The Annals of Statistics
1997, Vol. 25, No. 2, 642–661

ESTIMATING DISEASE ATTACK RATES IN HETEROGENEOUS INTERACTING POPULATIONS, WITH APPLICATIONS TO HIV VACCINE TRIALS[1]

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We describe models for infectious disease attack rates outside Aalen's multiplicative class and incorporating heterogeneity and interactions between subjects. Large-sample theory for the Nelson–Aalen estimator is developed, and its relevance examined in a simulation study. Planning for randomized, controlled clinical trials of prophylactic HIV vaccines partly motivated this work.

1. Introduction. Models appropriate for analyzing infectious disease transmission differ fundamentally from those suitable for chronic diseases. For chronic diseases, Aalen's (1978) multiplicative model, or its generalization, the relative risk regression model [Kalbfleish and Prentice (1980) and Andersen, Borgan, Gill and Keiding (1993)], is useful. In these models ramdomness in the intensity function is restricted to censoring, loss-of-follow-up or time-dependent covariates. The "baseline" intensity function is assumed deterministic. By contrast, for infectious diseases each individual's risk depends on the level of exposure to the infectious agent, which is not observable and may vary considerably between individuals and over time. In addition, contacts between individuals can generate dependences not seen in the chronic disease setting.

Large-scale randomized trials of HIV prophylactic vaccines are currently being planned [Dixon, Rida, Fast and Hoth (1993) and Rida and Lawrence (1995)]. Standard statistical methods based on Aalen's multiplicative model are likely to be used in the analysis of trial results. However, the issues considered above are salient in this context. The behaviors that put people at risk of contracting HIV are highly variable, and a host of biological factors influence both susceptibility to infection and infectiousness [DeGrutolla, Seage, Mayer and Horsburgh (1989), Jewell and Siboski (1990), Padian, Shiboski and Jewell (1990), Winkelstein, Lyman, Padian, Grant, Samuel, Wiley, Anderson, Lang, Riggs and Levy (1987)]. (As one instance, if individuals in the acute stage are more infectious than those in the chronic phase, most new cases might be due to contact with the former subgroup.) Recruit-

Received March 1995; revised December 1995.
[1] Research supported by NIAID Grants 5-R01-AI29168 and NO1-AI-45200.
AMS 1991 *subject classifications*. Primary 62F12, 60K35, 62P10; secondary 62M05, 62G30, 62E25.
Key words and phrases. Estimation in infectious diseases, interacting processes, asymptotics of Nelson–Aalen estimators, counting processes, vaccine trials, HIV disease.

ment in the trial might capture large parts of social networks; indeed, a substantial part of the "at risk" population in some communities might participate. As a result, many infections may be due to transmission from one trial participant to another.

Although infectious disease epidemiologists and epidemic modelers have long appreciated the random nature of hazards for infection, as well as the dependences induced by contacts, the impact of these features on distributional properties of commonly used statistics has not been thoroughly assessed. With the exception of Rida's (1991) work on asymptotic distribution theory under the relatively simple SIR model, we are not aware of any systematic approach to this problem. As exemplified by Becker (1989), large-sample distribution theory is often dispensed with by a reference to martingale limit theorems, without examination of whether the conditions of the theorems apply. For example, to apply the often-cited martingale central limit theorems of Rebolledo (1978, 1980), the variation process must converge to a deterministic function. However, in realistic transmission models, this process is a complicated function of all participants' infectious status indicators, which moreover are not independent. It is not difficult to construct examples for which convergence to a deterministic limit fails. Thus, to ensure validity of inferences in HIV vaccine trials, we must identify conditions under which the "standard" distribution theory applies, as well as develop practical guidelines for assessing whether these conditions obtain in communities participating in these trials.

In Section 2 we construct stochastic models of the infection counting process, focusing exclusively on the situation in which contacts are unobservable. Although counting processes in multiplicative models have been widely studied by statisticians [Andersen, Borgan, Gill and Keiding (1993) and Fleming and Harrington (1991)], our models are closer to the "interacting particle processes" known to probabilists and mathematical physicists [Liggett (1985), Spohn (1991) and DeMasi and Presutti (1991)]. For these processes the large-sample limiting dynamics is typically nontrivial and governed by infinite-dimensional evolution equations [Spohn (1991) and DeMasi and Presutti (1991)].

In Section 3 we prove limit theorems for a wide class of random variables related to our infection process, and in Section 4 we apply these to the Nelson–Aalen estimator of attack rates [Andersen, Borgan, Gill and Keiding (1993)] and related variance estimators. A central limit theorem justifies use of conventional Wald-type confidence intervals. In Section 5 we relax certain modeling assumptions and show that nonnormal statistics can dominate the large-sample limit. We also present a small simulation study. Finally, in Section 6 we state our conclusions and discuss directions for further research.

2. Models. We enroll n subjects at baseline. Let $N_i(t)$ be a right-continuous HIV infection status indicator for the ith subject at time t. Let $\varepsilon_i(t)$ be the right-continuous exposure counting process for the ith individual, $\varepsilon_i(t)$ being the number of exposures up to time t. Subjects are randomly

assigned (by a coin flip or electronic equivalent) to vaccine or control group at baseline. Let $V_i = 0, 1$ be a vaccine status indicator, $V_i = 1(0)$ meaning the subject was (not) vaccinated at baseline.

Let $\mathscr{G}_t$ be an increasing filtration on a probability space for which V_i, $\varepsilon_i(s)$ and $N_i(s)$, for $s \le t$, and some latent variables described below are measurable. We model the integrated intensity of the infection process $N_i(t)$ with respect to $\mathscr{G}_t$ by

$$\Lambda_i^{\mathscr{G}}(t) = \exp(\beta_{0i} + \beta_1 V_i) \int_0^{t-} (1 - N_i(s-))\, d\varepsilon_i(s). \tag{1}$$

The parameters $\beta_{0,i}$ and β_1 determine the probability of infection given exposure and vaccination status. Our model for vaccine effect is "Model One" of Smith, Rodrigues and Fine (1984), in which vaccination is assumed to drop the probability of infection in each exposure by a fixed factor.

