$ is the proportionality constant relating the relative risks of two strains $y_1$ and $y_2$ with $g(y_1 \mid v) - g(y_2 \mid v) = 1$. The assumption that vaccine protection decreases with divergence of the challenge strain from the prototype is incorporated by specifying $g$ nondecreasing. Methodology for hypothesis testing and estimation of $\beta$ and $F$ via maximum likelihood is described in Gilbert, Lele, and Vardi (1997).

3.5 Interpretation for Additional Explanatory Variables

We have elucidated the interpretation of the sieve models for the two-sample case in which vaccination status $V$ is the lone predictor. If additional covariates are included, the component regression parameters corresponding to $V$ are interpretable as strain-specific log odds ratios adjusted for the other covariates and, under the three assumptions of Section 3.2, can be reinterpreted as adjusted log ratios of strain-specific exposure–transmission relative risks. Applications include adjusting for duration of follow-up, stratifying by risk groups or other covariates, or additional vaccine arms. Concerning additional arms, it is important to distinguish between intercurrent vaccine failures (infected before complete immunization achieved) and breakthrough vaccine failures (infected after complete immunization achieved).

4. Estimation and Testing in the Categorical Models

4.1 MLR, Stereotype, and Adjacent Categories Linear Logit Models

The MLR, stereotype, or adjacent categories linear logit model of the response probabilities $\{\Pr(Y = y_s \mid x)\}$ can be fit using the method of maximum likelihood. Suppose that $n_s(x)$ sample points are observed at $x$ with response $Y = y_s$. Then the conditional likelihood is

$$L_C = \prod_{s=0}^{K-1} \prod_x \{\Pr(Y = y_s \mid x)\}^{n_s(x)},$$

(4.1)

where the product $\Pi_x$ is taken over observed $x$ values. The probabilities $\{\Pr(Y = y_s \mid x)\}$ from the MLR model (3.1) or from the stereotype model are substituted into (4.1) and then $L_C$ is maximized with respect to the parameters in the model. An iterative algorithm such as quasi-Newton is required. Standard programs are available, for example PROC CATMOD in SAS or the GLIM package (SAS, 1990; Payne, 1987). The log-likelihood is usually concave (Anderson, 1984), in which case maximization is straightforward. Large sample variance estimates of the parameter estimates can be obtained from the inverse information matrix.

If the sample size is small, the number of categories $K$ is large, or the data structure is sparse, then the accuracy of the large sample approximations is in question. The asymptotic methods tend to give inflated variance estimates, and occasionally the covariance matrix of the parameters is
singular, precluding asymptotic analysis (Hirji, 1992). Exact inferential procedures are an attractive alternative. Hirji (1992) developed an efficient method for computing exact conditional distributions of the sufficient statistics for the parameters of the adjacent categories linear logit model. This leads to exact tests and methods of computing exact parameter estimates and confidence intervals, which are implemented, e.g., in StatXact (Mehta and Patel, 1995).

For the two-sample problem in which vaccination status is the covariate, we consider testing the sieve null hypothesis \( H_0: \beta_s = 0 \) for all \( s \) that the vaccine confers uniform protection versus the alternative hypothesis \( H_1: \beta_s \neq 0 \) for some \( s \) that the vaccine protects differentially. Let \( l_0 \) and \( l_1 \) be the log likelihoods under \( H_0 \) and \( H_1 \), respectively. Then the usual argument shows that, for a nominal categorical response, the likelihood ratio statistic is asymptotically chi-squared with \( K - 1 \) degrees of freedom (cf., Wilks, 1938). Alternatively, an appropriate test can be formulated from the means and variances of the sufficient statistics of the MLR model parameters under the null hypothesis \( H_0 \). Following Zelen (1991), under \( H_0 \), the statistic

\[
\sum_{i=0}^{K-1} \frac{(N_v - N_{vI}) \left[ \frac{\hat{P}_{vi} + \hat{P}_{vI}}{2} \right]^2}{N_v s^2 \left[ \frac{\hat{P}_{vi} + \hat{P}_{vI}}{2} \right]^2}, \quad s^2 = \frac{N_{vI}}{N_I^2 (N_I - 1)} \frac{N_I^2 - 2N_I N_{vI} + N_{vI}}
\]

is asymptotically \( \chi^2_{K-1} \), where \( \hat{P}_{vi} \) is the maximum likelihood estimate of the \( i \)th cell probability conditional on vaccination status \( V \). This provides a simple, accurate test if the vaccine protects differentially.

