Interactions of Multiple Strain Pathogen Diseases in the Presence of Coinfection, Cross Immunity, and Arbitrary Strain Diversity

L. J. Abu-Raddad*
Vaccine and Infectious Disease Institute, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA

B. I. S. van der Ventel
Department of Physics, Stellenbosch University, Private Bag X1, Matieland 7602, South Africa

N. M. Ferguson
MRC Centre for Outbreak Analysis and Modelling, Department of Infectious Disease Epidemiology, Imperial College London, Norfolk Place, London W2 1PG, United Kingdom

(Received 11 October 2007; published 23 April 2008)

A model for coinfection in multiple strain infectious diseases is developed to incorporate coinfection statuses, immune and infection history, and cross immunity. It is solved for the symmetric interior equilibrium through the use of a ladder operator formalism inspired by quantum mechanical methods. We find that coinfection can fundamentally affects transmission dynamics with important epidemiologic and evolutionary consequences. It can significantly shift the distribution of age at infection for highly antigenically diverse pathogens so that in small host populations, an evolutionary strategy maximizing individual strain transmissibility might be less optimal than one which maximizes the total prevalence of all strains in the system. Alternatively, mechanisms which inhibit coinfection and thus increase total infection prevalence may be evolutionarily advantageous.

DOI: 10.1103/PhysRevLett.100.168102 PACS numbers: 87.19.X−, 87.10.−e, 89.20.−a

One of the most theoretically challenging problems in infectious disease epidemiology is that of interacting strains of the same pathogen, such as influenza [1] or dengue [2], or interacting diseases such as HIV/AIDS and malaria [3], at both the population and intrahost levels. The central problem in studying such systems is that of combinatorial complexity defined as the explosive growth in the number of state variables of the system with the linear increase in the number of strains or pathogens [4]. This impediment has sharply limited the analytical progress in understanding the dynamics and focused most theoretical efforts on studying systems with at most few strains. Other approaches studied the dynamics at the extremes of coinfection inhibition [5,6] or superinfection [7,8] at one side and arbitrary coinfection with no strain competition at the other side [9]. With coinfection inhibition no host can be infected by more than one strain at the same time while superinfection assumes a competitive hierarchy among the different strains but in such a manner that only one strain, the most virulent, can infect and take over the host. Meanwhile, arbitrary coinfection assumes that a host can be infected by more than one strain with no competition among these strains. These extremes bracket the more general problem, where the strains of a polymorphic pathogen of arbitrary diversity partially compete via cross immunity and direct competition during coinfection. Here we show that the more general problem is also amenable to analysis by using an operator formalism more commonly associated with quantum mechanics. Our analysis also has evolutionary implications. Classic evolutionary analysis tells us that selection acts to maximize the pathogen reproductive number R_0. However, our analysis indicates that for antigenically diverse pathogens which circulate in finite host populations, coinfection may mean that persistence is not necessarily maximized by maximizing R_0.

In the single strain susceptible, infected, and recovered (SIR) model [10], the population is divided into three compartments, giving the state variables of the system: susceptible (S), infected (I), and recovered (R). The state space for n cocirculating strains is complex as allowance must be made for individuals that are recovered, infected and immune from previous strain infections, but at the same time still susceptible to infections by the rest of the strains, although with varying strengths determined by the cross-immunity profile. Our model assumes lifelong immunity upon infection that depends on the previous infections but is independent of the order of such infections. Let the set $\mathcal{H} = \{1, 2, 3, \ldots, n\}$ label the n strains present in the system. The subsets of $\mathcal{H}$ can be used to label the various population compartments in the model. These compartments are mutually exclusive and there is no population overlap between the state variables. Excluding the overlap significantly complicates the model and sets it in contrast to other treatments of overlapping compartments [4,11,12]. Let $I_{\mathcal{J}}^{\mathcal{L}}$ represents the population that has recovered from all strain infections in the set $\mathcal{J}$, but currently infected by all strains in the set $\mathcal{L}$. Here $\mathcal{J} \subseteq \mathcal{H}$, $\mathcal{L} \subseteq \mathcal{H}\backslash\mathcal{J}$, implying $\mathcal{J} \cap \mathcal{L} = \varnothing$, and $I_{\varnothing}^{\varnothing}$ is the fully susceptible population that has no current or prior infections by any of the strains in $\mathcal{H}$. The symbol $\mathcal{H}\backslash\mathcal{L}$ stands for all elements in $\mathcal{H}$ with the exception of strains in $\mathcal{L}$. In this

