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Expected epidemiological impacts of introducing an HIV vaccine in Thailand: A model-based analysis

Karen Schneider, Cliff C. Kerr, Alexander Hoare, David P. Wilson*

The Kirby Institute for Infection and Immunity in Society, The University of New South Wales, Sydney, Australia

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ABSTRACT

Background: The RV144 trial conducted in Thailand was the first to demonstrate modest protective efficacy of an HIV vaccine. Its estimated initial efficacy was ~74%, but this waned considerably over time.

Methods: We developed a mathematical model to reflect historical and current HIV trends across different at-risk populations in Thailand. The model was used to estimate the expected number of infections that would be averted if a vaccine with outcome characteristics similar to the RV144 vaccine was implemented in Thailand at varying levels of coverage.

Results: In the absence of a vaccine, we projected roughly 65,000 new HIV infections among adults during the period between 2011 and 2021. Due to the waning efficacy of the vaccine, vaccination campaigns were found to have modest long-term public health benefit unless re-vaccination occurred. We forecast that an RV144-like vaccine with coverage of 30% of the population would lead to a 3% reduction in HIV incidence during the next 10 years. In comparison, 30% coverage of annual or biennial re-vaccination with the vaccine was found to result in 23% and 14% reductions in incidence, respectively. Coverage of 60% without re-vaccination resulted in a 7% reduction. Epidemiological outcomes were found to depend primarily on three factors: vaccination coverage, vaccine efficacy, and the duration of protection the vaccine provided.

Discussion: Due to the short duration of protection the vaccine provides without re-vaccination, our model predicts modest benefit from a vaccination campaign with an RV144-like HIV vaccine in Thailand. Annual or biannual re-vaccination is predicted to greatly increase the long-term public health benefits of a vaccination campaign. The feasibility of vaccine implementation, as well as its economic viability, remains to be determined.

1. Introduction

The development and distribution of a safe and effective vaccine is often considered the ideal way to control the spread of HIV. Extensive research using a range of different approaches has been conducted in efforts to develop such a vaccine [1], but the majority of human trials have yielded disappointing results [2–4]. A large community-based clinical trial conducted in Thailand was the first to report reduced HIV acquisition among vaccine recipients [5]. These results have renewed the prospect of the development of an effective HIV vaccine. The vaccine efficacy of this trial was reported to be 31.2% over the average 3.5 years of follow-up per person; however, it appeared to be in the order of 60–80% in the first year and waned thereafter [5]. While the findings of the RV144 trial are encouraging and have important implications for future HIV vaccine research, this vaccine's potential for long-term public health benefit remains controversial.

The trial reported that vaccine efficacy appeared to be lower for people with higher risk of infection, i.e. people who reported sharing needles, multiple sex partners, commercial sex work, a partner of the same sex, an HIV-infected partner, or symptoms of a sexually transmitted disease [5]. Therefore, the trial authors concluded that the vaccine may reduce the risk of HIV infection in a population with largely heterosexual risk. Since the global HIV pandemic is chiefly driven by heterosexual transmission, mass vaccination with an RV144-like vaccine could thus be a feasible prevention strategy. However, due to its relatively short-lived efficacy, effective re-vaccination may be essential for its ability to have long-term public health benefits.

The aim of the current study is to estimate the expected long-term population-level impact in reducing the spread of HIV through

* Corresponding author at: CFI Building, Corner Boundary and West Streets, Darlinghurst, Sydney, NSW 2010, Australia. Tel.: +61 2 9385 0900; fax: +61 2 9385 0920.
E-mail addresses: KSchneider@kirby.unsw.edu.au (K. Schneider), CKerr@kirby.unsw.edu.au (C.C. Kerr), AHoare@kirby.unsw.edu.au (A. Hoare), DWilson@kirby.unsw.edu.au (D.P. Wilson).

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the introduction of an RV144-like vaccine. A number of mathematical models have previously been used to investigate the general epidemiological impact of partially effective HIV vaccines (for example [6–10]). In the current study we developed a compartmental mathematical model to forecast the total number of infections averted in the Thailand setting due to the introduction of vaccine programs using an RV144-like vaccine [11]. This allowed us to investigate the importance of vaccination coverage, vaccine efficacy, the duration of protection provided by the vaccine, and the potential impact of providing re-vaccination.

