Title: Beyond instantaneous partnerships in compartmental models of HIV transmission: re-examining assumptions and a new model for partnership duration

Authors: Jesse Knight[1], …[1], and Sharmistha Mishra[1]

[1]Institute of Medical Science, University of Toronto

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Abstract

Highlights

- Review assumptions and limitations of current models of the force of infection
- Develop a new force of infection model to accurately represent repeated contacts
- Apply current and proposed models to HIV transmission in eSwatini
- Illustrate key differences in inferred drivers of transmission under each model

1 Introduction

The force of infection — or incidence — equation defines the rate of new infections among a susceptible population. As the core of most transmission models, this equation specifies the assumed mechanistic relationships between incidence and factors of interest, such as contact rates or the probability of transmission. The assumptions underpinning a force of infection equation are therefore key determinants of the modelled transmission dynamics, and ultimately evidence generated by the model.

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2 Current Models of the Force of Infection

$\langle 1 \rangle$ **Binomial Per-Partnership:** A common model for the force of infection in HIV transmission models is currently:

$$\lambda_i^{\langle 1 \rangle}(t) = \sum_{jhk} Q_{ijk} \left(1 - (1 - \beta_{hk})^{A_k}\right) \frac{I_{jh}(t)}{N_j} \tag{1}$$

where: β_{hk} is the per-contact (sex act) probability of transmission from individuals in infection stage h via partnership type k; Q_{ijk} is the rate of type-k partnership formation by individuals in group i with those in group j (includes "mixing" between groups); A_k is the number of contacts per type-k partnership; and $I_{jh}(t)/N_j$ is the proportion of group j who are in infection stage h (prevalence).

The term $1 - (1 - \beta)^A$ represents the probability of transmission per-partnership, which we denote B (Figure 1a, purple). This probability is derived from the binomial distribution for n transmissions after A independent, equal probability contacts:

$$P(n) = \binom{A}{n} \beta^n (1 - \beta)^{A-n} \tag{2}$$

Since transmission can only occur once, B is defined via the probability of "escaping" infection:

$$\begin{aligned} B &= 1 - P(n = 0) \\ &= 1 - \binom{A}{0} \beta^0 (1 - \beta)^A \\ &= 1 - (1 - \beta)^A \end{aligned} \tag{3}$$

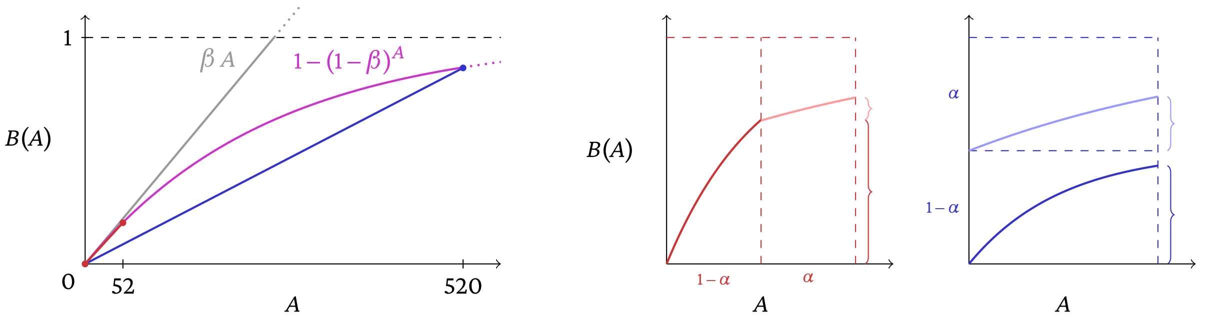
$\langle 1b \rangle$ **Binomial Per-Partnership-Year:** Many applications of model $\langle 1 \rangle$ define the probability of transmission B per-partnership-year, and thus effectively choose partnership duration $\delta = 1$ year, total contacts $A = F$ (contact frequency per-partnership), and partnership formation rate $Q \geq 1$, even for long-duration partnerships. We denote the model allowing $\delta > 1$ as $\langle 1a \rangle$ and that with $\delta = 1$ as $\langle 1b \rangle$, which is more common. As the "true" values of δ, F, and/or β increase, model $\langle 1b \rangle$ can be substantially different from $\langle 1a \rangle$. Figure 1a further illustrates two tangents, whose slope represents the applied yearly transmission rate QB for $\delta = 1$ (red) vs 10 (blue) year partnership durations, with $\beta = 0.34\%$ [3] and contact frequency $F = 52$ per-year. The yearly transmission rate for $\delta = 1$ is nearly double the rate for $\delta = 10$, and the binomial adjustment has almost no effect over 1 year, $B(A \mid \delta = 1) \approx \beta A$.

