

What could re-infection tell us about R_0 ? A modeling case-study of syphilis transmission

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ABSTRACT

Many infectious diseases can lead to re-infection. We examined the relationship between the prevalence of repeat infection and the basic reproductive number (R_0). First we solved a generic, deterministic compartmental model of re-infection to derive an analytic solution for the relationship. We then numerically solved a disease-specific model of syphilis transmission that explicitly tracked re-infection. We derived a generic expression that reflects a non-linear and monotonically increasing relationship between proportion re-infection and R_0 and which is attenuated by entry/exit rates and recovery (i.e. treatment). Numerical simulations from the syphilis model aligned with the analytic relationship. Re-infection proportions could be used to understand how far regions are from epidemic control, and should be included as a routine indicator in infectious disease surveillance.

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1. Introduction

Infectious disease surveillance systems use observed data to gauge epidemic spread, persistence, and control (Wolicki et al., 2016). Most surveillance relies on per-capita rates of diagnosed cases to characterize disease persistence, with or without the help of disease transmission models (Bansal, Chowell, Simonsen, Vespignani, & Viboud, 2016). Many infectious diseases can be acquired more than once and transmission models that explicitly capture re-infection demonstrate their influence on peak incidence (Barros & Pinho, 2017; Brewer, Peterman, Newman, & Schmitt, 2011; Martinello et al., 2017; Mutsaka-Makuvaza et al., 2018). However, what remains unknown is whether and how observed cases of re-infections could help characterize how far a locale may be from epidemic control (Barros & Pinho, 2017).

Re-supply of susceptible individuals is important in the persistence of infectious disease transmission and the loss of herd immunity. The replenishing of the susceptible population through treatment, and consequent re-infection, is of particular interest in the study of syphilis epidemics. Rates of syphilis continue to rise across the globe and particularly in industrialized

Abbreviations: S-I-S, susceptible-infectious-susceptible; S-I-R, susceptible-infectious-recovered; S-E-I-R-S, susceptible-exposed-infectious-recovered-susceptible.

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settings, where the proportions of new diagnoses that represent re-infection are also increasing (Fenton et al., 2008). As a result, syphilis screening and other interventions are now being directed towards those with a history of documented syphilis to prevent re-infection at the individual-level, and incidence at the population-level (Lapple, Wylie, Ross, & Plourde, 2017).

Re-infection is a part of the natural history of many infectious diseases, with or without treatment. For example, infections naturally cleared by the host without conferring protective immunity are often abstracted as “S-I-S” (susceptible-infectious-susceptible) systems leading to cycles of infection and re-infection (Anderson & May 1991). When infections confer a protective immunity that is aborted by treatment – we shift systems from “S-I-R” (susceptible-infectious-recovered) to “S-I-R-S” (Anderson & May 1991).

Syphilis is a sexually transmitted infection whose natural history without treatment follows an “S-E-I-R-S” system, with a short exposed (E) period following inoculation and before infectiousness. Treatment aborts the transition from infectiousness during early syphilis to a ‘recovered’ or clinically latent phase, wherein the pathogen (*T.pallidum*) remains in the body but cannot be transmitted to a sexual partner. Debate surrounds the duration of waning immunity following treatment in the “recovered” or latent phase of syphilis. While many epidemic models of syphilis use an average of 1–10 years of a waning or partial immunity following treatment of the latent stage (Gray et al., 2010; Pourbohloul, Rekart, & Brunham, 2003; Tuite & Fisman, 2016), empirical data on how fast protective immunity is lost remain scarce (Magnuson et al., 1956). What is known, however, is that clinical cases of re-infection have been documented following treatment at all stages of syphilis (Ogilvie et al., 2009).

Models of syphilis interventions suggest that a prioritized approach to those with a history of treated infection could be more efficient at reducing transmission, compared with applying the same intervention to all susceptible persons (Tuite et al., 2017). These findings hint at re-infection as a marker of epidemic emergence and persistence – and raise questions about whether the proportion re-infection could tell us about how far we are from epidemic control. We therefore sought to determine if the proportion re-infection could be used to characterize the underlying transmission dynamics, specifically the basic reproductive number R_0 of epidemics with re-infection like that of syphilis.

