MODELING

Coinfection: Doing the Math

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A transmission model clarifies the effects of influenza on pneumococcal pneumonia and bridges the gap between individual animal experiments and human epidemiological data (Shrestha *et al*., this issue).

Coinfection of hosts with more than one microorganism is ubiquitous in natural systems, but its effects are not simple. Upon coinfection with multiple parasites (defined here as infectious organisms that cause harm to their hosts), a range of within-host outcomes may occur, including host pathological changes and immune responses as well as effects on the individual parasites (Fig. 1). Some outcomes have effects at the population level, while others are confined to individuals (*1*, *2*). Now, Shrestha *et al*. use a mathematical approach to dissect the confounding effects of coinfection with the influenza virus and the bacterium *Streptococcus pneumoniae* (*3*).

In laboratory models and in studies of individual host pathology or immune response, coinfection often results in host or parasite responses beyond the simple additive effects of the two species (*1*, *4*, *5*). However, the extent to which such changes scale to population-level effects is a matter for debate (*6*). Coinfection-induced changes in host susceptibility and parasite-transmission potential can be observed in laboratory settings, but often, epidemiological signatures of these effects (such as changes in infection-peak height or duration) are equivocal. Biotic and abiotic environmental factors influence host-to-host parasite transmission (e.g., climate and vector availability). Once an infectious agent reaches a new prospective host, his or her susceptibility could be affected by host genetics, physical condition, and behavior. There are two possible consequences of such environmental and host influences: (i) these factors break the link between the individual-host and the population-level effects of coinfection or (ii) coinfection properties in one host could be retained in subsequent hosts, thus scaling the effects to the population level; still, the epidemiological signatures of these effects could be obscured by influencing factors (*6*). In many systems, and particularly in humans, experimentation cannot be used as a method to tease apart these possibilities. Instead, mathematical tools must be developed to achieve this aim (*7*).

In laboratory investigations with animal models, influenza has been shown to increase both susceptibility and pathological response to subsequent pneumococcal infection (*5*, *8*); similarly, there is little doubt that influenza virus exacerbates the pathology that results from pneumococcal coinfection in human subjects (*9*). However, epidemiological studies of coinfected human populations have not yielded such clear results, leading to questions of whether and how the within-host dynamics of the coinfection scale to the population level.

In their new work, Shrestha *et al*. take a mathematical approach by using a mechanistic transmission model within a Bayesian likelihood-based inference framework to determine the role of within-host coinfection dynamics. The authors model influenza virus as a potential driver of the epidemiological dynamics of *Streptococcus pneumoniae* infection in human populations. This approach is based on a fairly simple and well-known structure, an adapted SIRS model (where S = susceptible, I = infected, and R = recently recovered). However, the model has been applied in a new way to address questions about the scaling of coinfection dynamics from the individual to population level.

The SIRS model takes into account the coinfection with influenza by subdividing the susceptible and infected compartments of the model into influenza-infected and uninfected hosts. This model is then applied to two years of weekly epidemiological records of influenza and pneumococcal pneumonia hospitalizations in Illinois, USA. Using this framework, the authors formally tested three potential hypotheses for the role of influenza in driving the pneumococcal epidemiology. The three alternative hypotheses are not mutually exclusive; all have the potential to be supported or indeed, unsupported (suggesting no effect of influenza): (i) The transmission hypothesis assumes that individuals recently infected with influenza will have a higher contribution to pneumococcal

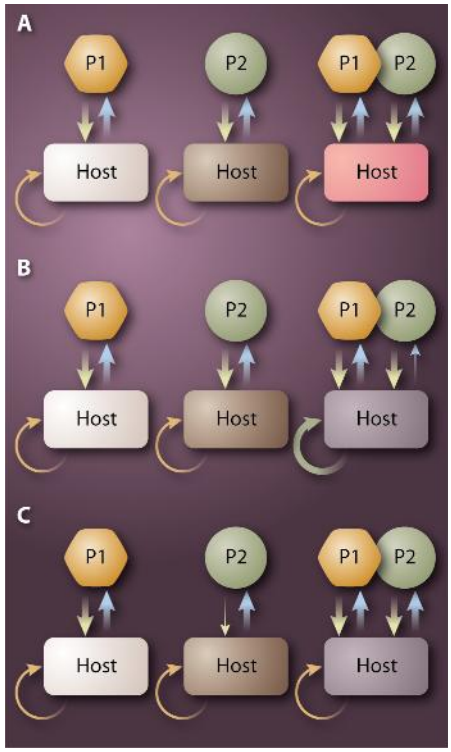

Fig. 1. Is one plus one more than two? Shown are the potential within-host and between-host consequences of coinfection. Two parasite species are represented by P1 (orange) and P2 (green). Yellow arrows, infection of host by parasites; blue arrows, host effect on a parasite and/or direct parasite-parasite interactions; orange or green circular arrows, transmission between hosts. Host effects (boxes) of P1 and P2 are shown in white and brown, respectively; simple additive effects of P1-P2 coinfection are shown in purple. (**A**) Coinfection exacerbates host pathology (pink box) but has no consequences for parasite dynamics or host susceptibility to infection; thus there is no change in between-host transmission. (**B**) Coinfection either causes direct interactions between parasites or induced changes in the host (e.g., immune responses) that alter the dynamics of one or both parasite species (thin blue arrow for P2); the ultimate effect is a change in transmission potential for one or both parasites, resulting in between-host effects (thick green circular arrow). (**C**) Coinfection alters host susceptibility to the second infecting agent (change from thin to thick yellow arrow for P2). Although there is no inherent change in either parasite's capacity to transmit between hosts, the next P1-infected host has an increased risk of P2 infection (a between-host effect). Null case (not shown): Coinfection has a purely additive effect on the host, the parasites have no effect on one another, and coinfection does not change the host response to either parasite.