2. Methods

2.1. Model

This section briefly describes the mathematical model that was developed to track the number of adults in Thailand according to different population risk groups, disease states and vaccination status; full details are provided in Appendix A. The disease state stratifications are: susceptible (i.e. uninfected), infected (further stratified based on CD4 count into CD4 $\geq$ 500, 350 $\leq$ CD4 < 500, 200 $\leq$ CD4 < 350, and CD4 < 200), and on treatment (either first- or second-line antiretroviral therapy (ART)). It is assumed that people living with HIV and a CD4 count below 350 are eligible for ART. A schematic diagram of the structure of the 14 health states in the model is shown in Fig. 1A. In order to capture the waning efficacy of a vaccine, the model incorporates a rate at which vaccinated people, who have partial protection to acquiring HIV, revert to become unprotected by the vaccine and then have the same per-capita risk of acquiring HIV as unvaccinated people. The rate of this reversion from vaccinated to no vaccine-conferred protection is 72.24% per year, as observed in the trial [5]. The efficacy of protection assumed for vaccinated people was 73.6%; that is, the per-capita rate of HIV acquisition for susceptive vaccinated people was 73.6% less than susceptible people who were not protected with the vaccine. We refer the reader to the accompanying editorial article of this Special Issue for explanation of these vaccine characteristics which are representative of the RV144 vaccine.

Since the risk behaviors and infection levels differ substantially between different sub-population groups in Thailand, the model was constructed with seven sub-populations: male and female injecting drug users (MIDUs and FIDUs, respectively), female sex workers (FSWs), male clients of FSWs (MCs), men who have sex with men (MSM), and low-risk males (LRMs) and females (LRFs) who do not fit into one of the other categories (Fig. 1B). For all population risk groups, we tracked the number of people in each of the 14 health states (Fig. 1A). As such, the model consisted of 98 compartments (98=[2 uninfected/susceptible states + 4 CD4 states $\times$ 3 treatment states] $\times$ 7 population groups).

The sexual and injecting mixing between the population subgroups are illustrated in Fig. 1B. Sexual partnerships were classed as being either regular or casual. Sexual behaviors – including the estimated numbers of partnerships and sexual acts per partnership

