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Inferring pathogen type interactions using cross-sectional prevalence data: opportunities and pitfalls for predicting type replacement

Irene Man[a,b*], Jacco Wallinga[a,b], Johannes A. Bogaards[a,c]

a Center for Infectious Diseases Control, National Institute for Public Health and the Environment, Bilthoven, The Netherlands;

b Department of Medical Statistics and Bioinformatics, Leiden University Medical Center, Leiden, The Netherlands;

c Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, The Netherlands;

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*Corresponding author: Address: RIVM, P.O. Box 1, 3720 BA Bilthoven, The Netherlands, Telephone: + 31 30 274 2561, E-mail: irene.man@rivm.nl

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Abstract

Background: Many multi-valent vaccines target only a subset of all pathogenic types. If vaccine and non-vaccine types compete, vaccination may lead to type replacement. The plausibility of type replacement has been assessed using the odds ratio (*OR*) of co-infections in cross-sectional prevalence data, with $OR > 1$ being interpreted as low risk of type replacement. The usefulness of the *OR* as a predictor for type replacement is debated, as it lacks a theoretical justification, and there is no framework explaining under which assumptions the *OR* predicts type replacement.

Methods: We investigate the values that the *OR* can take based on deterministic *S*usceptible-*I*nfected-*S*usceptible and *S*usceptible-*I*nfected-*R*ecovered-*S*usceptible multi-type transmission models. We consider different mechanisms of type interactions, and explore parameter values ranging from synergistic to competitive interactions.

Results: We find that $OR > 1$ might mask competition because of confounding due to unobserved common risk factors and cross-immunity, as indicated by earlier studies. We prove mathematically that unobserved common risk factors lead to an elevation of the *OR*, and present an intuitive explanation why cross-immunity increases the *OR*. We find that $OR < 1$ is predictive for type replacement in the absence of immunity. With immunity, $OR < 1$ remains predictive under biologically reasonable assumptions of unidirectional interactions during infection, and an absence of immunity-induced synergism.

Conclusions: Using the *OR* in cross-sectional data to predict type replacement is justified, but is only unambiguous under strict assumptions. An accurate prediction of type replacement requires pathogen-specific knowledge on common risk factors and cross-immunity.

Keywords: pathogen types; interactions; multivalent vaccines; type replacement; cross-sectional prevalence; odds ratio; confounding

Introduction

Studying and predicting the effects of vaccination against pathogens with many types can be challenging if the types interact with each other.[1] With a vaccine that immunizes against only a subset of pathogen types, vaccination may indirectly affect the types that are not targeted. Vaccination against the vaccine types may increase or decrease the prevalence of the non-vaccine types, depending on whether the interactions between the vaccine and non-vaccine types are competitive or synergistic. If the interactions are synergistic, vaccination may decrease the prevalence of the non-vaccine types since it also takes away the synergistic effects that the non-vaccine types receive from the vaccine types. If the interactions are competitive, vaccination may increase the prevalence of the non-vaccine types so that the non-vaccine types replace the vaccine types.[2-4] Such replacements have been observed after the introduction of vaccination against pathogens like *Haemophilus influenzae* and *Streptococcus pneumoniae*.[5-7] For human papillomavirus (HPV), it is still unclear if different genotypes interact and whether vaccination will lead to type replacement.[8,9]

To assess the risk of type replacement before the introduction of vaccination, investigators have searched for evidence of competition between the vaccine and non-vaccine types in epidemiologic studies. We focus on cross-sectional prevalence studies that provide information on patterns of co-occurrence of pathogen types. Co-occurrence can be defined as co-infection by different virus types (e.g. for HPV) or as co-carriage of different bacterial types (e.g. for *S. pneumoniae*), depending on the application. Once the meaning of co-occurrence is defined, type interactions can be quantified by the observed number of co-occurrences. Deviations of this quantity from the expected number of co-occurrences under independence can be interpreted as evidence for interactions. A common measure of association that expresses the extent of such deviation is the odds ratio (OR) of co-occurrence, with positive (negative) associations being considered indicative of synergistic (competitive) interactions.

Although this qualitative interpretation of associations has an intuitive appeal, it may not be consistent with the underlying mechanisms of interactions, leading to incorrect assessment of the risk of type replacement. While some competitive mechanisms induce negative associations, others, such as cross-immunity, have been shown to induce positive associations.[10,11] Even if the underlying mechanism of interactions agrees with this intuitive interpretation, type interactions may be confounded by unobserved risk factors or routes of transmission that are shared by

multiple types, leading to a bias toward positive associations.[8,11,12]

For HPV, various cross-sectional prevalence studies from the pre-vaccination era found co-infections to occur more often than expected, expressing positive associations, but few noteworthy differences between type-specific associations are reported.[13-15] Such co-infection patterns are usually explained in terms of unobserved common risk factors, with low risk of type replacement according to the intuitive interpretation. However, it is not clear to what extent competitive interactions may be masked by common risk factors, and therefore whether type replacement following HPV vaccination is plausible. Moreover, it remains to be demonstrated whether unobserved common risk factors have the same effect on each type-specific association, and can be corrected for.

Although the validity of using the OR of co-occurrence for inferring type interactions has been studied before,[10,11,16] its methodologic basis is not yet well established. In this paper, we 1) derive the OR as an estimator of interactions in acquisition and clearance; 2) present a proof for positive bias due to unobserved common risk factors; and 3) provide a novel explanation how cross-immunity induces positive associations. Ultimately, our goal is to assess the usefulness of co-occurrence patterns of pathogen types in cross-sectional prevalence data for predicting type replacement.

The OR as an estimator of the interaction parameters

A *S*usceptible-*I*nfected-*S*usceptible model with two pathogen types

We first consider a *S*usceptible-*I*nfected-*S*usceptible (*SIS*) model with two pathogen types in a closed population (fig:SIS_structureA).[3,17] In this population, individuals are susceptible or infected with respect to each of the two types so that there are $2^2 = 4$ different infection states. We encode each of the infection states by a notation in which the i-th letter indicates the status with respect to the i-th type: S for susceptible and I for infected. In formulae, each of $\{SS, IS, SI, II\}$ denotes the proportion of individuals in the corresponding state in the population. Together, they give the joint distribution of the two types.

In this model, individuals without any infections, the susceptibles, become infected by type 1 at rate $\lambda_1 = c\beta_1(IS + II)$ and by type 2 at rate $\lambda_2 = c\beta_2(SI + II)$, where c is the contact rate and β_i the probability of acquiring type i given established contact with an infected individual.

Types interact through two mechanisms: acquisition and clearance. Due to interactions in acquisition, individuals already infected by one type acquire an infection of the other type at an adjusted rate that is k times λ_1 or λ_2. The interaction parameter k is essentially the rate ratio of acquiring infections of one type among individuals that are already infected by the other type (exposed) compared to the acquisition among susceptibles (unexposed). Similarly, due to interactions in clearance, individuals that are infected by both types clear infections at an adjusted rate that is h times the clearance rate of individuals that are infected by only one type, μ_1 or μ_2. The interaction parameter h is therefore the rate ratio of clearing infections of one type among individuals infected by the other type (exposed) compared to the clearance among individuals not infected by the other type (unexposed). Interactions in acquisition (clearance) can be either independent, synergistic, or competitive by choosing k to be $=$,$>$, or <1 ($\frac{1}{h}$ to be $=$, $>$, or <1) as given by Table 1.

The following system of differential equations describes how $\{SS, IS, SI, II\}$ changes over time:

$$\begin{cases} \frac{dSS}{dt} = -(\lambda_1 + \lambda_2)SS + \mu_1 IS + \mu_2 SI \\ \frac{dIS}{dt} = \lambda_1 SS - (\mu_1 + k\lambda_2)IS + h\mu_2 II \\ \frac{dSI}{dt} = \lambda_2 SS - (\mu_2 + k\lambda_1)SI + h\mu_1 II \\ \frac{dII}{dt} = k\lambda_2 IS + k\lambda_1 SI - h(\mu_1 + \mu_2)II \end{cases} \quad (1)$$

The stationary distribution

$\{SS, IS, SI, II\}$, as governed by (1), always stabilizes at an equilibrium as time progresses. This occurs for any given set of model parameters. We assume that the model parameters are chosen such that both types are present (coexisting) at the equilibrium.

Equilibria in the deterministic setting are closely related to stationary distributions in Markov processes, since both are stable in time. In this paper, we consider the setting in which a cross-sectional dataset consists of individuals sampled from a stationary distribution that coincides with the equilibrium of the system described by (1).

As we are interested in the cross-sectional setting, we focus on the equilibrium and neglect transient dynamics of $\{SS, IS, SI, II\}$. By solving the linear system that governs the equilibrium (see eAppendix A), we obtain the following simple expression in terms of $\{\lambda_1, \lambda_2, \mu_1, \mu_2, k, h\}$:

$$\begin{cases} SS = (h\mu_1\mu_2)/C \\ IS = (h\mu_2\lambda_1)/C \\ SI = (h\mu_1\lambda_2)/C \\ II = (k\lambda_1\lambda_2)/C, \end{cases} \quad (2)$$

where $C = h\mu_1\mu_2 + h\mu_2\lambda_1 + h\mu_1\lambda_2 + k\lambda_1\lambda_2$ is the normalizing constant. Note that the derivation of (2) does not depend on how λ_i is defined in terms of the contact rate and transmission probabilities so that (2) holds as long as the model has the structure depicted in Figure 1A.

Result I: The OR is an exact estimator of the composite of the interaction parameters, $\frac{k}{h}$.

The OR is defined as the ratio of the odds of one type in presence of the other type, relative to the odds of this type in absence of the other type:

$$OR = (\frac{II}{SI})/(\frac{IS}{SS}) \quad (3)$$

To compute the OR, (2) is substituted in (3). This substitution yields $OR = \frac{k}{h}$, a function of the composite of the interaction parameters. If only one mechanism of interactions is operating, i.e. $h = 1$ or $k = 1$, the OR reduces to k or the reciprocal of h as shown in Figure 2A and Figure 2B, respectively. An alternative proof of $OR = \frac{k}{h}$ based on reversibility can be found in eAppendix A.

