Supplementary Information Appendix

Population level impact of an imperfect prophylactic HSV-2 vaccine

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Model equations and description. Our model consists of a system of eight differential equations for each risk group:

$$\frac{dS(i)}{dt} = \mu(1-f)N_0(i) - \mu S(i) - \Lambda^{S(i)}S(i) + \omega V(i) - \eta S(i)$$
$$\frac{dI_S(1,i)}{dt} = \Lambda^{S(i)}S(i) - \mu I_S(1,i) - \pi_1 I_S(1,i)$$
$$\frac{dI_S(2,i)}{dt} = \pi_1 I_S(1,i) - \mu I_S(2,i) - \pi_2 I_S(2,i) + \pi_3 I_S(3,i)$$
$$\frac{dI_S(3,i)}{dt} = \pi_2 I_S(2,i) - \mu I_S(3,i) - \pi_3 I_S(3,i)$$

(1)

$$\frac{dV(i)}{dt} = f\mu N_0(i) - \mu V(i) - (1-VE_S)(1+r)\Lambda^{S(i)}V(i) - \omega V(i) + \eta S(i)$$
$$\frac{dI_V(1,i)}{dt} = (1-VE_S)(1+r)\Lambda^{S(i)}V(i) - \mu I_V(1,i) - \pi_1 I_V(1,i)$$
$$\frac{dI_V(2,i)}{dt} = \pi_1 I_V(1,i) - \mu I_V(2,i) - \pi_2' I_V(2,i) + \pi_3' I_V(3,i)$$
$$\frac{dI_V(3,i)}{dt} = \pi_2' I_V(2,i) - \mu I_V(3,i) - \pi_3' I_V(3,i)$$

The index i stands for an i-sexual risk population where $i = 1,2,3,4$ represent low, low to intermediate, intermediate to high, and high risk groups respectively. The population is stratified into two classes based on vaccination status: un-vaccinated (S), and vaccinated (V) classes. Here $S(i)$ and $V(i)$ are the HSV-2 susceptible populations belonging to the group of unvaccinated and vaccinated, respectively. The $I_S(\alpha,i)$ and $I_V(\alpha,i)$ are the HSV-2 infected unvaccinated and infected vaccinated populations, respectively. The index α marks the stage of HSV-2 pathogenesis; $\alpha = 1,2,3$ stand for primary, latent (*no shedding*), and reactivated (*shedding*) stages, respectively. The $N(i)$ are the population sizes of each i-risk group, and $N_0(i)$ are the corresponding initial population sizes. The ω represents the rate at which the

vaccine wanes in vaccinated individuals and its inverse, assuming an exponential waning of vaccine immunity, is the duration of protection of the vaccine ($T = \frac{1}{\omega}$). We assume a constant birth rate in the model and we do not stratify the population explicitly according to age. The μ is the rate of entering and leaving the sexual activity group and its inverse is the duration of the sexual life span ($L = \frac{1}{\mu}$). The sexual life span constitute those individuals in the age range 15-49 [1, 2].

Vaccination is administered in the model in two different ways: adolescence vaccination and mass vaccination. Adolescence vaccination is administered for a fraction f of the population before entering sexual activity. Meanwhile mass vaccination is administered by vaccinating all of the susceptible population at some rate η. Here η denotes the average rate at which the susceptible population is being vaccinated. The reciprocal (η^{-1}) provides the average waiting time before vaccination.

In addition to the parameters f and η, vaccination is parameterized in the model through the vaccine efficacies [3, 4]: VE_S which is the classical vaccine efficacy of reducing susceptibility to HSV-2 infection, VE_I which is the vaccine efficacy of reducing HSV-2 infectivity *during shedding* for those who were vaccinated prior to their infection, and VE_P which is the vaccine efficacy of reducing disease reactivation (disease progression efficacy).

For completeness we include in the model the possibility of behavioral dis-inhibition due to changes in the perception of risk among those vaccinated. The parameter $r \in [0, \infty)$

parameterizes the relative increase in risk behavior experienced by vaccinated individuals after vaccination.

