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-

backs to our strategy of estimating (additional) nonstationarity of the incubation distribution as part of the backcalculation procedure, we believe that it can be defended against some of the additional criticisms raised by the discussants. Brookmeyer's "near nonidentifiability" depends on dismissing the smoothness structure as a minor part of the estimation procedure. Although the imposition of structure can thinly mask essential nonidentifiability in some situations, as pointed out by Kalbfleisch and Lawless (1988, 1989) for an AIDS-related application, this is not the case here. The smoothness requirement is essential to the procedure, and without it the issue of ill-posedness would present extreme numerical problems, apart from any nonidentifiability concerns, as is the case for backcalculation with a stationary incubation. With the smoothness assumption introduced, calculation of confidence intervals based on thousands of simulations shows no sign of the numerical instability Brookmeyer expects, because the roughness penalties eliminate it. We can see this by considering the random sample curve in Figure 1. If we imagine a departure starting in 1986 that leads to the same cumulative number of infections as for the hemophiliac curve, we see that such a curve would be much less plausible than the one fitted and would be much "rougher." The corresponding estimate of β would also be "rougher." Furthermore, a useful interpretation of Table 1 would be available even if the estimates *were* unstable. We would still have four different nonstationary incubation models that are generally consistent with what is known about incubation distributions and how they are changing, and these would still lead to equally good fits to the AIDS-incidence data while producing very different patterns of past infections. Thus, our basic interpretation of Table 1 would remain unchanged.

Karon and Satten complain that β is not interpretable in terms of treatment prevalence and effectiveness, and Carlin and Gelman also note the lack of interpretability. Modeling nonstationarity directly in terms of calendar time, however, does have some advantages. It results in a parsimonious model, and it does not require assuming away other sources of nonstationarity, such as evolution of the virus or changes in the characteristics of the HIV-infected population. In addition, the influence of calendar time can be directly estimated from data, such as followup of an infected cohort, by allowing it to be a time-varying covariate. In contrast, estimating the influence of treatments in a cohort is problematic because of, for example, self-selection and lack of intensive followup, while extrapolation from clinical trials to long-term, population-wide effects is even more suspect than extrapolation from cohorts. We note that Karon and Satten's inability to assess which β's are consistent with available data on treatments seems to contradict their earlier claim that enough is known about treatment-induced nonstationarity. The bottom line here is the influence on AIDS incidence, so knowing enough must entail knowing something about the overall effect in the population, which the parameter β estimates. We prefer Gail and Rosenberg's assessment that there continues to be "much uncertainty" in this area. Interpretations based on incorrect assumptions, however explicit, may be of questionable merit. We do support Karon and Satten's proposal to use estimation of β to check the adequacy of an external estimate of nonstationarity. For example, our inability to obtain an adequate fit using the treatment incubation model with $\beta = 0$ ($\lambda_\beta = \infty$) suggests that the model may be inaccurate (although the fault could lie in the stationary part).

It may be helpful to stress here that projecting AIDS incidence and joint estimation of infection rates and nonstationary effects are related but somewhat different tasks. A primary feature of our strategy for accommodating nonstationarity is that it may improve the accuracy of backcalculated projections without necessarily producing accurate estimates of nonstationarity parameters. Improvement in accuracy may be achieved by mitigating the effects of incorrect assumptions or incubation inputs through use of a more flexible model.

We note that there are difficulties with the simple use of treatment-based models of nonstationary effects on incubation. First, it is not immediately apparent why one should restrict the modeling of nonstationary phenomena to treatment effects when there are clearly other important temporal sources of influence on incubation. Attempts, however, to model successfully all plausible nonstationary factors will quickly dissipate backcalculation's advantages over transmission dynamics models. Second, even if one accepts that treatment efficacy is the primary, if not sole, form of incubation nonstationarity, it seems to us implausible to assume that these treatment effects are themselves stationary. Clearly, there have been and will continue to be changes in the kinds of therapies available, access to treatment regimens, treatment effects, and treatment practices. In particular, we are skeptical about the possibility that a simple nonstationary adjustment to the hazard for the onset of AIDS in an advanced stage of HIV disease can adequately model the effects of therapies. Thus, if one adopts the treatment-based model approach to the exclusion of other strategies, one is committed to an almost continuous process of model modification that presents an extremely complex procedure, at least if one is interested in working prospectively.

Brookmeyer's comments about nonidentifiability and about extrapolation for recent infection rates serve to emphasize the importance of how structure is imposed on θ. It may now be time to move beyond regarding

the structure of θ as merely a technical detail or device and to try seriously to reflect reasonable notions of what is plausible. We believe that our roughness penalty is a step in this direction. It reflects a common concept of smoothness with second differences and it facilitates the fitting of early exponential growth (as suggested by theoretical epidemic models) by measuring roughness on the log scale. Other approaches, however, are numerous. Jeremy Taylor (personal communication) has suggested using third differences because this would give more prior weight to θ's that go up and then back down (quadratic on the log scale). Carlin and Gelman's prior is another possibility, as are the approaches of Pagano et al. (1992a) and of Becker, Watson and Carlin (1991). In addition, there are many parametric models, such as those of Gail and Rosenberg and of Solomon and Wilson. To the extent that these different methods produce different results, they constitute an additional source of variation that must be considered and that can potentially be reduced by careful consideration of prior information about θ and evaluation of which assumptions are truly reasonable.