fashion the host population has been divided into compartments according to the level of coinfection $\mathcal{L}$ or immune and infection history $\mathcal{J}$. The birth and immigration term of the fully susceptibles is introduced through a constant rate b. The loss of population by death is introduced through a constant rate μ. Implicitly, we are assuming no infection induced-mortality. The recovery from infection is introduced through a constant rate ν_l. Potentially each strain has its own recovery period ν_l^{-1}. Infections are acquired through a mass action term $\Lambda^i I_{\mathcal{J}}^{\mathcal{L}}$ where Λ^i is the force of infection for each strain i

$$\Lambda^i = \beta_i \sum_{\mathcal{J}\subseteq\mathcal{H}\setminus\{i\}} \sum_{\mathcal{L}\subseteq\mathcal{H}\setminus\{\{i\}\cup\mathcal{J}\}} I_{\mathcal{J}}^{\mathcal{L}\cup\{i\}}, \tag{1}$$

and β_i is the transmissibility of strain i. Cross immunity (or enhanced susceptibility) enters the model through a reduction (or enhancement) of the susceptibility of the population $I_{\mathcal{J}}^{\mathcal{L}}$ to infection by a factor $\sigma^i_{\mathcal{J},\mathcal{L}}$. This parameter provides a measure of the distance between strain i and the immune history represented by the set $\mathcal{J}$ of past infections and coinfection statuses represented by the set $\mathcal{L}$. These assumptions lead to the following system of coupled nonlinear differential equations expressed compactly using set notation:

$$\dot{I}_{\mathcal{J}}^{\mathcal{L}} = b\delta_{\mathcal{J},\varnothing}\delta^{\mathcal{L},\varnothing} - \mu I_{\mathcal{J}}^{\mathcal{L}} - \sum_{i\notin\mathcal{J}\cup\mathcal{L}} \Lambda^i \sigma^i_{\mathcal{J},\mathcal{L}} I_{\mathcal{J}}^{\mathcal{L}} + \sum_{l\in\mathcal{L}} \Lambda^l \sigma^l_{\mathcal{J},\mathcal{L}\setminus l} I_{\mathcal{J}}^{\mathcal{L}\setminus l} - \sum_{l\in\mathcal{L}} \nu_l I_{\mathcal{J}}^{\mathcal{L}} + \sum_{j\in\mathcal{J}} \nu_j I_{\mathcal{J}\setminus j}^{\mathcal{L}\cup\{j\}}. \tag{2}$$

Here the third term is the rate of infection by strain i (which increments the level of coinfection), the fourth term is the rate at which infection adds individuals to the class, the fifth term represents recovery from infection with a strain in $\mathcal{L}$, while the last term is the rate at which recovery from an additional infection adds infection to the class.

The equilibrium is obtained in Eq. (2) by setting $\dot{I}_{\mathcal{J}}^{\mathcal{L}} = 0$. It is formidable to solve for the equilibrium at an arbitrary number of strains n. A tractable problem is to study the interior equilibrium of the uniform (symmetric) n strain problem where all strains share the same properties, i.e., $\nu_i = \nu$ and $\beta_i = \beta$ for all i. Here all variables with the same "history" are equal: $I_{\mathcal{J}}^{\mathcal{L}} = I_{\mathcal{J}'}^{\mathcal{L}'}$ for any $\mathcal{L}$, $\mathcal{L}'$, $\mathcal{J}$ or $\mathcal{J}' \subseteq \mathcal{H}$ provided the number of elements in $\mathcal{L}$ and $\mathcal{L}'$ are equal and the number of elements in $\mathcal{J}$ and $\mathcal{J}'$ are also equal. Consequently, it is appropriate to rearrange the system to accommodate the "strain blindness" of the variables with respect to which strains they represent, i.e., $I_{\mathcal{J}}^{\mathcal{L}} = I_j^l$ where the superscript l stands for the number of elements in the subset $\mathcal{L}$ (coinfection number), and the subscript j stands for the number of elements in the subset $\mathcal{J}$ (recovery number). Λ is now identical for all strains and is a function of the form $\Lambda = F(I_j^l)$. The equation of motion reduces to