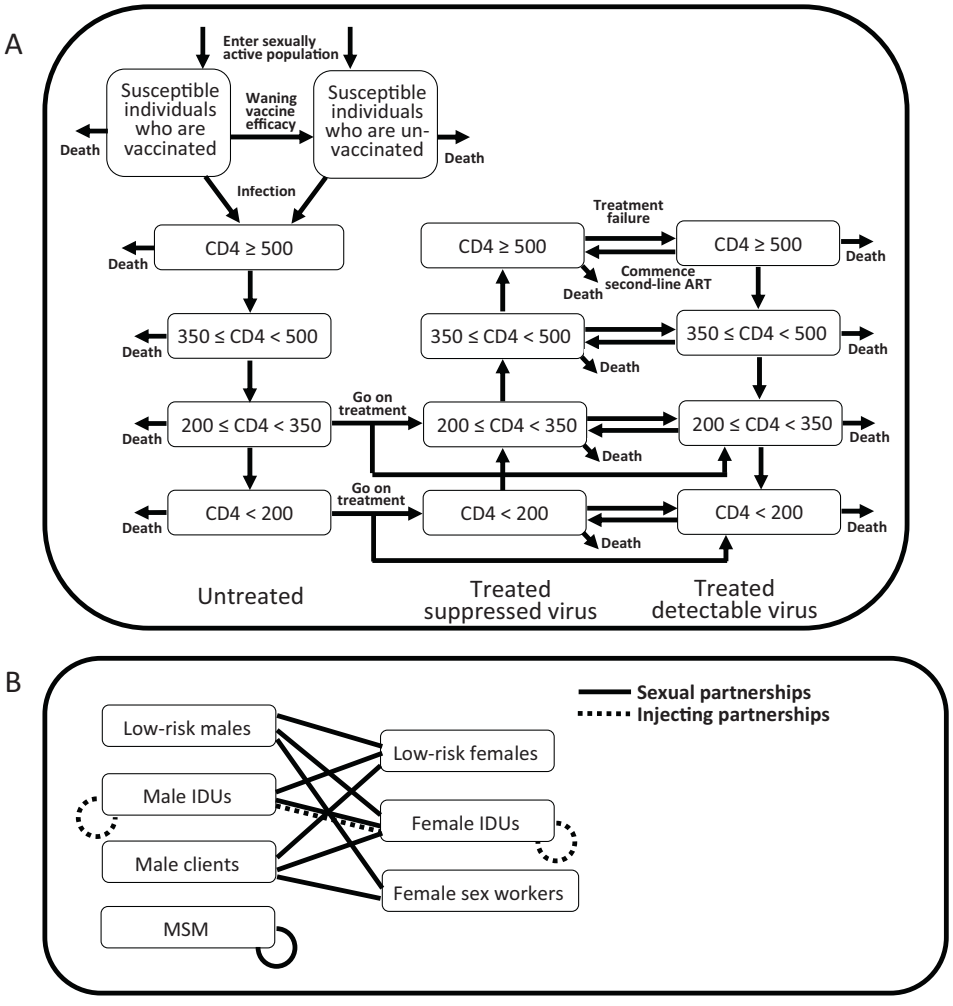

Fig. 1. (A) Schematic diagram of the disease states described by the model. (B) Schematic diagram of population groups and partnerships in the model.

and the probability of condom use – were dependent on population group, whether the sexual interaction was casual or regular, and whether it was a same- or opposite-sex interaction. The probability of sexual transmission was dependent on the sex of the people involved, the disease/treatment state of an infected partner, vaccination status, circumcision status, and sexual behaviors. The probability of transmission through injecting was dependent on the average frequency of using contaminated equipment. All transmission risks were also dependent on the rate of contact with HIV-infected people. Further details on the model's transmission dynamics, parameter values, and assumptions are provided in Appendix A.

2.2. Experimental design

The model simulated a series of different vaccination scenarios over a 10 year period. These scenarios represented coverage levels of 30%, 60%, and 90% of the susceptible population applied equally across all population risk groups. Separate analyses were conducted for scenarios that included re-vaccination every one, two, or five years. We assumed each re-vaccination would give the same level and duration of protection as the initial vaccination, at the level and duration reported in the RV144 trial [5].

In order to estimate the conditions that would have the most public health benefit, we also simulated scenarios with different vaccine properties by varying the vaccine's biological efficacy and the length of time for which it conferred protection.

2.3. Uncertainty and sensitivity analyses

As described in Appendix A, an optimized parameter set was established using a trust-region-reflective algorithm [12] implemented in MATLAB R2009a (The Mathworks, Natick, MA), constrained to bounds defined by experimental values relevant to Thailand as reported in the literature. This procedure varied all model parameters within the limits of experimental uncertainty until accurate HIV prevalence estimates were generated: 0.77% among LRM, 0.77% among LRF, 37.5% among MIDU, 35.3% among FIDU, 24.9% among MSM, 3.2% among FSWs, 4.7% among MC, and 1.4% overall (see Appendix A). To obtain uncertainty estimates, 1000 parameter sets were generated by Latin hypercube sampling [13] of the optimized parameter set, with an assumed uncertainty of ±20% in each parameter [14]. We pre-defined acceptable overall HIV prevalence bounds to ensure that our model was calibrated to accurately represent the epidemiology in Thailand [15]. We selected the sets of parameters that ensured that all population groups matched these estimates and reproduced the epidemic in Thailand. The model was then run using these parameter sets until a steady HIV prevalence was achieved. This steady state was used to simulate the initial conditions for the year 2011. Then the model was run from 2011 to 2021 to simulate the HIV epidemic under each vaccination campaign scenario.

