Is population-level perversity a likely outcome of mass vaccination against HIV?

Chris Sattlberger/SPL

Robert Smith and Sally Blower recently considered the population-level impact of disease-modifying HIV vaccines.[1] On the basis of a mathematical model, they pointed to the theoretical possibility that such vaccines might ultimately lead to an increased HIV prevalence—an outcome referred to as population-level perversity.

Using a model based on actual data from cohort studies, we concluded that disease-modifying vaccines will have a negligible impact on R_0, the basic reproduction number of HIV.[2] As such, vaccination cannot be expected to alter the endemic equilibrium that ensues from a natural AIDS epidemic. Disease-modifying vaccines may nonetheless be highly beneficial, because they bring about an improved prognosis for the individual HIV-infected person and a postponement of HIV spread at the population level.

Whereas Smith and Blower's analysis hinged on a time-independent measure (the fitness ratio), ours took into account the temporal dynamics of HIV infection in the individual and of HIV spread in a population. By using a model in which both disease progression rate and infectivity were related to the time course of viral load, we were able to calculate R_0 for individuals with different prognoses. We found very small differences in R_0, indicating that HIV-infected individuals with a short life expectancy naturally cause as many secondary infections as HIV-infected individuals with an improved life expectancy.[2] Because the virological determinant of increased survival with a vaccine—ie, a low amount of circulating virus—is naturally related to a decreased infectivity, we expect no change in R_0 as a direct result of vaccination.

Monkey studies have demonstrated that the key mechanism of a disease-modifying HIV vaccine involves the induction of cytotoxic T lymphocytes (CTLs) that can temporarily control viral replication following challenge with a pathogenic virus. Here is a clear analogy with the natural course of HIV infection, wherein a low viral load after primary infection predicts relatively good survival. However, viral escape from CTL recognition is the rule rather than the exception and long-term control of viraemia is extremely rare, both in vaccinated monkeys and in HIV-infected individuals.[3,4] Natural history thus strongly suggests that the inability of CTL-based vaccines to provide long-term control over viral replication in monkeys is relevant to disease-modifying HIV vaccines for human beings.

Timely introduction of a vaccine may nonetheless substantially postpone the peak incidence of infection and mortality from AIDS-related causes in a natural epidemic.[2] This population-level benefit can be in the order of several decades for realistic values of R_0. Our findings have been confirmed by Perelson and colleagues,[5] who developed a sex-structured and age-structured model including the transmission of vaccine-escape mutants.

There is no reason to suspect an increased transmission of HIV following vaccination, unless the type and amount of sexual activity in the population alters dramatically due to perceived protection by the vaccine.[1,5] Therefore, counselling and prevention efforts remain crucial to any AIDS control programme. In conclusion, population-level perversity is not a likely outcome of mass vaccination against HIV.

Johannes A Bogaards, W Marijn van Ballegooijen, Gerrit Jan Weverling, Maarten C Boerlijst, Jaap Goudsmit
JAB and GJW are at Crucell, Leiden, Netherlands; WMvB and MCB are at the Section of Population Biology, Institute for Biodiversity and Ecosystem Dynamics, Faculty of Science, University of Amsterdam, Netherlands; JG is chief scientific officer at Crucell, Leiden, and professor in Poverty-related Communicable Diseases at the Academic Medical Center, University of Amsterdam.
Correspondence to: Professor Jaap Goudsmit, Center for Poverty-related Communicable Diseases, Department of Internal Medicine, Academic Medical Center, Meibergdreef 15, Amsterdam, 1105 AZ, Netherlands. Tel +31 71 5248 755; fax +31 71 5247 853; j.Goudsmit@crucell.com

1 Smith RJ, Blower SM. Could disease-modifying HIV vaccines cause population-level perversity? *Lancet Infect Dis* 2004; **4:** 636–39.
2 van Ballegooijen M, Bogaards JA, Weverling GJ, Boerlijst MC, Goudsmit J. AIDS vaccines that allow HIV-1 to infect and escape immunologic control: a mathematic analysis of mass vaccination. *J Acquir Immune Defic Syndr* 2003; **34:** 214–20.
3 Goudsmit J, Bogaards JA, Jurriaans S, et al. Naturally HIV-1 seroconverters with lowest viral load have best prognosis, but in time lose control of viraemia. *AIDS* 2002; **16:** 791–93.
4 Barouch DH, Letvin NL. HIV escape from cytotoxic T lymphocytes: a potential hurdle for vaccines? *Lancet* 2004; **364:** 10–11.
5 Davenport MP, Ribeiro RM, Chao DL, Perelson AS. Predicting the impact of a nonsterilizing vaccine against human immunodeficiency virus. *J Virol* 2004; **78:** 11340–51.

