Comment

Mitchell H. Gail and Philip S. Rosenberg

We congratulate Bacchetti, Segal and Jewell on an authoritative account of many aspects of backcalculation, including especially their use of nonparametric methods with smoothing. This flexible approach was applied to modeling both the infection curve, $I(s)$ and secular changes in $D_{ij}R_{jk}$ as $R_jD_{ij}\exp(\beta_j + S(j))$. It is reasonable to interpret $S(j)$ as a seasonal effect on reporting and the smoothed sequence $\{\beta_j\}$ as reflecting secular changes in the incubation distribution, D_{ij}, in view of evidence that the completeness of reporting has remained high since 1987 and may have even improved where active surveillance has been implemented (see Table 4 in Buehler, Berkelman and Stehr-Green, 1992). The analyses of Bacchetti, Segal and Jewell provide new insights into the contribution of seasonal effects to overdispersion. Their findings of negative values of (β_j) beginning in mid-1987 (Figure 2) indicate that incubation distributions are lengthening after that time, as is also implied by the treatment model of Brookmeyer (1991).

While we agree that it is important to explore a wide range of plausible incubation distributions when using backcalculation, we believe that the three-parameter Weibull model derived from hemophiliacs is misleading. Bacchetti, Segal and Jewell (1992a) estimated this distribution using followup through October 1988 on the assumption that only one member of that cohort had received zidovudine (AZT) by then. However, a review of the treatment histories revealed that over one-third of the severely immunodepressed AIDS-free patients in this cohort (CD4+ levels below 200 cells/μL) received AZT between January and June 1988 (Rosenberg et al., 1991b). This may explain why the estimated median of this distribution is much more than 13 years (Figure 2 in Bacchetti, Segal and Jewell, 1992a). The corresponding estimate of 1,742,000 cumulative infections in the United States (Table 1) greatly exceeds other estimates based on backcalculation and seroprevalence surveys, and the corresponding estimated infection curve (Figure 1) exhibits much higher recent rates of infection than suggested by studies of seroincidence in cohorts of gay men and injecting drug users.

We take this opportunity to review some of the contributions that backcalculation has made to our understanding of AIDS epidemiology. Very little information is available on the "natural history" incubation distribution, F, beyond 6 years because AZT was introduced in March 1987 and AZT and other treatments have been used increasingly since then (see Figure 1 in Gail and Rosenberg, 1992). This scant information on F may seem insufficient, but most infections that took place before mid-1987 occurred within 7 or 8 years of that time. Thus the empirical data on F covered much of the important range of backcalculations before mid-1987.

Applications of backcalculation to data through mid-1987 were useful in several respects. First, backcalculation provided a simple conceptual framework to relate epidemiologic data on F, on AIDS incidence and on the prevalence of infection. Second, backcalculation led to short-term projections of AIDS incidence that were robust to changes in the incubation distribution (Brookmeyer and Gail, 1986, 1988; Brookmeyer and Damiano, 1989; Taylor, 1989). Third, although backcalculated estimates of cumulative infections were known to be highly sensitive to the choice of F (Brookmeyer and Gail, 1986, 1988; Taylor 1989; Rosenberg and Gail 1990), plausible ranges estimated from backcalculation for the number infected in the United States based on data through mid-1987 (e.g., 0.71 to 1.38 million in Rosenberg et al., 1991a) were in broad agreement with estimates based on surveys in selected populations (e.g., 0.90 to 1.27 million in Table 14 of Centers for Disease Control, 1987b). Because both results were subject to large random and systematic errors, it was reassuring that these estimates were based on entirely independent data sources and methods of analysis.