The progression of HSV-2 in the unvaccinated class of the population is described by π_1, the rate of progression from primary to latent stage, π_2, the rate of reactivation (the rate of progression from latent to reactivated stage), and π_3, the rate of deactivation (the rate of progression from reactivated to latent stage). Durations of each of the three stages are represented (in days) by the parameters τ_1, τ_2, and τ_3. A single *cycle* of HSV-2 infection is defined here as the average duration of a single period of reactivation (shedding) plus the consecutive period of latency (no shedding) before the next reactivation. The reactivation and latency cycle is assumed to have a frequency of χ cycles per year and we assume viral shedding only during primary infection and reactivations. The shedding frequency takes the value of ξ. Because the critical parameter here is the shedding frequency irrespective to the pattern of shedding [5], without loss of generality we assume χ=4 [5]. Because the duration of one cycle (in days) is $365/\chi$ then the duration of latency between reactivations is given by:

$$\tau_2 = 365\frac{1-\xi}{\chi}, \qquad (2)$$

whereas the duration of reactivation within the cycle is given by:

$$\tau_3 = 365\frac{\xi}{\chi} \qquad (3)$$

The rates of progression π_α (per year) of HSV-2 from one stage to the other are derived from the durations of each stage τ_α, $\alpha = 1,2,3$ using:

$$\pi_\alpha = \frac{365}{\tau_\alpha} \tag{4}$$

The vaccine efficacy of reducing shedding frequency (VE_P) is assumed to reduce ξ to $(1-VE_P)\xi$. Consequently this reduction causes expansion of latency at the expense of reactivations within a cycle. The HSV-2 progression rates in the vaccinated class are π_2' and π_3', and they are given by:

$$\begin{aligned} \pi_2' &= \frac{\chi}{1-(1-VE_P)\xi} \\ \pi_3' &= \frac{\chi}{(1-VE_P)\xi} \end{aligned} \tag{5}$$

The rates $\Lambda^{S(i)}$ are the HIV forces of infection (hazard rates of infection) experienced by each susceptible population $S(i)$:

$$\Lambda^{S(i)} = \rho_{S(i)} \sum_{j=1,2,3,4} \sum_{\alpha=1,2,3} \mathcal{G}(i,j) \left(\frac{t_{I_S \to S}(i,\alpha,j)\rho_{I_S(\alpha,j)} I_S(\alpha,j)}{\tilde{\rho}_N(j)} + \frac{t_{I_V \to S}(i,\alpha,j)\rho_{I_V(\alpha,j)} I_V(\alpha,j)}{\tilde{\rho}_N(j)} \right) \tag{6}$$

where

$$\rho_{V(i)} = (1+r)\rho_{S(i)}$$

$$\rho_{I_V(\alpha,j)} = (1+r)\rho_{I_S(\alpha,j)}$$

In these expressions, the vaccinated class of individuals experiences a fractional increase in sexual risk behavior r relative to the unvaccinated class. The $\rho_{V(i)}$ and $\rho_{S(i)}$ describe the *effective* new sexual partner acquisition rate for the vaccinated and unvaccinated susceptible populations. The $\rho_{I_V(\alpha,j)}$ and $\rho_{I_S(\alpha,j)}$ are the *effective* new sexual partner acquisition rates for the vaccinated and unvaccinated infected populations. Note that we use the term effective rate of partner change, as opposed to rate of partner change, since this parameter does not merely reflect the actual rate at which individuals change their partners, but also represents other behavioral mechanisms that effectively enhance this quantity such as concurrency and topology of sexual networks [6-8], as well as variability in risk behavior [9].