Transmission Modifiers: Factors that alter the probability of infection, such as condom use, circumcision, and STI co-infection, are usually added to (3) assuming a relative probability R and constant proportion of contacts affected α. For multiple modifiers, B is often defined as:

$$B = 1 - \prod_m (1 - R_m \beta)^{\alpha_m A} \tag{4}$$

where: $\sum_m \alpha_m = 1$; some R_m may represent the product of multiple factors; and a dummy term $R_m = 1$ can apply to the proportion of contacts without any modifier. In (4), "$\alpha_m = 50\%$ condom use" is modelled as 50% of contacts in all partnerships protected by a condom, *not* all contacts in 50% of partnerships protected by a condom. To model the latter, B may be defined instead as:

$$B = \sum_m \alpha_m \left(1 - (1 - R_m \beta)^A\right) \tag{5}$$



(a) Models of probability of transmission: linear vs binomial and per-partnership vs per-partnership-year

(b) Transmission modifier affecting: some contacts in all partnerships vs all contacts in some partnerships

Figure 1: Probability of transmission B vs number of contacts (sex acts) A. (a) Illustrates linear (grey) vs binomial (purple) models for B, and compares the applied yearly *rate* of transmission QB (tangents) for $\delta = 1$ (red) vs $\delta = 10$ (blue) year partnership durations, with fixed contact frequency $F = 52$ per-year, and $\beta = 0.34\%$ from [3]. (b) Compares interpretation of a transmission modifier with $R = 0.3$ effect and $\alpha = 0.5$ coverage as: some contacts in all partnerships (red) from (4) vs all contacts in some partnerships (blue) from (5); sum of brace heights gives the modelled B.

which is effectively a weighted average. It can be shown that (4) $\geq$ (5), because any large probability of transmission has disproportionate influence on (4), even for a small proportion of contacts affected (α or $1-\alpha$), whereas this influence is bounded by α or $1-\alpha$ in (5), as shown in Figure 1b. Figure A.1 explores the conditions under which difference between (4) and (5) are greatest. These conditions can be summarized as: when $R < 1$, $0.5 < \alpha < 1$, and A is large; or when $R > 1$, $0 < \alpha < 0.5$, and A is large, but not too large. Although differences rarely exceeded 20% in our analyses, the more appropriate equation should likely be selected based on a factor's interpretation.

$\langle 2 \rangle$ **Binomial Time Interval:** Another model for the force of infection further generalizes the idea of escaping infection to consider risk from all partnerships simultaneously. Drawing on the distinction between (4) and (5), the most appropriate equation for this model would be:

$$\lambda_i^{\langle 2\rangle}(\Delta_t) = 1 - \prod_k \left(1 - \sum_{jh} \left(1-(1-\beta_{hk})^{Q_{ijk}A_k\Delta_t}\right)\frac{I_{jh}(t)}{N_j}\right) \tag{6}$$

which is technically a probability ≤ 1, not a rate as in $\langle 1\rangle$. A simple version of this model was introduced in [4], where the dependence on time period Δ_t was explicitly noted. In principle, this model is more precise than $\langle 1\rangle$, provided that Δ_t is matched to the timestep of the numerical solver. However, and the added precision may be insignificant as Δ_t is usually small. Moreover, much like $\langle 1\rangle$, subsequent adaptations of this model have used a period of $\Delta_t = 1$ year, and then applied the resulting λ_i as a rate over smaller timesteps.[1] This adaptation then reduces transmission vs $\langle 1b\rangle$, since all contacts across all partnership-years are considered in one binomial model.

[1] One possible reason that Δ_t in (6) has not been used correctly could be that: most numerical solvers for systems of ordinary differential equations pass only t (not Δ_t) to the derivative computing function, and may use adaptive Δ_t for precision while solving — including: `scipy.integrate.odeint` in Python, `deSolve::lsoda` in R, and `ode45` in MATLAB.

