Modelling HIV vaccination

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Two aspects of the biology of HIV raise particular questions about the testing and use of a prophylactic vaccine. First, few, if any, people mount an immune response that is strong enough to clear their infection. It is therefore unlikely that a highly effective vaccine will be available soon. Second, HIV is mostly spread through sexual intercourse. Its rate of transmission in a community thus depends strongly on the sexual behaviour within that community. While molecular immunologists and virologists have been busy constructing candidate vaccines, mathematical epidemiologists have been constructing models to investigate their potential impact. All the models grapple with questions raised by the two special properties of HIV. These questions fall into two groups: those relating to the design and interpretation of clinical trials, and those relating to the community-wide impact of a vaccine.

Imperfect vaccines and efficacy trials

The goal of a vaccine-efficacy trial is to estimate how well a vaccine works. This is done by comparing the incidence of infection in a vaccinated group with that in a control group. The standard definition of vaccine efficacy, \( E \), is:

\[
E = 1 - \left( \frac{\text{incidence rate in vaccinated group}}{\text{incidence rate in unvaccinated group}} \right)
\]

For example, if there were five cases among the vaccinated group for every 100 cases among the control group, the efficacy of the vaccine would be estimated as 95%. In a very influential paper (that was apparently the outcome of a class exercise), Smith et al.\(^1\) discuss how different mechanisms of vaccine failure ought to be detected in clinical trials. They recognize that a vaccine can fail in different ways: it might give complete protection to some people and none to others; alternatively, it might reduce (but not eliminate) everybody's probability of infection on exposure. They show that, in calculating the vaccine efficacy, the appropriate measure of incidence in vaccinated and unvaccinated groups is determined by the manner in which the vaccine fails. For a vaccine that completely protects some people and does nothing for others, the appropriate measure is the total number of cases over the course of the trial (also called the cumulative incidence). For a vaccine that gives only partial protection to everybody, the appropriate measure is the number of cases per susceptible person per unit of time (also called the 'force of infection' or 'hazard'; see Table 1).

Halloran and coworkers\(^2\) have called these two types of vaccine 'all-or-nothing' and 'leaky' (Table 1), and have calculated examples of how much difference it would make if the incorrect definition of incidence was used in a trial. Figure 1 summarizes one set of such calculations. The correct definition of incidence gives the true efficacy of the vaccine; using the incorrect definition yields estimates of the vaccine efficacy that diverge away from the true value over time.

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cases caused by one infectious case introduced into a
community where everybody else is susceptible. If we
denote by $R_0$, the basic reproductive rate for an un-
vaccinated person when everyone else is susceptible,
and by $R_p$ the reproductive rate in a community where
a fraction $p$ has been vaccinated, we can express $R_p$ in
terms of $R_0$ and parameters describing the properties
of the vaccine. Three different types of vaccine failure
can be combined into a single summary measure that
we call 'vaccine impact', $\phi$ (Ref. 5). Like Smith et al.,
we consider the case of vaccines working in some people,
but not in others (this we call 'take'). We also consider
the case of the vaccine giving incomplete protection
(that is, reducing the degree of susceptibility) to those in
whom it takes (this we call 'degree'). We add the possi-
blility that vaccine-induced immunity might wane over
time (this we call 'duration'). We have shown that, for a
vaccine that takes in a fraction $\epsilon$, gives a degree of
protection $\psi$ (that is, reduces the per-exposure prob-
bility of infection by an amount $\psi$), and gives pro-
tection that lasts, on average, for a time $1/\omega$, in a
population in which individuals have a mean duration of
sexual activity $1/\mu$, the overall measure of vaccine
impact, $\phi$, is:

$$\phi = \epsilon \psi \mu / (\mu + \omega)$$

The vaccinated reproductive rate, $R_p$, for a popu-
lation that receives this vaccine with a coverage $p$ (that
is, a fraction $p$ are vaccinated) is then:

$$R_p = (1 - \phi p) R_0$$

Impact, $\phi$ is the amount by which vaccine cover-
se should be reduced when calculating the impact a vac-
cine will have on transmission in the community. It is
therefore a generalization of the well-established con-
cept of vaccine efficacy, which includes the possibility
that vaccine-induced immunity might not be permanent.
Below, we show how to calculate $\phi$ when vaccine fail-
ures have a different natural history of HIV infection
from people who have never seroconverted. As $\phi$ de-

dends linearly on $\epsilon$ and $\psi$, vaccines that are imperfect in
take or degree of protection have a lower population-
level impact than that of an ideal vaccine in an intui-

tively obvious way. The relationship between the du-

ation of protection and the population-level impact is
not so intuitively clear. As illustrated in Fig. 2, vaccine
impact is very sensitive to the duration of protection.
A vaccine that gives perfect protection that wanes with
a half-life of 10 years is only as good as a vaccine that
fully protects 30% of people for the rest of their lives.