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transmission (Fig. 1B); (ii) the susceptibility hypothesis assumes that individuals are more susceptible to pneumococcus if they are infected with influenza (Fig. 1C); and (iii) the pathogenesis-impact hypothesis assumes that influenza infection only influences the severity of clinical symptoms of the pneumococcal infection in individuals and that this, in turn, causes an increase in the probability of reporting. In hypothesis 3, there is no effect on between-host transmission or infection (Fig. 1A).

For each influenza-effect hypothesis, the model included a term that modulated the relevant process (transmission, susceptibility, reporting) as a ratio that described the influenza effect relative to the baseline of uninfected individuals. The transmission function for the transmission hypothesis was modulated by the term θ, susceptibility was modulated by the hazard term ϕ, and altered pathology was accounted for by the term ξ, which modulated the probability of reporting pneumococcal pneumonia cases (which was assumed to increase with severity of the disease). In each case, the null hypothesis was that influenza had no influence, meaning that the modulation terms for transmission, susceptibility, or pathology reporting would be equal to 1, inferring no difference between influenza-infected and uninfected individuals. When any of these terms was significantly greater than 1, the alternative hypothesis, that influenza did have an influence, was accepted. This approach yielded maximum likelihood estimates and 95% confidence intervals for each focal term. The authors found that only ϕ was significantly greater than one, indicating that influenza infection induced an increase in *S. pneumonia* susceptibility but did not suggest changes in transmission or pathology (as measured by increased reporting).

The authors then examined one- to three-week time windows for the influenza effect on subsequent transmission of *S. pneumonia* but found nothing to suggest that influenza could influence a subsequent pneumococcal infection that occurred more than a week later. Therefore, the interaction predicted between the parasite species was transient but significant and caused a substantial (~100-fold) increase in infection risk, which equated to up to 40% of cases of pneumococcal pneumonia being attributable to influenza coinfection during influenza peaks; this, in turn, equated to between 2 and 10% of pneumococcal infections on an annual basis. Using simulations of their model and comparing these to their two years of epidemiological records, the authors found that the seasonal pattern of pneumococcal infection could be captured without incorporating influenza, but the interannual variability in the numbers of pneumococcal pneumonia cases could only be captured if influenza coinfection was incorporated in the model.

As a final step, the authors determined the impact of this demonstrated epidemiological effect by simulating artificial influenza datasets with a range of interannual influenza epidemic peak sizes. Using these data as a covariate in their model, the authors then assessed the effect on predicted pneumococcal pneumonia hospitalizations. This analysis revealed a likely cause for the apparent disparity between the clear individual-level effects of influenza and the apparent lack of effect seen in the raw epidemiological data. Indeed, the magnitudes of the predicted pneumococcal pneumonia hospitalization peaks were relatively insensitive to the interannual variation in influenza, such that a twofold increase in the influenza peak resulted in only a 25% increase in the magnitude of the pneumococcal peak. This relatively small change in pneumococcal peak size could easily be overlooked in natural datasets but does not imply a small effect of influenza: The 100-fold increase in influenza risk equated to an estimated total of 3249 influenza-related pneumococcal hospitalizations in the two-year Illinois epidemiological dataset.

Shrestha *et al.* have chosen to focus on one side of the influenza-pneumococcus relationship, but there is evidence, at least from mouse models, that influenza viral titers are also affected by the presence of a *S. pneumoniae* infection (*10*). The current approach could be extended to explore the potential role of pneumococcus infection on influenza epidemiology. Indeed, variations of this modeling approach have great potential to be applied to a wide range of other coinfection systems and may offer a tool with which to determine what form the interaction between infecting species may take. It remains unclear whether this modeling approach can distinguish unidirectional interactions from those in which both parasite species have effects on each other (directly or indirectly through the host). What the approach does offer is a quantification of the epidemiological effect, which has not previously been possible.

The majority of large-scale disease control programs are aimed at single parasite species. Further, current estimations of infection risk take only a cursory account of coinfection, and estimators of disease severity [for example, Disability-Adjusted Life Years (DALYs)] consider the consequences of coinfection as simply additive. The links between parasite interactions, infection risk, and host pathology under conditions of coinfection are still poorly understood. largely because of the absence of suitable tools for the accurate detection of parasite interactions and for quantitative prediction of their consequences. Shrestha *et al.* bring us one step closer to a solution by adding a new tool to this assessment portfolio. A next step will be to model unidirectional and multidirectional interactions, because knowing which parasites drive infection dynamics in a system will help determine how best to target limited resources for efficacious control strategies.

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