The OR as a predictor for type replacement

The outcome of vaccination

We investigate whether the OR correctly predicts the outcome of vaccination. We introduce the following indicator function to denote the outcome of vaccinating against type 2 (vaccine type) for the prevalence of type 1 (non-vaccine type):

$$\Phi = \begin{cases} +, \text{if the prevalence of type1 decreases,} \\ 0, \text{if the prevalence of type1 stays unchanged,} \\ -, \text{if the prevalence of type1 increases;type replacement.} \end{cases}$$

Hence, $\Phi = +$ denotes a beneficial (and $\Phi = -$ an unfavorable) impact on the non-vaccine type due to vaccination against the vaccine type. We simulate vaccination by reducing the probability of acquiring type 2 throughout the entire population and investigate whether $OR >, =, < 1$ correctly predicts $\Phi = +, 0, -$, respectively.

In the simulations, different parameter values of k and h, ranging from competitive to synergistic interactions, lead to different outcomes of vaccination Table 2. If one mechanism of interactions is independent ($k=1$ or $\frac{1}{h}=1$), Φ is determined by the parameter value of the other mechanism of interactions with respect to 1. If both mechanisms of interactions are operating, we found the outcome of vaccination to be determined by the value of $\frac{k}{h}$ with respect to 1. As such, with both mechanisms operating in opposite directions, one being competitive and the other synergistic, the outcome of vaccination is determined by the strongest of the two (i.e. the parameter that deviates the most from 1).

Result II: The OR is a predictor for type replacement.

As $OR=\frac{k}{h}$ and the value of $\frac{k}{h}$ with respect to 1 determines the value of Φ, the OR is a predictor for the outcome of vaccination; $OR>,=,<1$ predicts $\Phi=+,0,-$, respectively. This correspondence justifies the intuitive interpretation of the OR.

If the assumptions of the model are violated, the OR may no longer be a predictor for the outcome of vaccination. In case the interactions are not symmetric among types, the OR becomes a weighted average of the type-specific interaction parameters. If the vaccine type is competitive towards the non-vaccine type, but the non-vaccine type is synergistic towards the vaccine type, $OR>1$ may hold even though type replacement does occur. Nevertheless, in less extreme cases of asymmetry, e.g. if the vaccine and non-vaccine type are both competitive or both synergistic towards each other but with different strength, the OR still correctly predicts the outcome of vaccination.

Positive bias due to unobserved common risk factors

Individuals may differ in risk of infections because of differences in genetic disposition or behavior. Some risk factors are common for all pathogen types. If a common risk factor is not observed nor adjusted for, it may confound the previous result of the OR being an estimator of $\frac{k}{h}$ and a predictor for type replacement. Using an example with unobserved heterogeneity in susceptibility, we illustrate the confounding effect due to unobserved common risk factors and explain why the bias is towards positive associations.

Heterogeneity in susceptibility

We consider a heterogeneous Susceptible-Inected-Susceptible model in which each individual is assigned an unobserved susceptibility level z, which influences his/her susceptibility for both types. The variation of z in the population is captured by the density function $f(z)$.

As this model comprises an extra dimension, z, the proportions of different infection states at the equilibrium become functions of z: $\{SS(z), IS(z), SI(z), II(z)\}$. To be consistent with the notations of the previous model, we let $\{SS, IS, SI, II\}$ be the proportions of all individuals in the corresponding infection states regardless of the value of z, i.e. for $A = SS, IS, SI, II$:

$$A = \int_0^\infty A(z)dz \tag{4}$$

We assume homogeneous mixing between individuals with different susceptibility levels. To model transmission, we define the global force of infection as $\lambda_1 = c\beta_1(IS + II)$ and $\lambda_2 = c\beta_2(SI + II)$. We then define the individual-specific force of infection to be the product of the individual-specific multiplier, z, and the global force of infection: $z\lambda_1$ and $z\lambda_2$. In fig:SIS_structureB, the infection dynamics of the population with susceptibility level z is shown. The corresponding system of differential equations can be found in eAppendix B.

The crude and the adjusted OR

If the susceptibility level is not observed, the crude OR is computed without distinguishing between individuals with different susceptibility levels:

$$OR = (\frac{II}{SI}) / (\frac{IS}{SS}) \tag{5}$$

For the hypothetical situation in which we could observe the susceptibility level, we define the adjusted OR to be the OR evaluated at each z:

$$OR(z) = (\frac{II(z)}{SI(z)}) / (\frac{IS(z)}{SS(z)}) \tag{6}$$

For each fixed susceptible level, z, the corresponding system of differential equations follows the same structure as the one of the homogeneous Susceptible-Inected-Susceptible model, where λ_i in (1) is replaced by $z\lambda_i$. Hence, for each z, the adjusted OR remains an estimator of $\frac{k}{h}$.

Result III: The crude OR over-estimates the composite of interaction parameters, $\frac{k}{h}$, and is not a sensitive predictor for type replacement.

The crude OR has a bias towards positive associations: $OR > \frac{k}{h}$ (see Figure 2A and Figure 2B). The proof of $OR > \frac{k}{h}$ in the case of independent interactions $(k = \frac{1}{h} = 1)$ can be found in eAppendix B. The proof invokes Chebyshev's integral inequality,[18] which formalizes a sufficient condition for a positive bias. In this example of heterogeneity in susceptibility, this condition requires the marginal probability of being infected to be either increasing or decreasing with z for both types. This condition is satisfied since the higher the susceptibility level, the higher the probability of being infected.

Since the crude OR over-estimates $\frac{k}{h}$, $OR > 1$ does not necessarily correspond to $\Phi = +$. However, $OR < 1$ still corresponds to $\Phi = -$. In other words, $OR > 1$ cannot rule out the possibility of type replacement, but $OR < 1$ can predict it.

Using $OR = 1$ as a threshold to distinguish between the presence and absence of type replacement leads to an incorrect prediction. However, there is no other threshold value for the OR that can produce a correct prediction, since the value of the OR at $\Phi = 0$ also depends on the chosen model parameters such as β_i and μ_i. Figure 3 shows the varying value of the OR under independence for different combinations of β_1, β_2 (on the left) and μ_1, μ_2 (on the right). This dependency on type-specific parameters suggests that different type-to-type combinations may require different adjustments for the same unobserved common risk factors.

Unobserved heterogeneity in other variables, that are either negatively or positively correlated with being infected with respect to both types, also leads to a positive bias of the OR for $\frac{k}{h}$. For instance, heterogeneity in contact rate or clearance rate also lead to an over-estimation of $\frac{k}{h}$, since the sufficient condition for positive bias we propose is satisfied. With assortative mixing according to such a common risk factor, we expect an even stronger positive bias.[19]

Different forms of bias due to type-specific or cross-immunity

The results obtained under the *S*usceptible-*I*nected-*S*usceptible model may not hold if natural infections trigger immune responses that protect the host against future infections. In general, immunity can be type-specific or cross-protective. For HPV, the strength of naturally

acquired immunity is still a topic of discussion as is the possibility of cross-protection to related genotypes.[20] For *S. pneumoniae*, naturally acquired immunity is thought to build up with age and likely plays a minor role in transmission dynamics among toddlers, but might mask competition among adults.[21]

In this section, we analyze how type-specific immunity and cross-immunity affect the estimation of interaction parameters and the prediction of type replacement. We study the two *S*-usceptible-*I*nfected-*R*-ecovered-*S*usceptible (*SIRS*) models depicted by Figure 4A and Figure 4B. The corresponding systems of differential equations can be found in eAppendix C. In both models, we incorporate type-specific immunity by expanding the infection dynamics to *SIRS* with regard to each type, where state *R* (for *R*ecovered) represents the immune state. The number of infection states now becomes $3^2 = 9$. Individuals enter state *R* after clearance of infection and exit due to waning of immunity at rate γ_i for type i. After losing immunity, individuals return to state *S*. In the *SIRS* model given by fig:SIRS_structureA, we keep the "*SI*"-part of the infection dynamics the same as in the previous *SIS* model, including how types interact in acquisition and clearance. Hence, current infections of one type affect susceptibility for and clearance of the other type. In the *SIRS* model given by fig:SIRS_structureB, we let past infections of one type affect susceptibility for and clearance of the other type. Such a mechanism of interactions is called indirect, since current infections of one type indirectly, through recovery, affect the other type. Indirect interactions, if competitive, correspond to cross-immunity, in which case being immune for one type offers protection to the other type. We consider direct and indirect interactions in separate models, since they lead to qualitatively different kinds of bias.

After incorporating the immune state, the definition of the *OR* as given under result I becomes:

$$OR = \left(\frac{II}{SI + RI}\right) / \left(\frac{IS + IR}{SS + SR + RS + RR}\right) \tag{7}$$

This definition matches the empirical setting where one cannot distinguish between susceptible and immune individuals.

Result IV: With type-specific immunity, the *OR* is a biased estimator of the composite of the interaction parameters, $\frac{k}{h}$.

In the *SIRS* model with direct interactions (Figure 4A), the *OR* remains an unbiased

estimator of $\frac{1}{h}$, but not of k unless $k=1$ (see Figure 2A and Figure 2B). $OR=1$ still constitutes a valid boundary between synergy and competition, however, the OR over-estimates k if $k<1$ and under-estimates k if $k>1$. Jointly, the OR becomes biased for $\frac{k}{h}$ (see eAppendix C for the proof).

Result V: With cross-immunity, the correspondence between the OR and the composite of the interaction parameters, $\frac{k}{h}$, is reversed.

In the $SIRS$ model with indirect interactions (Figure 4B), we consider cross-immunity as a composite of competition in both acquisition and clearance: past infections of one type hinder the acquisition and accelerate the clearance of the other type. We found that parameter values corresponding to cross-immunity ($k<1$ and $\frac{1}{h}<1$) induce positive associations ($OR>1$). Conversely, the opposite outcome of negative associations ($OR<1$) holds if interactions are synergistic ($k>1$ and $\frac{1}{h}>1$). Hence, the correspondence between the OR and $\frac{k}{h}$ is reversed (Figure 2A and Figure 2B).

We can understand this reversion by juxtaposing the two $SIRS$ models. In both models, the OR is computed using the same definition, with in the numerator (N): $\{SS, SR, RS, RR\}$ and $\{II\}$, and in the denominator (D): $\{IS, IR\}$ and $\{SI, RI\}$. In the direct $SIRS$ model, interactions in acquisition affect the transitions from states in (D) to states in (N), which is reversed in the indirect $SIRS$ model. Correspondingly, in the direct $SIRS$ model, increasing k increases the flow from states in (D) to states in (N) and leads to an increase in the OR (Figure 2A dotted line), whereas in the indirect $SIRS$ model, increasing k leads to a decrease in the OR (Figure 2A, dashed line). Analogously, increasing $\frac{1}{h}$ leads to an increase in the OR in the direct $SIRS$ model (Figure 2B, dotted line) and a decrease in the OR in the indirect $SIRS$ model (Figure 2B, dashed line). Given that $OR=1$ at $k=\frac{1}{h}=1$, inducing cross-immunity by decreasing k and $\frac{1}{h}$ from 1 leads to $OR>1$.