Authors' reply

We agree that Jaap Bogaards and colleagues' question "is population-level perversity a likely outcome of mass vaccination against HIV?" is an interesting question to consider, but unfortunately we do not yet have the necessary data that would enable us to answer this question. In our analysis we addressed a rather different question—specifically "could disease-modifying HIV vaccines cause population-level perversity?"[1] We had two key findings. Firstly, we showed that if disease-modifying vaccines were given to uninfected individuals then these preventive vaccines could make the epidemic worse (even if risk behaviour did not increase) if they provided only a low degree of protection against infection and/or generated high "fitness ratios". We defined the fitness ratio as the relative number of secondary infections caused by an infected vaccinated individual in comparison with an infected unvaccinated individual.[1] Secondly, we quantified under what specific conditions disease-modifying vaccines would make HIV epidemics worse, if risk behaviour either increased or decreased.

Mathematical models are extremely useful health-policy tools for evaluating possible outcomes of complex situations. The first epidemic model of imperfect preventive HIV vaccines was developed over a decade ago,[2,3] and showed that imperfect preventive HIV vaccines may fail in a number of ways, by generating a low "take", and/or providing a low degree of protection against infection, and/or waning.[1–7] Imperfect preventive vaccines may also act as disease-modifying vaccines (ie, the vaccines may modify pathogenesis such that infected vaccinated individuals survive longer than unvaccinated infected individuals).[3] The effects of preventive disease-modifying vaccines on the temporal dynamics of an HIV epidemic can be viewed in real-time by running our web-based model (http://www.biomath.ucla.edu/faculty/sblower). In our previous analysis we determined that predicting the epidemic-level impact of a preventive disease-modifying vaccine is complex and depends upon the degree to which the vaccinated individuals are protected against infection, the degree to which viral load is reduced in vaccinated infected individuals (by comparison with unvaccinated infected individuals), the magnitude of increase in survival time in vaccinated infected individuals (by comparison with unvaccinated infected individuals), and the magnitude of change in risk behaviour in both vaccinated and unvaccinated individuals. Our mathematical analyses enabled us to evaluate the effects of complexity and quantify the relations among these parameters. Importantly, we were able to calculate that if a vaccine caused a 1·5 $\log_{10}$ reduction in the viral load of vaccinated infected individuals (by comparison with unvaccinated infected individuals) then the epidemic-level impact of disease-modifying vaccines would always be beneficial (assuming that risk behaviour does not increase).[1]

Phase III clinical trials of preventive disease-modifying vaccines will be used to evaluate whether disease-modifying vaccines increase survival time. We suggest that when clinical trials are conducted data should also be collected to measure the effect of the vaccine on reducing viral load. The results on viral load reduction should then be evaluated—using the quantitative framework that we have developed—to predict the population-level impact of the vaccine. We have shown that population-level perversity is a possible outcome of mass vaccination against HIV, even in the absence of increases in risk behaviour.[1] Only when we have data on viral load reduction from phase III clinical trials of preventive disease-modifying vaccines will it be possible to answer the question that has been posed by Bogaards and colleagues. Based upon our previous analyses, we strongly recommend that only a preventive disease-modifying vaccine that causes substantial reductions in viral load is used to control HIV epidemics.

Sally M Blower, Robert J Smith
SMB is at the Department of Biomathematics and UCLA AIDS Institute, David Geffen School of Medicine at UCLA, Westwood, CA, USA. RJS is at the College of Veterinary Medicine, The University of Illinois at Urbana-Champaign, Urbana, IL, USA. Correspondence to: Dr Sally Blower, Department of Biomathematics and UCLA AIDS Institute, David Geffen School of Medicine at UCLA, 1100 Glendon Ave PH2, Westwood, CA 90024, USA. Tel +1 310 794 8911; fax +1 310 794 8653; sblower@mednet.ucla.edu

1 Smith RJ, Blower SM. Could disease-modifying HIV vaccines cause population-level perversity? *Lancet Infect Dis* 2004; **4:** 636–39.
2 McLean AR, Blower SM. Imperfect vaccines and herd immunity to HIV. *Proc R Soc Lond B Biol Sci* 1993; **253:** 9–13.
3 Blower SM, McLean AR. Prophylactic vaccines, risk behavior change and the probability of eradicating HIV in San Francisco. *Science* 1994; **265:** 1451–54.