The parameters $t_{I_S \to S}(i,\alpha,j)$ and $t_{I_V \to S}(i,\alpha,j)$ stand for HSV-2 transmission probability per partnership in a partnership between a susceptible member and an infected member of the unvaccinated and vaccinated populations, respectively. These transmission probabilities are expressed in terms of HSV-2 transmission probability per coital act per HSV-2 stage in this partnership ($p_{I_s(\alpha,j)\to S(i)}$), the number of coital acts per HSV-2 stage in this partnership (n_α), and the duration ($d_{I_S(\alpha,j)\to S(i)}$) of this partnership. For example using the binomial model, $t_{I_S \to S}(i,\alpha,j)$ is given by the expression:

$$t_{I_S \to S}(i,\alpha,j) = 1 - \left(1 - p_{I_s(\alpha,j)\to S(i)}\right)^{n_\alpha d_{I_S(\alpha,j)\to S(i)}} \qquad (7)$$

We define the vaccine efficacy in reducing infectivity *during shedding* (VE_I) in terms of the fractional reduction in the transmission probability per partnership according to

$$t_{I_V \to S}(i, \alpha, j) = (1 - VE_I) t_{I_S \to S}(i, \alpha, j) \tag{8}$$

The mixing among the four risk groups is dictated by the sexual-mixing matrix $\mathcal{G}(i, j)$ which provides the probability that an individual in risk group j would choose a partner in risk group i [10], and it has an assortative and proportional components. The mixing matrix is given by the expressions

$$\mathcal{G}(i, j) = e\delta_{i,j} + (1 - e)\frac{\tilde{\rho}_N(j)}{\sum_{k=1,2,3,4} \tilde{\rho}_N(k)} \tag{9}$$

Here, $\delta_{i,j}$ is the identity matrix and the parameter $e \in [0,1]$ measures the degree of assortativeness in the mixing. At the extreme $e = 0$, the mixing is fully proportional while at the other extreme $e = 1$, the mixing is fully assortative as individuals choose partners only from within their risk group. The risk groups are defined using the data of the Four City study [2]. Female sex workers and their male clients constitute the high risk group. Meanwhile, the populations with more than one non-spousal, one non-spousal, and no non-spousal partnerships in the previous year characterize the intermediate to high, low to intermediate and low risk groups, respectively. The $\tilde{\rho}_N(j)$ represents the total rate of partnerships acquired by individuals of risk group j and is given by

$$\tilde{\rho}_N(j) = \rho_{S(j)} S(j) + \rho_{V(j)} V(j) + \sum_{\alpha=1,2,3} \rho_{I_S(\alpha,j)} I_S(\alpha, j) + \sum_{\alpha'=1,2,3} \rho_{I_V(\alpha',j)} I_V(\alpha', j) \tag{10}$$

For the Kisumu, Kenya simulations we used the general population survey of the Four City study [2] to fit HSV-2 prevalence levels in the year 1997-1998 for the sexually active population.

Measures of HSV-2 vaccination impact at the population level. The basic reproduction number for a population with no vaccination (f =0) is given by

$$R_0 = \frac{L\rho}{L+\tau_1}\left[\tau_1 t_1 + \frac{L(1-\xi)(\xi+L\chi)}{L\chi+\xi(1-\xi)}t_2 + \frac{L^2\chi\xi}{L\chi+\xi(1-\xi)}t_3\right], \qquad (11)$$

where t_1, t_2, and t_3 are the transmission probabilities per partnership from HSV-2 infected and unvaccinated individuals to susceptible and unvaccinated individuals. The parameters ρ, L, τ_1, ξ, and χ are the effective partnership acquisition rate of unvaccinated individual, the average sexual life span, the average duration of HSV-2 primary infection, average shedding frequency of unvaccinated but infected individuals, and the average frequency of latency and reactivation cycles, respectively. On the other hand the basic reproduction number in the partially vaccinated population (R_{0V}) is given by

$$\begin{aligned} R_{0V} \;=\; & R_0 \;+\; \frac{L^2\rho}{(L+\tau_1)}\frac{fT}{(L+T+rfT)} \\ & \times\left\{(1+r)^2(1-VE_I)(1-VE_S)\left(\frac{\tau_1}{L}t_1+t_2\right)-\frac{\tau_1}{L}t_1-(1-\xi)t_2-\xi t_3\right. \\ & +\frac{\xi^2(1-\xi)}{\xi(1-\xi)+L\chi}(t_3-t_2) \;+\; (1+r)^2(1-VE_I)(1-VE_S)(1-VE_P)\xi \\ & \left.\times\left(1-\frac{\xi(1-(1-VE_P)\xi)}{L\chi+(1-VE_P)\xi(1-(1-VE_P)\xi)}\right)(t_3-t_2)\right\} \end{aligned} \qquad (12)$$

where VE_S, VE_P, and VE_I are the vaccine efficacies of reducing: susceptibility, shedding frequency, and infectivity *during* shedding, respectively. The parameters f, r, and T are the fraction of the population administered adolescence vaccination, their relative increase in risk behavior after vaccination, and the average duration of vaccine protection respectively.