2. Methods

Our investigation into the relationship between proportion re-infection and R_0 included two components. We conducted a theoretical analysis of a generic ‘S-I-S’ system with re-infection followed by numerical simulations of a more complex model to capture the natural history of untreated and treated syphilis. Both models were compartmental deterministic systems of coupled differential equations.

2.1. Generic re-infection model

We expanded the standard ‘S-I-S’ model by separating initial and repeat infections into four states: S_1 , I_1 , S_2 , and I_2 (Fig. 1a). The open population was homogeneous and remained stable with balanced births and deaths. Individuals entered the population (for example, at the onset of sexual activity) as S_1 , move into compartment I_1 during their first infection, and then recover (for example via treatment) into S_2 – and then remain within the ‘ S_2 - I_2 - S_2 ’ cycle following re-infection (I_2) and treatment.

The differential equations are as follows:

$$\frac{dS_1}{dt} = \mu N - \beta(I_1 + I_2)S_1 - \mu S_1. \quad (1)$$

$$\frac{dI_1}{dt} = \beta(I_1 + I_2)S_1 - \rho I_1 - \mu I_1. \quad (2)$$

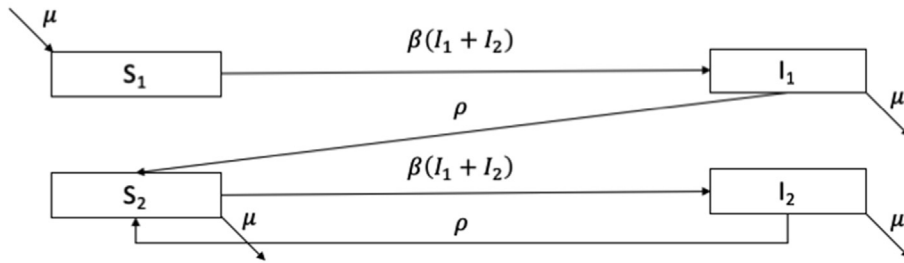
$$\frac{dS_2}{dt} = \rho(I_1 + I_2) - \beta(I_1 + I_2)S_2 - \mu S_2. \quad (3)$$

$$\frac{dI_2}{dt} = \beta(I_1 + I_2)S_2 - \rho I_2 - \mu I_2. \quad (4)$$

where μ is the entry and exit rate, N is the population, β represents the probability of transmission, and ρ is the per capita rate of treatment applied at the same value to the first (I_1) or a repeat infection (I_2).

Appendix details the derivation of an explicit relationship between R_0 and the prevalence of re-infection, defined as $I_2/(I_1 + I_2)$. We set the right-hand-side of the differential equations to 0 to identify the disease-free and endemic equilibria. Following van den Driessche and Watmough, we derived an expression for R_0 (van den Driessche, 2017; van den Driessche & Watmough, 2002). Then by expressing the endemic equilibrium in terms of R_0 , we derived the relationship between R_0 and the prevalence of re-infection. Finally, we studied the local stability of this fixed point.

