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those long gone from the lab and having achieved independent distinction, he remained a source of advice, support, and wisdom. For those outside his group, he also was a mentor of sorts. He had a special ability to explore the depths of a study presented at a lecture through questions that frequently uncovered aspects missed by the investigator. He was justly famous for being able to ask the most probing questions and yet make the recipient feel like he or she was receiving an accolade, a reflection of Bill's modesty about his remarkable intellect.

In short, Bill Paul was the scientist's scientist. He had endless curiosity, an ability to remain focused on unraveling layer after layer of complexity in biology without losing his enthusiasm for the subject, and devotion to the careers of others and to the scientific enterprise as a whole. As noted above, some scientists merely add threads to the tapestry of biology, but with Bill's passing, we have lost a master weaver who was brilliant at seeing the essential patterns in the fabric of nature. For this special capacity, for his leadership, and for his friendship, he will be missed tremendously.

Despite his passing, Bill has provided one final gift to our field in his new book, aptly titled 'Immunity' and just published in September 2015. He wrote this book 'to introduce both the general readers and potential students of immunology' to the field. Who better to do this than Bill Paul, an extraordinary scientist, mentor, friend, and 'mensch'.

Acknowledgments

The authors are all supported by the Intramural Research Program of the NIH.

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http://dx.doi.org/10.1016/j.it.2015.10.001

Science & Society

Understanding Herd Immunity

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Individual immunity is a powerful force affecting host health and pathogen evolution. Importantly, the effects of individual immunity also scale up to affect pathogen transmission dynamics and the success of vaccination campaigns for entire host populations. Population-scale immunity is often termed 'herd immunity'. Here we outline how individual immunity maps to population outcomes and discuss implications for control of infectious diseases. Particular immunological characteristics may be more or less likely to result in a population level signature of herd immunity; we detail this and also discuss other population-level outcomes that might emerge from individual-level immunity.

From Individual Immunity to Herd Immunity

Because of the feedbacks inherent in infectious disease dynamics, individual immunity has a long shadow: infection of one individual simultaneously increases the risk of infection for other individuals in the population by increasing their exposure, but also reduces the number of susceptible individuals that can be infected because that infected individual will develop individual immunity. For many pathogen life histories, there is a threshold proportion of the population that must be susceptible for the pathogen to successfully spread (Figure 1). Conversely, if the proportion of the population that is immune (by vaccination or natural infection) exceeds the threshold the incidence of the pathogen will decline. This is known as the 'herd immunity threshold' and arises because a subset of the susceptible population benefits from 'indirect protection' by the immunization of individuals that surround them (Figure 1). They will be less likely to be exposed to infection because most of the individuals that they encounter already have been, and are therefore immune and will not transmit the infection. Indirect protection alters the dynamics of pathogen transmission over the course of an outbreak and epidemics slow down and then turn over as a result.

For strongly immunizing infections, the key parameter that defines the herd immunity threshold is R_0, or the number of new infections generated by the first infectious individual in a completely susceptible population (Figure 1). For measles, for example, an infectious individual who has arrived in a population where no one else has ever experienced measles (or measles vaccine) is expected to infect, on average, 15 individuals during the infectious phase. In the simplest analysis, the critical proportion of the population that must be immunized to achieve elimination, or p_c, is defined by $p_c = 1 - 1/R_0$. Thus, the more inherently transmissible a pathogen is, the greater the proportion of the population that must be vaccinated to drive it locally extinct. In reality, a unique threshold for immunization associated with pathogen extinction in all populations is unlikely [1], as the basic model includes simplifying assumptions such as homogenous mixing within the population (rather than the age-dependent contact rates reported in [2] and through the year [3]) and