In (6), the prevalence of infection I_{jh}/N_j is modelled as "all contacts in some partnerships" like (5), not "some contacts in all partnerships" like (4). As with transmission modifiers, this distinction is often ignored, and using the latter assumption allows the following simplification of (6):

$$\lambda_i^{\langle 2 \rangle}(\Delta_t) = 1 - \prod_{jhk} (1 - \beta_{hk})^{Q_{ijk} A_k \Delta_t \frac{I_{jh}(t)}{N_j}} \tag{7}$$

A further adaptation of (7) first computes a weighted average per-contact transmission probability β_{hk} given the prevalence of each infection stage among partners:

$$\lambda_i^{\langle 2 \rangle}(\Delta_t) = 1 - \prod_{hk} \left(1 - \sum_j \beta_{hk} \frac{I_{jh}(t)}{N_j} \right)^{Q_{ijk} A_k \Delta_t} \tag{8}$$

which often yields almost identical results to (7) ($<$ 1% difference in our exploration).

⟨3⟩ Pure Rate: As shown in Figure 1a, the binomial adjustment in models ⟨1-2⟩ has negligible effect when β, A, and/or Δ_t are sufficiently small, at which point $B(A) \approx \beta A$. For completeness, and since it will be useful later, we define a final model ⟨3⟩ as:

$$\lambda_i^{\langle 3 \rangle}(t) = \sum_{jhk} Q_{ijk} A_k \beta_{hk} \frac{I_{jh}(t)}{N_j} \tag{9}$$

which effectively ignores partnership duration δ. We further introduce an alternate parameterization to QA: partnership formation *rate* Q and *number* of contacts per-partnership A — CF: *number* of concurrent partnerships C and contact *frequency* per-partnership F. For a given partnership duration δ, we have $F = A/\delta$, and $C = \delta Q$; thus, the total contact rate in both parameterizations is the same: $QA = CF$.

Limitations of Models ⟨1-3⟩: Models ⟨1-3⟩ span a continuum of trade-offs. At one extreme, model ⟨1a⟩ appropriately reduces the proportion of infections transmitted via long-duration partnerships; however, in doing so, the reduced rate of transmission QB effectively *delays* transmission in such partnerships, possibly resulting in underestimated infection prevalence. At the other extreme, model ⟨3⟩ ignores partnership duration, and thus likely overestimates the proportion of infections transmitted via long-duration partnerships; however, no transmission is delayed by any binomial adjustment. In the middle, models ⟨1b⟩ and ⟨2⟩ include a small reduction in proportion of transmission via long-duration partnerships and a small associated delay in transmission.

A final limitation affecting all models ⟨1-3⟩ is that: newly infected individuals may immediately transmit infection in the same partnership by which they were infected — i.e. to an already infected partner. This transmission is possible because, in frequentist compartmental models, the infection status of partners is always averaged across the pool of available partners, so a "fraction" of even one single partner is always susceptible (Figure 2a). In reality, infections transmitted via long-duration partnerships become "trapped", unless individuals have additional partners, or the partnership ends. Thus, prevalence immediately increases, but incidence may not increase proportionally until some time later.

3 Proposed Model

We developed a new model for the force of infection in compartmental models which aims to overcome the limitations of models ⟨1-3⟩. Below we describe the conceptual basis for the model, followed by the equations.

3.1 Conceptual Development

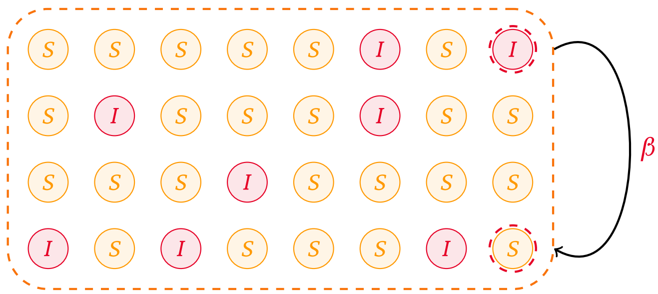
Consider a population of 32 individuals in 16 partnerships with 25% infection prevalence, at the moment of one transmission (Figure 2b). Initially, infection prevalence among partners of susceptible S (6/24) and infectious I (2/8) individuals are equal. Immediately after transmission, the prevalence decreases to 5/23 among partners of S but increases to 4/9 among partners of I, reducing incidence. Next, two events are possible: a) another transmission among the remaining discordant partnerships, yielding 4/22 prevalence among partners of S and 6/10 among partners of I, further reducing incidence; or b) the partnership from the first transmission ends and both individuals form new partnerships at random, yielding prevalence 9/32 among partners of both S and I (on average), increasing incidence. Effectively, models ⟨1-3⟩ all assume that (b) occurs first, but this assumption may be invalid, especially for long-duration partnerships. Other partnerships may begin/end too before (a) or (b), but the proportions of discordant partnerships would remain unchanged, on average.

