

## DISCUSSION

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The subject of this session is one of the main topics addressed by a recent National Research Council (NRC) report, *AIDS: Sexual Behavior and Intravenous Drug Use*<sup>1</sup>. Much of what I will say, and in particular my comments on the CDC paper, will be based on this report. The committee was chaired by Lincoln Moses and staffed by Charles Turner. A special panel on statistical issues was also set up, chaired by Jane Menken, and Ron Brookmeyer and I were members. The committee has obviously not seen or heard the papers being presented at today's session, so my comments therefore should not be interpreted as those of the committee, the Institute of Medicine, or the National Research Council.

The NRC report stressed the importance of going beyond counting AIDS cases to monitoring the spread of HIV in the population so I am glad to see this session on the ASA program. The need to look at HIV rather than AIDS is not a new idea any more, but it is an important one. The rationale is fourfold. First, the current number of AIDS cases is an out-of-date indicator of the present state of the epidemic; because of the long and variable latency period, new AIDS cases reflect old cases of HIV infection. Second, some people infected with HIV never develop the specific symptoms required for them to be counted by the AIDS surveillance system, but still suffer and die from HIV related illnesses. Recent developments indicate that there are even treatment options for people who have not yet developed overt symptoms. Third, HIV infected persons without overt symptoms infect others and thereby contribute to the spread of the epidemic. Finally, and most generally, the future magnitude of the AIDS epidemic will depend on the current extent and spread of HIV in the population.

The NRC panel and committee felt that this does not mean that the AIDS monitoring system can be neglected. Recently, the congressional General Accounting Office has also questioned the quality of the AIDS surveillance system, especially possibly large amounts of underreporting<sup>2</sup>. There is a substantial and probably increasing time lag between diagnosis of a case and reporting of it to CDC. Furthermore, changing the CDC AIDS definition in 1987 has complicated the analysis of trend data. In this regard, the NRC committee called for methodological studies to assess reliability and validity of categorization by mode of transmission. These data are crucial because they identify the populations that must be targeted to control spread of the epidemic. Given the difficulty in obtaining accurate information on sexual behavior, one must at least consider the possibility that there could be errors in these data. The committee felt that it would be good to know something about the magnitude and direction of these errors in order to interpret AIDS case data.

Coming back to HIV, the committee asked itself what is currently known about the number of people currently infected with HIV. In discussing plans to get more and better data, as in the papers in this session, this is clearly the place to start. We found that most currently available estimates of HIV prevalence are based on convenience samples of one sort or another. There are many estimates

for particular population groups, defined by risk factors (e.g. male homosexual sex, IV drug use, hemophilia, heterosexual sex with persons at risk), source of sample (blood donors, applicants for military service, patients at STD clinics, newborns), geographical location, and demographic groups. There is substantial variation along all of these dimensions, but these data stop short of telling us the prevalence in the U.S. or in well-defined subpopulations.

Some people believe that trends in these data could tell us something about trends in prevalence in the general population, but the committee was not convinced. The characteristics of measurement techniques have almost surely changed over time as our knowledge of the biology of AIDS grew. Furthermore, the populations being tested are not likely to be the same.

Discussions of the source, direction, and magnitude of the biases are more or less conjectural. To remedy this, the committee suggested that studies be carried out to document these biases as well as possible. If done well enough, such studies might lead to a way to adjust for some sources of bias. Furthermore, because some of the differences could be due to different testing procedures and standards, the committee felt that there needs to be a federal program to monitor the lab work for HIV testing.

Despite all of these problems with AIDS and HIV prevalence data, the committee found two more or less valid estimates of overall prevalence in the U.S. The first estimates comes from combining HIV prevalence estimates in population subgroups<sup>3</sup>. In essence, the best estimates of both HIV prevalence and numbers of homosexuals, IV drug users, and so on are multiplied and added across all the groups. There are two obvious problems with this method: estimating HIV prevalence, and estimating the number of people in each group.

The second method has been called "back-calculation"<sup>4</sup>. This method uses the number of AIDS cases that have been diagnosed over time plus estimates of the distribution of incubation period. With these two pieces of information, one can calculate backwards to find out how many people had to be infected in the past to yield the observed AIDS cases. This method is sensitive to the estimated incubation distribution, to biases in AIDS surveillance data, and to assumptions about past and future patterns of HIV infection.

