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.

Victor De Gruttola and Marcello Pagano are Associate Professor and Professor, Department of Biostatistics, Harvard School of Public Health, 677 Huntington Avenue, Boston, Massachusetts 02115.

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.

John M. Karon and Glen A. Satten are statisticians in the Division of HIV/AIDS (E-48), National Center for Infectious Diseases, Centers for Disease Control, Atlanta, Georgia 30333.

Bacchetti, Segal and Jewell (BSJ) have described many of the important issues in implementing backcalculation and in interpreting results. They have also proposed some potentially important extensions to the methodology. We appreciate the opportunity to comment on some apparent differences between our approach and theirs concerning implementation and interpretation of backcalculation procedures.

STATISTICAL VERSUS EPIDEMIOLOGIC MODELING

BSJ point out (Section 2.5) that modeling the HIV epidemic requires choosing how much information to incorporate about the natural history of HIV-related disease and the transmission of HIV infection. We agree that, in general, backcalculation is much more useful for reconstructing the history of the epidemic and predicting its future than either extrapolation or mathematical epidemiologic models. The issue then becomes how much substantive information should be incorporated explicitly into backcalculation. We advocate incorporating more substantive information about the HIV epidemic than do BSJ.

The effect of therapy on the incubation-period distribution is an example of the difference between our approach and theirs. BSJ state that "good external estimates of . . . nonstationarity . . . are generally not available" (Section 3.3). We believe, however, that reasonably reliable estimates of this effect are available. Data from both clinical trials (Volberding et al., 1990; Leoung et al., 1990) and cohorts (Graham et al., 1991; Longini, Clark and Karon, 1993) demonstrate that medical therapy can reduce the hazard for AIDS by 50%–65% in severely immunosuppressed persons [HIV-infected persons who have not developed AIDS and have a $CD4^+$ T-lymphocyte cell (T-cell) count $< 200/\mu L$]. This effect can be included explicitly in the incubation-period distribution (Brookmeyer, 1991; Longini, Clark and Karon, 1993; Rosenberg, Gail and Carroll, 1992).

Because the decision to use therapy is often based on a patient's $CD4^+$ T-cell count, we recommend using a model for the incubation-period distribution that is based on stages defined by these counts and that includes the effect of therapy; examples are models developed by Brookmeyer (1991) and Longini et al. (1991). Incorporating the effect of therapy requires making an assumption about the duration of the therapeutic effect; current models generally assume that the therapeutic effect lasts indefinitely (Brookmeyer, 1991; Longini, Clark and Karon, 1993). These models also prescribe the proportion of persons receiving therapy based on data such as those summarized by Rosenberg et al. (1991a).

Instead of modeling the therapy effect, BSJ introduce methodology that allows for an unspecified time trend in the incubation-period distribution through model parameters (their β's) that are estimated from backcalculation. This procedure requires fewer assumptions, but the results are hard to interpret, making it difficult to assess whether the estimated effect is consistent with external data (such as the proportion of immunosuppressed persons using therapy). For example, even if their estimated time-dependent trends (Figure 2) are not affected by time trends in reporting, their estimated trends may reflect changes in both efficacy and the proportion of immunosuppressed persons receiving therapy. It would be difficult to ascertain whether the estimated β's could correspond to a plausible combination of assumptions about the efficacy of therapy and the proportion of immunosuppressed persons receiving therapy.

The agreement of assumptions and estimates with data is an important part of model checking in backcalculation. In making the Public Health Service's AIDS-case projections for the United States, we have found it essential to use backcalculation models that make explicit assumptions so that we can interpret why results vary across models. We suggest using a model that includes explicit assumptions about the efficacy of therapy and about the proportion of immunosuppressed persons using therapy, as well as BSJ's β parameters. The values of these parameters would then indicate whether the data can be fit well under the assumptions made.

THE INCUBATION-PERIOD DISTRIBUTION AND MARKER FORMATION

BSJ describe the problems in estimating the incubation-period distribution. Reliable estimates of this distribution are hard to obtain because the time from HIV infection to AIDS diagnosis is relatively long and highly variable. In addition, most current estimates of the incubation-period distribution are based on cohorts recruited before 1985 and contain relatively few persons infected after that year. Our views are less pessimistic than BSJ's expressed in Section 2.3. Longini et al. (1991, 1993) have shown that a good model for the incubation-period distribution, including treatment effects, can be obtained from a cohort consisting mostly of HIV-seroprevalent persons. Their procedure is based on characterizing the incubation-period distribution as a series of stages defined by a marker such as the $CD4^+$ T-cell count. This type of procedure can estimate the incubation-period distribution before any of the seroincident persons develop AIDS. Making full use of seroprevalent cohort members is important, as HIV incidence has been relatively low in cohorts studied to date and may well remain low in cohorts recruited in the future.