Predicting type replacement in presence of immunity

In the indirect $SIRS$ model, the OR is not predictive for type replacement due to the reversed correspondence between the OR and $\frac{k}{h}$. In the direct $SIRS$ models, if both mechanisms of interactions are operating in the same direction, i.e. either $k>1, \frac{1}{h}>1$ or $k<1, \frac{1}{h}<1$, the outcome of

vaccination is also still determined by the value of $\frac{k}{h}$ with respect to 1. For more complicated situations in which the two mechanisms of interactions operate in opposite directions, i.e. either $k<1, \frac{1}{h}>1$ or $k>1, \frac{1}{h}<1$, the outcome of vaccination also depends on the type-specific parameters. For example, if current infections of one type increases the susceptibility for the other type (synergy, $k>1$) but accelerate clearance of the other type (competition, $\frac{1}{h}<1$), the outcome of vaccination may be $\Phi = -$ while $OR>1$, masking type replacement. In Figure 5, this discrepancy is shown by the differences between the Φ-map and the OR-map in the upper left and the lower right quadrants.

Discussion

In this paper, we studied the usefulness of co-occurrence patterns of pathogen types in cross-sectional prevalence data for predicting type replacement. We confirmed the OR of co-occurrence as an estimator of interactions in acquisition and clearance in models, either SIS or $SIRS$, with direct interactions. This correspondence between the OR and the interactions is reversed in the setting of a $SIRS$ model with indirect interactions, that is, when natural immunity against one type modifies the infection dynamics of another type.

We found that $OR>1$ can be caused by various mechanisms, namely direct synergistic interactions, cross-immunity or confounding due to unobserved common risk factors. As $OR>1$ can be caused by cross-immunity, it cannot preclude type replacement. On the other hand, we confirm $OR<1$ being predictive for type replacement in the setting without immunity, even under confounding by unobserved common risk factors. With immunity, it is predictive for type replacement only if 1) different mechanisms of interactions do not act in different directions; and 2) natural immunity against the vaccine types does not promote infections of the non-vaccine types. Such immunity-induced synergism is rare, but has been reported for different strains of the dengue virus in the form of antibody-dependent enhancement.[22]

The conditions, identified by our models, under which $OR<1$ is predictive for type replacement may not be generalizable if we depart from the model assumptions we considered. For instance, the predictive power of $OR<1$ for type replacement may disappear under asymmetric interactions among types. Although mild asymmetry (e.g. if one type experiences stronger competition from another type than vice versa), may retain the predictive power, more extreme

asymmetry (e.g. if one type is synergistic towards another type from which it experiences competition) may not. Furthermore, we did not consider within-host competition for transmission, which affects the transmission capacity in co-infected relative to singly infected individuals. In addition, natural immunity may result in a mix of direct and indirect interactions, different than in the *SIRS* models considered here, further complicating the interpretation of the *OR*.

Other model assumptions on contact patterns and transmission may lead to different interpretation for the *OR*. For example, the *S*usceptible-*I*nected-*R*ecovered-*S*usceptible model of Malagon et al. allows simultaneous acquisition when susceptibles are partnered with co-infected individuals.[11] Their model yields $OR > 1$ even if the type interactions are independent, in contrast to our *SIRS* models, which find $OR = 1$. This bias of the *OR* under independence arises because simultaneous acquisition is itself a mechanism that enhances the co-occurrence of types.

We assumed cross-sectional prevalence data to be sampled from an epidemiologic equilibrium in which a stable prevalence of infections is maintained. This stationary assumption is reasonable in the pre-vaccination era for endemic pathogens, like *S. pneumoniae* and HPV, and is commonly assumed in transmission modelling.[23] After the introduction of vaccination, this assumption is violated until the prevalence has re-established at a new equilibrium. When the prevalence oscillates through the years but has a seasonal pattern, other statistical methods using time series to infer type interactions might be more suitable.[22]. Furthermore, individuals reach the stationary distribution only after being at risk for some time in practice. The time required to achieve stationary depends on the speed of the transmission process and may differ between pathogens.

For HPV, there have been many studies on pre-vaccination cross-sectional data that used the *OR* to infer competitive interactions.[13-15] These studies usually adjust for possible unobserved common risk factors by either including person-specific random effects or by comparing each type-to-type *OR* to the pooled *OR*. After adjustment, most studies find $OR > 1$ or fail to find systematic deviations of the type-to-type *OR*'s from the pooled *OR*. However, conclusions concerning type replacement should be drawn cautiously in view of alternative explanations for these findings, including cross-immunity between types, which entails a risk of type replacement. Furthermore, adjustment for unobserved common risk factors need not be similar among types. Essentially, previous models account for unobserved risk factors by assuming a random effect that is the same for all pairs of types. Our results show that random effects could be different for each

type-to-type OR. Whether or not such differences among type-to-type combinations are practically negligible depends on the application. If not, one may resolve to random effects models that also account for differences between types.[24]

HPV vaccines have demonstrated to be cross-protective for some non-vaccine HPV types that are phylogenetically related to the vaccine types.[25-28] Such cross-protection may substitute the competitive pressure by the vaccine types on the non-vaccine types and counterbalance type replacement. Including cross-protection would alter the outcome of vaccination in our analyses. For some scenarios with $OR<1$ calculated from the pre-vaccination prevalence, type replacement may be mitigated or even prevented by cross-protection if cross-protective efficacy is strong enough. Consequently, while $OR<1$ predicts the potential for type replacement, type replacement need not occur in the presence of vaccine cross-protection.

For other pathogens, it is less common to use the OR of co-occurrence in a cross-sectional setting to study type replacement. We only know of Bogaert et al., who studied the possibility of *Staphylococcus aureus* replacing *S. pneumoniae* after the introduction of PCV-7.[29] For *S. pneumoniae* serotypes, we know of no studies on patterns of co-occurrence in the setting we discuss before PCV-7 was introduced.

We note that our models predict a stable equilibrium frequency distribution of $50\%-50\%$ when applied to epidemiologically indistinguishable types. Hence, they are not neutral from a population-genetic point of view as described by Lipsitch et al., who argued that non-neutral models are unsatisfactory in explaining the long-term coexistence of types when the evidence for competition is compelling.[30] Thereupon, various neutral models have been suggested, all assuming a form of competition, for example, by limiting the number of types that a host can carry or by inducing homologous immunity. Yet, a neutral model that intrinsically assumes competition may not be appropriate for developing the framework to test for signs of competition, since it has no natural representation for the absence of competition, in contrast to our ecologically non-neutral models. Furthermore, a stable coexistence of $50\%-50\%$ frequency is not a problem if one assumes types that are independent of each other. Even if types are epidemiologically indistinguishable (e.g. if they share the same transmission route and have similar infection cycles), it is reasonable that they converge to the same frequency if they are not interfering with each other during infection or transmission.

So far, only a few studies have commented on the validity of using the OR of co-occurrence to predict type replacement. This study is the first to provide conditions under which the OR is an estimator of interactions and under which it is predictive for type replacement. Furthermore, our contribution provides analytical proofs and intuition for earlier findings, such as the manifestation of unobserved confounding and the reversed relationship between the OR and type replacement due to cross-immunity.

Type replacement following vaccination may have detrimental impact on public health. Prediction of type replacement based on the OR of co-occurrence in cross-sectional studies has an intuitive appeal, which is mathematically grounded. However, when knowledge of the underlying mechanisms of interactions and the structure of confounding is lacking, observed patterns of co-occurrence allow for various explanations. Hence, the settings in which the OR unambiguously indicates the possibility of type replacement is narrowed down to pathogens in endemic equilibrium, with a well understood infection cycle and natural immunity. As such, to assess vaccination effects on the prevalence of non-vaccine types, post-vaccine surveillance studies remain essential because potential pitfalls in predicting type replacement are pervasive.

References

1 Balmer O. and Tanner M. Prevalence and implications of multiple-strain infections. Lancet Infect Dis, 11(11):868_878, 2011.

2 Mclean A. R. Vaccination, evolution and changes in the e_cacy of vaccines: a theoretical framework. Proc Biol Sci, 261(1362):389_393, 1995.

3 Lipsitch M. Vaccination against colonizing bacteria with multiple serotypes. Proc Natl Acad Sci U S A, 94(12):6571_6576, 1997.

4 Elbasha E. H. and Galvani A. P. Vaccination against multiple HPV types. Math Biosci, 197(1):88_117, 2005.

5 Ribeiro G. S., Reis J. N., Cordeiro S. M., and et al. Prevention of Haemophilus in_uenzae type b (Hib) meningitis and emergence of serotype replacement with type a strains after introduction of Hib immunization in Brazil. J Infect Dis, 187(1):109_116, 2003.

6 Hicks L. A., Harrison L. H., Flannery B., and et al. Incidence of pneumococcal disease due to nonpneumococcal conjugate vaccine (PCV7) serotypes in the United States during the era of widespread PCV7 vaccination, 1998_2004. J Infect Dis, 196(9):1346_1354, 2007.

7 Weinberger D. M., Malley R., and Lipsitch M. Serotype replacement in disease after pneumococcal vaccination. Lancet, 378(9807):1962_1973, 2011.

8 Plummer M., Vaccarella S., and Franceschi S. Multiple human papillomavirus infections: the exception or the rule? (editorial commentary). J Infect Dis, 203(7):891_893, 2011.

9 Pons-Salort M., Thiébaut A. C., Guillemot D., Favre M., and Delarocque-Astagneau E. HPV genotype replacement: too early to tell (correspondence). Lancet Infect Dis, 13(12):1012, 2013.

10 Durham D. P., Poolman E. M., Ibuka Y., Townsend J. P., and Galvani A. P. Reevaluation of epidemiological data demonstrates that it is consistent with cross-immunity among human papillomavirus types. J Infect Dis, 206(8):1291_1298, 2012.

11 Malagon T., Lemieux-Mellouki P., Laprise J.-F., and Brisson M. Bias due to correlation between times-atrisk for infection in epidemiologic studies measuring biological interactions

between sexually transmitted infections: a case study using human papillomavirus type interactions. Am J Epidemiol, 184(12):873_883, 2016.

12 Tota J. E., Ramanakumar A. V., Jiang M., and et al. Epidemiologic approaches to evaluating the potential for human papillomavirus type replacement postvaccination. Am J Epidemiol, 178(4):625_634, 2013.