A fourth success of backcalculation before mid-1987 was the failure of the model (our Figure 1). The definition of AIDS was broadened after August 1987 to include dementia, wasting syndrome and extrapulmonary tuberculosis, as well as presumptive, rather than biopsy-proven, diagnoses of certain other conditions in seropositive subjects (Selik et al., 1990). This revision caused a pronounced increase in AIDS diagnoses amounting to 26% in the last quarter of 1987 (Selik et al., 1990). To avoid confusion, Gail, Rosenberg and Goedert (1990) studied a "consistently defined" AIDS series (squares in our Figure 1) for U.S. gay men based on the surveillance definition in use before 1987 but adjusted to include an estimate of those people diagnosed initially under the new criteria who would later be diagnosed with consistent AIDS. All series were

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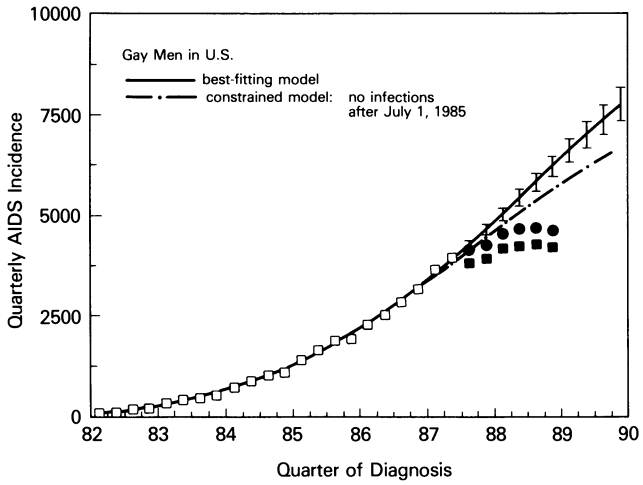

FIG. 1. *Consistently defined AIDS (squares) and all AIDS (circles) among U.S. gay men. The best-fitting backcalculation projection (solid line) based on AIDS-incidence data through June 1987 and the backcalculated projection constrained to have no infections after July 1, 1985 (dot-dash line), exceed observed AIDS incidence beginning in mid-1987. Further details are in the text and in Gail, Rosenberg and Goedert (1990).*

adjusted for reporting delays. It is seen that the backcalculated projections (solid line, our Figure 1) greatly exceed the observed consistent series after mid-1987 (solid squares). Even if one counts all AIDS under the expanded-surveillance definition (solid circles), backcalculated projections exceed AIDS counts. Constraining the backcalculated infection curve to go to zero in mid-1985 reduced the overshoot in projections by only about one-third.

The suddenness of the departure from previous trends beginning in mid-1987 suggested either a sudden failure in the surveillance system, for which no evidence has surfaced, or a sudden change in the incubation distribution. It is unlikely that earlier changes in the infection curve can produce the abrupt changes seen in our Figure 1, because changes in the infection curve are smoothed out by the convolution process. Gail, Rosenberg and Goedert (1990) and Rosenberg et al. (1991b) reviewed evidence from clinical trials that demonstrated the effectiveness of AZT and other treatments in delaying AIDS onset. They also gathered data on the amount of AZT in use in various risk groups and argued that the amount of treatment in use in certain risk groups, such as gay men, was sufficient to produce much of the change seen in our Figure 1, at least for the one-year period beginning in mid-1987. Other risk groups that had little access to AZT, such as injecting drug users, showed no such improvements in AIDS-incidence trends. Although the precise contribution of treatment to the sudden changes in AIDS-incidence trends is hard to quantitate (Segal and Bacchetti, 1990), the unexpected failure of simple backcalculation models led to a number of studies on the amount of treatment in use in various groups and to a new perspective on changes in AIDS-incidence trends. In particular, the sudden improvements seen in some subgroups beginning in mid-1987 did not necessarily imply that the number of infections was much smaller than previously believed, as suggested by naive backcalculation models that did not allow for secular changes in F.

Backcalculation is more problematic for incidence data beyond mid-1987 for several reasons. Models need to take secular changes in the surveillance definition and in the incubation distribution into account. "Treatment" models (Brookmeyer, 1991; Rosenberg, Gail and Carroll, 1992) and the model of Bacchetti, Segal and Jewell account for secular changes in F by modulating an underlying "natural-history" incubation distribution. The reliability of all these approaches diminishes for incidence data in the 1990s, because one requires knowledge of the natural history more than 10 years after infection, where there are no natural-history data. Moreover, there is much uncertainty about the current extent and types of treatments in use, the effectiveness of treatments in general use, as compared to clinical trial settings, and the duration of treatment benefits.