With these two estimates, we are in a unusual but somewhat fortuitous situation. Two very different methods yield estimates of "about one million" people currently infected with HIV. Both estimates have severe but different problems. Neither estimate alone would be very convincing, but the substantial differences in the assumptions needed for each separate estimate, and the convergence of results, increases our confidence. The committee would not be surprised, however, if the true number of people infected with HIV were 0.5 or 2 million.

Following on this, it is good that the estimates presented by Meade Morgan this morning, based on different data, are in this same range. At some point, however, given that the first estimates have come out to be about one million, one wonders whether a new estimate in that range is really an independent observation or if it reflects subconscious adjustments to get it into that range.

These are the results against which we need to compare a national seroprevalence estimate. What will we say if the direct national estimate is substantially below 0.5 million or above 2.0 million? This calculation also gives us some idea of the kind of precision we need in the direct national estimate, that is, better than a factor of 2.

### **The National Household Seroprevalence Survey**

The NHSS is one of the two main attempts underway to get a better estimate of HIV prevalence in the U.S. Since the need for this information is so great, this project deserves serious attention from the statistical community. My general sense is that the people planning and implementing this survey are doing an excellent job in the face of great adversity. To quote from the paper: "The design of the NHSS poses a significant challenge for survey methodologists not only because of the special methodological issues but also because of the complex social attitudes and political issues surrounding AIDS and HIV infection." The survey's designers have carefully thought out the potential sources of bias and developed very good ideas about how to test them. They have also learned to work carefully with local health officials and other community leaders to smooth what would otherwise be a rocky path.

I have two questions about the survey design. First, should the focus be on overall HIV prevalence or prevalence in specific groups, defined by risk behaviors? The paper seems to indicate that risk data are being gathered primarily to increase the accuracy of the overall HIV prevalence estimate. This could be done by using related data to disproportionately stratify the sample for increased efficiency, by using risk data to look for differential response rates, and by controlling to proportions from outside the NHSS.

There are, however, a number of problems with this approach. Asking question about sexual behavior and drug use could increase individual response problems. Local advisors don't like the use of these factors in sample design. And there are no other reliable data for controlling these factors, especially since Congress zeroed out the budget for the adult sexual behavior survey. If overall prevalence estimates were the goal, I would suggest that the survey's designers consider dropping the risk factor questions in order to get better response rates and not jeopardize the study.

My sense, however, is that the real potential value of the study lies in getting risk-group specific prevalence estimates. As I said before, we already have a pretty good idea of overall prevalence. If the NHSS estimate came out much below 0.5 million or above 2 million, we would question its accuracy. We don't have risk-group specific HIV prevalence rates from other sources, but sorely need them for targeting efforts and for modeling. The CDC family of surveys will tell us something about this, but not the complete picture.

My second questions is whether cooperation with community leaders in the design of the study will make it impossible to do well. I find this very frustrating. Some of the best ideas for variance reduction and bias control (seeding the sample, clustering and oversampling from high-risk groups) can't be done because of community advice. This is very short-sighted and may cripple the major attempt to help the communities concerned through better prevention efforts and eventually lower HIV infection rates. The NRC committee felt that the NHSS is clearly an important but also a difficult project. It commended the exploratory spirit and applauded the strategy of using experiments to test whether such a survey might provide useful direct estimates

of HIV prevalence. The committee felt that the results of these experiments should guide the ultimate decision about whether to go ahead with a full-scale survey.

### **The CDC "comprehensive family of surveys"**

The "family of surveys" is seen as a complement to the national seroprevalence survey with much more geographical detail and information on known, identified risk groups. The current status report by Meade Morgan reflects many clever and thoughtful ideas, especially the way that multiple, relatively independent estimates of the same quantity are compared.

The NRC committee, however, while supportive of the CDC efforts, said that the plans for selecting these samples used in family of surveys needs careful rethinking. With the exception of the survey of newborns, "these surveys cannot characterize (with knowable margins of error) the prevalence or incidence of HIV infection in any well-defined population," the committee said<sup>4</sup>.