Several discussants emphasize their view that backcalculated estimates from some of the incubation distributions appear to be inconsistent with external information about HIV-infection rates in the United States or Australia. We are certainly glad that external data are becoming available, although it is still possible to be quite skeptical about their accuracy. It is important to realize, however, that one cannot simply dismiss one or two of the estimates in Table 1 and thereby vindicate the accuracy of backcalculation. Any additional accuracy is the result of combining backcalculation with external information about θ. Also, the four incubations considered do not constitute an exhaustive or even systematic exploration of what may be plausible concerning incubation distributions in various populations. Thus, at this point, we cannot immediately conclude that there is no plausible incubation distribution that would lead to a backcalculated θ with 1.7 million cumulative infections (by the end of 1990) along with lower recent infection rates consistent with purportedly accurate external estimates. We continue to argue that a more systematic approach is needed. External information on infection rates, together with AIDS-incidence data, can provide valuable information about the incubation distribution in a population (Bacchetti, 1990), so approaches that combine estimation of both θ and the incubation distribution may be able to make the best use of such external information. The Bayesian approach of Carlin and Gelman is promising, but computational difficulties and the specification of a suitable incubation prior remain obstacles.

Our original reason for examining incubation data from three cohorts was to produce a meta-estimate. We therefore developed methods to fit data from two or more cohorts, allowing for separate infection curves but a common incubation distribution (Bacchetti et al., 1993). Having done this, however, we were then able to use likelihood ratio tests to assess whether the assumption of a common incubation was warranted. These tests showed significant differences, based only on the available cohort data, not on model extrapolation. That the differences were statistically significant is all the more impressive because of the small sample sizes noted by Brookmeyer. We felt that it would be more productive to follow the data than to cling to our preconceived notion of a common incubation, so we abandoned work on a meta-estimate and began to explore the implications of heterogeneous incubation distributions. In retrospect, unlike Brookmeyer, we consider that heterogeneity was to be expected, given the wide individual variation and very different characteristics of different risk groups. It is therefore important to consider the population under study, and the various subgroups that make it up, when choosing a suitable incubation prior or set of sensitivity analyses. It is also certainly important to explore which cofactors may explain the heterogeneity. Such exploration is currently under way for the San Francisco City Clinic Cohort.

The stage models advocated by Karon and Satten do not address the uncertainty caused by potential heterogeneity of incubation distributions. They do make good use of data from prevalent subjects, but at the cost of estimating more parameters and relying on strong assumptions. We are not aware of any published examination of these assumptions, and it seems safe to say that there is currently more uncertainty regarding the parameters and structure of such models than about the overall incubation distribution. We should also point out that other existing procedures for incubation estimation also allow for the effective use of data from prevalent subjects. Aside from allowing the possibility of projecting numbers of individuals in pre-AIDS stages and the accommodation of treatment-based models based on the assumed stages, the contribution of this approach to the overall accuracy of backcalculation remains unclear.

Concerning the possible use of AZT by members of the hemophiliac cohort, we note that ending followup at June 1987 produces a three-parameter incubation estimate that is very similar to the one used here, although Weibull models would differ substantially. Our decision to use all follow-up data was based on a prominently published paper, using the same data we did, that claims to report on the natural history of HIV infection in the cohort and that specifically states that only one subject received AZT before developing AIDS (Goedert et al., 1989). To our knowledge, no retraction or correction of that paper has appeared.

Because observing trends in markers of disease pro-

gression is very indirect, we are skeptical about its ability to produce accurate estimates of HIV incidence at low cost. In addition, it would seem to be subject to the same sampling biases as seroprevalence surveys or the direct measurement of seroconversion that we have proposed. The costs of adding our direct measurement to current surveys are those of splitting the samples, storing half, and performing ongoing record linkage to identify repeaters. This hardly seems prohibitive in light of the clear statistical advantages of having repeat samples. It would therefore seem prudent to employ this relatively simple approach in addition to others being contemplated.

Backcalculation from AIDS deaths would certainly require the improvement of AIDS-death surveillance, but this may well be possible and worthwhile. Because the recording of deaths is fairly complete, intensive followup on samples from computerized death certificates could provide a systematic assessment of the completeness of AIDS-death surveillance, thereby increasing its value. The patchwork of completeness studies on diagnosis surveillance, based largely on death certificates, is less satisfactory than what might be possible for deaths. In addition, death might be a more stable and biologically meaningful endpoint. As acknowledged, backcalculation based on AIDS deaths would be even less able to estimate recent infection rates, but this deficiency could be made up by other methods.

