

ers in commercial settings as well as from those representing government and academia. Industry-based researchers have a substantial record of aggressively pursuing and developing HIV/AIDS science and technologies. Third, they can accelerate research communications by encouraging publication of discoveries and results on electronic information (Internet) highways—keeping in mind requirements for a peer review system and its evolution.

We join others in applauding the policy plans and suggest the changes will do much to attract imaginative people and to support productive lines of inquiry. That, in turn, will drive advances in HIV/AIDS science and medicine. Build it and they will come.

**Howard B. Urnovitz**

**Roy W. Stevens**

*Calypte Biomedical Corporation,  
1440 Fourth Street,  
Berkeley, CA 94710, USA*



### **AIDS: Modeling Epidemic Control**

We would like to comment on the report by Sally Blower and Angela McLean "Prophylactic vaccines, risk behavior change, and

the probability of eradicating [human immunodeficiency virus] HIV in San Francisco" (2 Sept., p. 1451). They use a mathematical model of disease transmission to explore the possibility of eliminating (1, 2) HIV in that city. They conclude that, for certain parameter values, and under the model's assumptions, elimination of the virus would be unlikely or impossible, even with 100% vaccination coverage. There are, however, key factors Blower and McLean do not include in this study that make the potential use of a prophylactic HIV vaccine attractive.

First, the only efficacy characteristic included in the model is the reduction of susceptibility to infection. The most important effect of many vaccines, however, is to prevent or reduce clinical disease or to reduce shedding of the disease agent in already infected persons. For example, oral polio vaccine may not always prevent infection by wild polio virus, but it prevents paralytic disease and reduces intestinal and nasopharyngeal viral shedding of wild polio virus (3). Inactivated polio vaccine has a similar, but less dramatic effect on reducing viral shedding (3). In the case of chicken pox, many vaccinated persons become infected, but symptoms, when they occur, are mild (4). A further example is the unexpected success of

*Haemophilus influenzae* type b vaccine, which decreases transmission by reducing nasopharyngeal carriage of the virus in infected, vaccinated persons (5). This is beneficial to unvaccinated younger children and infants. HIV viremia is generally high during the primary infection period (for example, the first 3 to 12 weeks of infection) and then drops precipitously (6). In the HIV pandemic, there is evidence that transmission often occurs during this period (7). Reduced infectiousness decreases the intensity of an epidemic in proportion to the reduction of viral shedding and the fraction of the target population that is vaccinated. Including this relation in the model could reduce to a plausible percentage the vaccination coverage that would be required to eliminate HIV.

Second, Blower and McLean imply that reduction of HIV incidence could be a secondary goal if elimination of the virus proves to be impossible. Reduction of incidence and overall morbidity is more often the *primary* goal of a vaccination program than is elimination, and we believe that HIV vaccines should be judged on this basis. A vaccine against primary chicken pox, for example, would not eliminate varicella-zoster virus because of the reservoir of latent virus that reactivates to produce shingles (2, p. 22).

There's only one way  
to purify peptides—  
with your eyes open.



Third, HIV vaccine trials are being planned that include counseling about the possible low efficacy of any vaccine candidates. Even if such counseling does not result in a substantial reduction in risky sexual behavior, it could provide a counterbalance if some subjects were otherwise inclined to increase unprotected sexual contacts after immunization (8). This possible result of counseling was not discussed by Blower *et al.* in conjunction with use of the vaccine.

**Ira M. Longini Jr.**

**M. Elizabeth Halloran**

Department of Biostatistics,  
Emory University School of Public Health,  
Atlanta, GA 30322, USA

#### References and Notes

1. A recent consensus among infectious disease professionals (2) is that the term "eliminate" (not "eradicate") should be used when referring to the removal of an infectious agent from a limited geographical area.
2. Centers for Disease Control, *Morb. Mortal. Wkly. Rep.* **42** (suppl. RR-16), 2 (1993).
3. R. W. Sutter and P. A. Patriarca, in *Measles and Poliomyelitis*, E. Kurstak, Ed. (Springer-Verlag, New York, 1993), chap. 22, pp. 279–294.
4. C. J. White *et al.*, *Pediatr. Infect. Dis. J.* **11**, 19 (1992).
5. A. K. Takala *et al.*, *ibid.* **12**, 593 (1993).
6. S. J. Clark *et al.*, *N. Engl. J. Med.* **324**, 954 (1991); E. S. Daar *et al.*, *ibid.*, p. 961.
7. J. A. Jacquez, J. S. Koopman, C. P. Simon, I. M. Longini, *J. AIDS* **7**, 1169 (1994).