13 Rositch A. F., Poole C., Hudgens M. G., and et al. Multiple human papillomavirus infections and type competition in men. J Infect Dis, page 709, 2011.

14 Chaturvedi A. K., Katki H. A., Hildesheim A., and et al. Human papillomavirus infection with multiple types: pattern of coinfection and risk of cervical disease. J Infect Dis, 203(7):910_920, 2011.

15 Mollers M., Vriend H. J., van der Sande M. A., and et al. Population-and type-speci_c clustering of multiple hpv types across diverse risk populations in the Netherlands. Am J Epidemiol, 179(10):1236_1246, 2014.

16 Pons-Salort M., Letort V., and Favre M. e. a. Exploring individual HPV coinfections is essential to predict HPV-vaccination impact on genotype distribution: a model-based approach. Vaccine, 31(8):1238_1245, 2013.

17 Auranen K., Mehtälä J., Tanskanen A., and Kaltoft M. S. Between-strain competition in acquisition and clearance of pneumococcal carriage-epidemiologic evidence from a longitudinal study of day-care children. Am J Epidemiol, 171(2):169_176, 2010.

18 Mercer P. R. More calculus of a single variable. Springer, 2014.

19 Lemieux-Mellouki P., Drolet M., Brisson J., and et al. Assortative mixing as a source of bias in epidemiological studies of sexually transmitted infections: the case of smoking and human papillomavirus. Epidemiology Infect, 144(7):1490_1499, 2016. doi: 10.1017/S0950268815002915.

20 Gravitt P. E. The known unknowns of HPV natural history. J Clin Invest, 121(12):4593_4599, 2011.

21 Principi N., Terranova L., Zampiero A., and et al. Oropharyngeal and nasopharyngeal sampling for the detection of adolescent Streptococcus pneumoniae carriers. J Med Microbiol, 63(3):393_398, 2014.

22 Shrestha S., King A. A., and Rohani P. Statistical inference for multi-pathogen systems. PLoS Comput Biol, 7(8):e1002135, 2011.

23 Keeling M. J. and Rohani P. Modeling infectious diseases in humans and animals. Princeton University Press, 2008.

24 Coull B. A. and Agresti A. Random e_ects modeling of multiple binomial responses using the multivariate binomial logit-normal distribution. Biometrics, 56(1):73_80, 2000.

25 Malagón T., Drolet M., Boily M.-C., and et al. Cross-protective e_cacy of two human papillomavirus vaccines: a systematic review and meta-analysis. Lancet Infect Dis, 12(10):781_789, 2012.

26 Apter D., Wheeler C. M., Paavonen J., and et al. E_cacy of human papillomavirus 16 and 18 (HPV-16/18) AS04-adjuvanted vaccine against cervical infection and precancer in young women: _nal event-driven analysis of the randomized, double-blind PATRICIA trial. Clin Vaccine Immunol, pages CVI00591_14, 2015.

27 Kavanagh K., Pollock K. G., Cuschieri K., and et al. Changes in the prevalence of human papillomavirus following a national bivalent human papillomavirus vaccination programme in Scotland: a 7-year crosssectional study. Lancet Infect Dis, 17(12):1293_1302, 2017.

28 Woestenberg P. J., King A. J., van Benthem B. H., and et al. Bivalent vaccine e_ectiveness against typespeci_c HPV positivity: evidence for cross-protection against oncogenic types among Dutch STI clinic visitors. J Infect Dis, 2017. doi: 10.1093/infdis/jix582 [Epud ahead of print].

29 Bogaert D., van Belkum A., Sluijter M., and et al. Colonisation by Streptococcus pneumoniae and Staphylococcus aureus in healthy children. Lancet, 363(9424):1871_1872, 2004.

30 Lipsitch M., Colijn C., Cohen T., Hanage W. P., and Fraser C. No coexistence for free: neutral null models for multistrain pathogens. Epidemics, 1(1):2_13, 2009.

Figure 1: The structure of two SIS models for two pathogen types with interactions in acquisition and clearance indicated by dashed arrows. We encode each of the infection states by a notation in which the i-th letter indicates the status with respect to the i-th type: S for susceptible and I for infected. The susceptibility is assumed to be homogeneous in A and heterogeneous in B. B depicts only the subpopulation with susceptibility level z.

Figure 2: The crude OR as an estimator of the interaction parameter for acquisition (k) in A and the reciprocal of the interaction parameter for clearance ($\frac{1}{h}$) in B. Homogeneous SIS model (solid): unbiased estimation. Heterogeneous SIS model (dashed-dotted): over-estimation. $SIRS$ model with direct interactions (dotted): over-estimation of $k<1$ and under-estimation of $k>1$, unbiased estimation of h (overlapped by the solid line). $SIRS$ model with indirect interactions (dashed): reversion bias.

Figure 3: The crude OR under independence in the heterogeneous SIS model depends on type-specific parameters. A: it varies as β_1 and β_2 vary, while $\mu_1=\mu_2=1$ in A. B: it varies as μ_1 and μ_2 vary, while $\beta_1=\beta_2=\frac{4}{7}$. For both A and B, $c=3$ and $f(z)$ is a discrete distribution with 20%-80% mass at $z=0.2$ and $z=1.8$, respectively.

Figure 4: The structure of two $SIRS$ models for two pathogen types with direct interactions in A and indirect interactions in B indicated by the dotted arrows. The transition rates not affected by type interactions are omitted. The dark gray areas indicate the terms in the numerator (N) of the OR, whereas the light gray areas indicate the terms in the denominator (D) of the OR, where

$$OR=\frac{II\cdot(SS+SR+RS+RR)}{(SI+RI)\cdot(IS+IR)}=\frac{(N)}{(D)}.$$

Figure 5: The outcome of vaccination and the OR agree when both mechanisms of interactions operate in the same direction (the upper right and lower left quadrants), but may differ when the two mechanisms operate in different directions (the upper left and lower right quadrants). $\Phi=-\ (+)$ denotes the (non-)occurrence of type replacement by the non-vaccine type. The line $\frac{k}{h}=1$ depicts the boundary between $\Phi=+$ and $\Phi=-$ in the homogeneous SIS model.

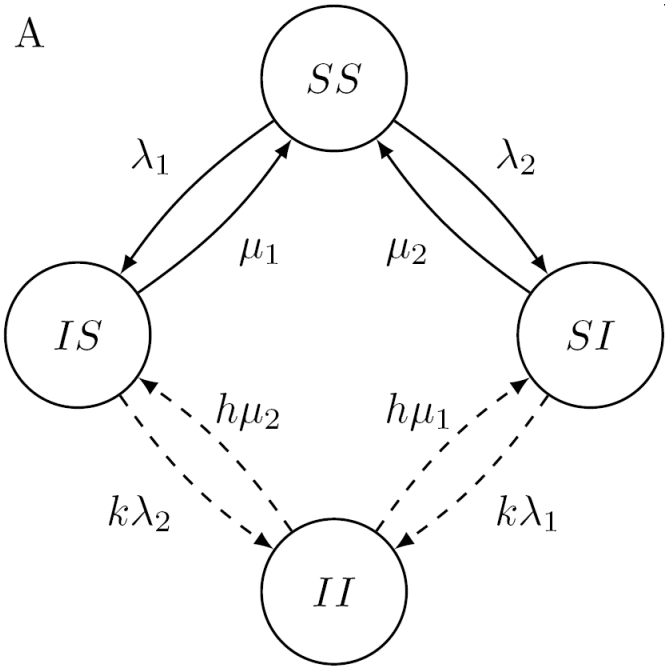
Table 1: Parameter values for interaction parameter k and h corresponding synergistic, independent, and competitive interactions.

	synergy	independence	competition
acquisition	$k>1$	$k=1$	$k<1$
clearance	$\frac{1}{h}>1$	$\frac{1}{h}=1$	$\frac{1}{h}<1$

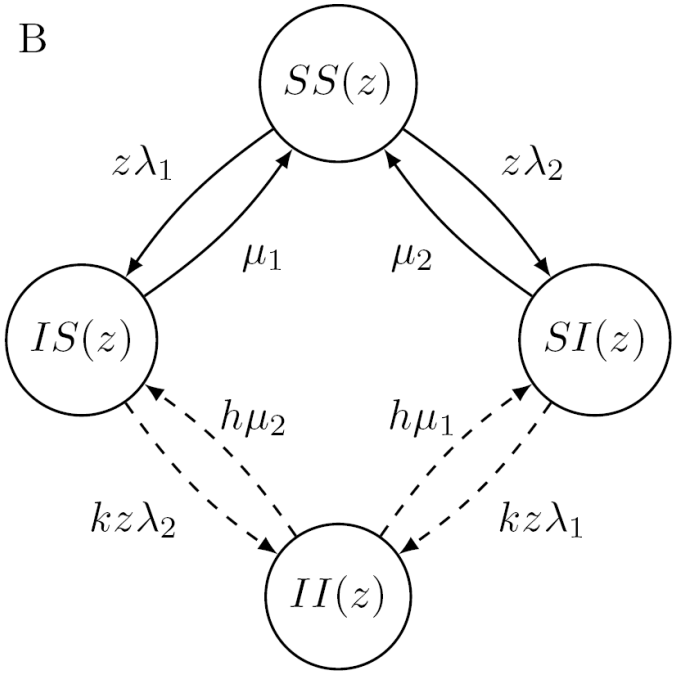
Table 2: Parameter values for the interaction parameters k and h corresponding $\Phi = +, o, -$.