Both expressions for R_0 and R_{0V} were derived using the dominant eigenvalue of the next-generation matrix [11, 12].

The vaccine utility [13] (Φ) is obtained from R_0 and R_{0V} using McLean and Blower [14] definition of vaccine impact ($\Phi = \frac{1}{f}\left(1 - \frac{R_{0V}}{R_0}\right)$):

$$\begin{aligned}\Phi \;=\; & \frac{1}{R_0}\frac{L^2\rho}{(L+\tau_1)}\frac{T}{(L+T+rfT)} \\ & \times\left\{\frac{\tau_1}{L}t_1 + (1-\xi)t_2 + \xi t_3 - (1+r)^2(1-VE_I)(1-VE_S)\left(\frac{\tau_1}{L}t_1 + t_2\right)\right. \\ & -\frac{\xi^2(1-\xi)}{\xi(1-\xi)+L\chi}(t_3-t_2) \;-\; (1+r)^2(1-VE_I)(1-VE_S)(1-VE_P)\xi \\ & \left.\times\left(1-\frac{\xi\left(1-(1-VE_P)\xi\right)}{L\chi+(1-VE_P)\xi\left(1-(1-VE_P)\xi\right)}\right)(t_3-t_2)\right\}\end{aligned} \tag{13}$$

Finally the vaccine infection fitness [13] (Ψ) is defined by the ratio

$$\Psi = \frac{R_{I_V}}{R_{I_S}}, \tag{14}$$

where R_{I_V} is the number of secondary infections that an infected vaccinee would cause in a partially vaccinated but infection-free population and R_{I_S} is the number of secondary infections that an infected unvaccinated individual would cause in the same population. Both of these numbers are obtained from the elements of the next-generation matrix [11]. The Ψ is given by:

$$\Psi = (1+r)(1-VE_I)\frac{L\chi+\xi(1-\xi)}{L\chi+(1-VE_P)\xi\left(1-(1-VE_P)\xi\right)} \times \frac{\left[\begin{array}{l}\xi(1-VE_P)\left(1-(1-VE_P)\xi\right)\left(\tau_1(t_1+t_2+t_3)+L(2t_2+t_3)\right)+\\ L\chi\left(t_1\tau_1+(3L+2\tau_1)\left(t_2-(1-VE_P)\xi t_2+(1-VE_P)\xi t_3\right)\right)\end{array}\right]}{\left[\begin{array}{l}\tau_1\xi(t_1+t_2+t_3)(1-\xi)+3L^2\chi\left(t_2(1-\xi)+t_3\xi\right)+\\ L\left(t_1\chi\tau_1+t_3\xi(1+2\chi\tau_1-\xi)+2t_2(1-\xi)(\chi\tau_1+\xi)\right)\end{array}\right]} \quad (15)$$

Vaccine utility states and desirable values of summary measures. Following our earlier work on HIV vaccination [13], we classified the *vaccine utility* at the population-level into three categories. The vaccine is *definitely beneficial* (deduced by $\Phi > 0$ [13]) if it reduces endemic equilibrium values for disease prevalence, incidence (absolute number of incident infection per year), and incidence rate (number of incident infections per susceptible individual per year) compared to their values without vaccination. (We did not include disease mortality in the criteria due to the chronic nature of the HSV-2 infection.) The vaccine would be *partially beneficial* ($\Phi = 0$) if at least one but not all of these values were reduced upon achieving equilibrium after vaccination and *perverse* ($\Phi < 0$) if none of these equilibrium values were reduced, or increased, after vaccination. Therefore, it is desirable for vaccines to be beneficial ($\Phi > 0$). Also it is desirable for vaccines to have the basic reproduction number with vaccination

below sustainability threshold (i.e. $R_{0V} < 1$). The vaccine, by satisfying this criterion, would impact HSV-2 chains of transmission in the general population. Moreover, a vaccinee infection fitness that is considerably below one (i.e. $\Psi < 1$) is an indicator of a substantial reduction in the secondary infections caused by the infected and vaccinated individuals compared to the infected and unvaccinated individuals.