For modeling purposes we next introduce a subfiltration of $\mathscr{G}_t$, call it $\mathscr{F}(t)$, generated by the $N_i(s)$, $s \le t$, the V_i's and the latent variables. By the innovation theorem [Aalen (1978)], the intensity with respect to a subfiltration is given by the expectation of (1) conditional on $\mathscr{F}_t$, which will be of the form

$$\lambda_i^{\mathscr{F}}(t) = \exp(\beta_{0i} + \beta_1 V_i)(1 - N_i(t-))\phi_i^{\mathscr{F}}(t). \tag{2}$$

We next divide the exposure intensity into contributions from contacts within the cohort and "external" contacts, and model them as

$$\phi_i^{\mathscr{F}}(t) = \sum_{j=1}^{n} \gamma_{i,j}(t) N_j(t-) + E_i(t-), \tag{3}$$

where the component-wise positive $\gamma_{i,j}(t)$ represents the intensity of contacts between subjects i and j, and $E_j(t)$ is a positive random vector of "external risk rates." For simplicity, we assume that both the extracohort exposure rate and the intercohort contact matrix are time independent, and the external risk rate variables are almost surely bounded by some constant K_E.

Finally, we model the contact matrix as

$$\gamma_{i,j} = \frac{1}{n} F(C_i, C_j), \tag{4}$$

where the C_i represent "contact propensities" of the study subjects making contacts within the cohort (which we assume are almost surely bounded by some constant K_C). We denote by F a polynomial in two variables which is positive on the square $[0, K_C]^2$:

$$F(x, y) = \sum_{p,q=1}^{d} a_{p,q} x^p y^q \ge 0. \tag{5}$$

(The latter is not a serious restriction, as any continuous function can be uniformly approximated by a polynomial on this domain.) The factor of $1/n$ is included in (4) to avoid comparing trials in which subjects have different

mean numbers of contacts per unit time. A simple but not uninteresting case is $\gamma_{i,j}$ proportional to $C_i \times C_j$ (i.e., $\alpha_{1,1} \equiv \alpha$, all others 0), reflecting the intuition that if two subjects double their activity, their chance of meeting increases by a factor of 4.

We summarize our model assumptions as follows:

ASSUMPTION 1. The notation $\{(N_1, \ldots, N_n), \{\mathscr{F}\}\}$ represents a multivariate counting process with intensity $\lambda_i^{\mathscr{F}}(t) = (1 - N_i(t-))\phi_i^{\mathscr{F}}(t)\exp(\beta_{0i} + \beta_1 V_i)$, where $\phi_i^{\mathscr{F}}(t)$ is given by $(1/n)\sum_{j=1}^{n} F(C_i, C_j)N_j(t-) + E_i$.

ASSUMPTION 2. The (C_i, E_i) are i.i.d. random variables with arbitrary distribution supported on $[0, K_C] \times [0, K_E]$.

ASSUMPTION 3. The V_i are i.i.d. Bernoulli and are independent of the (C_i, E_i).

After choosing the random variables (V_i, C_i, E_i) and fixing them, the process can be constructed by standard Markov process techniques.

Finally, since we focus here on the heterogeneity in contacts, we drop the variability in infection given exposure by setting $\beta_{0i} \equiv 0$ and, for simplicity, we write $\theta \equiv \exp(\beta_1) \equiv \exp(\beta)$. Our interest is in estimating θ (or, equivalently, β). Note that $\theta = 0$ represents a perfect vaccine, and $\theta = 1$ a totally ineffective one.

3. Limit theorems. In this section we prove large-sample limit theorems under Assumptions 1–3 for a large class of random variables related to the infection process. We apply these results to estimators of attack rates, standard errors and other interesting quantities in Section 4. Although we work in an infinite-dimensional context, it turns out that both the deterministic process derived from the law of large numbers and the Gaussian process derived from the central limit theorem are expressible in terms of a finite-dimensional subspace of deterministic functions. These functions are in turn governed by a system of ordinary differential equations.

We begin by introducing a sufficiently rich class of random variables. Let $B_0 \equiv B(\Omega_0)$ denote the space of bounded continuous functions on $\Omega_0 \equiv \{0, 1\} \times [0, K_C] \times [0, K_E]$. Given $f \in B_0$, we write $f = f(v, c, e)$, and make B_0 a Banach space with the uniform norm. Let $L(B_0)$ denote the space of bounded linear functionals on B_0. Although a well-known Banach space in its own right if given the total-variation norm, in order to make efficient use of existing theorems concerning infinite-dimensional processes we think of it as contained in a larger space of "generalized functions" [Gelfand (1964), DeMasi and Presutti (1991) and Schwartz (1950)].

Given $f \in B_0$, define a random variable by

$$X_n(f, t) \equiv \frac{1}{n}\sum_{i=1}^{n} f(V_i, C_i, E_i)(1 - N_i(t)). \tag{6}$$

These variables describe the key characteristics (vaccination status, contact propensity and external exposure risk) of the uninfected population at time t.

A finite-dimensional subspace spanned by these variables plays a central role in the dynamics. Let

$$
\begin{aligned}
I_n(p,t) &= \frac{1}{n}\sum_{i=1}^{n} C_i^p N_i(t), \\
J_n(q,t) &= \int_0^t I_n(q,s)\,ds
\end{aligned}
\tag{7}
$$

for $1 \le p \le d$, where $d \equiv \deg(F)$, the degree of the polynomial appearing in (5). These functions measure the rate and integrated contact propensity of the infected population at time t. We will show that the large n limits of these quantities, denoted by $I(p,t)$ and $J(p,t)$, respectively, together with the distributions of (V, C, E), govern the limits of all the random variables defined in (6).

For the first theorem we also require the following functions. Define a functional on $R^{d+1} \times B_0$ by

$$
G(x, y_1, \ldots, y_d; f) \equiv \left\langle \exp\left[-(1 - v + \theta v)\left(xe + \sum_{p=1}^{d} y_p c^p \right) \right] f \right\rangle, \tag{8}
$$

where $\langle \cdot \rangle$ denotes expectation with respect to the joint distribution of (V, C, E). Also define d ordinary functions of real variables defined in terms of (8):

$$
G_q(x, y_1, \ldots, y_d) \equiv \langle c^q \rangle - G(x, y_1, \ldots, y_d; c^q). \tag{9}
$$

THEOREM 3.1. *Assume zero infected individuals at $t = 0$. In terms of the (bounded, continuous) solution of the system of ODE's*

$$
\frac{dJ(q,t)}{dt} = G_q\left(t, \sum_r a_{\cdot,r} J(r,t) \right), \tag{10}
$$

with zero initial conditions, define

$$
X(f,t) \equiv G\left(t, \sum_r a_{\cdot,r} J(r,t); f \right). \tag{11}
$$

Then the following limit holds for any $f \in B$, t and $\delta > 0$:

$$
\lim_{n \to \infty} P\left[\sup_{0 \le \tau \le t} |X_n(f,\tau) - X(f,\tau)| > \delta \right] = 0. \tag{12}
$$

We actually prove a stronger result than expressed in (12): the so-called "weak convergence" [Billingsley (1968)] of the $X_n(\cdot,\cdot)$ process to the deterministic process defined in (11). As one consequence, the limits hold also for random stopping times which have deterministic limits, a result we exploit in Section 5.