	$\Phi = +$	$\Phi = o$	$\Phi = -$
Independent in clearance	$k > 1$	$k = 1$	$k < 1$
Independent in acquisition	$\frac{1}{h} > 1$	$\frac{1}{h} = 1$	$\frac{1}{h} < 1$
Both operating	$\frac{k}{h} > 1$	$\frac{k}{h} = 1$	$\frac{k}{h} < 1$

Figure 1A and 1B

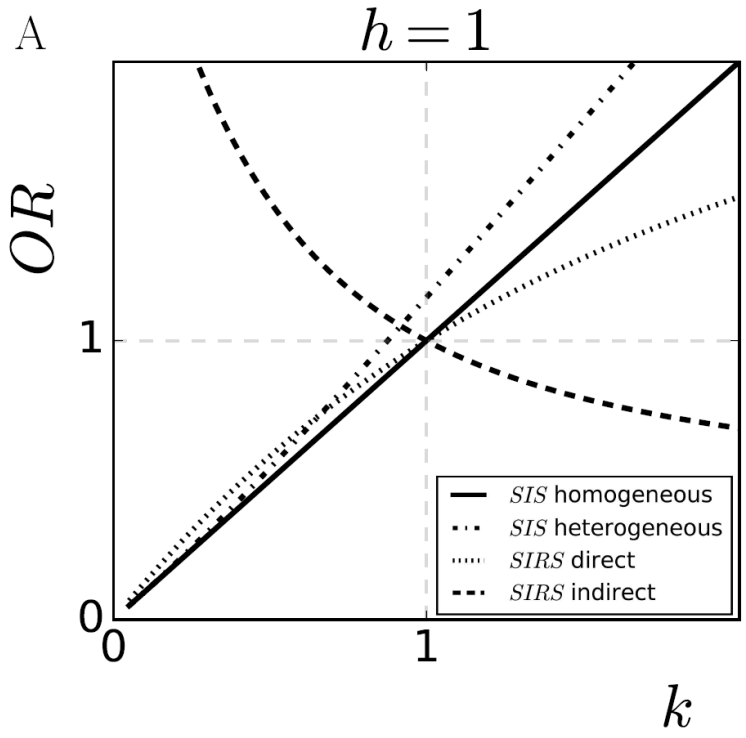


Homogeneous population



Heterogeneous population

Figure 2A and 2B



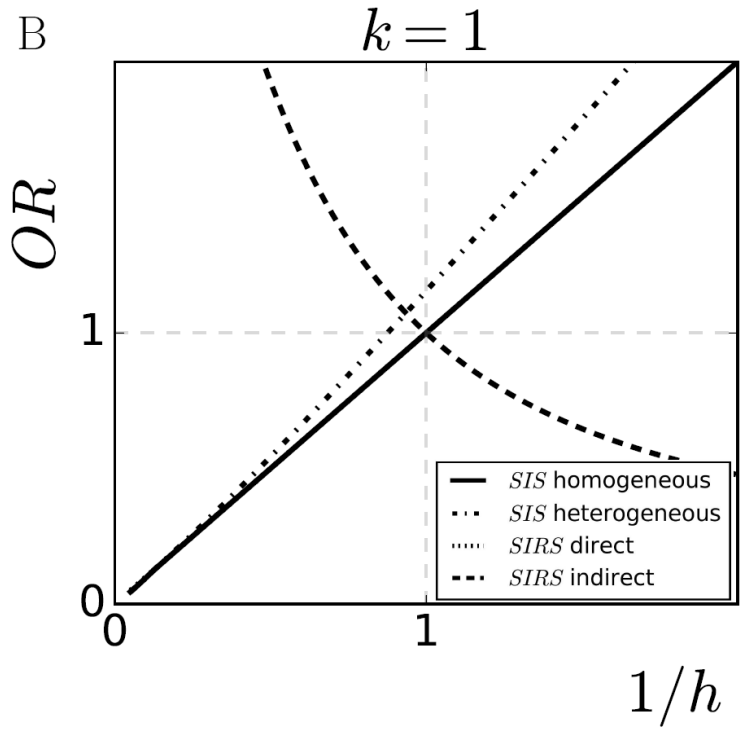


Figure 3

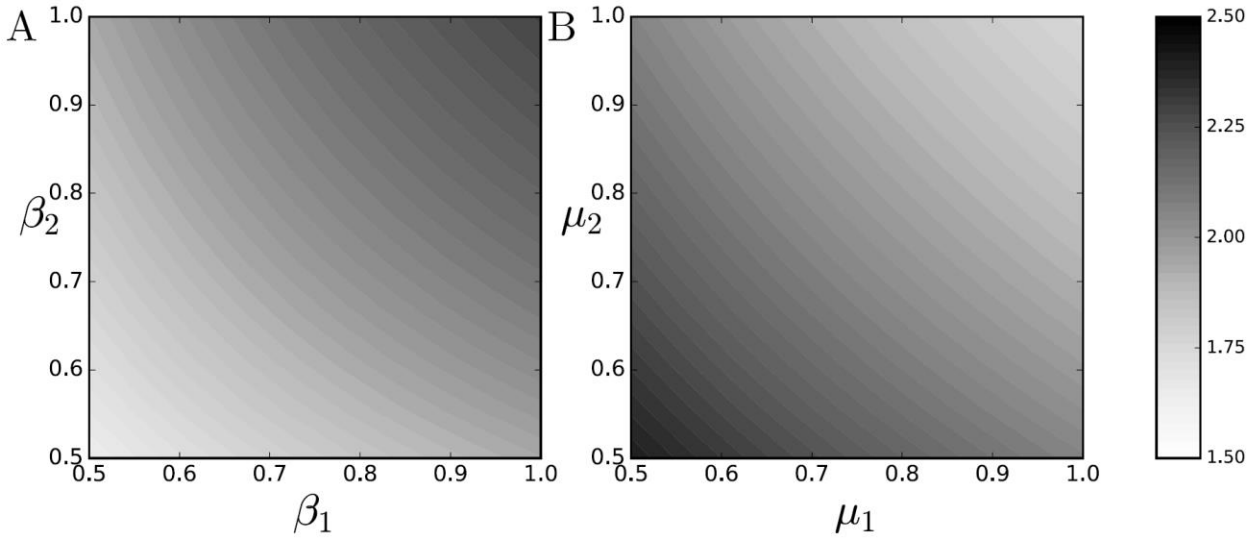
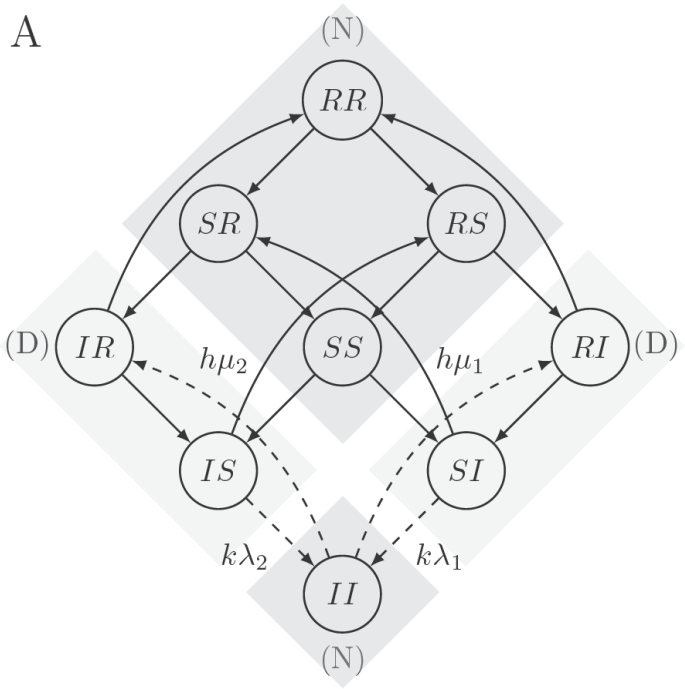
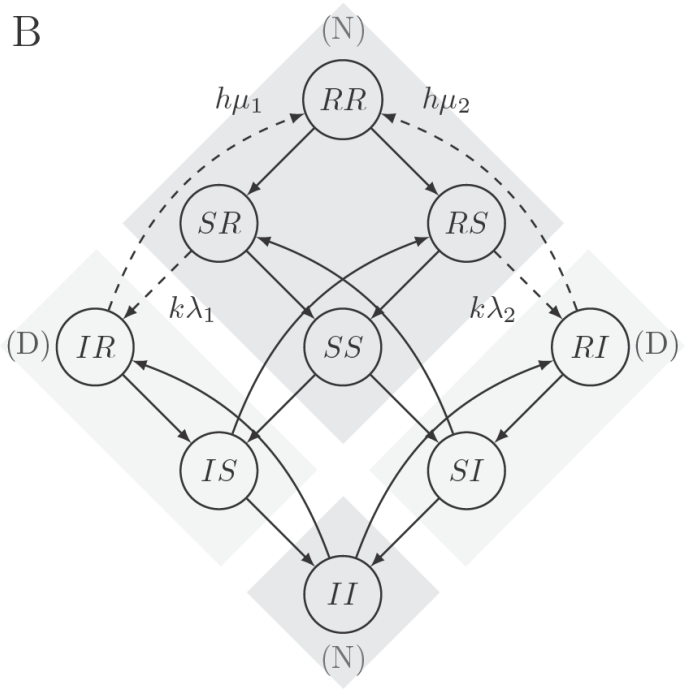

A
B
1.0
0.9
0.8
0.7
0.6
0.5
β_2
β_1
μ_2
μ_1
0.5
0.6
0.7
0.8
0.9
1.0
2.50
2.25
2.00
1.75
1.50

Figure 4A and 4B

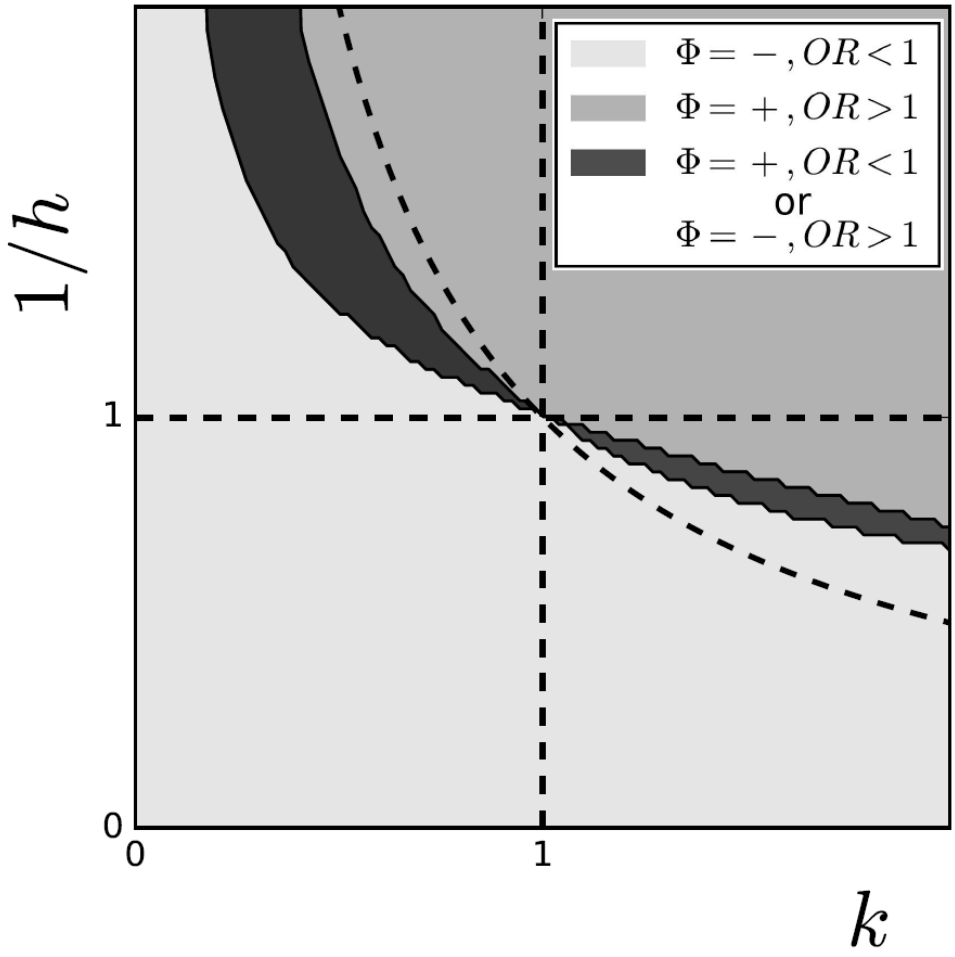


Direct interactions



Indirect interactions

Figure 5



eAppendix A The homogeneous SIS model

A.1 The linear system at the equilibrium

The equilibrium of the homogeneous SIS model in terms of $\{\lambda_1, \lambda_2, \mu_1, \mu_2, k, h\}$ can be obtained by solving the following linear system.