Use of a staged infection-time distribution has addi-

tional advantages. Satten and Longini (1992) have shown that in some cases, information on the variation over time in the proportion of HIV-infected persons in various $CD4^+$ T-cell stages can be used to reconstruct the HIV-incidence history of a population. Persons with relatively high $CD4^+$ T-cell counts provide more information on recent HIV incidence than do persons diagnosed with AIDS. Hence, constraining a backcalculation to reproduce the proportional distribution of persons in $CD4^+$ T-cell stages (or in a restricted set of stages, e.g., those with $CD4^+$ T-cell counts $>500/\mu L$) observed in a survey or by HIV reporting may improve the estimate of recent HIV incidence obtained from backcalculation.

ESTIMATES OF HIV INCIDENCE

Different backcalculation methods tend to give similar estimates of HIV incidence and prevalence through the mid-1980s. In contrast, different backcalculation methods can give very different estimates of recent HIV incidence and hence very different estimates of current HIV prevalence (CDC, 1990). Backcalculation cannot be expected to give a precise estimate of HIV incidence for the most recent 2–3 years because most HIV-infected persons do not develop AIDS within 3 years after infection. As a result, estimates of recent HIV incidence cannot be accepted as reliable without external validation.

AIDS-surveillance data and HIV-serosurvey data suggest that some of BSJ's HIV-incidence estimates for 1990 (Figure 1) are too high, while others are too low. AIDS-surveillance data indicate that there are now approximately 50,000 deaths per year in HIV-infected persons in the United States (CDC, 1992c). The CDC's HIV serosurveys generally show little change in HIV seroprevalence in the United States (CDC, 1991b), suggesting that during the last few years, approximately 50,000 persons per year were infected with HIV. This estimate is consistent with the estimate of 40,000 to 80,000 new infections per year in 1989 derived from HIV incidence in U. S. Army active duty personnel (CDC, 1990). The data therefore suggest that approximately 5,000 new HIV infections per month have occurred during the last several years, a substantially different estimate from those in BSJ's models of either <1,500 or >8,000 new HIV infections per month during 1990 (Figure 1). BSJ's four models provide qualitatively very different estimates of recent HIV incidence. In order to evaluate which model is likely to provide the most reliable estimate, we need to compare specific assumptions about the time dependence of the incubation-period distribution with data (e.g., from clinical trials and cohorts on the efficacy and use of therapy). Trends in the β's alone (Figure 2) do not provide this information.

We would like to obtain two different estimates related to recent HIV incidence, the current incidence per unit time in a population, and the trend in incidence. BSJ suggest estimating HIV incidence by testing successive samples using stored serum from persons whose blood is drawn for other reasons. Such procedures have been considered, but at least four major issues would need to be resolved. First, potential ethical and confidentially concerns would have to be resolved to the satisfaction of an institutional review board. Second, most seroprevalence surveys sample persons at elevated risk for HIV infection (e.g., hospitalized patients, persons attending sexually transmitted disease clinics, and persons in treatment for injection drug use). An estimate of HIV incidence obtained from these surveys is unlikely to be representative of a larger population. Third, risk information is not available in some of these surveys (such as that of hospitalized patients). Fourth, although HIV-incidence *trends* in these surveys may be generalizable, it may be possible to monitor these trends at much lower cost by observing trends in markers of disease progression. The best understood marker for progression, the $CD4^+$ T-cell count, requires fresh plasma and hence cannot be obtained from a serosurvey. These are markers which can be measured in serum, including β2-microglobulin. We are studying the time dependence of β2-microglobulin levels in HIV-infected individuals. If these levels were known to increase monotonically over time at the population level, we could estimate a time trend in HIV incidence by monitoring the prevalence of HIV-infected persons with β2-microglobulin levels less than an approximately chosen value. With a better understanding of the increase in β2-microglobulin with time since HIV infection, we would be able to estimate the proportion of HIV-infected persons who have been infected during the last year (Satten and Longini, 1992).