$$\frac{1}{1+n\lambda}\delta_{j,0}\delta_{l,0} - I_j^l + A_j^l I_j^{l-1} + C_j^l I_{j-1}^{l+1} = 0, \tag{3}$$

where $A_j^l = l\lambda\sigma_{j,l-1}/(1 + lZ + (n-l-j)\lambda\sigma_{j,l})$ and $C_j^l = jZ/(1 + lZ + (n-l-j)\lambda\sigma_{j,l})$, for the case $j > 0$ and $C_j^l = 1/(1+n\lambda)$ for $j = 0$. Here, $Z = (1-e)/e$ and $\lambda = \Lambda/e$, where $e = \mu/(\mu+\nu)$ is the fraction of the infectious period to the lifetime of the host. $\sigma_{j,l}$ is the cross-immunity parameter for a population currently infected by l strains and recovered in the past from some other j strains.

Equation (3) suggests the use of a ladder operator formalism, in that the closed system of $(n^2 + 3n + 2)/2$ discrete population states are coupled dynamically to their nearest neighbors. To our knowledge this formulation is novel in the context of theoretical epidemiology, but has been used in statistical physics. Indeed, it was pioneered by Doi who demonstrated the ability to rewrite classical physics systems as quantum ones [13,14].

The population variables are then determined by the following recursion relation:

$$I_j^l = \sum_{l'=1,\ldots,l+1} f(j,l,l') I_{j-1}^{l'} \tag{4}$$

with $I_{-1}^l = C_j^{l'-1}\prod_{m=l'}^{l} A_j^m$. Geometrically, the solution for I_j^l is essentially an enumeration of all the possible paths that connect the fully susceptible population I_0^0 to the population I_j^l. The solution is in terms of the parameters A_j^l and C_j^l, and is independent of their functional form or specific dynamical content allowing a much wider applicability of this formalism. Since A_j^l and C_j^l depend on λ, the above formalism provides expressions for I_j^l in terms of λ which can then be substituted in $\lambda = F(I_j^l)$ to yield an equation in terms of one variable of the form $\lambda = F(\lambda)$. This equation can be solved numerically through successive approximations [5] by noting that $\lambda_{\text{eq}} = \lim_{p\to\infty} F_p(\lambda_0) \forall\ \lambda_0 \in (0,\infty)$.

We present a sample of results based on the above formalism. We decompose the cross immunity $\sigma_{j,l}$ into two parts $\sigma_{j,l} = \eta_j\phi_l$ where η_j is the cross-immunity parameter against acquiring new infections as a consequence of prior exposure and recovery from j different strain infections in the past, and ϕ_l is the cross-immunity parameter against acquiring new infections for a host that is currently infected by l strains. For the calculations in Fig. 1, we discuss the dynamics in a multiple strain system of an infectious disease where recovery from infection does not lead to cross immunity against other strains but where current infection by one or more strains can induce cross immunity against acquiring more coinfections by other strains. Accordingly, we are exploring the dynamics in the continuum between systems where no more than one strain infection can be present (coinfection inhibition) [5,15], akin to superinfection [7,8], and systems where the strains are noninteracting and multiple strain coinfec-

tions can overlap within the same individual (full coinfection) [9]. Hence, $\sigma_{j,l} = \sigma_{0,l} = \phi_l$. In addition, we assume a constant cross immunity, i.e., $\phi_l = 1$ if $l = 0$ and $\phi_l = \phi$ if $l > 0$ implying that cross immunity is constant against new coinfections after the first infection.

Figure 1 shows the total prevalence y_T (fraction of the population infected by any strain) in presence of cross immunity and coinfection as a function of the cross-immunity parameter ϕ for two values of $R_0 = \beta N/(\mu + \nu)$ [10] of 1.5 and 4 (N is the total population size). At small $R_0 = 1.5$, y_T increases gradually with ϕ starting from the limit of coinfection inhibition ($\phi = 0$) till it reaches a maximum at the limit of noninteracting strains with maximal coinfection ($\phi = 1$). This is what one would intuitively expect from a system straddling the continuum between the two extremes of coinfection. Nevertheless, at large $R_0 = 4$, a system with moderate degree of cross immunity can have total prevalence exceeding paradoxically both of the two extremes of coinfection. The resolution of this paradox lies in the age distribution at infection as described below.