$$\begin{bmatrix} 0 \\ 0 \\ 0 \\ 0 \end{bmatrix} = \begin{bmatrix} -(\lambda_1+\lambda_2) & \mu_1 & \mu_2 & 0 \\ \lambda_1 & -(\mu_1+k\lambda_2) & 0 & h\mu_2 \\ \lambda_2 & 0 & -(\mu_2+k\lambda_1) & h\mu_1 \\ 0 & k\lambda_2 & k\lambda_1 & -h(\mu_1+\mu_2) \end{bmatrix} \begin{bmatrix} SS \\ IS \\ SI \\ II \end{bmatrix} \tag{1}$$

A.2 An alternative proof of result I

To better understand how the OR reduces to $\frac{k}{h}$, we provide an alternative proof for result I using the reversibility of the model. A model is reversible if the net flow between any pair of states is zero, i.e. for any state A and state B, the flow from A to B equals the flow from B back to A. The flow from A to B is given by "the prevalence in A" times "the transition rate from A to B", so that we have the following detailed balance equation:

$$A \cdot q_{A\to B} = B \cdot q_{B\to A} \tag{2}$$

Checking the detailed balance equation for each pair of states in our model verifies its reversibility at the equilibrium. For example, the flow from SS to IS equals the flow from IS back to SS, i.e.

$$SS \cdot q_{SS\to IS} = \frac{h\mu_1\mu_2\lambda_1}{C} = IS \cdot q_{IS\to SS} \tag{3}$$

This detailed balance property links the prevalence of states, which appear in the definition of OR, to the interaction parameters, which appear in the definition of the transition rates, so that we have:

$$\begin{aligned} OR &= \frac{II}{SI} \Big/ \frac{IS}{SS} \\ &= \frac{q_{SI\to II}}{q_{II\to SI}} \Big/ \frac{q_{SS\to IS}}{q_{IS\to SS}} \\ &= \frac{k\lambda_1}{h\mu_1} \Big/ \frac{\lambda_1}{\mu_1} \\ &= \frac{k}{h} \end{aligned} \tag{4}$$

The first equality of (4) shows that the OR is a ratio between two ratios, $\frac{II}{SI}$ and $\frac{IS}{SS}$. The second equality evokes the reversibility, which translates these two ratios to ratios of transition rates between $\{II, SI\}$ and between $\{IS, SS\}$. These transition rates then reduce to $\frac{k}{h}$ according to the definitions. The reversibility is key to the correspondence $OR = \frac{k}{h}$, since the rest of the derivation follows according to the definitions.

eAppendix B The heterogeneous SIS model

B.1 The system of differential equations

$$\begin{cases} \frac{dSS(z,t)}{dt} &= -(z\lambda_1 + z\lambda_2)SS(z,t) + \mu_1 IS(z,t) + \mu_2 SI(z,t) \\ \frac{dIS(z,t)}{dt} &= z\lambda_1 SS(z,t) - (\mu_1 + kz\lambda_2)IS(z,t) + h\mu_2 II(z,t) \\ \frac{dSI(z,t)}{dt} &= z\lambda_2 SS(z,t) - (\mu_2 + kz\lambda_1)SI(z,t) + h\mu_1 II(z,t) \\ \frac{dII(z,t)}{dt} &= kz\lambda_2 IS(z,t) + kz\lambda_1 SI(z,t) - h(\mu_1 + \mu_2)II(z,t) \end{cases} \tag{5}$$

B.2 The proof of $OR > 1$ under independence

Here, we prove that the crude OR is greater than 1 if the interactions are independent ($k = h = 1$) at the equilibrium. Equivalently, we prove that the observed-to-expected ratio is greater the 1, i.e. $II > (IS + II)(SI + II)$. Let $f(z)$ be the density function of the susceptibility level so that $\int_0^\infty f(z)dz = 1$. For notational convenience, we also define the following normalized quantities for each z:

$$\begin{aligned} \pi_{II}(z) &= II(z)/f(z) \\ \pi_{I*}(z) &= \Big(IS(z) + II(z)\Big)/f(z) \\ \pi_{*I}(z) &= \Big(SI(z) + II(z)\Big)/f(z) \end{aligned}$$

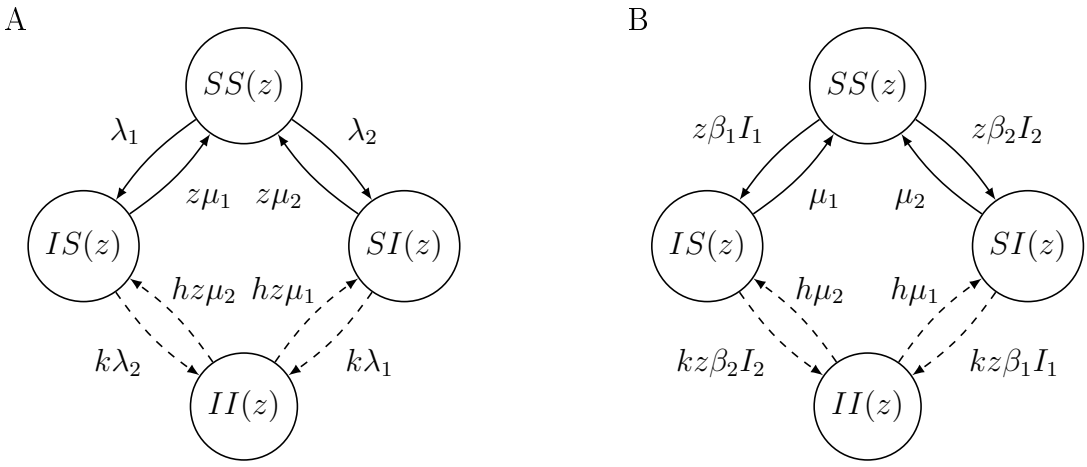
To verify $II > (IS + II)(SI + II)$, we expand the two sides of the inequality. The left hand side can be written as

$$\begin{aligned} II &= \int_0^\infty II(z)dz \\ &= \int_0^\infty \pi_{II}(z)f(z)dz \\ &= \int_0^\infty \pi_{I*}(z)\pi_{*I}(z)f(z)dz \\ &= \Big(\int_0^\infty f(z)dz\Big)\Big(\int_0^\infty \pi_{I*}(z)\pi_{*I}(z)f(z)dz\Big) \end{aligned} \tag{6}$$

The third equality is true, since for each value of z the corresponding system of differential equations follows the same structure as one of the homogeneous SIS, but with λ_i being substituted by $z\lambda_i$ (compare the system of ODE of the homogeneous SIS model and (5)). In the homogeneous SIS model, $OR = 1$ at $k = h = 1$. Hence, for each z, $OR(z) = 1$ at $k = h = 1$. Equivalently, $\pi_{II}(z) = \pi_{I*}(z)\pi_{*I}$. Lastly, the fourth equality holds, as $\int_0^\infty f(z)dz = 1$.

The right hand side can be written as

$$\begin{aligned} (IS + II)(SI + II) &= \Big(\int_0^\infty IS(z) + II(z)dz\Big)\Big(\int_0^\infty SI(z) + II(z)dz\Big) \\ &= \Big(\int_0^\infty \pi_1(z)f(z)dz\Big)\Big(\int_0^\infty \pi_2(z)f(z)dz\Big) \end{aligned} \tag{7}$$



Heterogeneous clearance rate Heterogeneous contact rate

eFigure 1: The structure of two heterogeneous SIS models for two pathogen types with interactions in acquisition and clearance indicated by dashed arrows. The clearance rate and contact rate are assumed to be heterogeneous in A and B, respectively. I_i denotes the proportion of individuals infected by type i throughout the whole population.

We have now arrived at the setting in which we can apply the weighted version of Chebyshev's integral inequality. This inequality says that for any continuous function $f(z) > 0$ on $[b, c]$, and continuous functions $\pi_1(z)$ and $\pi_2(z)$ on $[b, c]$ that are both increasing or both decreasing, the following holds:

$$\left(\int_b^c f(z)dz\right)\left(\int_b^c \pi_1(z)\pi_2(z)f(z)dz\right) > \left(\int_b^c \pi_1(z)f(z)dz\right)\left(\int_b^c \pi_2(z)f(z)dz\right) \quad (8)$$

The last step is to prove that $\pi_1(z)$ and $\pi_2(z)$ are both increasing in z. For each z, $\pi_i(z)$ at the equilibrium satisfies $z\lambda_i(1-\pi_i(z)) = \mu_i\pi_i(z)$, which can be rewritten as $\pi_i(z) = \frac{z\lambda_i}{(z\lambda_i+\mu_i)}$. As $\pi_i(z)$ has a strictly positive derivative, i.e. $\frac{d\pi_i(z)}{dz} = \frac{\lambda_i\mu_i}{(z\lambda_i+\mu_i)^2} > 0$, $\pi_i(z)$ is increasing.

