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Expected epidemiological impact of the introduction of a partially effective HIV vaccine among men who have sex with men in Australia

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ABSTRACT

A trial of the ALVAC-AIDSVAX HIV vaccine was recently found to be partially effective in preventing HIV transmission among study participants in Thailand. The success of this trial means that vaccination may become a viable intervention for the prevention of HIV infection in the medium-term future. Assuming that the vaccine has similar relative protective effectiveness per exposure event for reducing transmission among men who have sex with men (MSM) in high-income settings we investigated the potential population-level impact of rolling out such a vaccine among MSM in New South Wales, Australia. Using a detailed individual-based transmission model that simulates a population of sexually active MSM it was found that one-off intervention of 60% or 30% coverage of a vaccine with characteristics like the ALVAX-AIDSVAX vaccine would likely reduce the cumulative incidence of HIV by 9.6% and 5.1%, respectively, over a 10-year period. Due to the waning of vaccine efficacy, a booster vaccination could be required to maintain this reduction in incidence over the long term. If the previously vaccinated population is given a booster vaccine, with the same protection conferred as with the initial vaccination, every 5 years or every 2 years then the cumulative incidence over 10 years for 60% coverage could be reduced by 14.4% and 22.8%, respectively. Such a weak vaccine, with boosting, may be a potential intervention strategy for the prevention of HIV infection in MSM in high-income countries if further trials show boosting to be safe, acceptable, and cost-effective. However, the moderately low population-level impact suggests that a public health strategy involving such a vaccine should be supplemented with other biomedical and educational strategies.

1. Introduction

The holy grail of HIV prevention research is the development of an effective vaccine. Prior to September 2009 all attempts to demonstrate a viable HIV vaccine had been unsuccessful with nearly all clinical trials of vaccine candidates having failed [1–3] with some potentially increasing the risk of HIV acquisition [4,5] and there was little expectation of a viable HIV vaccine becoming available in the near future. The field experienced a breakthrough with the RV144 trial, for the first time reporting a vaccine to be successful in reducing the rate of HIV-1 infection [6]. This trial was a community-based randomized control trial of 16,402 healthy male and female primarily heterosexual volunteers in Thailand who were enrolled to receive 4 injections of ALVAC-HIV plus two booster injections of AIDSVAX B/E over a 24-week period [6]. Over the 3-year period of the trial the overall vaccine efficacy was found to be 31.2% (95% CI 1.1–52.1%; $P = 0.04$) [6]; however, this efficacy appeared to be higher at initiation of vaccination and then waned over time. While the results of this trial have been controversial [7] and need to be confirmed, they have re-invigorated the biomedical HIV prevention field as it raises the possibility of a partially effective HIV vaccine becoming available to be rolled out to individuals at risk of HIV infection.

Given that a partially effective vaccine does not completely prevent the acquisition of HIV and is much less effective than condoms, the likely population-level effect of the roll out of such a vaccine needs to be investigated. This overall impact will be dependent on the characteristics of the vaccinated population. In high-income countries such as the United States, United Kingdom, Western Europe and Australia the majority of HIV transmissions are due to anal intercourse between men who have sex with men (MSM) [8,9]. Within Australia, the region with the highest number of HIV diagnoses each year is the state of New South Wales (NSW) with approximately 70% of these cases attributed to homosexual transmission in recent years [8]. Over the last decade in NSW, as for most other homosexual populations in high income countries, there has been a relatively stable or even increase in the number of HIV diagnoses despite extensive public health and HIV

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awareness campaigns [8]. The roll out of a partially effective vaccine is then potentially useful in reducing the incidence of HIV in this population.

Mathematical modeling is the best approach for forecasting population-level impacts of implementing biomedical interventions assessed in clinical trial settings. However, models also need to be specific for populations or population groups of interest. To estimate the impact of a partially effective vaccine, potentially similar to the ALVAC-AIDSVAX strategy used in the Thailand trial, in preventing HIV infections in high-income MSM populations we developed a detailed HIV transmission model for MSM in NSW and investigated a number of vaccine roll out scenarios.