Synergy between vaccine efficacies. We investigated the synergy between different schemes of vaccine efficacies using the formula:

$$\text{synergy} = \frac{I_1 I_2}{I_{1,2} I_0} \tag{16}$$

where I_1, I_2, $I_{1,2}$, and I_0 are the values of incidence rate (number of incident infections per susceptible individual per year) for intervention scheme 1 alone, intervention scheme 2 alone, a combination of intervention schemes 1 and 2, and no intervention scheme, respectively. If the result in expression (16) is less than *one* then the two intervention schemes are *redundant* otherwise they are *synergetic*.

Sensitivity and uncertainty analyses. We performed sensitivity and uncertainty analyses to assess the robustness and sensitivity of our predictions to the uncertainty in the vaccine efficacies, behavioral parameters, and HSV-2 progression parameters used to parameterize the model. We examined the sensitivity of our vaccine mass intervention predictions both at the endemic equilibrium (long-term) and in 2020 (short-term) to variations of 1) 0 to 20% in the vaccine efficacy of reducing infectivity VE_I; 2) 21 to 39% in the vaccine efficacy of reducing

susceptibility VE_S , 3) 52.5 to 97.5% in the vaccine efficacy of reducing HSV-2 shedding frequency VE_P , 4) 6 to 36% in HSV-2 shedding frequency; 5) $\pm$ 15% in the fraction of the population in the highest risk group with a corresponding variation in the rest of the risk groups; 6) $\pm$ 15% in all values of the new sexual partner acquisition rates; 7) $\pm$ 15% in the degree of assortativeness in the mixing between the risk groups.

Figures S1-2 and S3-4 show the results of the sensitivity and uncertainty analyses with respect to our predictions at 2020 and at the endemic equilibrium, respectively. The analyses of the variability of excess prevalence, relative reduction in incidence, and excess incidence rate (incidence per 100 persons-years),were done by Monte Carlo sampling from the specified ranges of uncertainty in the tested parameters using the uniform distribution for 1000 runs of the model. The long-term and short-term predictions are largely invariable to the specified variations in the fraction of the population in the highest risk group, the rates of partner change, the level of assortativeness in the mixing between the risk groups, and the vaccine efficacy of reducing infectivity. Short-term predictions of excess prevalence, relative reduction in incidence, and excess incidence rate show large sensitivity to vaccine efficacy of reducing susceptibility and no sensitivity to shedding frequency. Long-term predictions are largely insensitive to the vaccine efficacy of reducing susceptibility. However, long-term predictions of excess prevalence, the relative reduction in incidence, and excess incidence rate are largely sensitive to the respective variation in vaccine efficacy of reducing shedding frequency, while only the last two quantities are largely sensitive to the respective variations in the HSV-2 shedding frequency.

These patterns of sensitivity show that the impact of the vaccine is not sensitive to the sexual behavior structure in the model and that if one of the efficacies dominates the effects on

infectious spread, its impact overshadows the effects of the rest of the efficacies. For example, the limited sensitivity to VE_I is a consequence of the fact that the impact of VE_P and VE_S is large enough that there is little room for the VE_I to yield an impact at the population level.

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Supplementary figures captions

Figure S1 Sensitivity and uncertainty analyses with respect to HSV-2 vaccine efficacies in the model for the calculation of Kisumu, Kenya. The values of excess prevalence, relative reduction in incidence, excess incidence rate at 2020 with respect to variations in (**A**) vaccine efficacy of reducing infectivity during shedding VE_I , (**B**) vaccine efficacy of reducing susceptibility VE_S , (**C**) vaccine efficacy of reducing shedding frequency VE_P .