4.2 Cumulative Logit and Proportional Odds Model

The parameters of the cumulative logit model, including the special case of the proportional odds model, can be estimated in a straightforward manner by weighted least squares using PROC CATMOD in SAS (SAS, 1990). The parameter estimates have an asymptotic multivariate normal distribution, from which variance estimates can be obtained. The sieve null hypothesis of uniform vaccine protection takes the same form as for the MLR model, i.e., \( H_0: \beta_s = 0 \) for all \( s \). This can be tested by a generalized Wald statistic, which is asymptotically chi-squared with \( K - 1 \) degrees of freedom. (See Koch et al., 1977, Appendix 1, for details.)

Notice that, for the proportional odds model, as well as for the adjacent categories linear logit model, the sieve null hypothesis is simply \( H_0: \beta = 0 \).

Data from all response categories are used for estimating each \( \beta_s \) in the cumulative models, but data from only the 0th and 9th response categories are used for estimating \( \beta \) in the MLR model. Thus, for ordered viral features with many categories, the cumulative models tend to give more precise estimates of \( \beta_s \).

5. Examples

5.1 HIV-1 Example

Genentech analyzed virus isolates of intercurrent (partially immunized) and breakthrough (fully immunized) infections among individuals vaccinated with their MN gpg120 subunit vaccine. They structured viral variation according to the hexapeptide tip of the V3 loop of the envelope protein. This tip is contained in the principal neutralization domain, a 35 amino acid region of the V3 loop that has been found to be the primary target of neutralizing antibodies in laboratory-adapted strains (LaRosa et al., 1990; Profy et al., 1990). The ordered categorical distance is defined as the number of substitutions or deletions to the prototype hexapeptide tip consensus sequence GPGRAF. The \( K = 3 \) response categories are defined as 0, 1, and 2 or more substitutions or deletions.

To date, there have been five breakthrough and four intercurrent infections among immunized trial participants. A randomized placebo group is not available, so we use three historical comparison groups, composed of 67 isolates from Berman et al. (1996b) (GNE), 28 isolates from the AIDS Vaccine Evaluation Group (AVEG), and 159 isolates from the Los Alamos National Laboratory (LNL). The comparison groups have similar tip sequence distributions, all skewed to the right, with high proportion of sequences matching the consensus sequence. Figure 3 shows frequency distributions and counts for the two immunized groups and the three comparison groups.

The frequency distributions suggest that the vaccine protects better against prototype strains. To formally investigate this, we apply the sieve analysis methods. Since the same conclusions are reached for the three comparison groups, we report results only for the Genentech (GNE) group.

The first task is assessing type-specific protection of a fully administered vaccine. For this, the four intercurrent isolates are excluded from the analysis. Consider the sieve null hypothesis that the
vaccine protects uniformly. The Breslow–Day statistic equals 2.49, with asymptotic p-value 0.11. The Kruskal–Wallis statistic is 2.30, with exact p-value 0.17. The null hypothesis is not rejected, perhaps due to low power, as there are only five breakthroughs. Next, the MLR, cumulative logit, adjacent categories linear logit, and proportional odds models are fit. The estimated parameters, standard errors, strain-specific odds ratios, 95% confidence intervals about the strain-specific odds ratios, and p-values are displayed in Table 2.

Using the approximations $OR(1) \approx RR(1)/RR(0)$ and $OR(2) \approx RR(2)/RR(0)$, the MLR model estimates that vaccine protection is $(43 \times 1)/(20 \times 2) = 1.07$ times better against challenge by strains with one substitution or deletion in the tip sequence and $(43 \times 2)/(4 \times 2) = 10.75$ times better against prototype strains than against strains with two or more alterations.

The cumulative logit model tells a similar story, estimating $\exp(\hat{\beta}_1) = RR(> 0)/RR(\leq 0) = 2.69$ and $\exp(\hat{\beta}_1) = RR(> 1)/RR(\leq 1) = 10.50$. Both models suggest significant and substantial differential protection against strains with at least two alterations in the tip sequence but no difference in protection against strains with only one alteration. The adjacent categories linear logit model fits the data poorly, as there is not a linear trend in estimated strain-specific log odds ratio. The proportional odds model also fits poorly, as seen by the fact that $OR(> 0) = 2.69$ and $OR(> 1) = 10.50$ are very different. Notice its precision gain, however—the standard error estimate of $\hat{\beta}$ is about half that for the nonscored cumulative logit model.

