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Guest Editors Commentary

Modeling the impact of RV144-like vaccines on HIV transmission

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Some 30 years after the public first became aware of AIDS, the need for a safe, effective, and affordable HIV vaccine remains compelling [1]. To date, the road to an HIV vaccine has been rocky, marked by the well-publicized failures of the first two candidates to reach large population trials. The first, a recombinant gp120 AIDSvax® B/E vaccine, proved ineffective [2,3]. The second, a recombinant adenovirus 5 gag/pol/nef HIV-1 vaccine, actually increased the risk of HIV acquisition among vaccinees relative to placebo recipients [4]. Then, just as vaccine developers were returning to their drawing boards [5], the bumpy road evened out. On 20 October 2009, results of RV144 – a large, long duration, expensive (≈120 million US$), community Phase III trial in Thailand evaluating a combination of two vaccines, ALVAC® HIV vaccine (a 4-dose prime) and the aforementioned AIDSvax® B/E vaccine (a 2-dose boost) – were announced at the AIDS Vaccine 2009 Conference in Paris, France. There were 51 infections in 26,507 vaccinated person-years versus 74 in 26,478 unvaccinated person-years (p = 0.04). Excluding 7 trial participants who were infected before vaccination, this prime-boost combination reduced the risk of HIV infection by 31.2% (95% CI, 1.1–51.2) overall compared to placebo [6].

In March of 2010, at the request of the Ministry of Public Health in Thailand, a consultation was co-sponsored by the WHO, UNAIDS, Global HIV Vaccine Enterprise, Thai Ministry of Public Health, and US Military HIV Research Program to address the utility of RV144 trial results, particularly public health and future access; ethical, regulatory, and community issues; science and vaccine development; and clinical trial design and statistics. Among the recommendations was to encourage modeling teams to estimate the cost and impact on the HIV epidemic of vaccine regimens with varying efficacy and durability, including a 31% efficacious general population vaccine with a 1-year duration of protection [7]. Accordingly, the editors invited modelers capable of evaluating the potential impact of RV144-like vaccines to investigate a common scenario with variations for a number of countries. This special issue of Vaccine contains several articles from this joint modeling exercise, along with several other HIV vaccine papers, most of which were presented at a satellite symposium, entitled ‘Preparing for the Availability of a Partially Effective HIV Vaccine’, held at the AIDS Vaccine 2010 Conference in Atlanta, USA.

In view of earlier disappointments [2-4], the RV144 trial results represent a significant scientific achievement, demonstrating for the first time that a preventive HIV vaccine is possible. Many questions remain, however, including (1) the immune correlates of protection in this community-based trial whose participants generally were at low risk of HIV infection; (2) whether, in view of the rapidly waning efficacy, booster doses could usefully maintain protection; (3) whether the vaccine was equally efficacious among those at higher risk of HIV infection; and (4) what lessons could be learned for combinations of partially effective biomedical interventions [8].

There are challenges inherent in analyzing observations from clinical trials and reporting their results [9], and the RV144 trial posed some unique challenges. Generally, vaccine efficacy is defined as the complement of the relative risk among vaccinated and unvaccinated persons, estimated as one minus the incidence rate ratio [10]. The 31.2% efficacy at 42 months – derived from the numbers reported above – is an average over the entire RV144 trial. The points in Fig. 1a illustrate estimates derived from cumulative infections and person-time at risk [see also 6, Table 1c]. These observations were analyzed and presented in this manner because, when HIV incidence is low, as in the Thai population studied, interval estimates of vaccine efficacy (the points in Fig. 1b represent infections and person-times at risk during successive 6-month intervals) may be so variable that patterns are difficult to perceive. This is the first challenge.

Several possible modes of vaccine action have been described [11]; vaccination may afford some degree of protection to all recipients; that is, vaccinees may be protected from infection, but only in some proportion of their exposures. Although such exposures might be sufficiently intimate for infection (e.g., contact with the body fluids of infectious persons), transmission might not occur if the dose of pathogens is too low. Alternatively, vaccination may take in some proportion of recipients; that is, some vaccinees may be protected from infection in all such exposures. Further, if vaccinated persons do become infected, they may be less infectious than unvaccinated people. The RV144 prime-boost regimen had no effect, however, on the early HIV-1 viral loads or CD4+ T-cell counts of participants who did acquire HIV post-vaccination [6]. Finally, as these two conceptual modes of protection are not mutually exclusive, the risk of infection per exposure could be reduced only in some vaccinees (i.e., some may be partially immune).
In this special issue about the potential impact of a modestly effective HIV vaccine in Thailand, South Africa, Australia, and the United States, two teams (Grey et al. and Hontelez et al.) modeled individuals, while the others modeled groups — for their purposes similar individuals. In models of groups, called compartmental or population-based models, exponentially distributed residence times (or sojourns) in the various compartments or states are easy to program — if we denote by \( N \) the number of people in any state, the \( per \ capita \) rate of change in this number, \( dX/dt \), is the reciprocal of the mean sojourn — and convenient because \( N \) may approach but will never become zero (or negative). Other distributions are more realistic biologically; the gamma (a statistical distribution describing times to randomly occurring events), for example, can be modeled as a sum of exponential distributions.