2. Materials and methods

While a number of models have previously been used to investigate the general impact of partially effective HIV vaccines (for example [10–12]) we developed a detailed individual-based stochastic computer model that has been specifically designed to assess the impact of HIV interventions in MSM in NSW, Australia [13]. This model was informed by the extensive behavioral and epidemiological data available for MSM in NSW (see the parameter table in supplementary material) and incorporates detailed sexual behavior such as the practice of serosorting (where men select sexual partners who disclose having the same HIV serostatus) and strategic positioning (where during unprotected anal intercourse between serodiscordant partners the HIV-negative partner takes the insertive position to reduce the risk of transmission) [14–16]. Many of the behavioral characteristics incorporated in the model are similar to characteristics of MSM populations in other high-income settings and thus the model results could potentially be used for informing discussions and implementation of vaccine strategies among MSM in other settings.

2.1. Model overview

The model simulates the sexual activity and breakup of regular, casual and group sexual partnerships in a population of 60,000 MSM who engage in anal intercourse, similar to the size of the identifiable MSM population in NSW, Australia [17]. Simulations of the formation, and breakup of sexual partnerships in the population of MSM are tracked over time. Model variables describing infection and disease status of HIV, disease progression, treatment status, level of sexual activity, partnership availability, and current sexual partners of each individual are updated in daily time-steps.

The model consists of four main components: (i) assigning population size and demographic characteristics such as age profiles and circumcision rates; (ii) detailed sexual behavior associated with regular, casual and group partner acquisition and serosorting as well as behavior within partnerships such as frequency of sex, strategic positioning and condom use; (iii) tracking HIV disease progression and rates of testing and treatment; and (iv) modeling transmission between discordant partners during sex based on the characteristics associated with the sexual encounter. All details of these components as well as data and assumptions for the model are presented in the supplementary material.

2.2. Model implementation and calibration

The model was implemented using Matlab® R2010b with each simulation tracking the dynamic sexual network, HIV transmission, and disease progression of HIV-infected individuals. After the initial phase of establishing simulated sexual networks and baseline HIV transmission (described in the supplementary material) the model was run for a time period representing the years 1996–2010 using the parameters in Table 1 of the supplementary material. The model was specifically calibrated to match the numbers of HIV diagnoses among MSM in NSW over this period. The mean trajectory of 50 model simulations accurately reflected the trends in HIV epidemiology and the number of HIV diagnoses in NSW gay men (as shown in Figures 1 and 2 of the supplementary material). The 10 simulations that best fit the NSW diagnoses data (according to a Pearson chi-squared test) were selected to forecast epidemic trajectories over the next 10 years under various vaccination scenarios (Figure 2 of the supplementary material).

2.3. Model of vaccine efficacy

To model the impact of a partially effective vaccine like the one used in the RV144 trial, we describe the efficacy of a vaccine (in terms of preventing HIV acquisition) within a vaccinated individual over time and the roll-out of vaccination in the population which is described by the proportion of MSM vaccinated and the time taken to vaccinate this proportion of men. As described in the accompanying editorial for this issue, an analysis of the results from the trial in Thailand show that the efficacy of the vaccine wanes over time but efficacy can be reasonably well fit by an exponential decay curve. We use this exponential decay curve to model the efficacy or protective effect of the vaccine within a vaccinated individual over time post vaccination. In our model, vaccinated individuals have a 73.6% reduction in the risk of acquiring HIV per-act at the time of vaccination. This vaccine efficacy (relative reduction in risk) wanes over time following an exponential decay with a half-life of 0.96 years (see accompanying editorial for more information). It is assumed that if vaccinated individuals become infected with HIV then there is no change in the probability of transmission to their HIV-negative sexual partners due to the vaccine.

For each vaccinated individual in the model, the time since they were vaccinated is recorded so that their vaccine efficacy can be calculated. It is assumed that individuals may be given a booster vaccine to compensate the waning effect of the initial vaccination. In the model, we simulate scenarios of no booster shots and also scenarios where booster shots are given to vaccinated individuals with a fixed probability once their time since vaccination reaches a specified time period. We assume following the booster shot, that vaccine efficacy within an individual returns to the same initial level as in their first vaccination (73.6%) and then wanes as before.

2.4. Vaccine intervention strategies

We simulated six vaccine interventions which started from the end of 2010 and were applied for the next 10 years. In all interventions a proportion of the current and entering MSM population is vaccinated within a roll-out period of 1 year. As for the other modeling papers in this issue, we simulated scenarios with a vaccine coverage of 30% and 60% with once-off vaccination for current sexually active gay men. We also simulated the impact of providing boosters to previously vaccinated men every 2 years or every 5 years. In each scenario, as men enter the population they are vaccinated with a probability matching the coverage rate of the corresponding scenario investigated so that the overall proportion of the population vaccinated is fixed at a constant value.