Sensitivity analyses were conducted by calculating partial rank correlation coefficients (PRCCs) between input parameters and the output variables produced by the model [14]. This allowed an assessment of which parameters had the strongest influence on the number of infections averted. Separate analyses were conducted for each population as well as overall. A PRCC may be interpreted the same way as a standard correlation coefficient as a measure to quantify the linear association between two variables, except that PRCCs control for the effects of the other variables in the system (in this situation, the other input model parameters). PRCCs are similar to Spearman correlation coefficients in that both are based on rankings of values for each variable. However, PRCCs provide more accurate estimates of the correlations between input and output

Table 1
Estimated primary epidemiological outcomes after 10 years of vaccination. Assumptions include a vaccine efficacy of 73.6%, waning at a rate of 72.24% per year, vaccination coverage of 60% among individuals entering the susceptible population, and no re-vaccination. Trends across population groups were similar for 30% and 90% vaccination coverage scenarios.

	All	Low-risk males	Low-risk females	Male IDUs	Female IDUs	MSM	Female sex workers	Male clients of sex workers
Infections averted (%) (IQR)	6.65 (6.58–6.72)	7.04 (6.99–7.08)	6.80 (6.77–6.84)	6.14 (6.00–6.27)	6.14 (6.01–6.27)	6.62 (6.55–6.68)	6.77 (6.74–6.81)	6.99 (6.94–7.03)
Cumulative incidence without vaccine (IQR)	63,568 (54,461–75,941)	8295 (6062–11,858)	12,238 (9042–17,037)	9553 (8038–10,891)	3102 (2607–3593)	25,131 (18,189–32,284)	852 (670–1105)	3582 (2679–4806)
Cumulative incidence with vaccine (IQR)	59,382 (50,837–70,924)	7717 (5635–11,024)	11,399 (8433–15,872)	8972 (7531–10,224)	2917 (2446–3374)	23,489 (16,949–30,079)	794 (625–1029)	3331 (2492–4468)
Prevalence in 2010 (%) (IQR)	1.56 (1.34–1.79)	0.57 (0.45–0.74)	0.54 (0.42–0.71)	38.7 (32.9–44.1)	35.7 (30.2–40.8)	25.7 (19.3–32.0)	2.88 (2.37–3.51)	2.09 (1.67–2.61)
Prevalence in 2021 (%) (IQR)	1.55 (1.33–1.78)	0.56 (0.44–0.74)	0.53 (0.41–0.71)	38.5 (32.7–43.9)	35.4 (30.0–40.6)	25.5 (19.1–31.9)	2.81 (2.31–3.43)	2.05 (1.63–2.57)