Again, in the same manner, heterogeneity in contact rate as given in eFigure 1A also yields $\pi_1(z)$ and $\pi_2(z)$ that are increasing in z. Since at the equilibrium $\pi_i(z)$ satisfies $z\beta_i I_i(1-\pi_i(z)) = \mu_i\pi_i(z)$, where z is now the varying contact rate and I_i is the proportion of individuals infected by type i. This equation can be rewritten as $\pi_i(z) = \frac{z\beta_i I_i}{(z\beta_i I_i+\mu_i)}$. I_i has the same value for all z at the equilibrium. As $\pi_i(z)$ has a strictly negative derivative, i.e. $\frac{d\pi_i(z)}{dz} = \frac{\beta_i I_i\mu_i}{(z\beta_i I_i+\mu_i)^2} > 0$, $\pi_i(z)$ is increasing.

At last, heterogeneity in clearance as given in eFigure 1B rate yields $\pi_1(z)$ and $\pi_2(z)$ that are decreasing in z. Since at the equilibrium $\pi_i(z)$ satisfies $\lambda_i(1-\pi_i(z)) = z\mu_i\pi_i(z)$, which can be rewritten as $\pi_i(z) = \frac{\lambda_i}{(\lambda_i+z\mu_i)}$. As $\pi_i(z)$ has a strictly negative derivative, i.e. $\frac{d\pi_i(z)}{dz} = \frac{-\lambda_i\mu_i}{(\lambda_i+z\mu_i)^2} < 0$, $\pi_i(z)$ is decreasing.

eAppendix C The $SIRS$ models

C.1 Force of infection

$$\begin{cases} \lambda_1 = c\beta_1(IS + II + IR) \\ \lambda_2 = c\beta_2(SI + II + RI) \end{cases} \tag{9}$$

C.2 Direct interactions

$$\begin{cases} \frac{dSS}{dt} &= -(\lambda_1+\lambda_2)SS + \gamma_1 RS + \gamma_2 SR \\ \frac{dIS}{dt} &= \lambda_1 SS - (\mu_1 + k\lambda_2)IS + \gamma_2 IR \\ \frac{dSI}{dt} &= \lambda_2 SS - (\mu_2 + k\lambda_1)SI + \gamma_1 RI \\ \frac{dII}{dt} &= \lambda_2 IS + k\lambda_1 SI - h(\mu_1+\mu_2)II \\ \frac{dRS}{dt} &= \mu_1 IS - (\lambda_2+\gamma_1)RS + \gamma_2 RR \\ \frac{dSR}{dt} &= \mu_2 SI - (\lambda_1+\gamma_2)SR + \gamma_1 RR \\ \frac{dRI}{dt} &= h\mu_1 II + \lambda_2 RS - (\mu_2+\gamma_1)RI \\ \frac{dIR}{dt} &= h\mu_2 II + \lambda_1 SR - (\mu_1+\gamma_2)IR \\ \frac{dRR}{dt} &= \mu_2 RI + \mu_1 IR - (\gamma_1+\gamma_2)RR \end{cases} \tag{10}$$

C.3 Indirect interactions

$$\begin{cases} \frac{dSS}{dt} &= -(\lambda_1+\lambda_2)SS + \gamma_1 RS + \gamma_2 SR \\ \frac{dIS}{dt} &= \lambda_1 SS - (\mu_1 + \lambda_2)IS + \gamma_2 IR \\ \frac{dSI}{dt} &= \lambda_2 SS - (\mu_2 + \lambda_1)SI + \gamma_1 RI \\ \frac{dII}{dt} &= \lambda_2 IS + \lambda_1 SI - (\mu_1+\mu_2)II \\ \frac{dRS}{dt} &= \mu_1 IS - (k\lambda_2+\gamma_1)RS + \gamma_2 RR \\ \frac{dSR}{dt} &= \mu_2 SI - (k\lambda_1+\gamma_2)SR + \gamma_1 RR \\ \frac{dRI}{dt} &= \mu_1 II + k\lambda_2 RS - (h\mu_2+\gamma_1)RI \\ \frac{dIR}{dt} &= \mu_2 II + k\lambda_1 SR - (h\mu_1+\gamma_2)IR \\ \frac{dRR}{dt} &= h\mu_2 RI + h\mu_1 IR - (\gamma_1+\gamma_2)RR \end{cases} \tag{11}$$

C.4 The proof of result IV

We show that the OR is an unbiased estimator of $\frac{1}{h}$ when there are only interactions in clearance, but is biased for interactions in acquisition. Together, the OR becomes a biased estimator of $\frac{k}{h}$.

If types interact only through direct interactions in clearance, $OR = \frac{1}{h}$ still holds due to a form of reversibility between $\{SS, SR, RS, RR\}$, $\{II\}$,$\{SI, RI\}$ and $\{IS, IR\}$. These four groups of states (as indicated by the four grey areas in Figure 4) coincide with the four factors appearing in the definition of the OR.

The result $OR = \frac{1}{h}$ can be derived in a similar way as (4). The corresponding detailed balanced equations are

$$\begin{aligned}(SS + SR) \cdot q_{SS \to IS} &= (IS + IR) \cdot q_{IS \to RS} \\ SI \cdot q_{SI \to II} &= II \cdot q_{II \to RI}\end{aligned} \tag{12}$$

Each equation of (9) corresponds to a pair of groups and describes the flow between them. For instance, the first equation corresponds to the pair $\{SS, SR, RS, RR\}$ and $\{IS, IR\}$. Note that state RS and state RR do not appear in the equation, since they do not have direct transitions to $\{IS, IR\}$. Note also that $SS \cdot q_{SS \to IS} + SR \cdot q_{SR \to IR}$ is written as $(SS + SR) \cdot q_{SS \to IS}$, since $q_{SS \to IS}$ and $q_{SR \to IR}$ are both equal to λ_1.

Furthermore, the following proportionality holds:

$$\begin{aligned}SI \cdot p &= SI + RI \\ (SS + SR) \cdot p &= SS + SR + RS + RR\end{aligned} \tag{13}$$

(10) links SI and $SS + SR$, which appear in the detailed balanced equations in (9), to $SI + RI$ and $SS + RS + SR + RR$, which appear in the definition of the OR. Hence, using (9) and (10), the derivation of $OR = \frac{1}{h}$ goes as follows:

$$\begin{aligned}OR &= \frac{II}{SI \cdot p} \Big/ \frac{IS + IR}{(SS + SR) \cdot p} \\ &= \frac{II}{SI} \Big/ \frac{IS + IR}{SS + SR} \\ &= \frac{q_{SI \to II}}{q_{II \to RI}} \Big/ \frac{q_{SS \to IS}}{q_{IS \to RS}} \\ &= \frac{\lambda_1}{h\mu_1} \Big/ \frac{\lambda_1}{\mu_1} \\ &= \frac{1}{h}\end{aligned} \tag{14}$$

If types only interact through direct interactions in acquisition, the OR becomes a biased estimator of k unless $k = 1$. $OR = 1$ still constitutes a valid boundary between synergy and competition, however, the OR over-estimates k if $k < 1$, and under-estimates k if $k > 1$. The bias arises as the reversibility breaks down for $k \neq 1$. The reversibility is violated, since $q_{SS \to IS} = \lambda_1$ and $q_{SR \to IR} = k\lambda_1$, disrupting the proportionality in (10) so that the derivation of (11) no longer holds.

Since the OR is biased for k, it is also biased for the composite of the interaction parameters, $\frac{k}{h}$.