3. Results

Our model produced relatively steady numbers of HIV incident cases and diagnoses over the next 10 years under current conditions with diagnoses closely reflecting incidence trends (due to the high testing rates within the MSM population in NSW). In Fig. 1a and b, the black curves represent the mean number of new HIV infections and mean number of annual diagnoses for the 10 baseline simulations (out of 50 simulations overall) that best fit the NSW

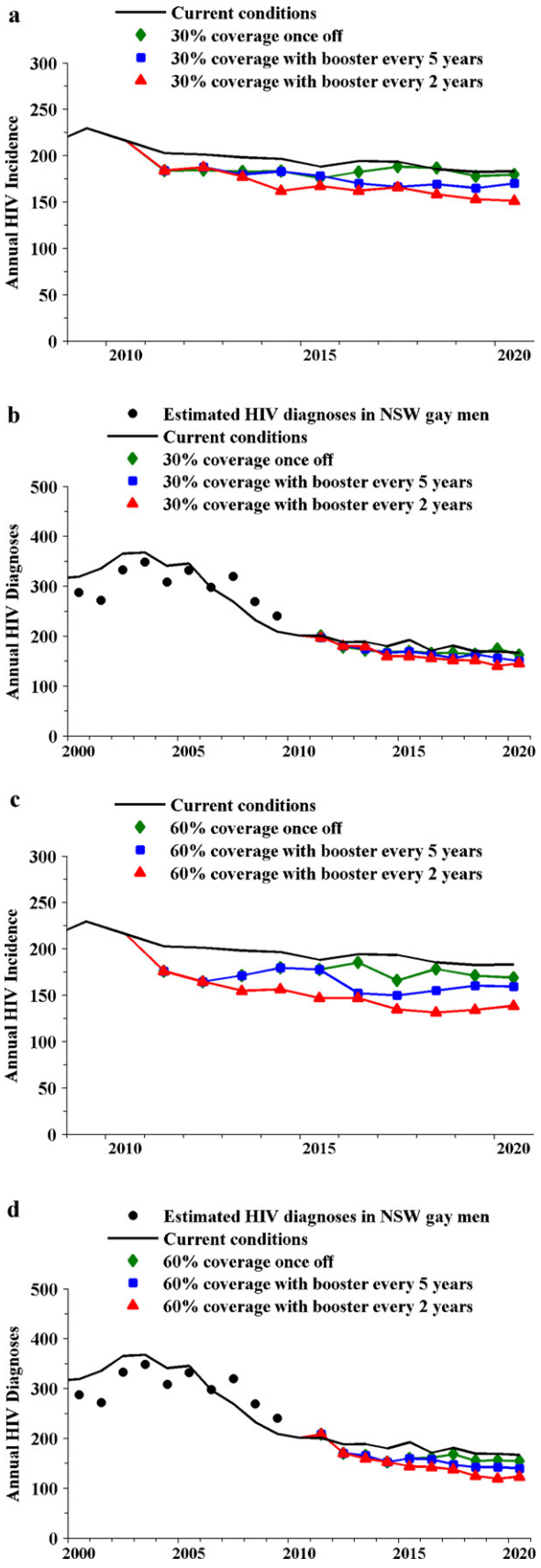

Fig. 1. Mean change in HIV incidence and diagnoses due to 30% ((a) and (b)) and 60% ((c) and (d)) of the population receiving a partially effective vaccine. (For interpretation of the references to color in the text, the reader is referred to the web version of the article.)