Figure S2 Sensitivity and uncertainty analyses with respect to the behavioral and HSV-2 progression parameters in the model for the calculation of Kisumu, Kenya. The values of excess prevalence, relative reduction in incidence, excess incidence rate at 2020 with respect to variations in (**A**) new sexual partner acquisition rates, (**B**) fraction of the population in the highest risk group, (**C**) assortativeness in the mixing between the risk groups, and (**D**) HSV-2 shedding frequency.

Figure S3 Sensitivity and uncertainty analyses with respect to HSV-2 vaccine efficacies in the model for the calculation of Kisumu, Kenya. The values of excess prevalence, relative reduction in incidence, excess incidence rate at endemic equilibrium with respect to variations in (**A**) vaccine efficacy of reducing infectivity during shedding VE_I , (**B**) vaccine efficacy of reducing susceptibility VE_S , (**C**) vaccine efficacy of reducing shedding frequency VE_P .

Figure S4 Sensitivity and uncertainty analyses with respect to the behavioral and HSV-2 progression parameters in the model for the calculation of Kisumu, Kenya. The values of excess prevalence, relative reduction in incidence, excess incidence rate at endemic equilibrium with respect to variations in (**A**) new sexual partner acquisition rates, (**B**) fraction of the population in

the highest risk group, (**C**) assortativeness in the mixing between the risk groups, and (**D**) HSV-2 shedding frequency.