8. M. E. Halloran, I. M. Longini, M. J. Haber, C. J. Struchiner, R. C. Brunet, *Stat. Med.* **13**, 357 (1993).

While mathematical models may be useful tools to explore the potential impact of vaccines and other interventions, their results should be interpreted carefully. Models may omit or misspecify important aspects of HIV spread and control. Furthermore, there are limited data at this time with which to estimate model parameters reliably.

As Blower and McLean point out, their model does not account for the heterogeneous risk behavior found among gay men. This heterogeneity has major implications for the spread and control of HIV. Dietz (1), for example, has derived an expression that accounts for the variation in the number of partners of HIV-infected individuals. This expression shows how a vaccination program that targets individuals with the highest risk behavior could have better results for public health than an untargeted approach. However, it may be difficult to identify and vaccinate such persons.

Models may be useful to conceptualize what one would like to learn from efficacy trials. Concepts like "vaccine take," however, may be difficult to define and measure. "Vaccine take" implies that there is a measure of immune response to vaccination

that indicates protection, but the correlates of protective immunity against HIV are unknown. For many vaccines, neutralizing antibodies have been shown to be protective, but for HIV, a cellular response may also be required. Furthermore, trials may demonstrate efficacy without establishing correlates, as is the case, for example, with pertussis vaccines.

If some degree of efficacy is demonstrated, long-term follow-up of trial participants would be required to assess the duration of protection. Repeated injections of vaccine may be necessary for long-term protection if immune responses wane. Furthermore, an HIV vaccine might be effective against viral strains that are similar to it, but provide little or no protection against those that are different. Over time, vaccination could set up a selection pressure such that dissimilar strains become more prevalent. Protection, therefore, could be diminished by a changing profile of circulating virus. This problem, however, might be solved by giving booster vaccines based on currently circulating strains, as is done for influenza.

Concern has been raised that widespread vaccination might lead to increased risk behavior so that the rate of HIV infection would actually increase. Preliminary data (2) from a study of two recombinant sub-

Here's one thing we all know—RPC works extremely well. But that doesn't mean an alternative purification technique may not be the better choice at times.

So keep your eyes open. After all, knowing what your options are keeps you from being restricted by the limitations of any one technique. Take a good look at what you're being offered.

You'll find Pharmacia Biotech offers an abundance of products for practically every purification technique. From RPC to size exclusion, ion exchange to IMAC, affinity and covalent chromatography, we've covered them all. So you can choose the technique that gives you the best results—purifying any type of peptide from any natural, synthetic or recombinant source. What's more, all our products—like

our six different RPC selectivities—come with complete technical data and support.

While we aren't the only supplier offering to help you purify peptides, very few in the purification business can match our experience. Now that's what we call providing support—enabling you to work with a variety of peptide purification techniques, no matter what your needs may be.

So if you're purifying peptides, don't let your choice of technique become routine. Take a closer look at your options and choose the one that gives you the best results.

To find out more about all Pharmacia Biotech has to offer you, just call us at 1 (800) 526 3593 in North America, or +46 18 16 50 11 from the rest of the world. As we said at the start, we believe you should keep your eyes open.



unit vaccines suggest that high-risk participants are not increasing their risk behavior. Data from interviews conducted by study clinicians (3) will be verified by an anonymous survey (4). While this observation is reassuring, alternative trial designs such as unblinded efficacy trials may be required to assess the impact of a vaccine under more realistic conditions. Halloran *et al.* (5) also have modeled the effect of behavior change on vaccine efficacy.

**Wasima Rida  
Patricia Fast  
Rodney Hoff  
Lewellys Barker**

Vaccine and Prevention Research Program,  
Division of AIDS,  
National Institute for Allergy and Infectious  
Diseases, National Institutes of Health,  
Bethesda, MD 20892-7620, USA

#### References

1. K. Dietz, *Stat. Methods Med. Res.* **2**, 23 (1993).
2. *AIDS Vaccine Evaluation Group Protocol 201* (Bethesda, MD, 1994).
3. J. McElrath and L. Corey, personal communication.
4. A. Sheon, personal communication.
5. M. E. Halloran, I. M. Longini, M. J. Haber, C. J. Struchiner, R. C. Brunet, *Stat. Med.* **13**, 357 (1994).

Response: We are pleased that our research on HIV prophylactic vaccines (1) generated

such interest, and we are happy to respond to the comments raised by our colleagues.