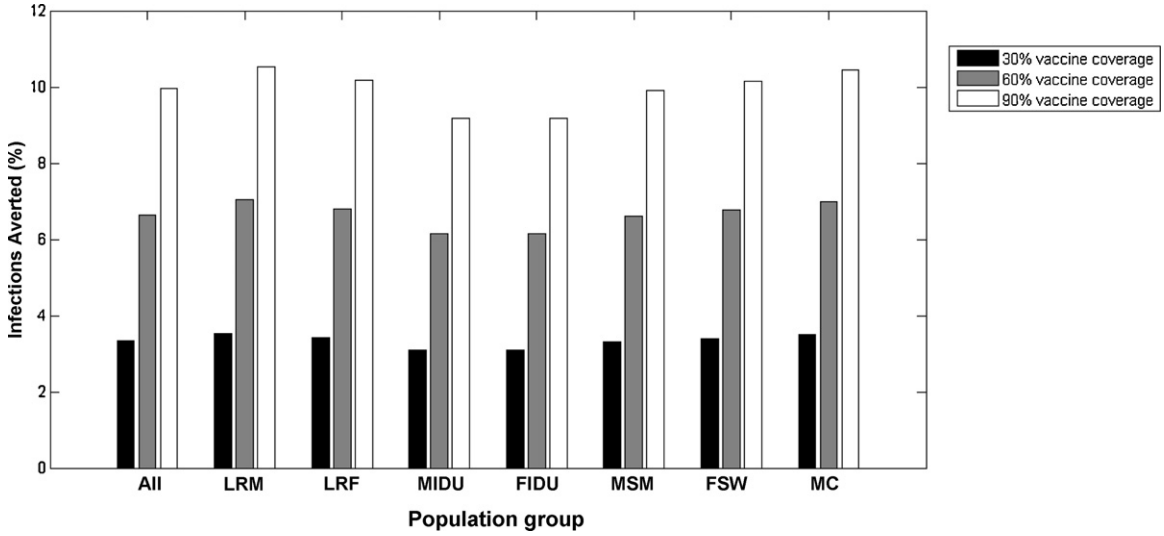

Fig. 2. Predicted percentage of infections averted after 10 years of vaccination overall and among population subgroups in Thailand. Assumptions include a vaccine efficacy of 73.6%, waning at a rate of 72.24% per year.

variables in cases where there are also correlations between input variables.

3. Results

Assuming no vaccine intervention or change in other current conditions, we projected a median annual incidence of 6357 (interquartile range [IQR]: 5446–7594) infections among adults aged 15–49 in Thailand, accumulating to approximately 63,568 (IQR: 54,461–75,941) new infections during the period 2011–2021. In our model, the majority of new infections were found to be among MSM (40%) and low-risk males and females (32%). In comparison, 20% of new infections were among IDUs, 1% among FSW, and 6% were among clients of FSW. The overall prevalence remained steady at ~1.6% (IQR: 1.3–1.8%).

Campaigns where individuals were vaccinated only once (i.e. when they entered the susceptible population) led to modest reductions in HIV incidence. Coverage rates of 30%, 60% and 90% led to an annual HIV incidence of 6287 (IQR: 5383–7509), 6217 (IQR: 5323–7425), and 6148 (IQR: 5265–7341), respectively. These values corresponded to 3.3% (IQR: 3.3–3.4%), 6.6% (IQR: 6.6–6.7%) and 9.9% (IQR: 9.8–10.0%) of infections being averted in each of the three scenarios.

Table 1 provides detail of the primary outcomes across all population groups for a vaccination scenario with 60% coverage and no re-vaccination. While modest reductions in incidence are observed for this scenario, it is apparent that IDUs were less likely to benefit from vaccination than other population groups (Fig. 2). Interestingly, this result is consistent with what was observed in the RV144 trial.

3.1. Efficacy and waning

Vaccine-related parameters (efficacy and waning) were further investigated to determine their independent effects on cumulative incidence in the model. Fig. 3A illustrates the relationship between the percentage of infections averted and vaccine efficacy across different vaccination coverage rates. When efficacy wanes at the level of magnitude observed by the RV144 vaccine, only marginal benefit can be observed by increasing vaccination coverage. Further, even if a vaccine was available with greater initial efficacy, it is unlikely that the vaccine could lead to any substantial impact with a similar rate of waning. For example, if efficacy was higher, at 80%, 90% or 100%, with 60% coverage and the same rate of waning, we estimated the overall number of infections averted after 10 years would be 7.3% (IQR: 7.2–7.4%), 8.4% (IQR: 8.3–8.4%), and 9.5% (IQR: 9.4–9.5%), respectively; similar results apply with 30% or 90%