For the central limit theorem we need the following operators. Define time-dependent linear operators $A(t), B(t)$: $B(\Omega_0) \to B(\Omega_0)$ by

$$[A(t)f](v,c,e) \equiv -(1 - v + \theta v) \times \left[ef(v,c,e) + \sum_{p,q} a_{p,q} I(q,t) c^p f(v,c,e) \right], \tag{13}$$

$$[B(t)(f)](v,c,e) \equiv \sum_{p,q} a_{p,q} X((1 - v + \theta v) c^p f, t) c^q. \tag{14}$$

Finally, define fluctuation variables by

$$Z_n(f,t) \equiv \sqrt{n}\,[X_n(f,t) - X(f,t)]. \tag{15}$$

THEOREM 3.2. *Let $Z(\cdot,t)$ be the Gaussian Markov process with paths in $C([0,\infty]; L(B))$ defined informally by the stochastic differential equations*

$$dZ(f,t) = [Z([A + B](t)f, t) - Z(B(t)f, 0)]\,dt + dB(f,t), \tag{16}$$

with, as initial conditions, Gaussian random variables with mean 0 and covariance

$$EZ(f,0)Z(g,0) = \langle fg \rangle - \langle f \rangle \langle g \rangle. \tag{17}$$

In (16), *$B(\cdot,t)$ is the Brownian motion process with covariance*

$$E\,dB(f,t)\,dB(g,s) = \delta_{t,s} X[-A(t)(fg), t]\,dt. \tag{18}$$

More precisely, $Z(\cdot,t)$ is the unique process with continuous paths and the indicated initial conditions, such that, for any $\phi \in C^\infty(R)$ and using the shorthand $\phi_t \equiv \phi(Z(f,t))$, the expression

$$\phi_t - \phi_0 - \int_0^t ds \big[(\phi')_s \{ Z([A + B](s)f, s) - Z(B(t)f, 0) \} - \tfrac{1}{2} (\phi'')_s X(A(t)(fg), s) \big] \tag{19}$$

is a mean-zero martingale [*Holley and Stroock* (1978)].

Then, for all $t \geq 0$, $f_1, \ldots, f_n$ in B_0 and $\xi_1, \ldots, \xi_n$ in R,

$$\lim_{n\to\infty} E \exp\Big[\sqrt{-1} \sum \xi_k Z_n(f_k, t)\Big] = E \exp\Big[\sqrt{-1} \sum \xi_k Z(f_k, t)\Big] = \exp\Big[-\tfrac{1}{2} \sum_{k,l} \operatorname{cov}(f_k, f_l; t, t)\, \xi_k \xi_l \Big], \tag{20}$$

where the limiting covariance

$$\lim_{n\to\infty} EZ_n(f,s)Z_n(g,t) \equiv \operatorname{cov}(f, g; s, t) \tag{21}$$

exists and satisfies

$$\frac{d}{dt}\operatorname{cov}(f,g;t,t) = \operatorname{cov}([A+B](t)f,g;t,t) - \operatorname{cov}(B(t)f,g;0,t) + X(-A(t)(fg),t) + (\textit{terms with } f \leftrightarrow g), \tag{22}$$

with initial conditions given in (17).

As for Theorem 3.1, the conclusion is actually much stronger than the single-time CLT stated in (20): weak convergence of the $Z_n(\cdot,t)$ process to the Gaussian Markov process defined in the theorem. In passing we remark that the operator $[A+B](t)$ occurring in the "drift" term in the stochastic differential equation (16) is the linearized right-hand side of the infinite-dimensional ODE governing the X-variables [see (29) below] performed around the solution $X(\cdot,t)$. This reflects the intuition that fluctuations are gentle perturbations of the deterministic evolution, and so propagate under the linearized equation.

PROOF OF THEOREM 3.1. Let $B \equiv B(\Omega)$ denote bounded continuous functions on $\Omega \equiv \{0,1\}^n \times \Omega_0$, the configuration space of the process. Let L_n: $B(\Omega) \to B(\Omega)$ be the generator of the Markov process used in the construction of $N_i(t)$, $0 \le t \le \infty$, so that, for $H \in B(\Omega)$ and for $\Delta_i H(N)$ denoting $H(N_1,\dots,N_i+1,\dots) - H(N_1,\dots)$, $L_n H(N_1,\dots)$ is given by

$$\sum_i (1 - V_i + \theta V_i)(1 - N_i)\left[\sum_j \frac{F(C_i,C_j)}{n} N_j + E_i\right] \times \Delta_i H(N). \tag{23}$$

By standard Markov theory [see Section 2.6.3 of DeMasi and Presutti (1991)],

$$H(t) = H(0) + \int_0^t L_n H(s)\,ds + M_{n,1}(t) \tag{24}$$

and

$$M_{n,1}^2(t) = \int_0^t \{L_n[H^2] - 2HL_nH\}(s)\,ds + M_{n,2}(t), \tag{25}$$

where the final terms in these equations are locally square-integrable, mean-zero martingales.

A straightforward computation using (24) gives the following result when applied to the X_n-variables:

$$\begin{aligned} &X_n(f,t) \\ &\quad = X_n(f,0) + M_{n,1}(f,t) \\ &\qquad + \int_0^t ds \Bigg\{ -\sum_{p,q} a_{p,q}\left[\frac{1}{n}\sum_j C_j^q - X_n(c^q,t)\right] \\ &\qquad\qquad \times X_n((1-v+\theta v)c^p f,t) - X_n((1-v+\theta v)ef,t)\Bigg\}. \end{aligned} \tag{26}$$

Another easy computation using (25) gives

$$EM_{n,2}^2(f,t) = \frac{1}{n}E\int_0^t \left[\frac{1}{n}\sum_i (1 - V_i + \theta V_i)(1 - N_i(s)) \right.$$

$$\left. \times \left(\frac{1}{n}\sum_j F(C_i, C_j)N_j(s) + E_i\right) f(V_i, C_i, E_i)^2\right] \tag{27}$$

$$\leq (\text{constant})\|f\|^2 t n^{-1}.$$

Hence, by Kolmogorov's inequality [Billingsley (1968)],

$$\lim_{n\to\infty} P\left[\sup_{0\leq\tau\leq t} |M_{n,2}(f,\tau)| > \delta\right] = 0. \tag{28}$$