Figure S1

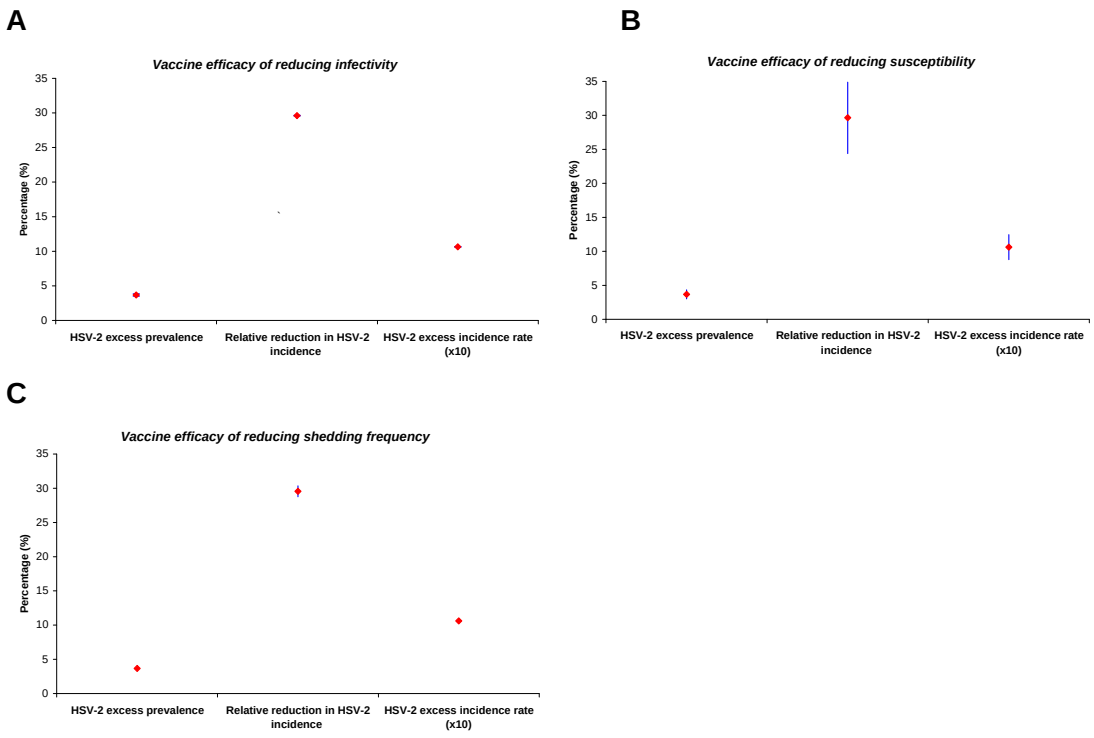

Figure S2

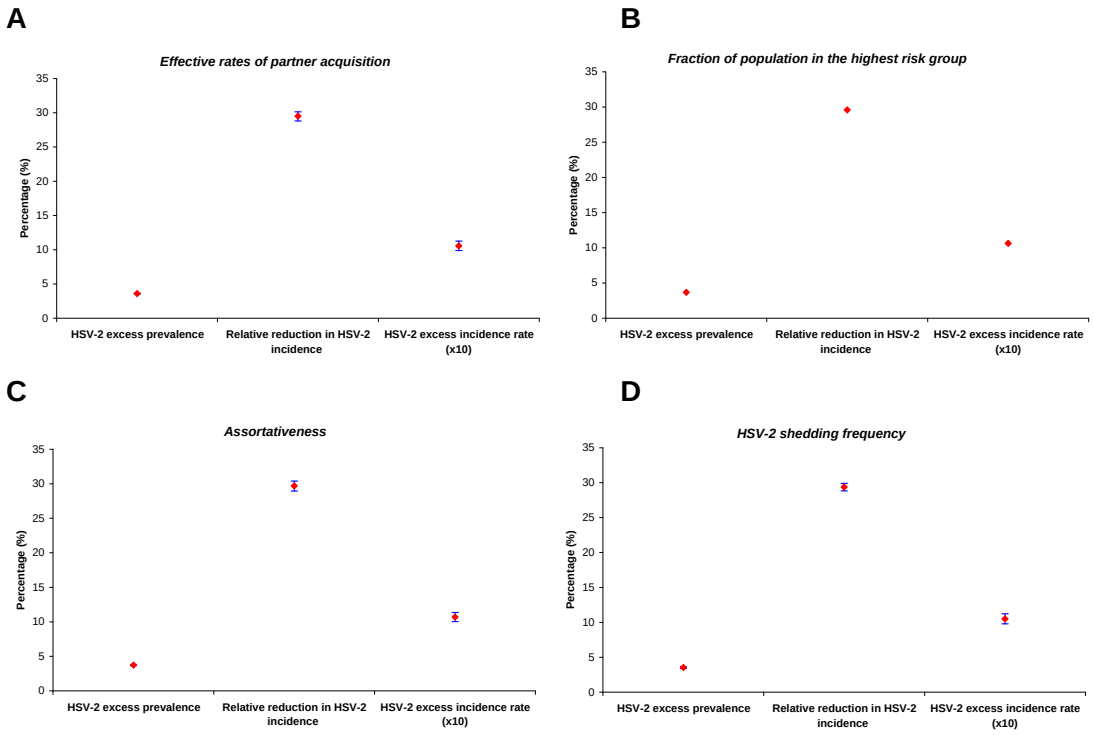