a. Generic Model



b. Disease Specific Model

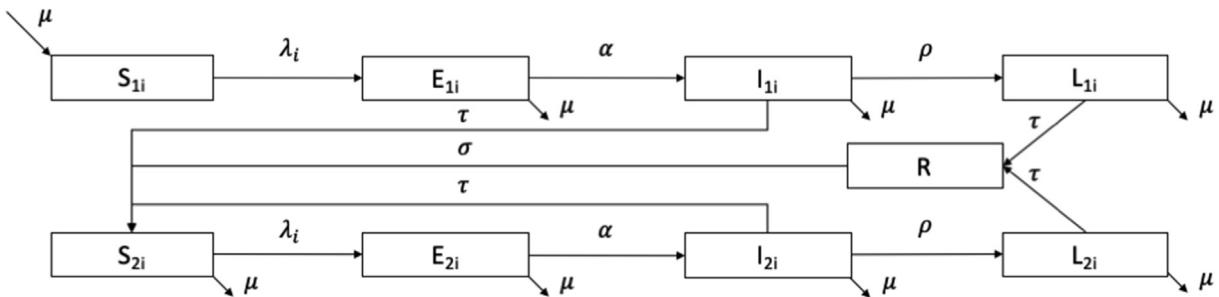


Fig. 1. Model schematic for the (a) generic and (b) disease specific models of re-infection. Each compartment represents a health state. The parameters describing the rate of transition between compartments of the disease specific model (b) are defined in Table 1. Force of infection λ_i is defined in Appendix. Parameters in the generic model are used only for theoretical analysis and are not assigned specific numerical values. The disease specific model reflects a simplified biology of syphilis infection and re-infection.

2.2. Disease specific syphilis model

To complement our theoretical analysis, we performed numerical simulations of the sexual transmission of syphilis to illustrate the range of observed epidemics among gay, bisexual, and other men who have sex with men (MSM) across Canada (Choudhri, Miller, Sandhu, Leon, & J, 2018; Public Health Agency of Canada, 2017). The model is detailed in Appendix.

We included the following compartments to represent a simplified version of the natural history of syphilis (Fig. 1b, Table 1): (Garnett et al., 1997) susceptible (S_1, S_2), exposed (E_1, E_2), infectious syphilis (I_1, I_2), and latent (non-infectious) syphilis (L_1, L_2). As with the generic re-infection model, we stratified the system into first time and repeat infections. Based on the current understanding of the natural history following treatment, we assumed that individuals treated in the I_1 compartment became immediately susceptible to future infections (i.e. moved into S_2). However, treatment while in the latent stage meant that individuals experienced a period of waning immunity before becoming susceptible to re-infection.

We included heterogeneity in risk via two sexual activity-levels (c_H [high-activity], and c_L [low-activity]), and assumed proportionate mixing when partnerships were formed (Garnett & Anderson, 1994). The population size stayed constant and individuals remained within their activity-levels and experienced the same testing/treatment rates irrespective of activity-level.

To examine the relationship between proportion re-infection and R_0 , we generated 4900 synthetic epidemics at equilibrium within the observed rates of annual diagnoses of infectious syphilis among MSM in urban centers across Canada (<1100 cases per 100,000 MSM) (Choudhri et al., 2018; Public Health Agency of Canada, 2017). We used biological and sexual behaviour data from the literature to parameterize the model (Table 1). We drew parameters from surveys of the MSM community across Canada, Canadian demographic data, and reviews of the biological properties of syphilis. To generate the synthetic epidemics, we used latin hypercube sampling across the following parameters assuming uniform distributions: biological probability of transmission per partnership (β); proportion of individuals in the high activity group (N_H/N), the ratio of partner change rate among the high and low activity groups (c_H/c_L); and the treatment rate (τ). To derive R_0 , we calculated the next generation matrix to find the dominant eigenvalue (Appendix) (van den Driessche, 2017; van den Driessche & Watmough, 2002).

Table 1
Parameters for the disease specific model of syphilis.