Applying the law of large numbers to (27) and the definition of weak convergence, we see that any limit $X(\cdot, t)$ in distribution of the $X_n(\cdot, t)$ process along any subsequence $n_k \to \infty$ will have the property that

$$X(f,t) = X(f,0) - \int_0^t G(f,s)\,ds, \tag{29}$$

where $G(f,t)$ equals

$$\sum_{p,q} a_{p,q}\left[\langle c^q\rangle - X(c^q,t)\right] X((1 - v + \theta v)c^p f, t) \tag{30}$$

$$- X((1 - v + \theta v)ef, t).$$

Rather than develop the appropriate machinery here to prove such limit points exist for our random measure-valued processes, we appeal to more general results. Regard $L(B_0)$ as a subspace of $D'(\{0,1\} \times [0, K_C'] \times [0, K_E'])$, $K_C' > K_C$, $K_E' > K_E$, a direct sum of spaces of generalized functions (or, in Schwartz's terminology, "distributions"); see Gelfand (1964) and Schwartz (1950). The spaces $D'(U)$, or $S'(U)$ (Schwartz-class distributions), where U is a differentiable manifold, are countable unions of Hilbert spaces and as such have particularly desirable properties for proving limit theorems in infinite-dimensional spaces [DeMasi and Presutti (1991) and Holley and Stroock (1978)]. We regard the process as living in $D([0,T], D'(\Omega_0))$, the space of right-continuous trajectories with left limits with values in $D'(\Omega_0)$, equipped with the Skorohod topology, as in DeMasi and Presutti (1991). That cluster points exist now follows from uniform boundedness of the compensators appearing in (24) and (25), by a minor modification of Theorem 2.6.2 in DeMasi and Presutti (1991) and Mitoma (1983). Furthermore, since individual jumps change each $X_n(f,t)$ only by a quantity of magnitude $O(\|f\|/n)$, it follows from Theorem 2.7.8 in DeMasi and Presutti (1991) that any such limiting process is supported on the space of continuous D'-valued trajectories. They will again be positive measures.

Hence we need only prove a uniqueness result for continuous solutions of (29) to conclude that such a process is supported on a single path—that is, the law of large numbers holds. Equation (29) embodies an infinite-

dimensional system of quadratic ordinary differential equations to which general theorems for existence and uniqueness of solutions might apply [Deimling (1977)]. However, in our case the solution can be found in closed form modulo a finite-dimensional system.

Observe that only products of the general variable with the special variables $I(q,t)$ appear. Temporarily assuming the $I(\cdot,t)$ and $J(\cdot,t)$ functions are known, we rewrite the equations to be linear with time-dependent coefficients; that is, we rewrite (29) as

$$X(f,t) = X(f,0) + \int_0^t X(A(s)f,s)\,ds. \tag{31}$$

The multiplication operators $A(t)$ commute for different t's. Hence exponentiating time integrals does not require product-integration theory but only ordinary operator exponentiation [Kato (1985)], for example, by convergent power series. Thus, to solve (29), we multiply both sides by an integrating factor, defining a new dependent variable by

$$\left[\exp\left\{-\int_0^t A(s)\,ds\right\}X(\cdot,t)\right](f). \tag{32}$$

This variable has zero time derivative, so

$$X(f,t) = \left\langle \exp\left[-(1-v+\theta v)\left\{et + \sum_{p,q} a_{p,q} J(q,t)c^p\right\}\right] f\right\rangle. \tag{33}$$

This yields (11). We next put $f = c^q$ for $q = 1,\ldots,d$ to get (10). We have reduced the proof to showing that the solution of the latter system is unique. However, uniqueness for a finite system of ODE's with C^1 and bounded right-hand sides, over any fixed time interval $[0,T]$, is standard [Birkhoff and Rota (1969)]. □

PROOF OF THEOREM 3.2. As in the proof of Theorem 3.1, it will be convenient to regard the process as a random signed measure living in $D'[\Omega_0]$. The existence and uniqueness of the limiting Gaussian Markov process with continuous paths defined by the martingale condition (19) is proven as in Holley and Stroock (1978).

To derive the weak limit of the fluctuation process, we proceed as in Theorem 3.1. Let $\phi(\cdot) \in C^\infty(R)$. Let $A_n(t)$ be the operator defined as $A(t)$ but with $I_n(\cdot,t)$ replacing $I(\cdot,t)$. Then writing $\phi(Z_n(f,t)) \equiv \phi_t$, applying the generator to ϕ_t and expanding to second order in quantities of order $n^{-1/2}$, we have that

$$\begin{aligned}(\phi_t - \phi_0) - \int_0^t ds\Bigg\{\phi_s'\sqrt{n}\left\{X_n(A_n(s)f,s) - \frac{\partial X(f,s)}{\partial s}\right\} \\ + \frac{1}{2}\phi_s'' X_n\left[-A_n(s)(f^2),s\right]\Bigg\}\end{aligned} \tag{34}$$

is a mean-zero martingale up to terms of order n^{-1}. To treat the term containing ϕ', add and subtract terms with each occurrence of $X_n(A_n(s)f, s)$ replaced by $X_n(A(s)f, s)$ in curly brackets and use (29) to obtain that

$$
\begin{aligned}
&(\phi_t - \phi_0) - \int_0^t ds \\
&\quad \times \Bigg\{ \phi'_s \Bigg[Z_n([A + B](s)f, s) \\
&\qquad - \sum_{p,q} a_{p,q} X_n((1 - v + \theta v)c^p f, t)\{Z_n(c^q, t) - Z_n(c^q, 0)\} \Bigg] \\
&\qquad + \tfrac{1}{2}\phi''_s X_n[-A_n(s)(f^2), s] \Bigg\} + O(n^{-1})
\end{aligned} \tag{35}
$$

is a martingale.

The existence of a weak limit of the fluctuation process $Z_n(\cdot, t)$ follows from the L^2-boundedness of the compensators which appear in (21); see DeMasi and Presutti (1991). The compensators can be written, up to negligible terms, as linear combinations of the fluctuation variables themselves; therefore the required bounds follow from L^2-bounds on these variables. These in turn follow from the proof of (22) below. By (36) and uniqueness results similar to those in Holley and Stroock (1978), any such limit point must be the law of the Gaussian Markov process described in the theorem.