$R_v$ can be used to calculate the theoretical vacci-
nation coverage needed to eradicate an infection. It can
also be used as a broader measure of the effect that a
given level of intervention will have even if eradica-
tion is not achieved. Vaccines with the same impact (and
hence the same coverage required for eradication) will
reduce the reproductive rate in a vaccinated population,
$R_v$, by the same amount if given at the same coverage.
Interestingly, this does not necessarily lead to identical
seroprevalence levels. Figure 3 shows how four vaccines
with the same impact lead to different seroprevalence
levels over time. Even the equilibrium levels are dif-
ferent for vaccines in which the degree of protection is
less than one.

We have extended vaccine impact, $\phi$, to include the
possibility that vaccine failures might have a different
natural history of HIV infection from people who have
never been vaccinated. Under these circumstances, the
duration element is removed from the calculations, as
we assume that anybody in whom the vaccine takes has
an altered course of infection (if they become infected).
To evaluate the potential effects of vaccines that de-
crease infectiousness, the potential trade-off between
decreased infectiousness and increased duration of
infectiousness must be examined explicitly. This trade-
off can be expressed in terms of a basic reproductive
rate for those vaccinated successfully, $R_v$. Reduced in-
feciousness makes $R_v$ smaller than $R_0$, but a longer
infectious period makes it larger. It is easy to show
(Box 1) that, for a population where a fraction $p$ have

{fig:1} Implications of vaccine failures for trials. Trials that use an inappro-
nropriate design could yield very poor estimates of the true effect of a vac-
cine. For a leaky vaccine (where everyone is somewhat protected), a trial
based on the force of infection (also called the hazard) is appropriate.
For an all-or-nothing vac-
cine (where everybody is either fully protected or not at all), cumulative inci-
dence is the appropriate measure. This example is from Halloran et al.,
and assumes a background force of infection of 0.05 per susceptible person per year and a true vac-
cine efficacy of 50%.


received a vaccine (which takes in a fraction \( \varepsilon \) and protects to degree \( \psi \)), the appropriate average of \( R_e \) and \( R_0 \) is:

\[
R_p = (1 - \varepsilon \psi) R_0 + (1 - \psi) \varepsilon p R_e
\]

A nice biological interpretation of this mathematical linear stability result is that \( R_p \) is the number of tertiary cases per secondary case (in the absence of density-dependent constraints). Halloran and colleagues derived this relationship for the special case in which everyone has been vaccinated (\( p = 1 \)).

Furthermore, if \( R_e = (1 - \xi) R_0 \), that is, vaccination reduces the lifetime infectiousness of a vaccine failure by an amount \( \xi \), the new summary measure of vaccine imperfection is:

\[
\phi = \varepsilon (\psi + \xi (1 - \psi))
\]

This has the reassuringly commonsensical biological corollary that reductions in susceptibility and reductions in infectiousness are interchangeable in their population-level impact.

Altered levels of infectiousness among vaccine recipients have important implications for the design of vaccine trials. In particular, methods to detect such an effect are needed; this is an aspect of trial design that is under intense study at the moment (I. Longini, pers. commun.).

**Behavioural change during trials**

The most obvious application of mathematics to the design of vaccine trials is in calculating how large the trial needs to be. Smith and colleagues have explained how this is done; the required study size is a function of the rate of HIV transmission in the community where...
Box 1. Deriving $R_p$

$R_p$ is the reproductive rate in a population where a fraction $p$ have received a vaccine. $R_e = 1$ is the eradication criterion. The normal definition of $R_p$ is the number of secondary cases per primary case in a susceptible population. We need to know what kind of primary case it is.

**Definitions**

The vaccine takes in a fraction $\psi$ and gives a degree of protection $\psi$ to those in whom it takes. $R_e$ is the basic reproductive rate: the number of new cases generated by one person who is never successfully vaccinated if everyone that he or she meets is unvaccinated. $R_p$ is the basic reproductive rate for vaccine failures. Vaccine failures are defined as people in whom the vaccine took, but who subsequently became infected.

**Secondary cases caused by a primary case**

Each primary case will cause $R_e(1 - \psi p)$ cases among unprotected people, and $R_e(1 - \psi p)$ cases among successfully vaccinated people, where $i = 0$ if the primary case is unvaccinated, and $i = v$ if the primary case is vaccinated.

**Tertiary cases caused by secondary cases**

Each case in a previously unprotected person will cause $R_e(1 - \psi v p)$ tertiary cases. Each case in a previously successfully vaccinated person will cause $R_e(1 - \psi v p)$ tertiary cases.