Parameter	Symbol	Unit	Default value or range used in sampling	Source
Population characteristics				
Population Size	N		366,279	Combined from adult (aged 15–64) male population in Canada (Statistics Canada, 2018b) (12 209 300) and estimated proportion of adult males who report sex with other men (0.03) (Statistics Canada, 2015)
Rate of entry into the modeled population	μN	Person/Year	5831	Population growth based on birth rate of males (Statistics Canada, 2018a) applied to proportion who have sex with other men
Syphilis natural history				
Transmission probability per sex act	β		Uniform (0.09, 0.64)	(Alexander & Schoch, 1949; Garnett, Aral, Hoyle, Cates, & Anderson, 1997; Moore, Price, Knox, & Elgin, 1963)
Incubation period	$1/\alpha$	Days	25	Garnett et al. (1997)
Infectious period	$1/\rho$	Days	154	Garnett et al. (1997)
Protective immunity period	$1/\sigma$	Years	5	Garnett et al. (1997)
Public health characteristics				
Per-capita treatment rate (per year)	τ		Uniform (0.1, 0.8)	Remis et al. (2010)
Partnership characteristics				
Average number of partnerships per year (per-capita partner change rate)	c_{avg}	Person	15	Generated from survey data - Lambda survey: M-Track Ontario second generation surveillance (2010) (Remis et al., 2010). In the model (Appendix), c_H refers to partner change rate in the high-activity group, and c_L in the low-activity group. The weighted average results in the default value of c_{avg} . Lower bound: Lambda, Upper bound: M-Track Ontario second generation surveillance (2010) (Remis et al., 2010)
Proportion of individuals in the high activity group	N_H/N		Uniform (0.079, 0.217)	Assumption
Ratio of high to low activity partnership numbers	c_H/c_L		Uniform (5, 10)	

3. Results

3.1. Generic model

From our analysis of the next generation matrix, R_0 for the generic model is equivalent to the standard SIS model with $R_0 = \frac{\beta}{\rho + \mu}$. Using the fact that a standard SIS model has an endemic equilibrium at $(S^*, I^*) = \left(\frac{1}{R_0}, 1 - \frac{1}{R_0}\right)$, we found that our general model has unique disease-free and endemic equilibria at

$$(S_1^{**}, I_1^{**}, S_2^{**}, I_2^{**}) = (N, 0, 0, 0) \text{ and } (S_1^*, I_1^*, S_2^*, I_2^*) = (S^*(1 - \kappa), I^*(1 - \kappa), S^*\kappa, I^*\kappa) \quad (5)$$

and where,

$$\kappa = \frac{R_0 + 1}{R_0 + 1 + \frac{\mu}{\rho} R_0}. \quad (6)$$

This means that at the endemic equilibrium, the proportion re-infection is

$$\frac{I_2^*}{I^*} = \kappa = \frac{R_0 + 1}{R_0 + 1 + \frac{\mu}{\rho} R_0}. \quad (7)$$

By analyzing the local stability of the two equilibria, we find that when $R_0 > 1$, the disease free fixed point is unstable and the endemic fixed point is stable. The opposite is the case when $R_0 < 1$.

Equation (6) indicates that R_0 increases with proportion re-infection via a non-linear monotonic relationship. Each incremental increase in the proportion re-infection indicates a larger and larger increase in R_0 . The non-linear relationship is illustrated in Fig. 2 under varying treatment rates (ρ) and assuming fixed exit rate (μ). The relationship is modified by the ratio of treatment and exit rates: a lower proportion re-infection may signal a large R_0 when the baseline treatment rates are low (Fig. 2) or when exit rates (such as turn-over in the high-activity population) are high.

3.2. Disease specific syphilis model

The R_0 of the syphilis model is given by (Appendix):