Consider next Fig. 2 where the dependence of y_T on the two forms of cross immunity is examined. In addition to constant ϕ_l cross immunity we assume constant η_j cross immunity ($\eta_j = 1$ if $j = 0$ and $\eta_j = \eta$ if $j > 0$). The rate at which y_T changes versus ϕ as opposed to η shows how the epidemic dynamics can depend differently on the two forms of cross immunity. The cross immunity against coinfection can be more influential in the interstrain dynamics than that of prior exposure cross immunity. Weaker coinfection cross immunity allows the pathogen to reach more segments of the population through coinfections of those who are already infected by at least one strain.

In Fig. 3 we display individual strain prevalence y_1 (fraction of the population infected by any one specific strain) and the total infection prevalence y_T at the two extremes of full coinfection and coinfection inhibition as a function of R_0. In the coinfection inhibition limit, both y_T^{no} and $y_1^{\text{no}} = y_T^{\text{no}}/n$ increase monotonically as a function of R_0 to the point of saturation. However, in the full coinfection limit y_T^{co} increases rapidly initially with R_0, but then peaks before declining and asymptotically tending to a low level. y_T in the coinfection inhibition model can be larger than that of full coinfection at large R_0. This result is perhaps counter-intuitive on the basis that the presence of coinfection yields an increased number of infections implying intuitively an increased number of infected individuals. The age distribution at infection is at the heart of this paradox. Since the average age at infection is given by $\tau_{\text{lifetime}}/R_0$ [10], a large R_0 (and hence a greater force of infection) implies an earlier age at infection. With coinfection and large R_0, hosts are exposed to most strains early in life, giving high multiplicities of infection at young ages, while with coinfection inhibition hosts have to experience infections sequentially, leading to a broad age distribution at infection and consequently a larger y_T. As R_0 increases, the dynamical difference between models with and without coinfection increases. This difference in behavior might be critical in interpreting total prevalence data for a multiple strain pathogen such as malaria, as one can be mistaken in assuming a positive or simple correlation between infection prevalence and R_0. Prevalence data need then to be supplemented with data on the multiplicity of infection (or within-host pathogen diversity) and the age-distribution of

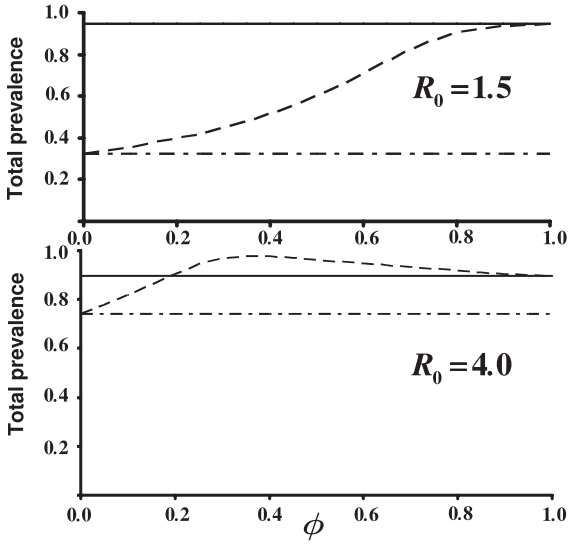

FIG. 1. The total prevalence y_T as a function of the cross-immunity parameter ϕ with $\eta = 1$, $e = 0.3$, and $n = 50$. The solid line represents the total prevalence with coinfection and no cross immunity, the dashed line the total prevalence with coinfection and cross immunity, and the long-dashed-short-dashed line the total prevalence with coinfection inhibition. Note that $\phi = 1$ imply no cross immunity while $\phi = 0$ imply total cross immunity.

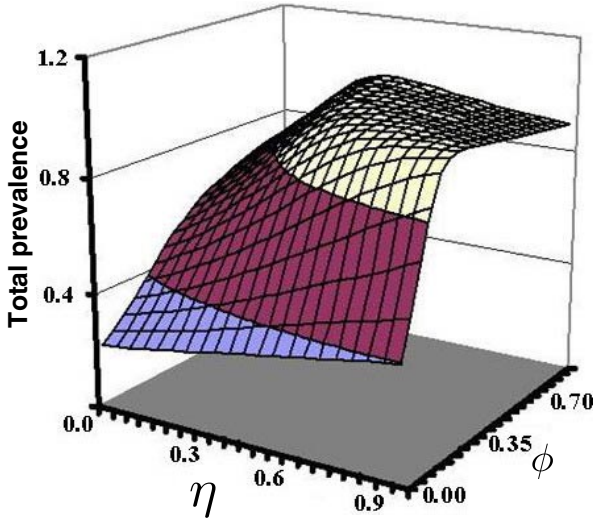

FIG. 2 (color online). The total prevalence in the presence of the two forms of cross immunity and coinfection as a function of the cross-immunity parameters ϕ and η. For this calculation $n = 50$, $R_0 = 4$ and $e = 0.3$.