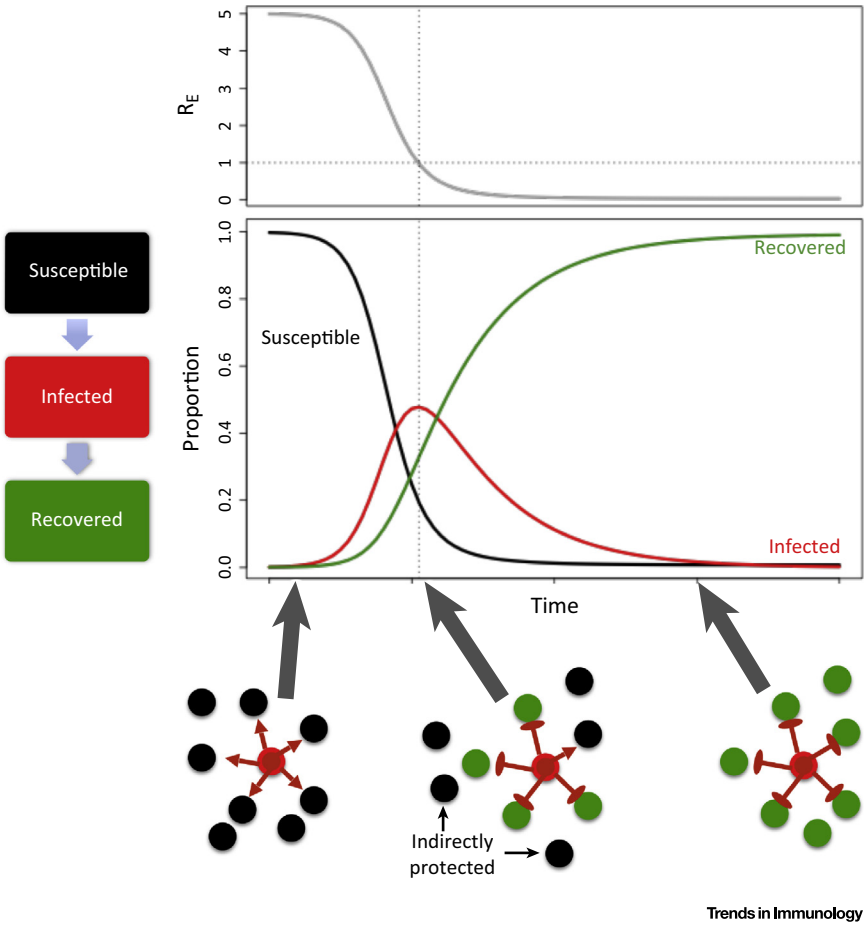

Figure 1. Herd Immunity in a Closed Population (Flow Diagram on the Left, No New Susceptibles Are Born and No One Leaves or Enters) for a Completely Immunizing Infection with $R_0 = 5$. The top panel shows R_E, the effective reproduction number, reflecting the number of new infected individuals per one infectious individual. R_E is defined by the product of R_0 and the proportion of the population that is susceptible. The bottom panel shows the proportion of individuals that are susceptible, infected, and recovered. Initially, everyone is susceptible (black line) and an infected individual is introduced. The infection spreads rapidly (red line) but reaches a threshold where new infected individuals can infect less than one susceptible individual ($R_E < 1$, top panel) as most of the population is now recovered and immune (green line). The few remaining susceptible individuals benefit from 'indirect protection'. These dynamics are illustrated in the schema below, where circles indicate individuals, colors indicate whether they are susceptible, infected, or recovered, arrows indicate successful transmission, and blocked arrows show individuals protected through their own immunity; indirectly protected individuals are also indicated. The herd immunity threshold is the fraction of the population that is susceptible at the point where R_E falls below 1 and the number of infectious individuals peaks, indicated by the dotted vertical line. Mathematically, this equates to $p_c = 1 - 1/R_0 = 0.8$.

homogenous vaccination coverage (rather than the inequity generally observed [4]). Demographic features will also affect the threshold, with higher vaccination coverage required to achieve this threshold in high-birth-rate contexts [5]. Nevertheless, the concept of herd immunity has provided a powerful benchmark for understanding the relative effort required for control of particular pathogens and for illuminating past successes such as smallpox elimination. Of course, sterilizing immunity as seen in measles is relatively rare across a diversity of important pathogens. There are numerous other life histories (for example, where immunity may wane and individuals return to susceptible status) that will generate different population consequences. However, as described below, even quite imperfect immunity following infection can manifest via herd immunity at the population level.