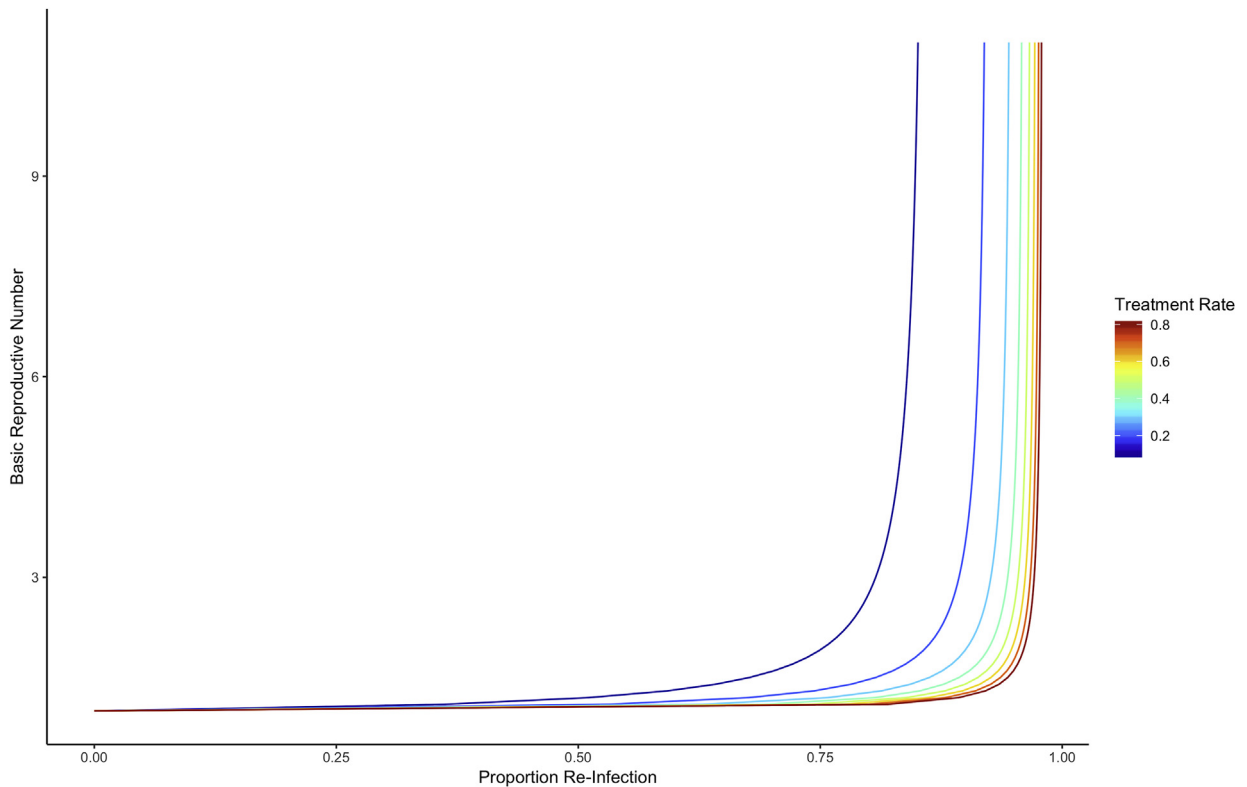


Fig. 2. Analytic relationship between proportion re-infection and R_0 , stratified by treatment rate. Results are based on the generic model.

$$R_0 = \frac{\alpha \beta (c_H g_H + c_L g_L)}{(\alpha + \mu)(\rho + \tau + \mu)} \quad (8)$$

Fig. 3 depicts R_0 for each modeled proportion re-infection from the synthetic epidemics stratified by the annual diagnoses of syphilis. The non-linear convex relationship between the proportion re-infection and R_0 is similar to that derived from the generic model (Fig. 2).

For a given R_0 , higher proportion re-infection and larger annual diagnoses cluster together (Fig. 3). We measure observed diagnoses by the number of treated syphilis cases per 100,000 individuals at equilibrium, which is captured by the formula $(I_0^* + I_1^*)\tau/N \times 100,000$. Fig. 3 also demonstrates that for a given proportion re-infection (for example, 60%), R_0 is larger with smaller “observed” epidemics (that is, epidemics with fewer annual diagnoses per 100,000 MSM). The reason for this is depicted in Fig. 4. Most of the smaller “observed” epidemics (annual diagnoses, 400–600 per 100,000 MSM) are constrained to very low treatment rates. In contrast, most of the larger “observed” epidemics (annual diagnoses, 800–1100 per 100,000 MSM) are constrained to medium/high treatment rates. The treatment rate also effects how sharply R_0 increases with proportion re-infection (Fig. 4). Low treatment rates are associated with a steeper increase in R_0 per increase in proportion re-infection.