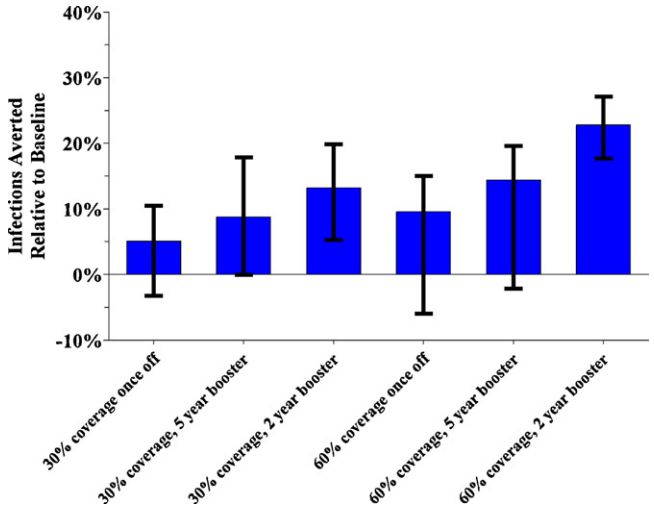

Fig. 2. Overall infections averted from 2010 to 2020 due to interventions using a partially effective vaccine. The thick blue bars represent the mean number of infections averted for each intervention from the 10 simulations while the thin black error bars represent the total range across all simulations. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

diagnoses data, respectively. Overall, our results indicate that vaccinating MSM in NSW, Australia, with a partially effective vaccine that wanes relatively quickly will likely have a very modest impact on the number of HIV infections unless a large proportion of the population is vaccinated and receives a regular booster vaccine.

3.1. Impact of once-off vaccination

Undertaking a vaccination program where a proportion of the current MSM population is vaccinated within 1 year (representing 2011 in our simulations) and MSM are vaccinated prior to becoming sexually active results in a small reduction in HIV infections in the following 10 years. The green lines with diamonds in Fig. 1a and b represent the change in annual HIV incidence and diagnoses, respectively, if 30% of the current and incoming population is vaccinated. In this once-off vaccination scenario a mean of 100.5 infections will be averted over the next 10 years relative to baseline for the 10 simulations. As shown in Fig. 2, this represents a 5.1% decrease in cumulative infections for this 10-year period (ranging from a 3.2% increase in infections to a 10.5% decrease across the 10 simulations). By 2020 there is only a minimal reduction in annual incidence and diagnoses with the main gains in averted affections occurring in the first few years. This is because the vaccine efficacy wanes to almost zero over the 10-year period in men vaccinated during 2011 and hence the conditions in 2020 are almost identical to those in the baseline scenario.

If 60% of the current and incoming population is vaccinated in a once-off scenario then we expect larger reductions in incidence and diagnoses (green lines with diamonds in Fig. 1c and d). In this larger coverage scenario, a mean of 186.8 infections were simulated to be averted over the next 10 years. This corresponds to a mean 9.6% decrease in cumulative infections, with a total range between a 6% increase and a 15% decrease for the 10 simulations (Fig. 2). As for the 30% coverage scenario, this decrease is not sustained over time due to the waning in efficacy in vaccinated men.

Vaccinating a higher proportion of men and rolling out the vaccine in a period shorter than 1 year yields a higher number of infections averted (results not shown) but the trends in annual incidence and annual diagnoses are qualitatively similar with a convergence towards the baseline scenario as the vaccine efficacy wanes in the model.

3.2. Impact of booster vaccinations

One way of maintaining the decrease in annual HIV incidence is for previously vaccinated men to receive a booster shot. If 100% of vaccinated men in the 30% coverage, once-off scenario receive a booster vaccine 5 years after their initial vaccination (blue lines with squares in Fig. 1a and b) then the model forecasts a mean 8.8% (−0.1 to −17.8%) decrease in the number of incident infections (or 171.8 cases) (see Fig. 2). When the coverage is increased to 60% and boosters are provided every 5 years there is a more substantial increase in the number of infections averted with a 14.4% decrease in cumulative infections (range 2.2% increase to 19.6% decrease).

Increasing the frequency of vaccine boosters is likely to further increase the number of HIV infections averted in the 2011–2020 period. If men previously vaccinated receive boosters every 2 years then in the 30% vaccine coverage scenario the model forecasted a 13.2% decrease in cumulative infections (Fig. 2: range 5.3–19.8% decrease), which corresponds to 256.1 infections averted. The number of infections averted is 1.5 times more than when boosters are given every 5 years and 2.55 times more than the once-off scenario. Finally, vaccinating 60% of the current population during 2011 and 60% of incoming MSM continuously with a follow-up booster vaccination every 2 years results in 440.8 averted HIV infections, a 22.8% decrease in cumulative infections over the 2011–2020 period (Fig. 2: range 17.7–27.1% decrease). The number of infections averted in this scenario is 1.6 times the number of infections averted when boosters are given every 5 years and 2.4 times the number in the corresponding once-off scenario. The simulated booster vaccination strategy has greater impact because it overcomes the waning effect of the model vaccine. Even under the most ambitious scenario (60% coverage and boosters for 100% of vaccinated every 2 years) the reduction in incidence over 10 years is still modest (22.8%). This level is below the efficacy reported in the trial (31% over 3 years) due to the waning effect of the partially effective vaccine and less than universal coverage.

