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.

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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

new diagnoses of AIDS in the year following the end of the data.

It is important to have estimates of the numbers of individuals in different stages of HIV disease. A natural extension of Brookmeyer and Liao's (1990b) incubation model to incorporate the availability of zidovudine to HIV-infected individuals with $CD4^+$ cells/mm^3 counts of 500 or less, is to split Brookmeyer and Liao's first stage into two: $CD4^+$ counts above 499 (stage 1), and $CD4^+$ counts in the range (200, 499) (stage 2). Wilson and Solomon (1991) describe a progressive multistage model for the incubation period which readily accommodates changes in treatment regimes at different stages of HIV infection over calendar time. The general approach also deals readily with changes in the definition of AIDS, especially if the data are still collected with the old definition before the change point.

THE AUSTRALIAN EXPERIENCE

AIDS surveillance systems and databases from countries other than the United States may not be as complex, nor as large, and it is of interest to compare and contrast various aspects of the use of backcalculation.

In Australia, new diagnoses of HIV infection and AIDS are routinely notified from all States and Territories to the National Centre in HIV Epidemiology and Clinical Research, Sydney. Reporting is supplemented by information on new zidovudine prescriptions and by some death-certificate checking. The data on AIDS are of relatively high quality compared with those of other western countries. Reporting is virtually complete by 18 months, and underreporting is currently estimated to be between 10% and 20%, depending on region and possibly on transmission category. The Australian data are almost certainly relatively more homogeneous than the U.S. data.

It is interesting that in recent work we completed for the purposes of the National Working Group on HIV Projections, the results from our parametric approach (Solomon et al., 1991) are very similar to the results obtained from the nonparametric approach of Becker et al. (1992). We view the different approaches as complementary rather than competing.

When we first analysed the Australian AIDS data in 1989, we found the monthly incidence data to be quite strongly correlated and no evidence of seasonal effects. Use of quarterly data minimises the autocorrelation effects, but the resulting estimates are still sensitive to the level of data aggregation, referred to in our introductory remarks.

In Australia, there is virtually no information on the incubation period, and so we are dependent on external data. We have applied the incubation distributions given in Bacchetti, Segal and Jewell (1992a) to the Australian data to the end of 1991, as reported by mid-1992 and with an adjustment to the 1991 data based on the assumption that the reporting delay would remain unchanged from 1990. We used our own treatment model fitted to quarterly data: the hazard of progression from one stage to the next is assumed to follow a Weibull distribution, with stage 1 mean 3.8 years, stage 2 exponential mean 4.5 years, stage 3 exponential mean 2 years and stage 4 clinical AIDS. It was assumed that treatment was available only to those in stage 3 and that the effect prolongs the mean incubation by 1 year. Details are described in Wilson and Solomon (1991). For the distribution of new HIV infections, we assumed a parametric quadratic exponential form, constrained to not fall below 150 per quarter.

Table 1 summarizes our "equivalent" results to those given in Table 1 of the article under discussion. Note that it is important to distinguish the blood-transfusion data which are quite different.

Information from studies of HIV incidence in cohort and clinic populations strongly suggests that the two incubation models that yield the lowest deviances are unrealistic. The "Hemophiliac Cohort" model predicts very slowly decreasing numbers of new infections that

TABLE 1
Australian version of Bacchetti, Segal and Jewell's Table 1 (*Section* 4.1.1)

Incubation model	Quarter of peak in infections	Cumulative infections (in hundreds) by month/year			Deviance	Predicted diagnoses* in quarter
		12/84	6/87	12/90		1/95
Treatment model**	1/85	52	110	131	57	222
Random sample	3/80	56	70	92	38	166
Multistage treatment model	3,4/83	77	93	110	57	201
Hepatitis B vaccine trial	1/85	52	105	130	46	148
Hemophiliac cohort	4/84	79	134	206	43	190

* Unadjusted for underreporting and using 1987 case definition.

** Weibull distribution with index 2, conditional mean before mid-1987 taken to be 10 years, increasing to 11 years after that date when treatment became available.

are too high, approximately 500 per quarter estimated during 1990. On the other hand, the "random sample" model predicts a very dramatic peak in infections for the last two quarters of 1980. Qualitatively these results do not depend on the use of a parametric formulation for new HIV infections, or on constraining the new infection rate.

It is interesting that approximately half of the lack of fit occurs in five distinct quarters. For the "treatment model" (and actually any model based on the Weibull distribution, with or without treatment effects), the lack of fit occurs in Q1, 1984, and Q4, 1985, both with too few observed cases, and in Q3, 1988, Q4, 1988, and Q2, 1990, all with too many observed cases. However, for the "Hepatitis B Vaccine Trial" model, the overfit occurs as just described, but now there is underfitting in the second quarters of 1985 and 1989, as well as 1990. The monthly observed data in each of these quarters are (8, 21, 9), (29, 44, 51) and (50, 44, 44). Also, three of the nine second quarters are overfitted by the model, indicating little evidence for any seasonal variation. It is interesting that part of the lack of fit appears to be driven by the incubation-period distribution. There are apparent outliers in the data too, but no explanation has been found for them.

DISCUSSION

Backcalculation is widely held by statisticians to be the most statistically respectable approach to both estimating the past HIV-infection curve and predicting the future course of the AIDS epidemic, but other methods should also be considered. In mathematical complexity and requisite assumptions, backcalculation lies between empirical curve fitting to observed AIDS-incidence data and models for the transmission dynamics of HIV infection. We reiterate that resources need to be devoted to considerable sensitivity analyses for backcalculation; experimental-design considerations may play a useful role here. On a related point, it seems essential to analyze the data in relatively homogeneous groups and to give predictions separately for geographical regions and transmission categories within regions.

There is considerable heterogeneity between individuals concerning the incubation distribution and the availability and effect of a variety of treatment regimes which have been evolving continuously over the recent past. It may be that the underreporting rate is decreasing as treatment becomes more readily available to those in earlier stages of HIV disease (at least in Australia) and HIV-infected individuals are more actively seeking treatment both at an earlier stage and because it is more efficacious. It is also possible that reporting delays are shortening because these individuals will then be monitored fairly closely.

An alternative way of modelling seasonal effects to that suggested by the authors would be to fit the first four terms of a Fourier series. That is, ignoring trend, replace the $S(j)$ or the $e^{S(j)}$ by

$$\alpha \cos\left(\frac{2\pi j}{12}\right) + \beta \sin\left(\frac{2\pi j}{12}\right) + \gamma \cos\left(\frac{4\pi j}{12}\right) + \delta \sin\left(\frac{4\pi j}{12}\right).$$

This model has the advantage of reducing the number of parameters to be estimated to four, or two if only the first two terms are fitted, but this is likely to be too restrictive. Serial correlation can also be incorporated, although it may be difficult to distinguish such correlation from trend. This model might also help to distinguish "true" seasonal effects from artifacts of the data-collection process.

It is not possible to remove all the uncertainty surrounding the epidemic, but statisticians can help provide information on which consensus decisions can be made together with social and medical scientists and others. As part of this process, it is important to incorporate external information, both objectively and subjectively, especially regarding the recent past. The available data on HIV disease, incubation and so on, represent an incomplete description of phenomena which are, on the whole, relatively poorly understood, and we should be aiming to bring as much knowledge as possible to bear on the problem.

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Rejoinder

Peter Bacchetti, Mark R. Segal and Nicholas P. Jewell

We thank the discussants for a number of insightful comments, as well as some useful additional background and discussion. Here, we respond to a number of the issues raised and provide some additional comments on a few points.

Although we emphasized in the paper some draw-