This scenario highlights how any partnership where transmission has occurred should be "removed" from the force of infection. In a compartmental (non-pair-based) model, these partnerships can be tracked as proportions of individuals: namely, all recently infected individuals *and* all recently transmitting individuals. If individuals have multiple concurrent partnerships ($C_i > 1$), then these individuals should not be removed entirely, but their effective numbers of partners should be reduced by 1. If multiple types of partners are considered, then only the type involved in transmission should be reduced. This adjustment can then be applied until the individuals change partners — an expected period of δ_k. However, during this period, these individuals should be modelled to progress as usual through different stages of infection, aging, etc.

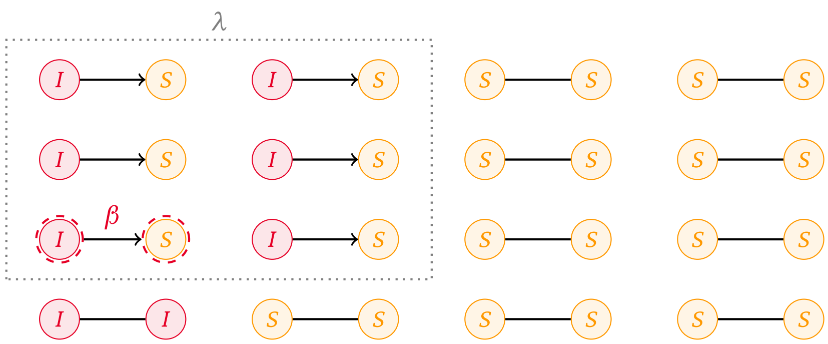
Using this conceptual basis, we propose a new stratification of modelled population, denoted $\bar{k}$. The stratum $\bar{k} = 0$ corresponds to no recent transmission, or all "new" partners. Other strata $\bar{k} > 0$ correspond to recent transmission via (to or from) partnership type k. Figure 3 illustrates the new stratification for an system with 5 modelled infection stages. Following infection, all individuals enter a stratum $\bar{k} > 0$ corresponding to the partnership type k by which they were infected. Thus, the rate of entry (from S_i) is λ_{ik}. Individuals may then transition from $\bar{k} > 0$ to $\bar{k} = 0$ upon forming a new partnership, at a rate δ_k^{-1}. Finally, individuals may re-enter any stratum $\bar{k} > 0$ if they transmit infection via partnership type k. We denote the corresponding rate as λ'_{ik}, representing the per-person rate of *transmission*, not *acquisition* as in λ_{ik}. This rate λ'_{ik} is not usually defined, but we develop the equations to do so below.

3.2 Equations

Since partnership duration is now considered separately, we start from the pure rate model ⟨3⟩. We adapt (9) to: integrate the changes to mixing due to changes in numbers of partners available; and track the rate of transmission *from* risk groups j and infection stages h.



(a) Frequentist approximation



(b) Pair-wise reality

Figure 2: Illustration of 32 individuals in a population with 25% infection prevalence, at the moment of one transmission (β)

Notation. S: susceptible; I: infectious; β: transmission event.

We begin by defining M_{ijk} as the absolute (not per-person) number of type-k partnerships between group i and group j. We assume that M_{ijk} can be defined by an arbitrary function f, with inputs M_{ik}, M_{jk}, and some parameter(s) θ_{ijk} specifying mixing patterns:

$$M_{ijk} = f(M_{ik}, M_{jk}, \theta_{ijk}) \tag{10}$$

We define M_{ik} (and likewise M_{jk}) as the total numbers of type-k partnerships "offered" by group i, across both susceptible and infected individuals in each infection stage h:

$$M_{ik} = M_{S,ik} + \sum_h M_{I,ihk} \tag{11}$$

We define $M_{S,ik}$ and $M_{I,ihk}$ as follows:

$$M_{S,ik} = S_i C_{ik} \tag{12a}$$
$$M_{I,ihk} = I_{ih,\bar{k}=k}(C_{ik} - 1) + \textstyle\sum_{\bar{k} \neq k} I_{ih,\bar{k}} C_{ik} \tag{12b}$$

The definition (12a) is hopefully familiar, while (12b) can be described as the sum of partnerships "offered" across states $\bar{k}$, where the partnership numbers C_{ik} of infected individuals in state $\bar{k} = k$ are reduced by 1.