Because of this, the committee recommended that, over time, efforts be made to reformulate these surveys as probability samples. Probability samples can include some especially important sites with probability one, so that local public health concerns can be served at the same time that precision is improved. Furthermore, as long as the samples refer to well-defined populations, national surveys can ask about membership in those populations, and thus provide the information needed to put the survey results in context.

Reformulating the sampling plan will not be easy, but the NRC committee felt that it must be done. To eliminate bias from the self-selection of facilities, the CDC should work closely with local health departments and health facilities to build confidence and develop a good plan for maintaining the confidentiality of records. More universal but anonymous testing of blood samples drawn for other purposes (as is currently being done in some areas for newborns) would help to reduce individual self-selection bias. Unless these samples are improved, public health officials in 1995 will know little more than we do today about how to slow the HIV epidemic.

### **Modeling the growth and spread of the HIV epidemic**

Statisticians model the AIDS epidemic for two basic reasons: to make predictions about the future burden of illness and health costs, and to evaluate possible interventions and develop strategies for preventing the spread. Each of these purposes calls for different model features and approaches. As a result, there is a continuum of models that have been proposed and developed for the spread of AIDS.

At one extreme, statistical models that are extrapolations of one sort of another deal with the most aggregate statistics and make almost no assumptions about behavior. The well-known CDC projections use this approach<sup>5</sup>. Such models might be good for forecasting the magnitude of the future burden of illness, at least in the short range, but have nothing to say about the value of potential interventions. They also make the least demands on data, and at least we know what the problems are. At the other extreme, epidemiological and demographic models specify the population in great detail in terms of demographic and behavioral subgroups and their interactions, demand large amounts of disaggregated data, and make many assumptions about behavior. These models may not be good for predictions but can give us qualitative results and help us to evaluate the relative effects of various interventions. They

often, however, demand more of the data (in terms of precision and availability for subgroups) than the data can support. It is sometimes said in such situations that even if a model's predictions are not quite right, its qualitative results are correct. This may be so in some instances, but I have never heard a convincing general argument that this is so, and I distrust it.

Clearly, we need to strike a balance between these two extremes.

My sense is that the RTI model is too complex for the data currently available. To their credit, the developers do make a strong attempt to make sure that the model is consistent with the observed AIDS surveillance data, adjusted for known deficiencies as much as possible, and the available epidemiological and biological evidence. Despite this, many model assumptions cannot be fully supported by current data or biological evidence. These include: (1) the distribution of the incubation period, (2) starting values for the number of susceptibles in each group and the year that the first infection occurred, (3) specification of the frequency of contacts within and across groups, infectiousness rates within and across groups, and so on, (4) the stability over time of most model parameters, and (5) adjustments for late and incomplete reporting that may be different by group and over time. It depends somewhat on how you count them, but there are many more degrees of freedom in the model than there are data points. The result is that the fit they get is only one of many possible fits.

I had an experience like this myself in fitting a similar model for only one population group with many fewer parameters or degrees of freedom. Despite this, I found three parameter sets that fit the observed data almost equally well, seemed biologically reasonable, but led to radically different projections of the epidemic. In one, HIV incidence peaked in the early 1980s, and in another, it was still growing exponentially in 2010<sup>6</sup>.

Despite such uncertainties, I think that the models can make a contribution in helping to better target interventions. It sometimes is the case, and investigation may show here, that robust qualitative results can be obtained even when quantitative predictions are very sensitive to model and parameter assumptions.

In particular, the RTI model has the potential to address two important issues: (1) the effectiveness of more specific interventions, especially targeting population subgroups for testing and counseling and other interventions, and improving condom use or other safety steps in only a part of the population; (2) heterogeneity in risk-related behavior and HIV incidence. For example, given U.S. conditions, is it

possible for the epidemic to sustain itself by heterosexual transmission alone, or, does there need to be a subpopulation that engages in high-risk behavior--homosexual sex or IV drug use? Knowing the answer to this would have important effects on planning an intervention campaign. If the second point were true, we could concentrate on the high-risk populations.

### Conclusion

In conclusion, I am glad to have had the opportunity to discuss these three papers. Learning more about the spread of the HIV infection is clearly an important aspect of our national effort to stop AIDS. These papers, although all very different, represent very strong efforts by good statisticians to deal with a very tough problem. They deserve to be congratulated on their successes and supported in their future efforts.

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