4. Discussion

These results have two key implications for surveillance of infectious diseases where repeat infections are possible. First, the proportion re-infection can be used to infer how far a population is from epidemic control in a given setting. This is because the larger the R_0 , the further an epidemic is from control, which would occur if $R_0 < 1$. Settings with smaller proportion re-infection would be closer to epidemic control, and vice versa. Due to the non-linearity of the relationship between these two quantities, the effect of reductions or increases in the proportion re-infection on R_0 is particularly dramatic when the proportion re-infection is high. For example, if we assume similar rates of syphilis treatment in two Canadian cities – the epidemic is harder to control in the city with the higher proportion re-infection. Although we did not perform any counterfactuals, this relationship would be consistent with other studies that suggest prioritizing interventions for those infected at least once could be an efficient control strategy (Tuite A, 2017).

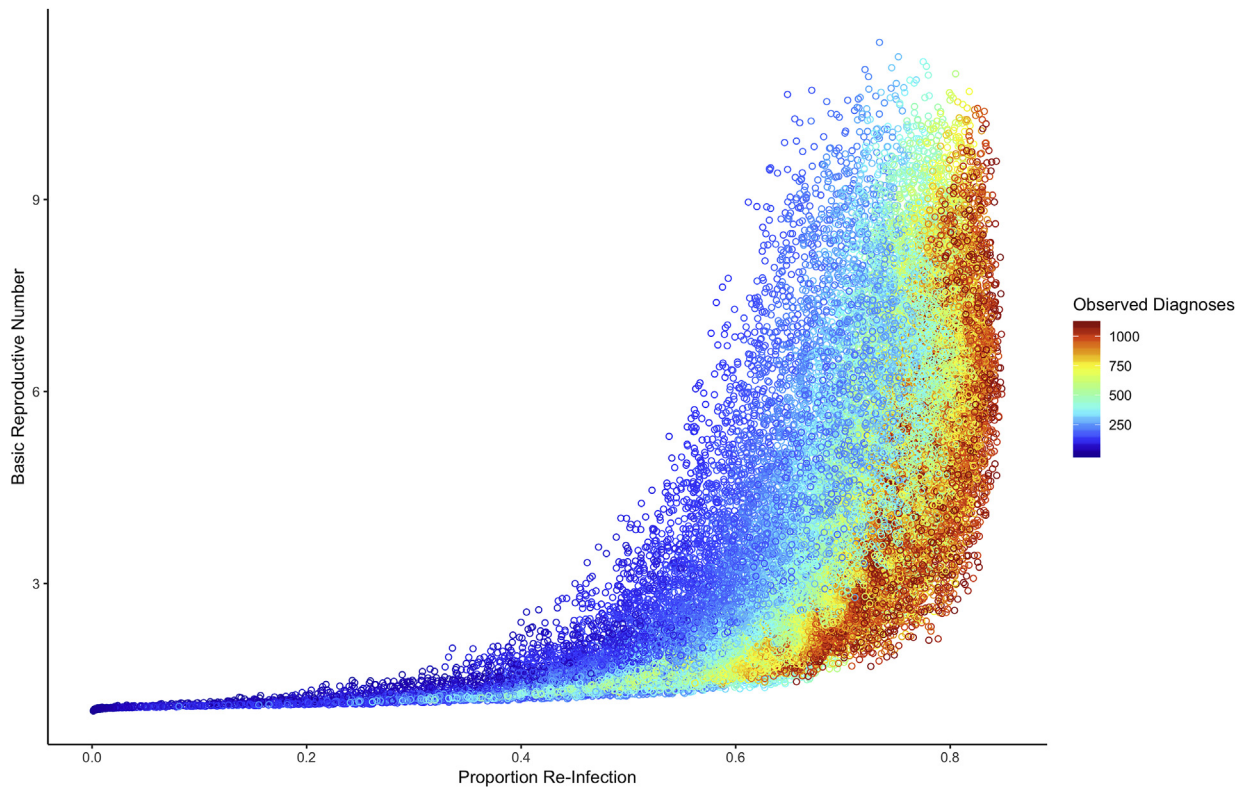


Fig. 3. Simulations of the relationship between proportion re-infection and R_0 by rate of diagnoses. Results are based on the disease-specific model. Diagnoses rates reflect cases per 100,000 individuals.