4 Blower SM, McLean AR. AIDS: modeling epidemic control. *Science* 1995; **267:** 1252–53.
5 Blower SM, Koelle K, Mills J. Health policy modeling: epidemic control, HIV vaccines and risky behavior. In: Kaplan EH, Brookmeyer R, eds. Quantitative evaluation of HIV prevention programs. New Haven: Yale University Press, 2002: 260–89.
6 Blower SM, Schwartz EJ, Mills J. Forecasting the future of HIV epidemics: the impact of antiretroviral therapies and imperfect vaccines. *AIDS Rev* 2003; **5:** 113–25.
7 Blower SM, Moss RB, Fernandez-Cruz E. Calculating the potential epidemic-level impact of therapeutic vaccination on the San Francisco HIV epidemic. *AIDScience* 2003; **3**(21).

Global climate change and malaria

We wish to respond to a number of statements made by Paul Reiter and colleagues[1] on our article on malaria and global warming,[2] in which we model duration of exposure to *Plasmodium falciparum* malaria and independently validate the model using 3791 presence/absence parasite surveys[3] collected across Africa. Although we recognise that an important component of science is open debate, Reiter and colleagues made some inaccurate statements and hence misrepresentations of our work that need to be addressed. For example, Reiter and colleagues comment that we have modelled "merely duration of the transmission season", which we interpret as "heightened transmission and increased incidence".[1] The first part of this statement is absolutely correct and modelling duration (and timing) of transmission season (for the first time at a continental scale) is exactly what we set out to achieve. The latter part of the statement regarding increased incidence is inaccurate as nowhere in the paper is incidence interpreted in the light of changes in person-months of exposure under global climate-change scenarios. The relation between population exposure and disease incidence is not straightforward and there are many contributing factors. To make such inference from our model—which is concerned with spatiotemporal population exposure—would not be valid.

Reiter and colleagues state that the model was based on a "mere 15 African locations".[1] This is incorrect. The relation between climate and malaria is complex and for this reason, four phases of model development were used to derive the final model. As discussed in the paper, the initial 15 studies were used to provide crude (first pass) climatic thresholds (within established biological ranges), which were subsequently refined by comparing various iterations of the model against historical published and unpublished maps and clinical case data. The final phase of model development involved extensive consultation and dialogue with experts from throughout Africa regarding areas of agreement, false negatives, false positives, and season duration. All four phases of this iterative development process contributed uniquely to the final model. A comparison between the model and historic maps and clinical case data used in the model building process is shown for southern Africa as an example (figure). None of the 3791 presence/absence parasite surveys were used in any way in the model development process, but were withheld to facilitate a true independent accuracy assessment of the final model after development.

Similarly, Reiter and colleagues then cite as a "greater failing" of the model our reliance on parasite ratio studies as the relations between parasite prevalence, clinical disease, and transmission season length are unlikely to be linear. Given that "parasite prevalence" was not used at all in the paper and that we make no attempt to infer prevalence from the predicted duration of transmission season, this constitutes another inaccurate statement by Reiter and colleagues. To reiterate, we used only presence/absence data from parasite surveys to independently validate the final model (after the development phase was fully complete) and do not use parasite prevalence in any way. That the relations mentioned above are not linear is undoubtedly true and is the subject of ongoing research in our programme and many others.

Reiter and colleagues question the use of contemporary population estimates on the grounds that populations are projected to increase and a greater proportion of people are projected to be living in urban areas over the coming century.[1] To include population projections in already uncertain climate projection scenarios would make it difficult to disaggregate the effects of climate from those of population and would result in an "accumulation of uncertainties".[4] Yet this question illustrates exactly the utility of such a model. We chose to model specific climate and population scenarios, but the transparency and reproducibility of the model means that it can be used as a baseline against which to evaluate changes in exposure under any combination of climate and/or population scenarios.