Finally, we prove formula (22) for the covariance of the fluctuation process. Applying the generator to the product $Z_n(f, t) \times Z_n(g, t)$ gives

$$
\begin{aligned}
&\frac{d}{dt} EZ_n(f, t)Z_n(g, t) \\
&\quad = EZ_n([A + B]f, t)Z_n(g, t) + EZ_n(f, t)Z_n([A + B]g, t) \\
&\qquad - EZ_n(B(t)f, 0)Z_n(g, t) - EZ_n(f, t)Z_n(B(t)g, 0) \\
&\qquad + X_n(-A(t)(fg), t) + O(n^{-1}).
\end{aligned} \tag{36}
$$

We regard (22) and (36) as equations for bilinear forms on $B(\Omega_0) \times B(\Omega_0)$, with $B(\Omega_0)$ given its natural Banach space norm. Since the operator $A(t)$ is contractive in this norm, (36) minus all terms containing $B(t)$ would imply a bound uniform in n on the solution. Since $B(t)$ is a finite-rank projection, standard theory for bounded perturbations of contractive operators in Banach spaces [Kato (1985)] gives existence, uniqueness and a bound on the solution independent of n. Hence we can pass to the limit as $n \to \infty$ in (36), and we have proved the final assertions in the theorem. □

4. Application: estimators of attack rates and vaccine efficacy. We introduce two infected population variables:

$$
N_v(t) = \sum_{i=1}^{n} V_i N_i(t), \qquad N_{1-v}(t) = \sum_{i=1}^{n} (1 - V_i) N_i(t), \tag{37}
$$

and two susceptible population variables (no censoring):

$$(38)\quad Y_v(t) = \sum_i^n V_i(1 - N_i(t-)), \qquad Y_{1-v}(t) = \sum_i^n (1 - V_i)\big[1 - N_i(t-)\big].$$

Define the jump intensities with respect to $\mathscr{F}_t$ in the two groups by $\lambda_v(t) = \alpha_v(t)Y_v(t)$ and $\lambda_{1-v}(t) = \alpha_{1-v}(t)Y_{1-v}(t)$, where, for example,

$$(39)\qquad \alpha_v(t) = \frac{\theta \sum_i^n V_i\big[1 - N_i(t-)\big]\big[\sum_j^n \big(\gamma_{i,j}N_j(t-) + E_j\big)\big]}{Y_v(t)}.$$

The estimable intensities are those with respect to the observable filtration, denoted by $\mathscr{F}_t^o$, and are given by $\lambda_v^o(t) = \alpha_v^o(t)Y_v(t)$ and $\lambda_{1-v}^o(t) = \alpha_{1-v}^o(t)Y_{1-v}(t)$, where, by application of the innovation theorem, we have

$$(40)\quad \alpha_v^o(t) = \frac{\theta\sum_i^n V_i\big[1 - N_i(t-)\big]\big[\sum_j^n \big(E\big[\gamma_{i,j} \mid \mathscr{F}_{t-}^o\big]N_j(t-) + E\big[E_j \mid \mathscr{F}_{t-}^o\big]\big)\big]}{Y_v(t)},$$

with a similar expression for $\alpha_{1-v}^o(t)$. We note that, for traditional multiplicative intensity models [Andersen, Borgan, Gill and Keiding (1993)], $\alpha_v(\cdot)$ and $\alpha_{1-v}(\cdot)$ are deterministic. However, in our model, these are complicated functions of the infection counting processes for all individuals in the cohort. The estimable intensities will also be random, since the conditional expectations in (40) will be even more complicated functions. Nevertheless, proceeding as for the deterministic case, a natural estimator of the integrated intensity function

$$(41)\qquad A_v(t) = \int_0^t \alpha_v(s)\, ds$$

is the Nelson–Aalen estimator

$$(42)\qquad \hat{A}_v(t) = \int_0^t Y_v(s)^{-1}\, dN_v(s),$$

which is just a sum over event times:

$$(43)\qquad \hat{A}_v(t) = \sum_{j:\,\tau_j \le t} Y_v(\tau_j)^{-1},$$

where τ_j is the infection time of the jth vaccinated subject. Note that (43) does not explicitly involve the (unobserved) contact process.

Since the integrated intensity function being estimated is random and not invariant over replicate trials, interpreting traditional frequentist inferential statements is problematic. We avoid this problem by taking the parameter to be estimated as the limiting value of $A_v(\cdot)$, denoted by $A_v^\infty(\cdot)$. Under Assumptions 1–3, this function is fixed and coincides with the limiting value of the Nelson–Aalen estimator. Another approach would be to take the "estimand" as the expected value of the integrated intensity. Unfortunately, this estimand depends on the size of the cohort and so is not invariant over trials of different sizes. Nevertheless, in situations where the limiting function $A_v^\infty(\cdot)$

is not fixed (i.e., when Assumptions 1–3 do not obtain), this may be the most appropriate target for inference.

Let

$$A_v^*(t) = \int_0^t \alpha_v(\tau) J_v(\tau)\, d\tau, \tag{44}$$

with a similar expression for $A_{1-v}^*(t)$, where $J_v(t) = I(Y_v(t) > 0)$. Then

$$\hat{A}_v(t) - A_v^*(t) = \int_0^t \frac{J_v(\tau)}{Y_v(\tau)}\, dM_v(\tau), \tag{45}$$

where $M_v(t)$ is the martingale from the decomposition of $N_v(t)$. As a first use of this martingale decomposition we obtain the limits of the attack estimates for both groups, as follows.

THEOREM 4.1. *The asymptotic limit of the Nelson–Aalen estimator of integrated intensity is given by*

$$\lim_{n\to\infty} \hat{A}_v(t) = -\log(2X(v,t)) \tag{46}$$

in distribution, where $X(v,t)$ *is defined in Theorem* 2.1 *with* $f(v,e,c) = v$, *with a similar equation for* $\hat{A}_{1-v}$ *with* v *replaced by* $1-v$.