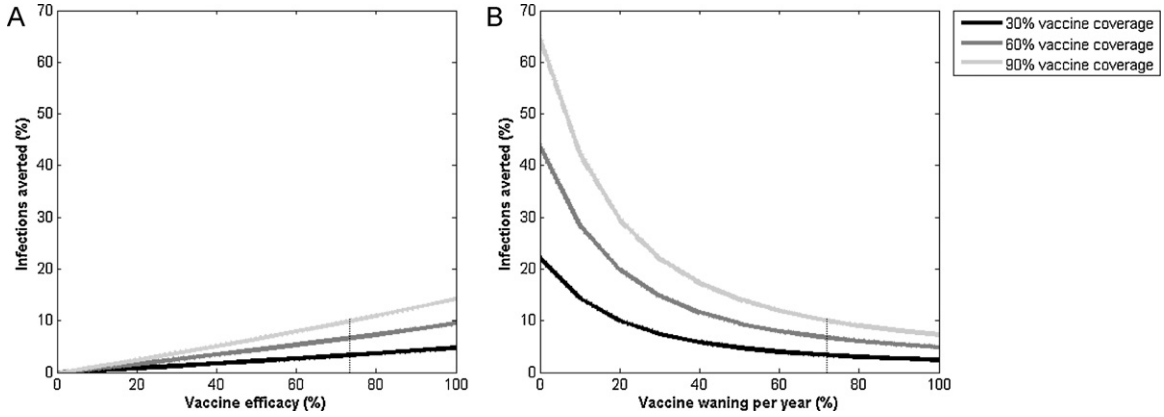

Fig. 3. Predicted percentage of infections averted after 10 years; dashed lines show default values. (A) Waning rate: 72.24% per year. (B) Vaccine efficacy: 73.6%.

Table 2
Partial rank correlation coefficients between model parameters and infections averted for each population subgroup. The correlation coefficient indicates the importance of the given parameter on the number of infections averted. Positive correlations indicate that increases in that parameter cause increases in the number of infections, negative correlations indicate decreased number of infections, and zero indicates no effect.

Infections averted in the overall population		
	Top four most important variables	Correlation coefficient*
Infections averted in overall population	Number of regular partners heterosexual men had per year	0.8612
	Efficacy of condoms	−0.7754
	Number of sexual acts among heterosexual regular partners per year	0.6569
	Baseline transmission probability for heterosexual partners (female-to-male)	0.6529

Infections averted for each population group		
Population group	Most important variable	Correlation coefficient*
Overall		0.8612
Low-risk males	Number of regular partners heterosexual men had per year	0.8927
Low-risk females		0.8966
Female sex workers		0.8770
Male clients of sex workers		0.8914
Male IDUs	Efficacy of cleaning injecting equipment	0.8887
Female IDUs		0.8879
MSM	Efficacy of condoms	−0.8715

* All p-values < 0.0001.

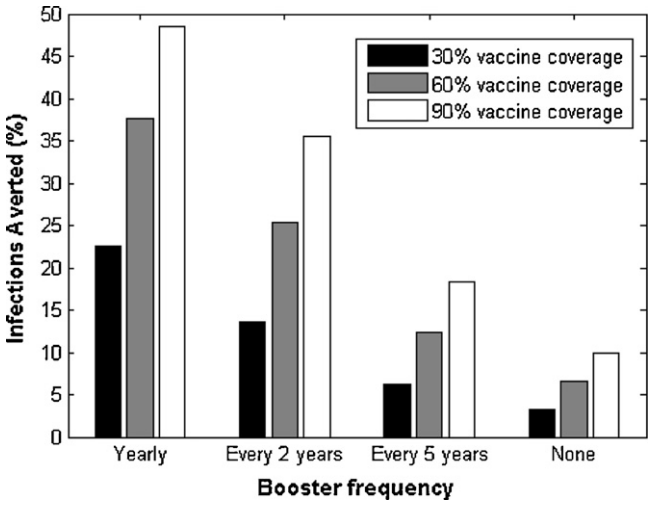

Fig. 4. Median percentage of infections averted. Assumptions include a vaccine efficacy of 73.6%, waning at 72.24% per year.

coverage rates. However, as illustrated in Fig. 3B, substantial public health benefits can be achieved if a vaccine has a lower rate of waning. For example, with efficacy and coverage levels at 73.6% and 60%, respectively, but the duration of vaccine protection by reducing waning from 72.24% per year to 20%, 10% and 0% per year, we estimated 19.8% (IQR: 19.6–20.0%), 28.4% (IQR: 28.1–28.6%), and 43.7% (IQR: 43.2–44.1%) of HIV infections could be averted after 10 years, respectively.

3.2. Re-vaccination

We simulated the expected impact of providing re-vaccination by assuming that it would confer the same amount and duration of protection as the first vaccination (Fig. 4). Based on our model, we estimate that an RV144-like vaccine applied with a coverage rate of 30% would lead to a 3.3% (IQR: 3.3–3.4%) reduction in the number of infections after 10 years. However, if 30% of the population were again re-vaccinated after 5 years, the total number of infections averted would increase to 6.2% (IQR: 6.2–6.3%). Further, re-vaccination every 2 years resulted in 13.5% (IQR: 13.4–13.7%) of infections being averted, while yearly vaccination would avert 22.5% (IQR: 22.3–22.7%) of infections over 10 years (Fig. 4).