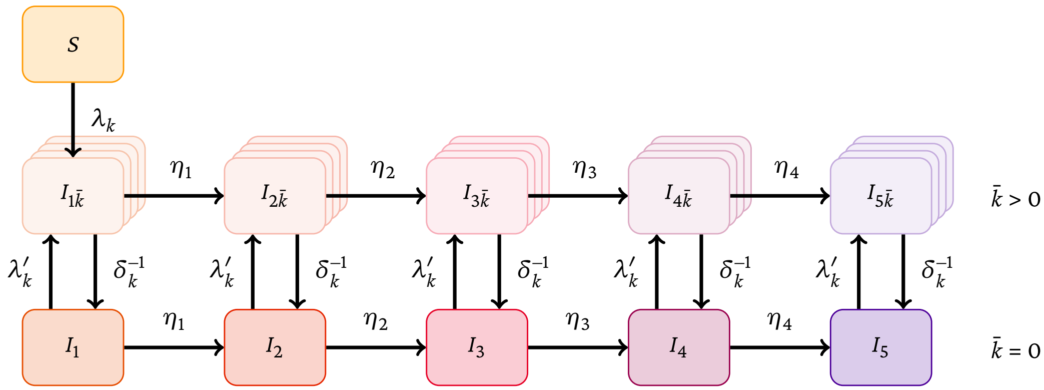


Figure 3: Illustration of a new stratification $\bar{k}$ to track proportions of individuals in partnerships where transmission has already occurred.

Notation. S: susceptible; I_h: infectious in stage h; k: partnership type; $\bar{k}$: new stratification; λ: force of infection to susceptible; λ': force of infection from infectious; η: rate of progression between infection stages; δ: duration of partnership.

Next, we define the absolute (not per-person) rate of transmission from group j and infection stage h to group i via type-k partnerships as:

$$\Lambda_{ijhk} = F_k \beta_{hk} M_{ijk} \frac{M_{S,ik}}{M_{ik}} \frac{M_{I,jhk}}{M_{jk}} \tag{13}$$

where the two fractions represent the proportions of all partnerships (M_{ijk}) formed by susceptible individuals in group i ($M_{S,ik}$) with infectious individuals in group j and infection stage h ($M_{I,jhk}$). Finally, we define the per-person transmission rates to i and from jh as follows:

$$\lambda_{ik} = \sum_{jh} \frac{\Lambda_{ijhk}(t)}{S_i} \tag{14}$$

$$\lambda'_{jhk} = \sum_{i} \frac{\Lambda_{ijhk}(t)}{I_{jh}} \tag{15}$$

For the purposes of solving the model, we can even skip division by S_i and I_{jh} in (14) and (15), since λ'_{ik} and λ'_{jhk} are immediately multiplied by S_i and I_{jh}, respectively, in the system of differential equations.

3.3 Comment

In the proposed approach, we do not explicitly model the proportion of infected individuals who recently transmitted or acquired infection via two *different* partnership types, (or two partnerships of the same type). If we did, the required size of the new dimension $\bar{k}$ would be 2^K, not $K + 1$. However, under frequentist assumptions, we can equivalently model two transmissions by one individual as one transmission each by two individuals, and thus allocate two proportions of $I_{jh\bar{k}=0}$ to $I_{jh\bar{k}=k_1}$ and $I_{jh\bar{k}=k_2}$ (one each), instead of just one proportion to $I_{jh\bar{k}=(k_1,k_2)}$.

In fact, $I_{jh\bar{k}=0}$ can be *negative*, because the dimension $\bar{k}$ is only relevant to (12b), and in all other contexts and equations, we first sum $I_{jh\bar{k}}$ across $\bar{k}$ to yield I_{hj}, which should be positive. Moreover, we can also have $I_{jh\bar{k}} > I_{jh}$, provided that $I_{jh\bar{k}} \leq I_{jh}C_{jk}$, reflecting the situation when more than 100% of I_{jh} have recently transmitted or acquired infection via at least one type-k partnership. This situation can only arise in the context of concurrent partnerships, $C_{jk} > 1$. In this case $I_{jh\bar{k}=0}$ *must* be negative, but it can be shown that (12b) still yields the correct value of $M_{I,ihk}$. With this perspective, the constraint $I_{jh\bar{k}} \leq I_{jh}C_{jk}$ may be intuitive, and it should be possible to guarantee for small enough timesteps, because $M_{I,ihk}$ approaches zero as $I_{jh\bar{k}}$ approaches $I_{jh}C_{jk}$ — i.e. all partnerships become concordant.