Figure S3

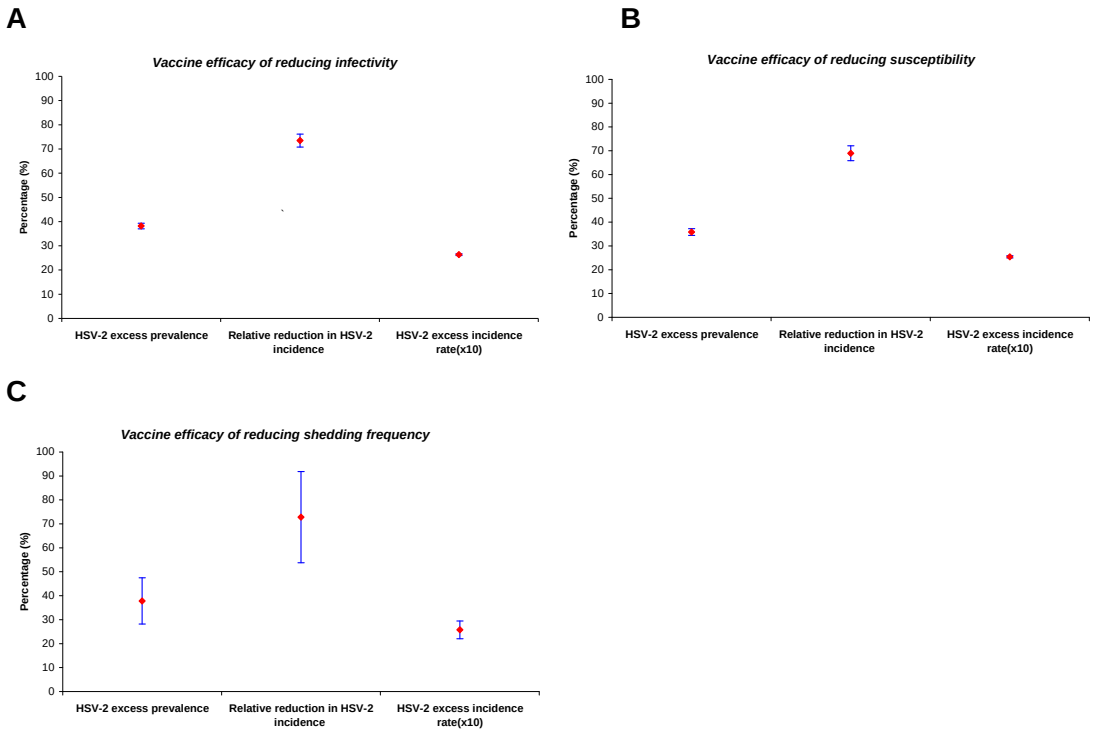
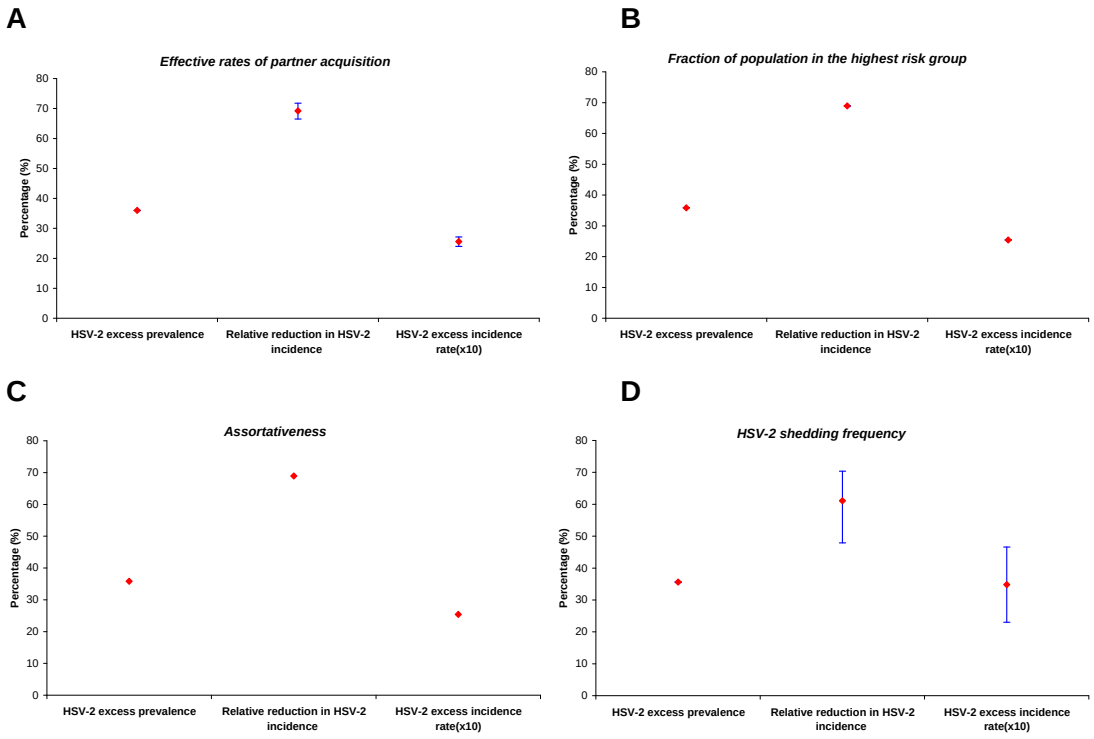
Figure S4