4. Discussion and conclusions

The recent success of the ALVAC-AIDSVAX vaccine trial in Thailand has generated considerable excitement in the HIV biomedical community and raises the prospect of a partially effective HIV vaccine becoming available in the medium-term future. Using an individual-based stochastic computer simulation model of HIV transmission we have shown that a partially effective HIV vaccine that is similar to the ALVAC-AIDSVAX vaccine can reduce the incidence of HIV within MSM populations, albeit by a fairly modest amount. While once-off vaccination campaigns could have an impact in reducing new infections, it is likely to be necessary to have booster vaccines to maintain reductions in HIV incidence over time. The frequency of boosters depends on the feasibility and acceptability within the target population, costs and desired epidemiological impact. However, given the relatively high rate of waning of the model vaccine under consideration in this study, 5-yearly boosting is possibly too infrequent and 2-yearly boosting may be necessary.

While our model is specifically calibrated to the MSM population in NSW in Australia, the sexual and clinical behaviors incorporated in the model are similar to behaviors in other high-income settings where HIV epidemics predominantly affect MSM and thus we would expect similar relative reductions in infections in comparable settings. However, a limitation of the model is its complexity which makes it difficult to undertake sensitivity and uncertainty analyses. The most important parameters in our model were found to be those describing the probability of HIV transmission during anal intercourse such as the sexual practice and behaviors of men during intercourse. While there is a large amount of data describing the sexual behavior of MSM in NSW (as discussed in the supplementary material) it is often difficult to translate these data into appropriate parameter values, particularly for those describing group sex partnerships, serosorting, and strategic positioning. However, by calibrating the model to the HIV epidemic in NSW MSM we were able to represent these behaviors while also accurately reflecting the trends in HIV epidemiology.

Our results indicate that a partially effective HIV vaccine could be just as effective as other biomedical interventions that are currently under consideration as components of public health responses to HIV epidemics, such as the use of antiretroviral treatment as a pre-exposure prophylaxis [18] or male circumcision [19] (though it is expected that circumcision would be relatively ineffective as a public health intervention in Australia as the majority of MSM engage in both receptive and insertive intercourse [20–22]). Our results highlight that partially effective vaccines that induce waning immunity could be used as legitimate public health interventions to reduce the number of HIV infections within a population but relatively frequent boosting is likely to be warranted. The roll-out of such a vaccine strategy would need to be complemented with other public health interventions to lead to noticeable population-level impacts in reducing HIV infections.

It is too premature to implement an intervention strategy around the ALVAC-AIDSVAX vaccine. Firstly, the results of the ALVAC and AIDSVAX vaccine trial in Thailand need to be reproduced, especially as there has been some controversy surrounding the significance of outcomes from the trial [7]. Secondly, the observed efficacy of this vaccine is moderate and other candidate vaccines may be developed in the near future that result in higher efficacy. Confidence in the vaccine and a full understanding of its benefits and risks is required before implementation. Thirdly, further evaluation of the impact of the introduction of a partially effective vaccine needs to be carried out. It is plausible that vaccinated individuals, believing they are protected by vaccination, may change their sexual behavior in a way that may counteract the protective effect of a vaccine. While there has been little evidence of behavior change for other interventions [18], this is particularly important for waning vaccines where changes in sexual behavior may last over a longer time than the duration of protection conferred by the waning vaccine. Thus social research investigating the likely acceptance and response of the introduction of a partially effective vaccine needs to be carried out so that any likely changes can be considered in future modeling studies and in programmatic and policy discussions. Fourthly, our results suggest that if partially effective vaccines wane over time then boosting of such a vaccine would be required to maintain the impact of the intervention over time and trials would be required to assess the immunological–biological and overall protective effects of different boosting frequencies. Finally, health economic analyses are necessary in order to determine the cost-effectiveness of using such a vaccine in large populations or prioritizing subpopulations in different settings.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.vaccine.2011.06.061.

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