**Tertiary cases per secondary case**

\[
\text{Total secondary cases} = R_e(1 - \psi v p)
\]

\[
\text{Total tertiary cases} = R_e(1 - \psi v p R_e(1 - \psi v p) + R_e(1 - \psi v p R_e(1 - \psi v p)
\]

\[
R_p = (1 - \psi p) R_e + (1 - \psi v p R_e
\]

$= \text{number of tertiary cases per secondary case}$

the study is based\textsuperscript{6}. Smith et al. point out that it is ethically necessary to counsel all participants in a study about reducing risky behaviour (a euphemism for unprotected sexual intercourse). Successful counselling reduces transmission, thus reducing the chance of detecting any effect of the vaccine in the study. This 'catch-22' implies that trials need to have a larger sample size, so that expected decreases in exposure resulting from successful counselling do not jeopardize the chance of detecting a beneficial effect of the candidate vaccine.

Successful counselling, leading to reductions in risky behaviour, poses one set of problems for trials. Unsuccessful counselling, leading to increases in risky behaviour, poses another. If everybody in a trial (both vaccinees and controls) increases their risky behaviour equally, the estimated efficacy of the vaccine should be unchanged. But what if trial participants get themselves tested for HIV and then act differently depending on the result of that test? It would be reasonable for trial participants who test HIV positive to assume that they are in the vaccine arm of the trial. If they then increase their risky behaviour while those receiving the placebo do not, the chances of the trial giving an accurate estimate of the efficacy of the vaccine are again jeopardized. Halloran and coworkers\textsuperscript{5} have calculated just how wrong the estimates might be for varying levels of behavioural change (Fig. 4). They point out that a trial that records exposure in some way would be much less prone to such problems.

Halloran et al.\textsuperscript{5} analyse in some depth the extent to which ill-designed trials might give a 'wrong' answer. The following factors are allowed to vary: the 'true' efficacy of the vaccine, its mode of action, the extent to which risky behaviour increases and the fraction of participants that change their behaviour. The authors summarize their findings: 'A good vaccine will look

**Fig. 4. Implications of changes in behaviour for trials.** Trials that fail to record exposure (sex acts, number of partners or some combination) are very vulnerable to changes in behaviour leading to increased exposure among the vaccinated group of the trial. This example from Halloran et al.\textsuperscript{5} assumes a background force of infection of 0.05 susceptible people per year (that is, each year 1 in every 20 susceptible people becomes infected) and a true vaccine efficacy of 50%. The vaccine is assumed to protect all recipients partially. The model trial uses the appropriate measure of incidence and has a thousand people in each group. All vaccinated individuals are assumed to increase their risky behaviour by the factor shown. The figure shows estimates of vaccine efficacy and 95% confidence intervals at 3 years (open circles) and 10 years (filled circles) after vaccination.
good under a variety of circumstances, while a poor vaccine will easily look worse than it is.'

**Behavioural issues during vaccine use**

If a prophylactic vaccine was to complete a large-scale vaccine-efficacy trial successfully, it would presumably be used rapidly in high-risk communities (at least in developed countries). What would be its impact? We modelled the impact of a vaccine in a community using parameters derived from population-based studies of the homosexual community in San Francisco, USA. As discussed above, we first addressed questions about the control, without eradication, of HIV in San Francisco. We then went on to consider what would happen if people increased their risky behaviour because of false sense of security endowed by the licensing of a vaccine. Figure 5 shows the relationship between vaccine impact, \( \phi \), behavioural change and the proportion of the community that would need to be vaccinated to eradicate HIV in San Francisco. We have also derived an expression to estimate the circumstances under which it would be possible for increases in risky behaviour to overwhelm the beneficial effects of a vaccine completely. For example, consider the case of a vaccine that gives 50% protection and is given to 60% of people. If they respond with a 40% increase in their risky behaviour, the epidemic would get worse, not better.

The great heterogeneity that exists in risky behaviour suggests that a vaccine might be targeted towards high-risk individuals and thus have a disproportionate effect. Heterogeneity in sexual behaviour and risk of infection changes the impact of a nontargeted vaccination programme, and the pattern of mixing in the population is crucial to the impact of a targeted campaign. However, careful longitudinal studies of risky behaviour show that membership of high-risk groups is not stable over time, and that the risk of acquiring HIV infection is very dependent on the sexual networks to which an individual belongs. This means that it could be very difficult to identify which people should be targeted. It is essential that these findings are taken into account when discussing targeted vaccination.

**Conclusions**

HIV, its treatment and prevention are rarely out of the news. Hopes rise and fall as vaccine and drug trials are announced or postponed. Basic science, too, provides sometimes hopeful, sometimes discouraging insights. The announcement early this year that some Gambian prostitutes have lymphocytes that might make them immune to infection with HIV was tremendously encouraging to everyone hoping for a preventative vaccine. The news that there are some people with apparent protective immunity to infection is an extremely important boost to confidence that one day there will be vaccines to protect against infection with HIV. Now, while such vaccines are in development, it is a good time to use mathematical models to question how they should be tested and, ultimately, how they should be used.

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**References**