The second challenge posed by the RV144 trial results is that, in estimating the impact of any intervention whose efficacy varies, one requires a function for efficacy at all times \( t \). Proportional hazards analysis of individual infections in the RV144 trial yields the relationship illustrated by the red or dashed line in Fig. 1b, whose equation is \( VE = 1 - \exp \left(-2.4 + 0.76 \times \log (t)\right) \), where \( t \) is time in days since vaccination (Don Stablein, personal communication). Solely for mathematical convenience, we approximated this survival function with that illustrated by the blue or solid line in Fig. 1b, whose equation is \( VE = 0.78 \times \exp \left(-0.06t\right) \), where \( t \) is time in months since vaccination. We fitted this equation to the interval estimates illustrated using Breslow’s approximation of the likelihood [12]. (For interpretation of the references to color in this figure the reader is referred to the web version of the article.)

Were efficacy to vary inversely with risk and the above-mentioned protective modes of vaccine action to be disjoint (mutually exclusive and exhaustive), one could conclude that vaccination afforded degree protection. Because members of subpopulations at higher risk of HIV exposure are by definition more frequently or intensely exposed, more of them would be infected during any period. If, in contrast, vaccination took in some proportion of recipients, there would be no such difference between those at higher and lower risk. While the inverse relationship between risk and efficacy is suggestive [6, Table 2], the efficacies by self-reported risk category do not differ significantly, nor does the greater point estimate among medium compared to low-risk groups make biological sense. Understanding the mode of vaccine action is the third challenge.

Finally, to ensure that results were comparable, we asked the modelers not only to employ the exponential function illustrated by the blue or solid line in Fig. 1b for efficacy at all times \( t \) since vaccination, but to report fractions of infections averted over a 10-year follow-up period by single mass vaccinations of 30% and 60% of sexually active adults. The temporal decay of vaccine efficacy led inevitably to explorations of the impact of booster vaccinations at 1- to 5-year intervals. Pending results of studies underway to determine if vaccinees respond immunologically to booster doses, the modelers simply assumed that vaccine efficacy could be restored by boosting. Another variation on the reference scenario was vaccinating persons attaining sexual maturity during follow-up. Given that the efficacies of this prime-boost combination among populations exposed to HIV via different modes of transmission are indistinguishable we did not specify a mode of vaccine action.

The modelers found that RV144-like vaccines would have modest impact, averting 5–15% of infections over 10-year periods, especially in countries with high incidence (see Andersson et al., Nagelleke et al. in this issue). Vaccination would be cost-effective in South Africa if the complete prime-boost regimen were priced around 150 US$ per person (see Hontelez et al. in this issue) whereas in the United States a price of 500 US$ per person would meet conventionally accepted cost-effectiveness thresholds (see Long and Owens in this issue). Because efficacy wanes so quickly, periodic boosting of immune responses would be necessary to sustain protection (see Schneider et al. in this issue). Two teams investigated prioritizing women sex workers, their clients, and people who inject drugs (see Long and Owens, Andersson and Stover in this issue), with the proviso that the RV144 trial was conducted in a lower-risk population. These teams found that prioritizing subpopulations at higher risk of HIV exposure was more efficient, even if efficacy were lower than observed in the RV144 trial, than vaccinating all members of the sexually active population. Grey et al.in this issue found comparable benefits among Australian men who have sex with men when they assumed that vaccination would be as efficacious in this sub-population as observed among heterosexuals in Thailand.

While mathematical models can estimate the population-level impact of partially efficacious vaccination strategies on HIV incidence in different settings, they may produce conflicting outcomes if methods, assumptions, and parameters vary. In this series of articles, we sought to examine the results of different modeling approaches when the teams made similar assumptions (e.g., the exponential function for efficacy), and assessed similar interventions (e.g., the impact of 30% versus 60% coverage among sexually active adults on 10-year HIV incidence) in various settings. The consistency of modeled findings, demonstrating that a vaccine that is modestly efficacious in a population at low risk of heterosexual HIV exposure could have tangible population-wide benefits, is encouraging. While such consistency suggests that these findings are robust, this exercise is but a first step in understanding the place of a partially effective vaccine in combination with other behavioral, structural, and biomedical HIV prevention approaches [13].

Mathematical models cannot be parameterized for every conceivable setting nor used to explore all possible HIV prevention...
programs, but modeling studies can refine and validate simpler decision-making tools. Modeling contributed in a tangible way to informed decision-making about male circumcision [14], refining a Decision Makers Programme Planning Tool [15]. Six countries in sub-Saharan Africa have completed facility-based costing studies and, in two further countries, studies are underway to estimate the requisite parameters. This user-friendly tool can estimate the cost and impact of a variety of programmatic approaches by varying, for example, speed of scale-up, key populations prioritized for tailored programs, and task-shifting or task-sharing modes of program delivery. Resource allocation tools that incorporate synergies from overlapping interventions and accommodate economies and diseconomies of scale can inform policy and programming [16]. Concerns about striking context-appropriate balances of treatment versus prevention programming, maximizing human and financial resources, and addressing equity issues also affect policy decisions. Mathematical models and tools derived from them bring yet another dimension to the decision-making process, provided their assumptions are transparent, reasonable, and accepted.

With RV144 as a benchmark and continued scientific progress, including the identification of several broadly neutralizing antibodies that target multiple strains of HIV [17,18], recent exciting developments in mucosal immunization against HIV-1 [19], and a novel vaccine candidate that significantly suppresses viral load after infection [20], the dream of a safe, effective, and affordable HIV vaccine seems more realistic than ever.

References