eAppendix D Computing codes

In Python 3.

```
import numpy as np
from scipy.integrate import odeint
import matplotlib.pyplot as plt
from matplotlib.patches import Rectangle

# Define the systems of differential equations SIS (homogeneous), SIRSdirect, SIRSindirect, SIS_inhomogeneous
def SIS(state, t, c, beta1, beta2, mu1, mu2, gamma1, gamma2, k1, k2, h1, h2):
    SS = state[0]
    IS = state[1]
    SI = state[2]
    II = state[3]

    lambda1 = c*beta1*(IS + II)
    lambda2 = c*beta2*(SI + II)

    dSS = -(lambda1 + lambda2)*SS + mu1*IS + mu2*SI
    dIS = lambda1*SS - mu1*IS - k1*lambda2*IS + h1*mu2*II
    dSI = lambda2*SS - mu2*SI - k2*lambda1*SI + h2*mu1*II
    dII = k1*lambda2*IS + k2*lambda1*SI - (h2*mu1 + h1*mu2)*II

    return [dSS, dIS, dSI, dII]

def SIRSdirect(state, t, c, beta1, beta2, mu1, mu2, gamma1, gamma2, k, h, m):
    k1, k2, h1, h2 = k, k, h, h
    # direct interactions
    SS = state[0]
    IS = state[1]
    SI = state[2]
    II = state[3]
    RS = state[4]
    SR = state[5]
    RI = state[6]
    IR = state[7]
    RR = state[8]

    lambda1 = c*beta1*(IS + II + IR)
    lambda2 = c*beta2*(SI + II + RI)

    dSS = - (lambda1 + lambda2)*SS + gamma2*SR + gamma1*RS
    dIS = - (k1*lambda2 + mu1)*IS + lambda1*SS + gamma2*IR
    dSI = - (k2*lambda1 + mu2)*SI + lambda2*SS + gamma1*RI
    dII = - (h2*mu1 + h1*mu2)*II + k1*lambda2*IS + k2*lambda1*SI
    dRS = - lambda2*RS + mu1*IS + gamma2*RR - gamma1*RS
    dSR = - lambda1*SR + mu2*SI + gamma1*RR - gamma2*SR
    dRI = - mu2*RI + h2*mu1*II + lambda2*RS - gamma1*RI
    dIR = - mu1*IR + h1*mu2*II + lambda1*SR - gamma2*IR
    dRR = mu1*IR + mu2*RI - (gamma1+gamma2)*RR

    return[dSS, dIS, dSI, dII, dRS, dSR, dRI, dIR, dRR]


def SIRSindirect(state, t, c, beta1, beta2, mu1, mu2, gamma1, gamma2, k, h, m):
    k1, k2, h1, h2 = k, k, h, h
    # indirect interactions (competition -> cross-immunity)
    SS = state[0]
    IS = state[1]
    SI = state[2]
    II = state[3]
    RS = state[4]
    SR = state[5]
    RI = state[6]
    IR = state[7]
    RR = state[8]
```

```
    lambda1 = c*beta1*(IS + II + IR)
    lambda2 = c*beta2*(SI + II + RI)

    dSS = - (lambda1 + lambda2)*SS + gamma2*SR + gamma1*RS
    dIS = - (lambda2 + mu1)*IS + lambda1*SS + gamma2*IR
    dSI = - (lambda1 + mu2)*SI + lambda2*SS + gamma1*RI
    dII = - (mu1 + mu2)*II + lambda2*IS + lambda1*SI
    dRS = - (k1*lambda2)*RS + mu1*IS + gamma2*RR - gamma1*RS
    dSR = - (k2*lambda1)*SR + mu2*SI + gamma1*RR - gamma2*SR
    dRI = - (h1*mu2)*RI + mu1*II + k1*lambda2*RS - gamma1*RI
    dIR = - (h2*mu1)*IR + mu2*II + k2*lambda1*SR - gamma2*IR
    dRR = h2*mu1*IR + h1*mu2*RI - (gamma1+gamma2)*RR

    return[dSS, dIS, dSI, dII, dRS, dSR, dRI, dIR, dRR]

def SIS_heterogeneous(state, t, beta1, beta2, mu1, mu2, k1, k2, z_cup, z_tilde, N_cup, N_tilde):
    S_cup = state[0]
    S_tilde = state[1]
    I1_cup = state[2]
    I1_tilde = state[3]
    I2_cup = state[4]
    I2_tilde = state[5]
    I12_cup = state[6]
    I12_tilde = state[7]

    E1_cup = I1_cup + I12_cup
    E2_cup = I2_cup + I12_cup
    E1_tilde = I1_tilde + I12_tilde
    E2_tilde = I2_tilde + I12_tilde
    l1 = beta1 * (E1_cup + E1_tilde)
    l2 = beta2 * (E2_cup + E2_tilde)

    dS_cup = - z_cup * (l1 + l2) * S_cup + mu1 * (N_cup - S_cup - E2_cup) + mu2 * (N_cup - S_cup - E1_cup)
    dE1_cup = - mu1 * E1_cup + z_cup * l1 * S_cup + k2 * z_cup * l1 * (N_cup - S_cup - E1_cup)
    dE2_cup = - mu2 * E2_cup + z_cup * l2 * S_cup + k1 * z_cup * l2 * (N_cup - S_cup - E2_cup)
    dI12_cup = dE1_cup + dE2_cup + dS_cup
    dI1_cup = dE1_cup - dI12_cup
    dI2_cup = dE2_cup - dI12_cup
    dS_tilde = - z_tilde * (l1 + l2) * S_tilde + mu1 * (N_tilde - S_tilde - E2_tilde) + mu2 * (N_tilde - S_tilde - E1_tilde)
    dE1_tilde = - mu1 * E1_tilde + z_tilde * l1 * S_tilde + k2 * z_tilde * l1 * (N_tilde - S_tilde - E1_tilde)
    dE2_tilde = - mu2 * E2_tilde + z_tilde * l2 * S_tilde + k1 * z_tilde * l2 * (N_tilde - S_tilde - E2_tilde)
    dI12_tilde = dE1_tilde + dE2_tilde + dS_tilde
    dI1_tilde = dE1_tilde - dI12_tilde
    dI2_tilde = dE2_tilde - dI12_tilde

    return [dS_cup, dS_tilde, dI1_cup, dI1_tilde, dI2_cup, dI2_tilde, dI12_cup, dI12_tilde]

# Get the equilibrium of a model with parameters: c, beta1, beta2, mu1, mu2, gamma1, gamma2, k1, k2, h1, h2
def equilibrium(plot, model, num_states, c, beta1, beta2, mu1, mu2, gamma1, gamma2, k1, k2, h1, h2):
    # Initialize joint distribution
    state0 = [1 / num_states] * num_states
    parameters = (c, beta1, beta2, mu1, mu2, gamma1, gamma2, k1, k2, h1, h2)

    # Set simulation length and step size
    t_0, t_e, t_step = 0, 1000, 0.10
    t = np.arange(t_0, t_e, t_step)

    # Simulate
    state = odeint(model, state0, t, args=parameters)

    # Plot the population dynamics in time
    if plot:
        E1 = []
        E2 = []
        if num_states == 4:
            [S, I1, I2, I12] = state
            E1 = I1 + I12
            E2 = I2 + I12
```

```
        else:
            [SS, IS, SI, II, RS, SR, RI, IR, RR] = state
            E1 = IS + II + IR
            E2 = SI + II + RI
        plt.figure()
        plt.ylim((0, 1))
        title = r'$k = {}, h = {}$'.format(k1, h1)
        plt.title(title, fontsize=15)
        plt.xlabel('t')
        plt.plot(t, E1, '-', color='red', label=r'$E_1$')
        plt.plot(t, E2, '-', color='blue', label=r'$E_2$')
        plt.legend()
    return state[-1,:]

# Plot the outcome of vaccination (Phi)
def plot_k_h_Phi_map(plot, model, num_states, c, beta1, beta2, mu1, mu2, gamma1, gamma2):

    num_step, start, end = 30, 0.1, 2.5
    parameters = np.linspace(start, end, num_step)          # candidate values for the interaction parameter k and 1/h
    x = np.repeat(parameters, num_step)                     # argument x for the Phi-map
    y = np.tile(parameters, num_step)                       # argument y for the Phi-map
    z1 = ["yellow"] * (num_step ** 2)                       # argument c for the Phi-map
    z2 = ["yellow"] * (num_step ** 2)                       # argument c for the or-map

    for i in range(num_step**2):

        k1, k2 = x[i], x[i]
        h1, h2 = 1 / y[i], 1 / y[i]
        # k1, k2 = x[i], y[i]
        # h1, h2 = 1, 1

        eps = 0.000001
        print(i, k1, h1)
        # print(i, k1, k2)

        prevalenceNVT = [0, 0]  # prevalenceNVT[0] = post, prevalenceNVT[1] = pre
        for l in range(len(beta2)):
            betaNVT = beta1
            betaVT = beta2[l]   # beta of the VT, l=0 pre-vaccination, l=1 post-vaccination

            # Simulate the equilibrium
            eq = equilibrium(plot, model, num_states, c, betaNVT, betaVT, mu1, mu2, gamma1, gamma2, k1, k2, h1, h2)

            odds_ratio = 0
            if num_states == 4:
                [s, i1, i2, i12] = eq
                prevalenceNVT[l] = i1 + i12           # state is + state ii
                if prevalenceNVT[l] > eps:
                    odds_ratio = (s * i12) / (i1 * i2)
            else:
                [ss, is_, si, ii, rs, sr, ri, ir, rr] = eq
                prevalenceNVT[l] = is_ + ii + ir      # state is + state ii + state ir
                if prevalenceNVT[l] > eps:
                    odds_ratio = ((ss + rs + sr + rr) * ii) / ((is_ + ir) * (si + ri))

        # Compute the odds ratio in the pre-vaccination era
            if odds_ratio != 0 and odds_ratio < 1:
                z2[i] = "red"
            elif odds_ratio != 0 and odds_ratio > 1:
                z2[i] = "green"

        # Compute the outcome of vaccination Phi
        if prevalenceNVT[0] < eps and prevalenceNVT[1] < eps :
            z1[i] = "yellow"
        elif prevalenceNVT[0] + eps > prevalenceNVT[1]:
            z1[i] = "red"
        elif prevalenceNVT[0] - eps < prevalenceNVT[1]:
            z1[i] = "green"
```

```
        else:
            z1[i] = "blue"


    # Plot Phi-map
    # red:      Phi = -
    # green:    Phi = +
    # yellow:   Phi = na,   NVT goes extinct in both the pre- and post-vaccination era
    # blue:     Phi = o
    plt.figure()
    plt.scatter(x, y, s=40, c=z1, alpha=1)
    plt.xlim(0, x[-1] + (end - start)/num_step)
    plt.ylim(0, y[-1] + (end - start)/num_step)
    plt.xlabel(r"$k$", size=28, position=(0.9, 0.1))
    plt.ylabel(r"$1/h$", size=28, position=(0.1, 0.7))
    class_colours = ['red', 'green', 'blue', 'yellow']
    class_names = [r'$-$', r'$+$', r'$o$', 'na']
    recs = []
    for i in range(0, len(class_colours)):
        recs.append(Rectangle((0, 0), 1, 1, fc=class_colours[i], alpha=1))
    plt.legend(recs, class_names)

    # Plot h=1/k, h=1 and k=1
    plt.plot(np.linspace(0, end, 100), 1/np.linspace(0, end, 100), '--', color='black', linewidth=5)
    plt.axhline(y=1, linestyle='--', color='black', linewidth=5)
    plt.axvline(x=1, linestyle='--', color='black', linewidth=5)

    # Save the plot
    filename = 'Plot_phi'
    plt.savefig('Figure/' + filename + '.png')

    # Plot or-map
    # red:      OR < 1
    # green:    OR > 1
    plt.figure()
    plt.scatter(x, y, s=40, c=z2, alpha=1)
    plt.xlim(0, x[-1] + (end - start) / num_step)
    plt.ylim(0, y[-1] + (end - start) / num_step)
    plt.xlabel(r"$k$", size=28, position=(0.9, 0.1))
    plt.ylabel(r"$1/h$", size=28, position=(0.1, 0.7))
    class_colours = ['red', 'green', 'yellow']
    class_names = [r'$OR<1$', r'$OR>1$', 'na']
    recs = []
    for i in range(0, len(class_colours)):
        recs.append(Rectangle((0, 0), 1, 1, fc=class_colours[i], alpha=1))
    plt.legend(recs, class_names)

    # Plot h=1/k, h=1 and k=1
    plt.plot(np.linspace(0, end, 100), 1/np.linspace(0, end, 100), '--', color='black', linewidth=5)
    plt.axhline(y=1, linestyle='--', color='black', linewidth=5)
    plt.axvline(x=1, linestyle='--', color='black', linewidth=5)


# Initialize parameters
c = 1                   # Contact rate
beta1 = 1.2             # Acquisition probability, non-vaccine type
beta2 = 2, 2.5          # Acquisition probability, vaccine type, [0]post- and [1]pre-vaccination era
mu1, mu2 = 1, 1         # Clearance rates
gamma1, gamma2 = 1, 1   # Rate of waning immunity
num_states = 9          # Number of infection states (= 4, 9)
model = SIRSdirect      # Model (= SIS, SIRSdirect, SIRSindirect)
plot = False            # If True, plot the population dynamics in time,
                        # where E_i(t) is the prevalence of type i at time i.

# Plot the map for the outcome of vaccination (Phi)
# Type 1 is the non-vaccine type (NVT)
# Type 2 is the vaccine type (VT)
plot_k_h_Phi_map(plot, model, num_states, c, beta1, beta2, mu1, mu2, gamma1, gamma2)
```