For a sieve analysis of all nine immunized infections, there are three ordered vaccine groups, control, partially vaccinated, and fully vaccinated. The standardized linear-by-linear association

---

**Figure 3.** Frequency distributions of HIV-1 infecting types.

**Table 2**

<table>
<thead>
<tr>
<th>Model</th>
<th>Category</th>
<th>$\hat{\beta}$</th>
<th>SE($\hat{\beta}$)</th>
<th>$\exp(\hat{\beta}) = \widehat{OR}$</th>
<th>95% CIa $\widehat{OR}$</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLR</td>
<td>1</td>
<td>0.72</td>
<td>1.25</td>
<td>1.07</td>
<td>(0.09, 12.56)</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2.38</td>
<td>1.13</td>
<td>10.75</td>
<td>(1.18, 98.16)</td>
<td>0.035</td>
</tr>
<tr>
<td>Cumulative logit</td>
<td>&gt;0</td>
<td>0.99</td>
<td>0.95</td>
<td>2.69</td>
<td>(0.42, 17.22)</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>&gt;1</td>
<td>2.35</td>
<td>1.05</td>
<td>10.50</td>
<td>(1.35, 81.96)</td>
<td>0.025</td>
</tr>
<tr>
<td>Adjacent categories</td>
<td>&gt;0</td>
<td>1.12</td>
<td>0.63</td>
<td>3.06</td>
<td>(0.90, 10.43)</td>
<td>0.074</td>
</tr>
<tr>
<td>linear logit</td>
<td>&gt;1</td>
<td>2.24</td>
<td>1.26</td>
<td>9.35</td>
<td>(0.80, 108.69)</td>
<td>0.074</td>
</tr>
<tr>
<td>Proportional odds</td>
<td>&gt;0</td>
<td>1.18</td>
<td>0.52</td>
<td>3.27</td>
<td>(1.17, 9.11)</td>
<td>0.024</td>
</tr>
<tr>
<td></td>
<td>&gt;1</td>
<td>1.18</td>
<td>0.52</td>
<td>3.27</td>
<td>(1.17, 9.11)</td>
<td>0.024</td>
</tr>
</tbody>
</table>

*a Ninety-five percent confidence intervals are derived from a normality approximation and the observed inverse information matrix.
statistic is 2.08, with two-sided asymptotic p-value 0.038 and two-sided exact p-value 0.046. Thus, there is a significant sieve effect with increasing vaccine dose.

There are two approaches to fitting the models to the three vaccine groups. The first is to let \( x = (1_{\text{intercurrent}}, 1_{\text{breakthrough}})^T \), in which case each \( \beta \) is two-dimensional, where the first (second) component is a log ratio of strain-specific relative risks for partial (full) vaccinees relative to nonvaccinees. The second approach accounts for the amount of vaccination by defining \( x \) to be a set of scores. We apply the second method, with equally spaced scores. The MLR model estimates with 95% confidence intervals are \( \exp(\hat{\beta}_1) = RR_{\text{inter}}(1)/RR_{\text{inter}}(0) = 1.05 \) (0.34, 3.23), \( \exp(\hat{\beta}_2) = RR_{\text{inter}}(2)/RR_{\text{inter}}(0) = 3.42 \) (1.18, 9.92), and \( \exp(2\hat{\beta}_1) = RR_{\text{break}}(1)/RR_{\text{break}}(0) = 1.09 \) (0.11, 10.45), \( \exp(2\hat{\beta}_2) = RR_{\text{break}}(2)/RR_{\text{break}}(0) = 11.67 \) (1.39, 98.41). The cumulative logit model estimates \( \exp(\hat{\beta}_1) = RR_{\text{inter}}(> 0)/RR_{\text{inter}}(\leq 0) = 1.66 \) (0.70, 3.94), \( \exp(\hat{\beta}_2) = RR_{\text{inter}}(> 1)/RR_{\text{inter}}(\leq 1) = 3.35 \) (1.23, 9.06), and \( \exp(2\hat{\beta}_1) = RR_{\text{break}}(> 0)/RR_{\text{break}}(\leq 0) = 2.76 \) (0.49, 15.56), \( \exp(2\hat{\beta}_2) = RR_{\text{break}}(> 1)/RR_{\text{break}}(\leq 1) = 11.19 \) (1.53, 82.10). The models suggest that partial vaccination, as well as full vaccination, protects significantly worse against strains with two or more alterations.