PROOF. A calculation similar to that for the martingale appearing in the proof of Theorem 3.1 establishes that the martingale in (45) goes to 0 in distribution. Thus $\hat{A}_v(\cdot)$ and $A_v^*(\cdot)$ have the same limit. Equation (46) therefore follows directly from Theorem 3.1, the bounded convergence theorem for integrals, the easily proved limits $J_v(t) \to 1$ and $X_n(v,0) \to 1/2$ and the computation

$$\begin{aligned}\int_0^t \frac{-X(A(s)v,s)}{X(v,s)}\, ds &= \int_0^t -\frac{d}{dt}\log(X(v,s))\, ds \\ &= \log(X(v,t)) - \log(X(v,0)).\end{aligned} \tag{47}$$

□

Equation (45) suggests defining the mean-squared error function to be

$$\bar{\sigma}_v^2(t) \equiv E\{\hat{A}_v(t) - A_v^*(t)\}^2 = \int_0^t E\left\{\frac{J_v(\tau)}{Y_v(\tau)}\alpha_v(\tau)\right\} d\tau. \tag{48}$$

An estimator of the latter quantity can be obtained by replacing $\alpha_v(\tau)\, d\tau$ by $d\hat{A}_v(\tau)$:

$$\begin{aligned}\hat{\sigma}_v^2(t) &\equiv \int_0^t J_v(\tau)(Y_v(\tau))^{-2}\, dN_v(\tau) \\ &= \sum_{\tau_j < t} Y_v^{-2}(\tau_j).\end{aligned} \tag{49}$$

Again, (49) has the advantage of not depending explicitly on the unobserved contact process. The results of Section 3 apply and give the following result.

THEOREM 4.2. *The variance estimators* $\hat{\sigma}_v^2(t)$ *and* $\hat{\sigma}_{1-v}^2$ *enjoy limits in distribution of the form*

$$\lim_{n\to\infty} N\hat{\sigma}_v^2(t) = \lim_{n\to\infty} N\bar{\sigma}_v^2(t) = \frac{1-2X(v,t)}{X(v,t)}, \tag{50}$$

with a similar expression for v *replaced by* $1-v$.

The proof is similar to that of Theorem 4.1.

Combining these results with standard martingale central limit theorems [DeMasi and Presutti (1991) and Andersen, Borgan, Gill and Keiding (1993)] yields the following theorem.

THEOREM 4.3.

$$\sqrt{n}\left(\hat{A}_v - A_v^*, \hat{A}_{1-v} - A_{1-v}^*\right) \to (U_v, U_{1-v}) \tag{51}$$

weakly in $D[0,t]^2$, *where* U_v *and* U_{1-v} *are independent Brownian motions with covariances given by* $\operatorname{cov}(dU_v(s), dU_v(t)) = \bar{\sigma}_v^2(t)\delta(s-t)\,dt$, *and similarly with* v *replaced by* $1-v$.

The error estimates in Theorem 4.2 refer to the variance of the Nelson–Aalen estimator centered around the random compensators. As explained above, one can regard the asymptotic limit of these compensators as the "target" to be estimated; if we do, the proper error estimate becomes

$$\tilde{\sigma}_v^2(t) \equiv E\left\{\hat{A}_v(t) - A_v^\infty(t)\right\}^2, \tag{52}$$

with a similar equation with v replaced by $1-v$. In general, these will be different from the estimates of Theorem 4.2. Theorem 3.2 applies and yields the following result.

THEOREM 4.4. *The errors in attack rates, with deterministic centering and assuming zero fluctuations in vaccinated/unvaccinated populations at* $t=0$, *enjoy limits of the form*

$$\lim_{n\to\infty} n\tilde{\sigma}_v^2(t) = \frac{\operatorname{cov}(v,v;t,t)}{X(v,t)^2}, \tag{53}$$

where $X(v,t)$ *is given in Theorem* 3.1, $\operatorname{cov}(v,v;t,t)$ *is the solution of* (22) *with* $f=g=v$, *whose existence and uniqueness were guaranteed in Theorem* 3.2, *and a similar result holds with* v *replaced by* $1-v$.

PROOF. An easy computation gives

$$\hat{A}_v(t) = H_n(Y_v(t)/n, Y_v(0)/n) = H_n(Y_v(t)/n, 1/2), \tag{54}$$

where

$$H_n(x,y) \equiv \sum_{k=[nx]}^{[ny]} \frac{1}{k} = \ln\left(\frac{y}{x}\right) + O\left(\frac{1}{n}\right). \tag{55}$$

The theorem then follows from Theorem 4.1 and the delta-method for computing variances applied to the function $-\ln(2x)$. □

A simple estimator of the true biological parameter β, which would be approximately unbiased at small values of t (i.e., if events are "infrequent"), is given by

$$\hat{\beta} = \log\left[\frac{\hat{A}_v(t)}{\hat{A}_{1-v}(t)}\right] \tag{56}$$

and has asymptotic limit

$$\lim_{n\to\infty} \hat{\beta} \equiv \beta(\infty) = \log\left[\frac{\log(X(v,t)) + \log(2)}{\log(X(1-v,t)) + \log(2)}\right]. \tag{57}$$

Thus the "model bias" is given by

$$\beta(\infty) - \beta = \beta(\infty) - \log(\theta). \tag{58}$$

This can be small for moderate contact propensities in the population (see Section 6). An estimate of standard error based on the Nelson–Aalen martingale variance can be formed and has asymptotics given by (let β^* be the compensator of $\hat{\beta}$):

$$\begin{aligned}
&\lim_{n\to\infty} nE\left[\hat{\beta} - \beta^*\right]^2 \\
&\quad = \lim\left[\frac{\hat{\sigma}_v^2(t)}{\left(A_v^\infty(t)\right)^2} + \frac{\hat{\sigma}_v^2(t)}{\left(A_{1-v}^\infty(t)\right)^2}\right] \\
&\quad = \frac{1 - 2X(v,t)}{X(v,t)\ln^2(2X(v,t))} + \frac{1 - 2X(1-v,t)}{X(1-v,t)\ln^2(2X(1-v,t))}.
\end{aligned} \tag{59}$$

An asymptotic result for the error with deterministic centering is

$$\begin{aligned}
&\lim_{n\to\infty} nE\left[\hat{\beta} - \beta(\infty)\right]^2 \\
&\quad = \frac{\operatorname{cov}(v,v;t,t)}{X(v,t)^2\ln^2(2X(v,t))} + \frac{\operatorname{cov}(1-v,1-v;t,t)}{X(1-v,t)^2\ln^2(2X(1-v,t))} \\
&\qquad + \frac{\operatorname{cov}(v,1-v;t,t)}{X(v,t)X(1-v,t)\ln(2X(v,t))\ln(2X(1-v,t))}.
\end{aligned} \tag{60}$$

Unfortunately, comparing (59) and (60) is difficult, since (22) cannot be solved exactly but requires a resort, for example, to perturbation expansions [Kato (1985)]. We note that, provided fluctuations in the vaccination assign-

ments are removed at baseline (e.g., by using permutation assignments), the first term in this expansion is simply the Nelson–Aalen limiting expression, so the expansion is around the standard statistical estimator. Examination of the next term in the expansion reveals that, to that level of approximation, the variance with deterministic centering is larger than that with random centering. We conjecture that this is true more generally but we are unable to provide a proof. Qualitatively, the difference in variance with deterministic centering (60) and that with random centering (59) is determined by the variability in the compensators and the covariance between the compensators and the associated martingales, which may not vanish in the interacting case.