Longini and Halloran and Rida *et al.* imply that we may have underestimated the potential beneficial impact of vaccines because we did not include the possibility that HIV-infected, vaccinated individuals may be less infectious than HIV-infected, unvaccinated individuals. We have discussed this issue (2), and believe that it is wrong to assume that a vaccine that reduces primary viremia would have no effect on the duration of infectiousness. Therefore, in order to evaluate the potential effects of vaccines that decrease infectiousness, it is necessary to explicitly examine the potential tradeoff between decreased infectiousness and increased duration of infectiousness (3). This tradeoff can be expressed in terms of a basic reproductive number for the successfully vaccinated,  $R_v$ . Reduced infectiousness will act to make  $R_v$  smaller than  $R_0$  (the basic reproductive number for unvaccinated people), but a longer infectious period would act to make it larger. One can show (4) that for a population where a fraction  $p$  have received a vaccine [which takes in a fraction  $\epsilon$  and protects to degree  $\psi$  (1, 2)], the appropriate average of  $R_v$  and  $R_0$  is

$$R_p = (1 - \epsilon p)R_0 + \epsilon p(1 - \psi)R_v$$

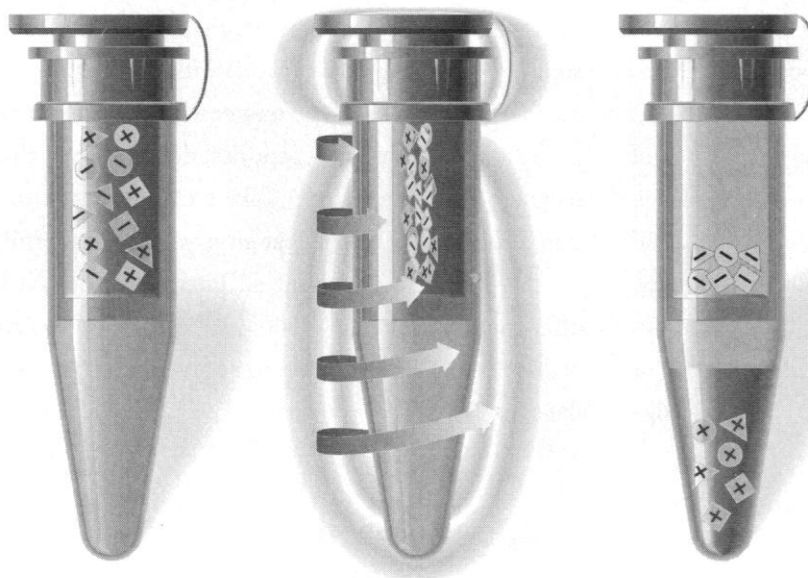
Here  $R_p$  is the effective reproductive number and summarizes transmission of infection in the community. Setting  $R_p = 1$  gives the eradication threshold, setting  $R_p = R_0$  gives the threshold at which the vaccine becomes detrimental.

Longini and Halloran are concerned that our analysis focused only on eradication (as defined by Anderson and May) and did not discuss noneradicating control. We have investigated the impact of noneradicating vaccination regimens (2). They also state that we did not consider the effects of counseling, which could counterbalance the tendency to increase unprotected sexual contacts. We disagree; our model did not specify the complex causal factors that determine risk behavior change, but we did analyze all of the possible behavioral outcomes (that is, if sexual behavior increased, decreased, or remained constant).

Rida *et al.* suggest that a targeted vaccine program could be more beneficial than a uniformly applied vaccination program. In theory we agree with this observation (1); however, previous empirical findings (5-7) lead us to believe that in the real world targeted HIV vaccination programs could be ineffective. Previously we have shown (by a statistical analysis of risk behavior data) that a gay man's risk of HIV infection

## A New Spin On DEAE-Based Separations.

# The Power Of DEAE. With A Twist.



Now you can achieve, on a microscale level, very fine separations of complex protein mixtures—fast. Introducing the Ultrafree®-MC DEAE centrifugal filter from Millipore. The only device that gives you the speed and ease of centrifugal filtration and the selectivity of an anion-exchange chromatography membrane.

How about a test spin? Call us for a free sample. US and Canada, 1-800-MILLIPORE ext. 8017. Japan, fax to (03) 3474-9141. Europe (fax to our Paris headquarters), +33.1.30.12.71.83.

**MILLIPORE**



is determined not only by his type of sexual activity and frequency of partner acquisition, but also by the probability of his selecting a seropositive partner (5), which is measured by the weighted seroprevalence of HIV in the community. Hence, we have demonstrated (by an empirical analysis) that an individual's choice of sex partner can be an important risk factor for HIV infection (5). These findings illustrate that, because sexual network data are rarely collected, a high-risk individual may be misclassified as a low-risk individual. Our statistical analyses have also revealed that individuals who have a high rate of partner acquisition also have periods of time in which the rate is low (6). Our results concerning sexual networks (which determine the probability of selecting a seropositive partner) and temporal variability suggest that it might often be impossible to identify all of the high-risk individuals. Furthermore, we have also shown that (even when a risk group is identified) the membership of the risk group is not stable over time (7). The problems of risk group identification and risk group instability mean that, in practice, a targeted vaccine program could be extremely ineffective.