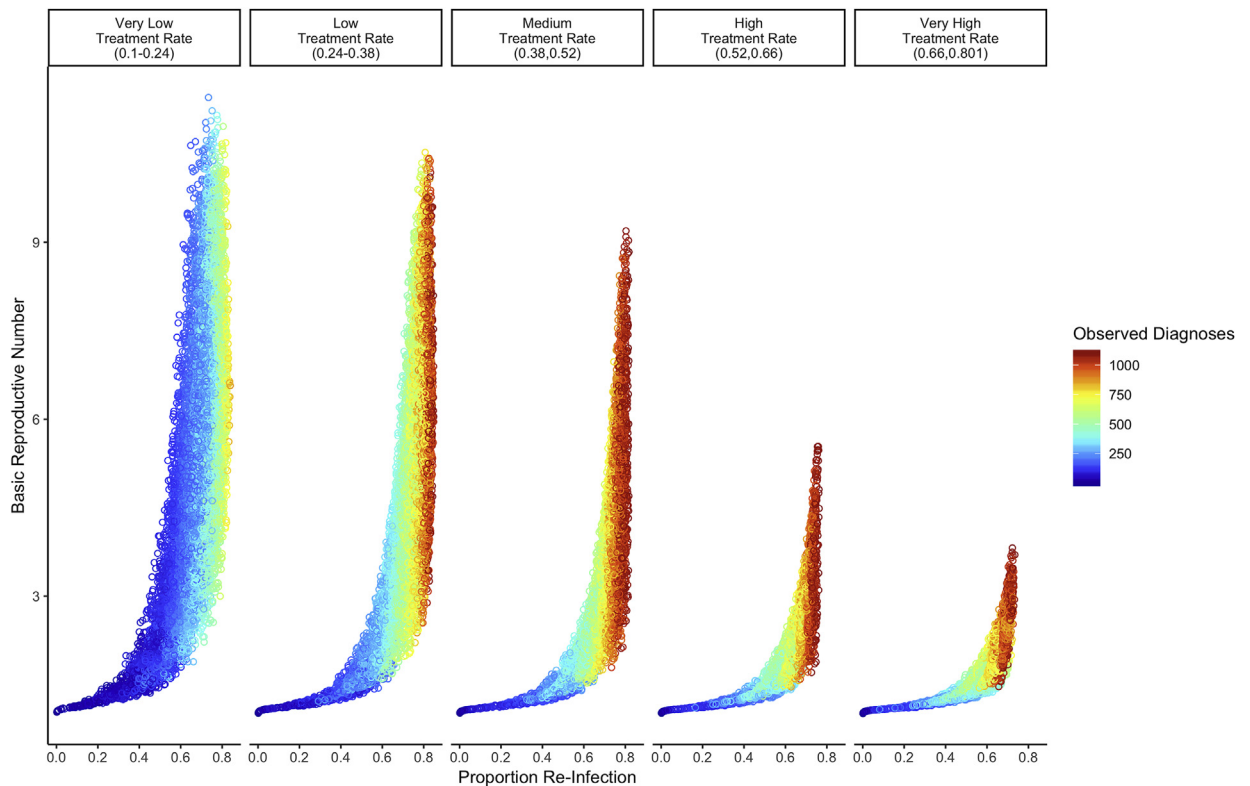


Fig. 4. Simulations of the relationship between proportion re-infection and R_0 stratified by treatment rates. Results are based on the disease-specific model. Diagnoses rates reflect cases per 100,000 individuals.