4 Experiment

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APPENDIX

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A Supplemental Results

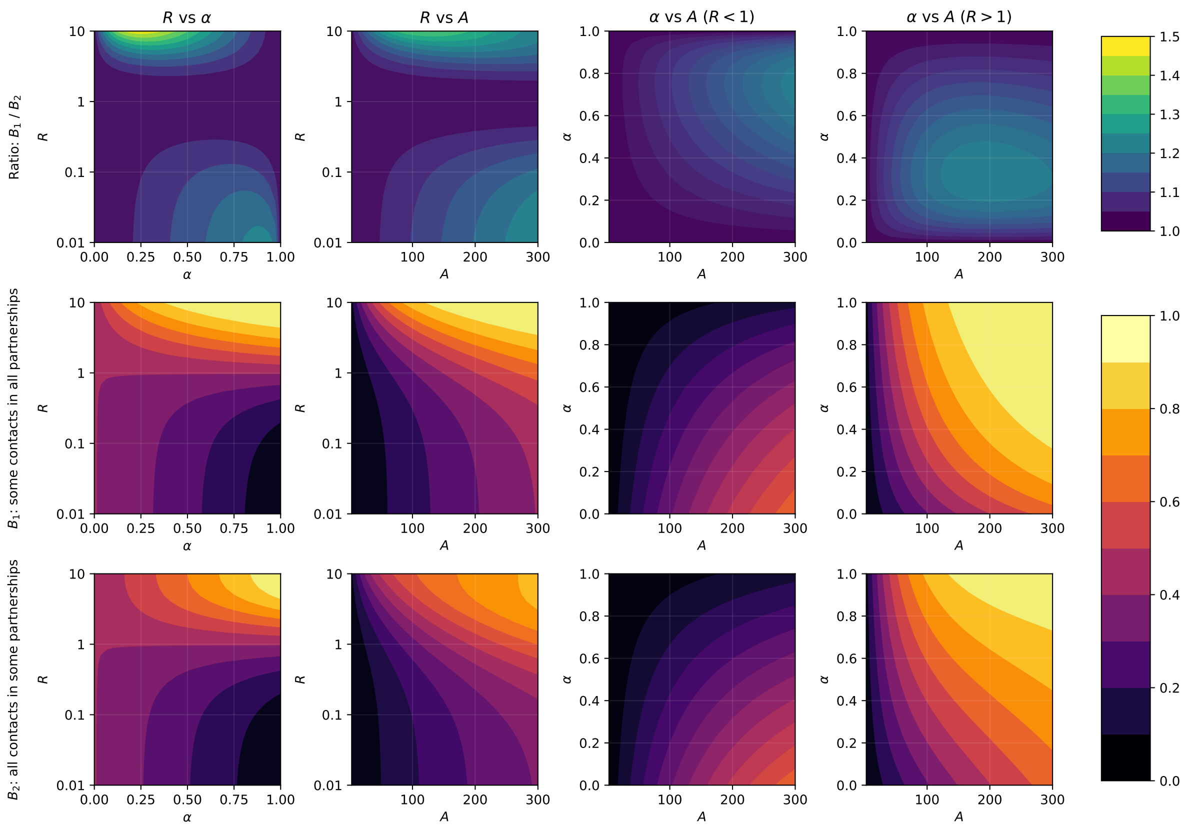

Figure A.1: Per-partnership probability of transmission B, in the presence of a transmission modifier R, calculated assuming either: B_1: α proportion of contacts in all partnerships modified; or B_2: all contacts in α proportion of partnerships modified. We observe $B_1 \geq B_2$.

β = 0.34% throughout [1]. For R vs α, A = 152; for R vs A, α = 0.5; for α vs A, $(R < 1) = 0.1$, $(R > 1) = 5$. For $0.1 < R < 3$, the ratio $B_1/B_2 \approx 1$. When $R < 1$, then B_1/B_2 is maximized with $A \rightarrow \infty$ and $0.5 < \alpha < 1$. When $R > 1$, then B_1/B_2 is maximized with $1 < A < \infty$ and $0 < \alpha < 0.5$.

References

[1] M. C. Boily, R. F. Baggaley, L. Wang, et al. "Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies". In: *The Lancet Infectious Diseases* 9.2 (2009), pp. 118–129.