Rida *et al.* also suggest that our parameter estimates are based on little or no data.

We disagree. Our analysis was specifically designed to investigate the potential effects of prophylactic vaccines in San Francisco. Consequently [as described in our report (1)], we obtained analytical results and parameter estimates from data from the San Francisco Young Mens Health Study (SFYMHS), a large, multistage probability sample of gay men conducted in 1993 in San Francisco (8). The sampling design of the SFYMHS provides a population-based estimate of HIV infection and sexual behaviors; consequently we believe that our parameter estimates are reliable and have external validity.

We do not believe that we have used our model to paint a bleak picture for HIV vaccines. We would like to stress that (as we pointed out) it is possible to eradicate HIV without any vaccine if the current levels of risk behavior can be reduced to certain (specified) levels. Mathematical models have great utility as epidemiological tools for evaluating the potential effects of HIV vaccines. We believe that models should be used to explore the possible outcomes before the real world is used as an experimental system.

**Sally Blower**

San Francisco General Hospital,  
University of California,  
San Francisco, CA 94143-1347, USA

**Angela McLean**  
Zoology Department,  
Oxford University,  
Oxford, United Kingdom

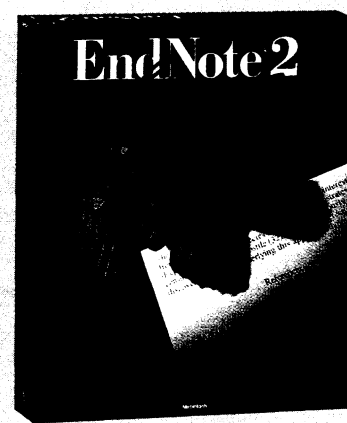
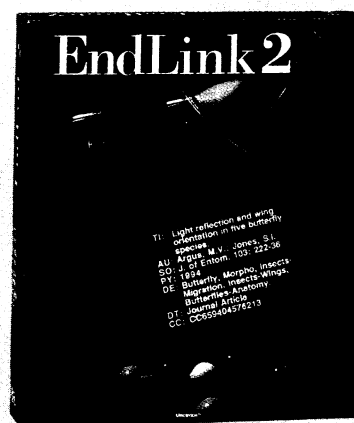
#### References

1. S. M. Blower and A. R. McLean, *Science* **265**, 1451 (1994).
2. A. R. McLean and S. M. Blower, *Proc. R. Soc. London Ser. B* **253**, 9 (1993).
3. R. M. Anderson, S. Gupta, R. M. May, *Nature* **350**, 356 (1991).
4. A. R. McLean, J. A. Wilson, S. M. Blower, in preparation.
5. S. Service and S. M. Blower, *Proc. R. Soc. London Ser. B*, in press.
6. S. M. Blower, M. C. Samuel, J. A. Wiley, *J. AIDS* **5**, 633 (1992).
7. S. M. Blower, G. J. P. van Griensven, E. H. Kaplan, *Epidemiology*, in press.
8. D. H. Osmond *et al.*, *Am. J. Public Health* **84**(12), 1933 (1994).

#### Corrections and Clarifications

In Claire O'Brien's News & Comment article "Priority initiatives squeeze science" (10 Feb., p. 782), David Porteous was incorrectly described as head of the Medical Research Council's (MRC's) Human Genetics Unit. He is head of the Molecular Genetics Section of the MRC's Human Genetics Unit.

# NEW! EndNote Plus 2.0



## Bibliographies made easy!

More than 75,000 researchers use EndNote to create bibliographies and organize references. Now version 2 makes this even easier with great new features such as term lists, new search options, and 240 journal styles! And to make it even easier, EndLink lets

you import references from more than 100 sources without typing a word!

**Niles & Associates, Inc.**  
800 Jones Street  
Berkeley, CA 94710

Voice: 800-554-3049  
Fax: 510-559-8683  
email: endnote@aol.com

Mail to Niles & Associates, Inc., 800 Jones St., Berkeley, CA 94710

☐ Yes! send me information about EndNote for...

☐ Mac Version 2.0      ☐ Windows Under Development      ☐ DOS Version 1.3.3 2.0 not available

Name \_\_\_\_\_

Address \_\_\_\_\_

City/State/Zip \_\_\_\_\_