The second implication for disease surveillance is the unexpected relationship between rates of observed cases and R_0 . Our synthetic epidemics clustered such that for a given proportion re-infection, lower rates of diagnosed syphilis were associated with a higher R_0 . Variations in treatment explain this counterintuitive finding. Since the rate of new diagnoses is a function of both the true incidence and the treatment rate, a low observed incidence could stem from either low incidence or low case detection rates. The epidemics with few observed cases and a high R_0 also are those with a low treatment rate, which means many infections remain undiagnosed. The result is that observed cases are a large underrepresentation of true incidence. Conversely, when treatment rates are high, the observed diagnoses rates more accurately reflect the true incidence, leading to a positive correlation between observed cases and R_0 . Increased treatment also reduces R_0 by shortening the duration of infectiousness. Taken together, this means that observed diagnosis rates, due to a dependence on both the true incidence and the treatment rate, is an unreliable proxy for R_0 and should not be used alone to assess how far a given setting is from epidemic control. While the difference between observed versus true incidence is well-established and its implications discussed (Rothman, Greenland, & Lash, 2008), especially in the context of increased testing over time (Miller, 2008), the use of observed cases to directly or inadvertently infer epidemic potential in the public health literature remains (National Collaborating Centre for Infectious Diseases, 2017; Public Health Agency of Canada, 2017). Our findings provide further evidence that when comparing observed per-capita syphilis rates between two cities, the city with the seemingly larger epidemic may not be the one with the epidemic that is more difficult to control.

Under the assumption that the treatment rate is the same for new and repeat infections, measuring proportion re-infection bypasses the challenges associated with using observed diagnoses to infer R_0 . Treatment rates affect the numerator and denominator of the proportion re-infection equally, meaning the observed proportion re-infection is equivalent to the true proportion re-infection given our assumptions. Analyzing the proportion re-infection could give a more accurate picture of the epidemic than the rate of new diagnoses, leading to a better understanding of R_0 . In fact, using the proportion re-infection and the observed diagnoses together gives the best estimate of R_0 . Our analytical relationship between R_0 and the proportion re-infection is stratified by the treatment rate. Since the observed diagnoses and the proportion re-infection also uniquely determine the treatment rate, stratifying our results by the observed diagnoses could thus narrow the inference on R_0 .

Interpretation of the findings is limited to the analytic and illustrative case study of syphilis transmission. The findings surrounding inference using proportion re-infection do not account for stochasticity—which are particularly important when considering smaller population size (Anderson & May 1991)—or plausible differences in testing and treatment rates among those with a prior history of infection versus those without (Workowski & Berman, 2006). Our model captures heterogeneity with respect to partner change rates but heterogeneity is limited to two risk-groups. We did not, however, calibrate the model to differences in observed cases between groups, nor did we include differences in syphilis testing and treatment rates by risk group. Important next steps include examining the role of additional heterogeneity, calibrated to city-specific data, on the predictive power of the relationship between proportion re-infection and R_0 in a given city. We also did not study the implications on trends in proportion re-infection over time and its relation to the effective reproductive number. Although findings can be expected to be similar given the relationship between the basic and effective reproductive numbers (Anderson & May 1991; van den Driessche, 2017), future work involves examining the utility of monitoring proportion re-infection alongside trends in observed cases to evaluate the impact of control strategies over time.

5. Conclusion

Using generic and disease-specific mathematical models that captured re-infection, we identified a relationship between proportion re-infection and R_0 . We derived a generic expression that reflects a non-linear and monotonically increasing relationship between proportion re-infection and R_0 and which is attenuated by entry/exit rates and recovery (i.e. treatment). Our findings highlight the potential for systematically reporting and using data on re-infection alongside observed diagnoses as part of disease surveillance for any pathogen that can cause repeat infections. In doing so, public health teams could gain a better understanding of the underlying disease dynamics, allowing them to identify settings and populations where more resources may be required to achieve local epidemic control.

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Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.idm.2019.09.002>.

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