3.3. Sensitivity analysis

We conducted a sensitivity analysis based on partial rank correlation coefficients to identify which model input parameters were most influential in giving rise to the variation observed in the model outputs. For a given vaccine scenario, the variation observed in the percentage of infections averted in the low-risk population was most sensitive to the following parameters: the number of regular partners, condom efficacy, and the frequency of sexual acts (Table 2). These parameters were also the most important ones among the population subgroups in which the primarily mode of transmission is heterosexual. The most important factor for infections averted among IDUs was the efficacy of cleaning injecting equipment, while condom efficacy was the most important factor among MSM (Table 2).

4. Discussion

Our study illustrated that the RV144 vaccine has the potential to reduce HIV incidence in Thailand, but only if its long-term efficacy can be improved via re-vaccination. With 30% coverage of the sexually active population, our model projected that 14% of infections could be averted after 10 years with biannual re-vaccination, while 23% could be averted with yearly re-vaccination. With 60% coverage, these reductions in incidence are estimated to become 25% and 38%, respectively. Our model suggests that vaccination campaigns would have close to negligible long-term effects in the absence of re-vaccination, with only 3% of HIV infections averted after 10 years with a coverage rate of 30%. Due to the short duration of protection that the RV144 vaccine provides, it appears that re-vaccination would be essential to provide long-term public health benefits. Even with low coverage rates, there will be extensive costs associated with developing and maintaining the infrastructure for a sustained vaccination campaign. Therefore, such a vaccine program may not be cost-effective as compared to other HIV prevention programs.

In our model, population-wide vaccination applied at equal coverage rates across all population groups resulted in different percentages of infections averted among the different subpopulations, ranging from 6.1% among IDUs to 7.0% among low-risk males (Table 1). This is consistent with the results of the vaccine trial which found lower levels of protection among population groups at higher risk of HIV acquisition. Interestingly, there was

a nearly linear negative relationship between prevalence and percent of infections averted (Spearman's $\rho = -0.9$, $p = 0.007$). We believe this is most likely due to a saturation effect in cumulative risk associated with multiple exposure events [16]. Individuals at highest risk may acquire HIV infection despite partial protection conferred by a biomedical intervention due to repeated risk exposure events that may not all be protected, whereas individuals at lower risk are more likely to have an infection prevented. However, for all population groups, a partially effective vaccine can have the effect of delaying, or averting, infection even if not completely preventing an infection from establishing.

There are several practical obstacles to implementing a vaccination campaign. For example, recent estimates predict low social acceptability and uptake for low-efficacy vaccines. A recently published meta-analysis reports significantly lower social acceptability scores (40% vs. 74%) for a moderately (50%) versus a highly (80–95%) effective HIV vaccine [17]. Since the RV144 vaccine would be categorized as low-to-moderately effective, achieving high coverage rates and convincing the general community to be vaccinated annually may be infeasible, especially among marginalized or at-risk population groups. Other potential deterrents include cost, side effects, and general fear of vaccines [17]. In addition, our model did not consider the potential for risk compensation, whereby there is an increase in risky behavior following the introduction of an intervention perceived to reduce risk, such as a vaccine. The effects of risk compensation are especially important given the low vaccine efficacy, since a very high-efficacy vaccine might result in near-zero infection probability regardless of behavior.

While there are several obstacles associated with vaccination campaigns, it is important to note that even low-to-moderate efficacy vaccines can have significant epidemiological impacts, potentially exceeding those of other biomedical interventions [18]. Our model predicts that it is possible to achieve a significant long-term public health benefit with an RV144-like vaccine if there is high coverage, sustained implementation, and re-vaccination. However, the rapid waning of efficacy observed in the RV144 trial is likely to be the greatest obstacle to its effective use in a vaccination campaign.

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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.2011.06.074.

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