5. Examples and simulations. In some populations, the limiting model dynamics with bounded contact rates may approximate finite-sample behavior. However, in others contact heterogeneity may be profound. These may be better approximated by models in which small subgroups exhibit extraordinary contact propensities.

Consider a bimodal distribution for contact propensity concentrated on two points $\{1, c_+\}$, with $c_+ = n/K$ and probability $P[C_i = c_+] = K/n$ for some positive K. The external risk is also K/n, and we put $F(c_i, c_j) = c_i c_j$. Call the individuals with the higher contact propensities the "superactives." Now let τ_{sa} be the (random) time at which the first superactive becomes infected. This time may exceed the length of the trial. If so, the number of infected cases at the trial's end $t = T$ will be small. Next suppose $\tau_{sa} < T$. Then, very quickly following τ_{sa}, for large n all the superactives become infected. Indeed, let n_+ denote the number of superactives enrolled and $n_{sa}(t)$ the number of superactives infected at time t. Then it is easy to show that, conditional on $n_+ > 0$ and $n_{sa}(t)/n_+ \geq f$ at time t, at time $t + \delta t$,

$$\frac{En_{sa}(t + \delta t)}{n_+} \geq 1 - \exp\left[-\frac{\theta c_+^2 n_+ f\, \delta t}{n}\right]. \tag{61}$$

For the indicated scaling, $c_+^2/n \to \infty$, so the superactive's epidemic is virtually instantaneous once it occurs. Afterwards the risk among "normals" equals their external (small) plus a fixed extra risk $n_+ c_+/n \approx$ (constant). Thus, conditional on $n_+ > 0$ and $\tau_{sa} < T$, over the interval $[\tau_{sa}, T]$ the trial closely resembles one treated in previous sections.

These statements become exact in the scaling limit, and we have the following informal theorem. The limiting distribution of numbers of infections, Nelson–Aalen estimate of attack rates and $\hat{\beta}$ are mixtures of Gaussians with parameters corresponding to a trial held over a fixed time interval, with constant external risk and bounded contact rates. The mixture distribution is over three quantities: the number of superactives enrolled (Poisson), the fraction of enrolled superactives that are vaccinated (binomial) and the time before the superactive's epidemic begins.

These results suggest running trials to a random time (say the time to reach a preselected case load) to at least partly resolve the mixture. Indeed,

this practice is common in large clinical trials with formal trial monitoring mechanisms. However, the random stopping time strategy would likely not resolve the mixtures for more complicated situations in which multiple, rarely interacting subgroups of "superactives" exist. We note that, under Assumptions 1–3, the theorems in Sections 3 and 4 still apply to randomly stopped processes provided the (properly rescaled) time scale has a limit law [Billingsley (1968)].

To further explore these issues, we conducted a small simulation study. We simulated vaccine trials using the models discussed in the previous sections, with the product form of the contact matrix and two distributions for contact propensities and external exposure intensities. For the asymptotically well-behaved case, we took the C_i's uniform on $[0, 10]$ and the E_i's uniform on $[0, 1]$. In the ill-behaved situation, we took the C_i's to have a bimodal distribution concentrated on $\{1, 100\}$ with $\Pr\{C_i = 1\} = 0.01$ and the E_i's uniform on $[0, 0.01]$. Two thousand subjects were randomized to have equal numbers in vaccine and placebo groups. The vaccine parameter θ was 1.0, 0.6 or 0.2. Our program simulated the infection process by generating, after each infection event time, n independent exponential random variables with parameters $\lambda_i^{\mathcal{F}}(t)$, computing the minimum $T_{\min}$ and recording an infection event at $t + T_{\min}$ for the associated individual. We generated 1000 replicate trials under each parameter configuration.

We ran the trials stopping either at a fixed time equal to the average time necessary to obtain a predetermined total of infections ($N_{\text{stop}} = 50$, 100 or 150 cases, respectively), these times having been computed from earlier runs, or stopping at a random time as discussed above. Some realizations with fixed time stopping ended with few (< 10) infections; we discarded these and tabulated the fraction of all runs (indicated by "s.f." or "success fraction") meeting this minimum information criterion.

We chose as the representative statistic $\hat{\beta}$ of Section 4, modified to be finite if either subgroup had zero infection rate at trial's end. We then computed the following quantities: $\overline{\beta}$, the average of $\hat{\beta}$ over the trials; "bias(model)," the average bias relative to the model parameter, $\overline{\beta} - \log(\theta)$; "bias($\infty$)," the average bias relative to the asymptotic limit (for bounded scenarios only) $\equiv \overline{\beta} - \lim \log[\hat{A}_v(\tau_N)/\hat{A}_{1-v}(\tau_N)]$, where τ_N represents stopping at a fixed fraction of 0.025, 0.05 or 0.075 times n. We computed the latter by numerically integrating (10) and using (46).

In addition, we computed the average standard deviation (SD) of $\hat{\beta}$ over the replicate trials; the average Nelson–Aalen estimated standard error (SE); the coverage rate of a Wald-type 95% confidence interval for β, recorded as rej $\pm$ (the fraction of trials in which $\hat{\beta} \pm 1.96 \times \text{SE} <$ or $> \beta$, respectively); and, finally, the coverage rate of a similar confidence interval for $\overline{\beta}$ recorded as Rej + or Rej − .

Results with fixed stopping time and uniform or bimodal contact propensities are reported in Tables 1 and 2. Bias in $\hat{\beta}$ is small for vaccines of low efficacy but increases for efficacious vaccines. Note that the relative risk has value θ at time 0 but is time dependent and converges to 1 as time increases.

TABLE 1
Simulated data from 1000 *trials with uniform contact distribution and fixed-time stopping rule*

θ	N_{stop}	bias(model)	bias(∞)	SD	SE	rej +	rej −	Rej +	Rej −
1.0	50	−0.004	−0.004	0.280	0.289	0.019	0.013	0.019	0.013
	100	−0.005	−0.005	0.198	0.198	0.016	0.032	0.017	0.029
	150	−0.004	−0.004	0.164	0.164	0.025	0.026	0.022	0.027
0.6	50	−0.024	−0.027	0.296	0.300	0.015	0.017	0.022	0.016
	100	0.003	−0.001	0.214	0.213	0.026	0.016	0.026	0.016
	150	−0.001	−0.008	0.172	0.171	0.019	0.025	0.024	0.024
0.2	50	−0.030	−0.037	0.436	0.397	0.038	0.018	0.046	0.014
	100	0.004	0.006	0.275	0.274	0.034	0.019	0.037	0.019
	150	−0.010	−0.028	0.231	0.221	0.021	0.025	0.034	0.020

The statistic $\hat{\beta}$ estimates the log-transformed ratio of time-integrated attack rates, resulting in bias with respect to the true "biological" parameter θ. This bias does not disappear in the large-sample limit, as Theorem 4.1 makes clear.