These results are open to criticism because of the small number of immunized infections and concern about the appropriateness of the comparison groups. Randomization would increase control group validity and justify interpreting the regression parameters as ratios of strain-specific relative risks of infection.

5.2 Hepatitis B Vaccine Trial Example

Since few immunized infections occurred in Genentech’s trial, we illustrate sieve analysis in a setting in which numerous infections occurred. In a Phase III, randomized, double-blind, placebo-controlled preventive vaccine efficacy trial of surface antigen HEPTAVAX hepatitis B vaccine among homosexual men in New York City, cases of hepatitis associated with hepatitis B, hepatitis A, or disassociated with hepatitis B or A were observed during the 2-year period of follow-up. (See Szmuness et al., 1981, for details.) The observed distributions of B, A, and non-A, non-B infections in the placebo and vaccine groups, with counts, are depicted in Figure 4.

The null hypothesis that the vaccine protects uniformly against B, A, and non-A, non-B hepatitis is strongly rejected by the sieve likelihood ratio test \( \chi^2 = 28.3, p < 10^{-6} \). Zelen’s test statistic (4.2) gives a similar result, \( \chi^2 = 26.1, p < 10^{-5} \). The MLR model estimates \( \exp(\hat{\beta}_1) = RR(A)/RR(B) = 7.0 \) ((2.7, 18.4), \( p = 0.0001 \)) and \( \exp(\hat{\beta}_2) = RR(\text{non-A, non-B})/RR(\text{B}) = 13.1 \) ((4.3, 39.3), \( p < 10^{-5} \)). We conclude that the vaccine protects much better against prototype hepatitis B than other hepatitis types, especially non-A, non-B hepatitis.

6. Power of the Ordered MLR Model

How many infections are necessary in order to detect differential protection? We discuss power for detecting a linear trend in the strain-specific log odds ratios. Three things must be prescribed for the power calculations: the structure of the viral variation, the number infected on the placebo

![Figure 4. Frequency distributions of hepatitis infecting types.](image-url)
and vaccine arms, and the baseline infecting strain distribution. The baseline distribution is the distribution of virus types expected among infected trial participants who did not receive the vaccine. We computed power using a four category ordered distance, like that used in Section 5.1, with an additional category for strains with three or more substitutions or deletions from prototype.

We assume two baseline distributions, uniform and skew. For the uniform distribution, the baseline infecting strains are specified to be equally represented in the four categories. The skew distribution is constructed from the aggregate data of the GNE, AVEG, and LNL isolates, yielding a 67, 23, 9, and 1% distributions of baseline infecting strains with values 0, 1, 2, 3+, respectively. Since, under the alternative hypothesis, a linear trend is assumed, specifying the log odds ratio for the last category determines the whole trend. We assume that the vaccine is 50% efficacious and that equal numbers of participants are randomized to receive vaccine and placebo preparations. Thus, the number of infected participants who receive the vaccine is roughly half the number of those who receive the placebo preparation. Finally, the calculations are performed for two sizes of trials: a definitive Phase III trial, which is sized to expect 200 infections in the placebo group, and a smaller screening trial, which is sized to expect 50 infections in the placebo group. The power calculations are performed using computer simulations. For the uniform and skew distributions, the smallest OR(3)’s that are detectable with 80 and 90% probability are listed in Table 3.

Since dynamics governing HIV-1 transmission are poorly understood, it is difficult to judge how likely it will be to achieve the odds ratios presented in Table 3. The HIV-1 example, with an estimated \( \hat{OR}(2) = 10.75 \), shows that differential protection is detectable without necessitating unreasonably large samples.

Notice that the power is comparable for the uniform and skew distributions.

7. Discussion

The utility of the sieve models for vaccine trial data is twofold. First, if the investigator wishes to assess if and to what extent vaccine protection depends on a particular viral feature chosen a priori, then the models can be used for statistical inference. In this case, the vaccine trial could be sized to detect differential protection. Alternatively, the sieve models can be used as hypothesis generating exploratory tools for identifying potential viral correlates of protection. This would proceed by fitting the models to the infecting strain data structured according to a variety of features. Those features deemed by the models to be most associated with differential protection are marked as candidate viral correlates of protection, which could be further investigated through basic laboratory research, vaccine challenge studies in animals, and independent vaccine trials in humans.