The presence of month effects is interesting in itself, and correcting for them has the potential to improve the accuracy of backcalculation. Not only is overdispersion reduced, but failing to correct can be expected to lead to projections that are too high if the case series used ends in March or June and too low if it ends in December. Month effects can be modeled using Poisson regression models that include terms to fit a smooth trend in addition to seasonal terms. Including circular terms, as proposed by Solomon and Wilson, may indeed help to distinguish biological from artificial causes of the patterns. Comparing patterns in different countries and in different subgroups in the United States may also shed light on the causes. Modeling serial correlation, as suggested both by De Gruttola and Pagano and by Solomon and Wilson, complicates the model somewhat but may not be necessary in situations where the residuals from simpler models show no such correlation, as we found here.

We believe that Gail and Rosenberg's characterization of inaccurate projections as a "success" is not justified. Clearly, the best success would have been accurate predictions that reflected what was known about treatment effects. The retrospective success they claim is not perfectly clear to us but seems to be based on the substantiation of treatment effects by the inaccuracy of some backcalculation projections. The

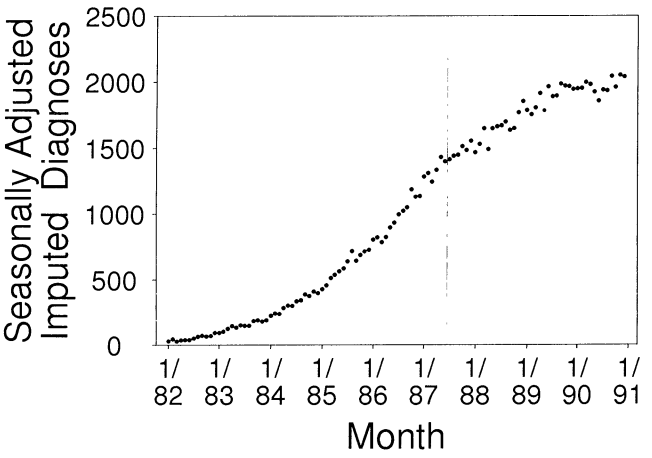

FIG. 8. *Monthly AIDS incidence among homosexual and bisexual men in the United States who were not also intravenous drug users. Counts are adjusted for reporting delay and month effects as described in Figure* 3, *with no adjustment for underreporting. The vertical line is between June and July* 1987.

existence of treatment effects, however, is obvious from what is known about preventive therapies. Since the advent of widely used treatments, and because the treatments were effective as shown in clinical trials, AIDS incidence must have decreased from what it would have been without any effective treatment. In order to claim more than showing the obvious with regard to the impact of treatment on AIDS incidence, backcalculation must accurately estimate the magnitude of the populationwide effect of treatment on AIDS incidence. We do not believe that the gap between predicted and observed in Gail and Rosenberg's Figure 1 provides the basis for such an estimate. Indeed, we believe that our Figure 2 makes a strong case that uncertainty about incubation prevents backcalculation from currently being able to produce such an estimate. Furthermore, using more recent monthly data and correcting for month effects produce a somewhat different picture. In Figure 8, there is much less indication of any sudden changes, and lowering the count for May 1987 by about 5% would erase any appearance at all of an "abrupt change." Thus, the impact of treatment may have been more gradual and less dramatic than their Figure 1 would indicate. This provides an example of the potential importance of correcting for seasonal effects in interpreting AIDS incidence.

Many of the statistical issues raised in our paper and by the discussants have implications beyond backcalculation. This is particularly true for questions surrounding the use of smoothing techniques, penalized likelihood, and Bayesian approaches. With regard to backcalculation specifically, the discussants' remarks amply illustrate the substantial range of opinions about incubation information, HIV-infection incidence models, and properties of the AIDS-reporting system.

The uncertainty surrounding each of these aspects of the backcalculation technique belies the "simple conceptual framework," noted by Gail and Rosenberg, which the method provides. Thus, despite the apparent simplicity of the statistical model used, great care must be taken in application of the methodology and interpretation of the results obtained. In general, we continue to argue for consideration of a broader class of models and more extensive examination of assumptions and quantitative inputs in implementing a backcalculation approach so that the analysis truly reflects the appropriate uncertainty and interpretations are subject to an appropriate amount of skepticism. We also urge future consideration of methods that take full advantage of available external data, including a variety of seroprevalence studies. In fact, it is perhaps overdue that backcalculation analyses employ such data in a more formal sense than currently. Finally, we note that with the change of the AIDS definition introduced at the beginning of 1993, new challenges to the problem of projecting frequencies of AIDS cases, HIV prevalence and infection patterns are upon us. The area promises to continue to be of great interest in the next few years.

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