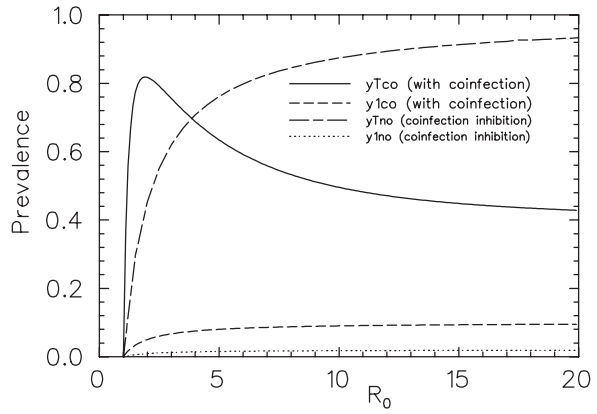

FIG. 3. Individual versus total prevalence. The total (y_T) and individual (y_1) strain prevalences, in the presence ($\phi = 1$) and absence ($\phi = 0$) of coinfection, as a function of the reproductive number (R_0). Here $n = 50$, $\eta = 1$, and $e = 0.1$.

infection—with attention being paid to the potential impact of coinfection.

Individual strain prevalence is an important determinant of the overall fitness of a pathogen strain in finite host populations. But might multiple strain pathogens, perhaps mediated by rapid genetic mixing between strains, evolve to maximize their total prevalence as opposed to their individual strain prevalence? Coinfection fundamentally affects this issue, as in the absence of coinfection, there are no differences in the qualitative behavior of the total compared to the individual prevalences. This evolutionary question is whether a ''local'' versus a ''global'' fitness measure is preferred. If a pathogen strain adopts the local strategy of evolving to maximize its own strain prevalence, then it should evolve to maximize R_0, at least until the point at which prevalence saturates. On the other hand, if the pathogen should adopt the global strategy of maximizing the total prevalence of infection in the system, then it would evolve to the low optimal value of R_0 which maximizes this fitness measure. A global strategy is suggestive of group-selection except perhaps in the case of pathogens where genetic mixing is sufficiently intense for kin-selection [16,17] to be a significant factor - something which may be the case for some bacterial and helminthic infections. In such cases, maximizing total prevalence maximizes the persistence of the pathogen overall. Persistence is fundamentally a stochastic phenomenon, and thus one not readily captured by deterministic evolutionary modelling. For highly diverse pathogens with many strains at low frequencies, the concept of selection fixating a maximally fit variant breaks down, and instead it is more useful to consider the evolutionary dynamics of the quasispecies of closely genetically related strains which are shaped by the competing pressures of selection, recombination or mutation and extinction [18]. In such a scenario, the fittest of the individual strains may not be even present as part of the quasispecies [19]. Nonetheless, without a mechanistic model that shows how selection for total as opposed to individual strain prevalence can arise, no definitive conclusions can be drawn. Situations where host populations are small (giving high probabilities of single strain extinction) and strains are highly genetically related (via recombination) perhaps represent the most likely context for such selection, but more work is needed to demonstrate this.

Thus a goal for future work is to combine the epidemiological dynamics of multiple strain infections with that of the evolutionary dynamics of selection to assess the evolutionary trends in pathogen evolution. We focused here on the former, but still our treatment provided evolutionary insights and implications. A natural extension of this work is to explore evolutionary dynamics more explicitly, with the incorporation of pathogen virulence, mutations, and strain generation.

The authors gratefully acknowledge the financial support of the Fred Hutchinson Cancer Research Center (L. A. R.); the Medical Research Council (L. A. R. and N. M. F.), the Royal Society and the Howard Hughes Medical Institute (N. M. F.); the National Research Foundation of South Africa (B.I.S.v.d.V).

*laith@scharp.org

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