Consider a candidate ordered categorical viral feature. Through dimensionality reduction, the MLR model provides a framework for investigating more finely how vaccine efficacy depends on the strain category definitions. The goal is to determine the subset of strains among the \( K \) strain categories that have distinct strain-specific vaccine efficacies. Tippett’s procedure (Koziol and Perlman, 1978) utilizes sequential likelihood ratio tests to guide the collapsing of response categories. Consider the hypotheses that there are two groups of \( \{\beta_s\} \) in the MLR model (3.1), i.e.,

\[
H_{(2,r)}: \beta_0 = \cdots = \beta_r = 0, \quad \beta_{r+1} = \cdots = \beta_{K-1} = \beta \neq 0 \quad (1 \leq r < K),
\]

with corresponding maximized log-likelihoods \( l(2;r) \). Tippett’s procedure gives a test of the hypothesis of two distinct groups, \( H_2 \) against \( H_0 \). Set \( l(2) = \max\{l(2;r)\} \). Under the assumption of independence between the \( K - 1 \) likelihood ratio statistics \( 2(l(2;r) - l_0) \), the statistic \( 2(l(2) - l_0) \) is asymptotically \( \chi^2_1 \). To test \( H_2 \) versus \( H_0 \) at the \( \alpha \) significance level, treat \( 2(l(2) - l_0) \) as a \( \chi^2_1 \) variate at the \( 1 - (1-\alpha)^{1/(K-2)} \) significance level. The maximizing value \( r^* \) of \( r \) above gives the

<table>
<thead>
<tr>
<th>( N_{pl}/N_{vl} )</th>
<th>Distribution</th>
<th>( OR(3) ) at 80% power</th>
<th>( OR(3) ) at 90% power</th>
</tr>
</thead>
<tbody>
<tr>
<td>50/25</td>
<td>Uniform</td>
<td>7.5</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td>Skew</td>
<td>7.9</td>
<td>10.4</td>
</tr>
<tr>
<td>200/100</td>
<td>Uniform</td>
<td>2.5</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>Skew</td>
<td>3.0</td>
<td>3.4</td>
</tr>
</tbody>
</table>

\(^a\) Results are based on 3000 replications of the tests. The nominal level is 0.05.
best division of the \( \{ \beta_s \} \) into two groups. If the hypothesis of two groups is accepted, then this procedure can be continued to test for three, four, or \( s \) groups of indistinguishable categories with corresponding maximized log likelihoods \( l(3), l(4), \) or \( l(s) \) defined similarly to \( l(2) \). Alternatively, Sambamoorti (1989) used an information theoretic criterion, a variation of the Akaike Information Criterion, to provide a consistent means of reducing the dimensionality in MLR models. Under mild smoothness hypotheses, Sambamoorti (1989) derived a strongly consistent estimator of the rank of the parameter matrix and of the set of indices of collapsible categories. This method, as well as Tippett’s procedure, provides insight for the example in Section 5.1, suggesting that categories 0 and 1 can be collapsed. An HIV-1 vaccine trial will provide data on a broad array of genotypical, phenotypical, and serotypical viral characteristics, and either of these methods may prove useful as exploratory tools for investigating how various features correlate with vaccine efficacy.

Methods for sieve analysis have been described for the case where viral characteristics are summarized by a univariate feature. However, it is clearly of interest to assess how vaccine efficacy depends jointly on two or more viral features or how it depends jointly on viral characteristics and other variables such as host characteristics. Elsewhere we show how the models developed here can be modified to model a multidimensional response. Potential applications of these multivariate models include a current HIV vaccine trial of Pasteur-Mérieux-Connaught’s vCP205 recombinant canarypox vector vaccine, which includes genes coding for env, gag, and pol, inference of how viral and host factors interact to affect vaccine protection, assessment of type-specific waning of vaccine protection, and investigation of type-specific vaccine suppression of viraemia.

Acknowledgements

We thank the anonymous referees and the editor for their valuable suggestions.

Résumé


References

Assessing Vaccine Protection Against HIV


Received November 1996; revised June 1997; accepted December 1997.