We note a similar situation for estimated standard error. In particular, SE reasonably approximates the standard deviation of $\hat{\beta}$ for low-efficacy vaccines but degrades with highly efficacious vaccines. With vaccine efficacy of 80%, SE greatly underestimates the true standard deviation of $\hat{\beta}$. The corresponding coverage rate of the 95% Wald-type confidence interval is generally good for weak vaccines but falls for vaccines with higher efficacy. This is apparently due to bias in $\hat{\beta}$ rather than non-Gaussian distributional shape since the coverage is close to nominal in most cases.

Results using the random stopping rule are reported in Tables 3 and 4. We find bias in $\hat{\beta}$ similar to that with fixed stopping time rule. However, with the random stopping time, the Nelson–Aalen-type estimator of standard deviation of $\hat{\beta}$ is quite accurate. The Wald intervals for β are only inflated due to bias in $\hat{\beta}$.

TABLE 2
Simulated data from 1000 *trials with bimodal contact distribution and fixed-time stopping rule*

θ	N_{stop}	s.f.	bias(model)	SD	SE	rej +	rej −	Rej +	Rej −
1.0	50	0.64	−0.005	0.262	0.266	0.026	0.020	0.028	0.020
	100	0.64	0.001	0.225	0.218	0.022	0.021	0.022	0.021
	150	0.66	0.003	0.204	0.208	0.022	0.024	0.021	0.024
0.6	50	0.62	0.018	0.243	0.228	0.043	0.021	0.031	0.026
	100	0.66	0.032	0.213	0.215	0.057	0.012	0.031	0.027
	150	0.73	0.038	0.189	0.202	0.053	0.008	0.025	0.024
0.2	50	0.66	0.117	0.384	0.264	0.150	0.013	0.035	0.031
	100	0.68	0.114	0.346	0.276	0.129	0.007	0.037	0.023
	150	0.74	0.101	0.401	0.270	0.160	0.013	0.052	0.032

TABLE 3
Simulated data from 1000 *trials with uniform contact distribution and random stopping rule*

θ	N_{stop}	bias(model)	bias(∞)	SD	SE	rej +	rej −	Rej +	Rej −
1.0	50	−0.003	−0.003	0.289	0.284	0.039	0.030	0.039	0.030
	100	0.011	0.011	0.207	0.200	0.032	0.027	0.032	0.027
	150	−0.001	−0.001	0.157	0.163	0.019	0.017	0.019	0.017
0.6	50	−0.002	−0.005	0.300	0.294	0.033	0.026	0.033	0.026
	100	−0.003	−0.001	0.207	0.206	0.018	0.023	0.018	0.023
	150	−0.005	−0.012	0.169	0.168	0.023	0.020	0.032	0.020
0.2	50	−0.047	−0.053	0.419	0.393	0.048	0.023	0.048	0.008
	100	0.002	−0.008	0.268	0.267	0.044	0.010	0.044	0.010
	150	−0.004	−0.021	0.215	0.216	0.028	0.017	0.037	0.009

6. Conclusions and directions for further research. An important open problem in the upcoming HIV vaccine trials will be to identify tractable analytical models with stable and interpretable parameters. In this paper we tried to capture the underlying complexity of the transmission mechanism in a probability model with latent variables and assess the impact on estimation. Our models do provide stable and interpretable parameters under some conditions (e.g., with suitably bounded contact heterogeneity), but not under others. Limited information from the trials will be available to check these homogeneity assumptions; hence developing practical criteria for using these results will be difficult.

Our experience has suggested a class of simpler models for the aggregate infection counting process that may be robust and stable even in the face of extensive heterogeneity. Consider the aggregate intensity involving unobserved latent variables and the process of averaging over these variables to induce an intensity with respect to the observable filtration. In simpler frailty models, the effect of the averaging is to induce a time dependence in the relative risk function on a time scale defined by cumulative "baseline"

TABLE 4
Simulated data from 1000 *trials with bimodal contact distribution and random stopping rule*

θ	N_{stop}	bias(model)	SD	SE	rej +	rej −	Rej +	Rej −
1.0	50	−0.001	0.290	0.284	0.038	0.033	0.038	0.033
	100	0.001	0.206	0.200	0.028	0.024	0.028	0.024
	150	0.003	0.167	0.163	0.028	0.024	0.028	0.024
0.6	50	0.067	0.290	0.291	0.036	0.018	0.019	0.018
	100	0.087	0.199	0.205	0.054	0.007	0.019	0.019
	150	0.061	0.166	0.167	0.053	0.008	0.022	0.021
0.2	50	0.216	0.355	0.358	0.133	0.003	0.038	0.009
	100	0.279	0.245	0.245	0.225	0.002	0.033	0.015
	150	0.228	0.197	0.201	0.249	0.002	0.032	0.015

intensity. However, in our situation, the "baseline" intensity function is a complicated function of the infection processes for the entire study cohort—see (41) of Section 4—and hence random. Rather than explicitly model this random function (as in Section 2), we might consider an approximate model for the intensity of the form

$$\lambda(t; v) = \lambda_0(t)\,\theta\big(v; t, \Lambda_0(t)\big), \tag{62}$$

where v is the vaccine/placebo group indicator, $\lambda_0(t)$ is a "baseline" intensity function with $\Lambda_0(t)$ denoting its integral to time t and θ is a deterministic relative-risk function to be estimated. Although similar in form to the usual relative-risk regression model, $\lambda_0(t)$ is random and will fluctuate over replicate trials. Nevertheless, the "time-dependent covariate," $\Lambda_0(t)$, can be stably estimated from data observed prior to t (e.g., by the Nelson–Aalen estimator), and this suggests an adaptation of well-known partial likelihood techniques for estimation of the fixed function θ.

Our small simulation study suggests that the relative risk function θ is stable in the face of considerable variability in λ_0. Developing a theoretical justification for the model in (62) together with more extensive simulation studies under conditions of substantial heterogeneity would be useful.

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