MODELING AIDS INCIDENCE

Most of BSJ's results are based on modeling AIDS incidence for all transmission risk groups combined. We prefer to model risk groups separately, as AIDS-incidence trends vary among these groups. In particular, AIDS incidence has been increasing relatively rapidly in cases with HIV infection attributed to heterosexual transmission but may have reached a plateau in men who have sex with men (whether injecting drug users or not), and in female and heterosexual male injecting drug users (CDC, 1992c).

We are skeptical of the need to model the monthly variation in AIDS-case counts, especially considering that the median incubation period is about 10 years, even though doing so improves the behavior of the standardized residuals. We would be interested in know-

ing whether the estimated monthly effects correspond to real variation in AIDS diagnoses over time, instead of just improving fit by adding flexibility. For example, we would discount estimated monthly effects that appeared to represent simply random variation over the calendar year. We would also be interested in knowing whether modeling monthly variation gives a better fit to annual AIDS-case counts and whether there is an advantage in modeling monthly rather than quarterly AIDS incidence.

PROSPECTS FOR THE FUTURE

The CDC expanded the AIDS-surveillance definition in January 1993 to include severe immunosuppression, as well as several life-threatening conditions beyond those in the 1987 surveillance definition (CDC, 1992b). Data from a large CDC study of persons in health care for HIV-related diseases (Farizo et al., 1992) show that the median time from the diagnosis of severe immunosuppression to an AIDS diagnosis (according to the 1987 surveillance criteria) is 15 months (CDC, 1992c). Expanding the surveillance definition will therefore reduce substantially the time from HIV infection to case report for persons reported based on a $CD4^+$ T-cell count. In addition, the proportion of persons reported based on severe immunosuppression may increase with time (after prevalent severely immunosuppressed persons are reported) as the use of $CD4^+$ T-cell counts increases in monitoring the health of HIV-infected persons in medical care.

BSJ's proposal to base backcalculation on mortality data is unlikely to be the best method for using data collected under the expanded surveillance system. Mortality information is less complete than information on persons diagnosed with AIDS. For example, approximately 8% of reported persons with AIDS diagnosed before 1986 have not been reported as dead (CDC, 1992a), although many of the apparent survivors probably are dead (Hardy et al., 1991). Estimating the number of HIV-associated deaths through death certificates yields fewer deaths than the number reported through AIDS surveillance (Buehler, Hanson and Chu, 1992). In addition, backcalculation based on mortality would give estimates of recent HIV incidence that are even less precise than backcalculation based on AIDS incidence because of the longer time from HIV infection to the event.

Instead of using mortality information, backcalculation methodology should be extended to use data reported under the expanded AIDS surveillance definition. Either a separate incubation-period distribution is needed for severe immunosuppression as the defining event or the incubation-period distribution must model severe immunosuppression as one or more stages before the occurrence of overt life-threatening disease. In addition, the CDC is obtaining surveillance data on all persons testing positive for HIV infection in some states. Marker data are available for some of these persons. We will be incorporating these data into backcalculation models to get better estimates of HIV incidence during recent years. Much progress has been made in using backcalculation to model the HIV epidemic, but challenging problems remain.

Comment

Patricia J. Solomon and Susan R. Wilson

INTRODUCTORY REMARKS

This paper is a useful addition to the literature on statistical methods for AIDS. Its emphasis quite properly reflects the authors' computationally intensive contributions which include many developments that are necessary for dealing with the U.S. data.

Patricia J. Solomon is Senior Lecturer, Department of Statistics, University of Adelaide, GPO Box 498, Adelaide SA 5001, Australia. Susan R. Wilson is Senior Fellow, Centre for Mathematics and Its Applications, Australian National University, GPO Box 4, Canberra ACT 2601, Australia.

We agree that sensitivity analyses are essential. Wilson, Fazekas de St. Groth and Solomon (1992) have also evaluated the sensitivity of estimates of past HIV incidence and future AIDS incidence to major uncertainties in the backcalculation method in the context of the Australian AIDS epidemic. In particular, we investigated sensitivity to the incubation-period distribution (Weibull and gamma), the new infection-intensity distribution (quadratic exponential, linear logistic and power) and the level of aggregation of the data (quarterly, six-month and yearly) used for analysis. Past and current estimates of HIV incidence and future estimates of AIDS were sensitive to all of these uncertainties, the least sensitive estimate being