Given these uncertainties, it is encouraging that different approaches to incorporating treatment effects (Brookmeyer, 1991; Rosenberg, Gail and Carroll, 1992) predict a plateauing of U.S. AIDS incidence between 1990 and 1994. The "stage" model of Brookmeyer (1991) leads to somewhat higher estimates of AIDS incidence and cumulative infections than the "time since infection" (TSI) model of Rosenberg, Gail and Carroll (1992), mainly because the stage model assumes that more treatment is in use and that treatment effects are stronger than in the TSI model (see Gail and Rosenberg, 1992). Rosenberg et al. (1992) used the TSI model to study AIDS-incidence trends in the District of Columbia. They estimated alarmingly high seroprevalence rates and identified a "second wave" of infections beginning in the mid-1980s among injecting drug users and people infected through heterosexual contact. Independent survey data on seroprevalence levels and trends confirmed these findings and led to a redirection and intensification of prevention efforts.

If the surveillance definition of AIDS remains stable, it may be possible to simplify backcalculation and to avoid treatment models by reestimating the incubation distribution from empirical data on cohorts infected since 1987. If the definition is broadened to include CD4+ lymphocyte levels below 200 cells/μL, estimates of the incubation distribution would need to be made separately for various groups, with attention given to the degree of access to medical care. Access to medical care affects not only how soon treatments are given but also, as Bacchetti, Segal and Jewell emphasize, how rapidly a diagnosis of AIDS is made. In this

setting, backcalculation would best be applied to subgroups and interpreted in light of external data specific to each group.

The analytical and diagnostic tools developed by the authors, and their insights on components of overdispersion and model uncertainty, will be valuable in future studies of AIDS-incidence trends by backcalculation.

Comment

Victor De Gruttola and Marcello Pagano

The authors should be congratulated on presenting a timely and authoritative review of an important topic. The long latency period of AIDS makes it challenging to use surveillance databases for assessing epidemic trends. It also makes a technique such as backcalculation, which makes use of this information, another option for projecting the epidemic. Surveillance databases provide the only direct source of information about the impact of treatments and of educaonal interventions on entire populations. The analytical approaches presented in this paper may improve the usefulness of AIDS surveillance in designing and evaluating large-scale vaccine trials. In addition, these techniques could help us learn more about changes in the age distribution of HIV incidence over time. Currently we know little about the HIV infection rates among adolescents, who may be at particularly high risk. This knowledge should be useful in planning and evaluating attempts at behavioral modification.

Detection of subtle features of the epidemics of HIV infection and AIDS depends on knowledge about the precision of estimates and projections. The authors have characterized the numerical instability of deconvolution processes and the sensitivity to changes in the parameters of the process. One issue that we believe deserves more attention, however, is the error introduced by assuming that the times of onset of AIDS are independent; this was deemed of secondary importance by the authors. The assumption is obviously incorrect; the number who develop AIDS today must affect the number who do so tomorrow. Based on our own work, we agree with the authors that, as in the linear least-squares problem, the impact of this error should not be felt in solving for the mean function or the projections; it will result in an overly optimistic estimated precision of the projections. It would be interesting to assess the impact of this assumption. The best way to do this might be to model a process with some dependencies built in (Pagano et al., 1992a), rather than perform simulations with the incorrect independence assumption built into the model.

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Comment

John M. Karon and Glen A. Satten

Two of the most important questions concerning the HIV epidemic in the United States are whether HIV incidence is falling or rising and how many persons are becoming infected each year. Because it is presently the only feasible method for estimating past HIV incidence, backcalculation is fundamental for our understanding of the epidemic. Backcalculation is also currently the best method for making AIDS case projections.

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