Evidence for Indirect Protection Afforded to Nonimmune Individuals

Since we seldom have detailed observations of chains of transmission (who infected whom) and too rarely know the background susceptibility of the people who were not infected during an outbreak, detecting indirect protection requires careful interpretation of population-scale incidence patterns. Data on fluctuations in the number of cases observed within a country or city are frequently available through public health surveillance and can provide indications of the action of indirect protection. One powerful source of evidence is short-term effects following vaccination introduction, where unvaccinated cohorts show reduced incidence and thus evidence of indirect protection (reviewed in [6]). Another source of evidence is changes in cycles of pathogen incidence over the longer term. Susceptible host depletion and replenishment should strongly affect the timing and magnitude of outbreaks where indirect protection is operating [7]. Accordingly, transition from annual to biennial dynamics was observed for measles after the end of the Baby Boom [8], in line with expectations for this strongly immunizing pathogen: low birth rates mean that susceptibles accumulate more slowly, and they also benefit from indirect protection resulting from a high proportion of immune individuals from the last cycle. For partially immunizing pathogens, indirect protection seems at first less likely. Nevertheless, observed changes in dynamics indicate that even the brief period of reduction in population exposure occasioned by partial immunity could result in indirect protection. For rotavirus, for example, the spatial pattern of timing of epidemics across the USA could be linked to a spatial pattern of birth rates [9], indicating the action of indirect proetection; and furthermore, the predicted

change from annual to biannual dynamics as a result of vaccination was observed. Similar observations can be made for respiratory syncytial virus (RSV) [10] and pertussis [11].

From Within Host to Population Scale

Immunity derived from either natural infection or vaccination can be highly variable, ranging from protection against only clinical disease to protection against only transmission or only carriage. When considering how within-host dynamics of the immune response to a particular pathogen might shape herd immunity at the population level, arguably the key aspect is the degree to which acquired immunity limits onward transmission. Imagine a pathogen where immunity considerably reduces symptoms ('disease') for infections occurring after the primary infection but has no effect on transmission. From the perspective of the pathogen, no individuals have been removed from the population (all the green individuals in Figure 1 would still be accessible to infection) and there is consequently no indirect protection and, accordingly, no herd immunity. Some recent work even suggests that disease-only-blocking vaccines could select for the evolution of increased virulence [12]. Again, transmission-blocking vaccines provide potentially the safest outcomes [13], which suggests that this should be a key focus in vaccine development to maximize positive impact.

Other Intricacies

It is well known that the interactions of within-host immune processes mean that one pathogen's dynamics may alter the direct protection experienced for other pathogens; this in turn may influence transmission at the population scale. This is particularly clear for immunosuppressive pathogens: there is evidence that HIV can affect acquisition of measles immunity [14] and therefore the potential for persistent transmission in populations with high HIV prevalence. Recent results also suggest that infection with measles may deplete memory of a range of other pathogens, thus weakening individual immunity and the potential herd-level effects [15]. Within-host immune interactions might also result in negative indirect effects: via antibody-dependent enhancement, infection with one dengue strain can leave individuals more vulnerable to infection with another, but also, potentially, more infectious placing others at higher risk for transmission [16].

Concluding Remarks

Individual immunity is such a powerful force that its consequences are felt beyond the individual at the population scale. The decline of an epidemic alone is insufficient to conclude the action of indirect protection and herd immunity: changes in transmission linked to behavior changes such as school holidays [3] or fluxes linked to agriculture [17] can result in such a pattern. However, as described here, changes in epidemiology following interventions such as targeted vaccination, and changes in epidemic cycles in response to vaccination or changes in birth rates, can indicate the indirect effect of herd protection. Identifying such signatures is important: indirect protection means that the return on every individual immunized is more than one individual, making immunization a powerful tool in public health. Importantly, these indirect benefits of vaccination reduce the population burden of infection, regardless of the distance from the herd immunity threshold, and indeed are strongest as the threshold for herd immunity is approached.

Acknowledgments

This work was funded by the Bill and Melinda Gates Foundation (C.J.E.M., B.T.G., M.F.), the RAPIDD program of the Science and Technology Directorate, Department of Homeland Security, and the Fogarty International Center, National Institutes of Health (C.J.E.M., B.T.G., M.F., A.L.G.).

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http://dx.doi.org/10.1016/j.it.2015.10.004

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