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THE NEED FOR MORE INTEGRATED EPIDEMIC MODELING WITH EMPHASIS ON ANTIBIOTIC RESISTANCE

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6.1 INTRODUCTION

Antibiotic resistance has become one of the greatest threats to public and patient health. Pathogens resistant to antibiotics can significantly decrease a physician's ability to treat infection and increase the probability of mortality in patients [3]. Estimates are that, per annum, a minimum of two million Americans contract antibiotic resistant infections, resulting in 23,000 deaths [18]. Decreases in the efficacy of antibiotics threaten to reverse a variety of major medical gains [60, 85]. For example, the ability to perform transplants and other surgical procedures are dependent on antibiotic effectiveness [28] and would be severely hampered in a post-antibiotic world. Overall, the annual economic cost to the US health care system of antibiotic-resistant infections is estimated to be $21–$34 billion [34, 64, 70]. Given the importance of this problem, from standpoints both of human health and economics, there is much to be gained from better understanding how resistant bacterial pathogens evolve and

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persist in human populations. Integrated computational models encompassing aspects of human behavior can improve our understanding of the evolution and the spread of resistance, offering a clearer picture of how ecology and epidemiology interact to spread antibiotic resistant pathogens, as well as insight into policy options to help contain the spread of resistance. Here the history of mathematical modeling of infectious diseases and a selection of its achievements and limitations is very briefly examined, followed by a discussion of the need to develop models of disease spread that incorporate individual behavior with reference to how this can improve models of bacterial pathogens.

6.2 MATHEMATICAL MODELING OF INFECTIOUS DISEASES

Mathematical models of infectious disease have been used since the eighteenth century to guide interventions to control disease [11]. At the beginning of the twentieth century, models explaining the dynamics of measles [41] as well as malaria [71] had been developed. Kermack and McKendrick then established the modern mathematical theory of infectious disease [49], clarifying in deterministic settings the threshold nature of epidemics and the central idea of herd immunity. Important factors such as the impact of stochasticity and critical community size on sustaining epidemics were later introduced [9, 10], as were further refinements describing the invasion and persistence of human pathogens [2, 40]. Similar techniques have been applied to the study of the spread of animal and plant diseases, both in agricultural and natural landscapes [17, 36, 39, 48, 75]. This has led to theories of how epidemics spread spatially, and how control measures should be deployed in a wide range of pathogens, host populations, and environments. As the global epidemic of antibiotic resistance has increased in recent years, mathematical models of the spread of antibiotic resistance have also been developed [4,5,26,27,59,68,69]. These models have elucidated important aspects of transmission in hospital settings, nursing homes, and other inpatient facilities.

The models underlying most theories on epidemic spread have generally been formulated as "SIR" models [43] in which individuals of the same epidemiological status are lumped together in homogeneous pools: S is the size of the susceptible class, I is the infectious, and R is the removed (e.g., dead or recovered). Control treatments are then modeled either through quantitative changes to model parameters, notably transmission rates and infectious periods, or by introducing additional transitions, such as when a vaccination program switches individuals from a susceptible to a removed class [2]. Like central idealizations in other fields—the simple harmonic oscillator or ideal gas in physics, or the Lotka–Volterra equations in ecology—the classical "SIR" differential equations are an elegant, tractable, and important foundation. And while they have been instrumental in understanding fundamental aspects of disease spread, just as in these other fields, they are not fully equal to the complexity of real-world settings, which amalgamate pathogen evolution, risk behavior, spatial dynamics, and policy. Classical modeling thus generally ignores heterogeneities between individuals, and simply cannot represent the direct interactions between individuals, which ultimately generate the patterns that emerge at the population level.

Despite these limitations, computational models have begun increasingly to include realistic descriptions of human behavior in understanding how diseases spread. The catalyst for this was largely sexually transmitted diseases where behavior (and modification of behavior) is most pronounced. Thus, factors such as heterogeneous sexual mixing rates [12, 44], rational responses to economic incentives [67], more realistic descriptions of risk-taking behavior [13–15, 29, 45], and the spread of fear and its impact on disease transmission [32] have all been examined within this classical modeling framework. More recently, models in this framework have examined the impact of behavioral responses of individuals on the spread of antibiotic resistance. For example, including heterogeneities in age-related mixing can dramatically affect the spread of community-associated strains of methicillin-resistant *Staphylococcus aureus* (CA-MRSA) [55], which has important implications for controlling the disease.

Computational power and speed has been one of the major limitations to modeling individual behavior that in recent years has been removed. This has allowed for the development of agent-based models that can include realistic contact networks [33, 62, 63] and examine how behaviors such as policy resistance to vaccination [83] impacts the spread of a disease. Individual-based models have also been developed to understand the complexity of bacterial strain interaction [21] as well as heterogeneties in malaria transmission and the impact this has on emergence and spread of drug resistance [52]. Despite these advances, there still exists room to innovate and integrate, particularly as individuals can behave in unexpected ways during epidemics. Epidemics are contexts fraught with fear, distrust of health authorities, and poor information. In such settings, understanding how people behave and how that behavior may affect transmission can guide decision making and policy options. While epidemiological modeling has come a long way in including behavior, many models posit that individuals behave rationally. The model of "rational behavior" can be misguiding in contexts, such as healthcare, where decision making must cope with great uncertainty in emotionally charged contexts. Systematic deviations from rationality have been repeatedly observed in both laboratory and field experiments (see, e.g., Refs. [42, 74]). These deviations are explained by decision heuristics that can both approximate rational choices as well as yield irrational biases [37], for example:

1. *Representativeness Heuristic*. People may rely on this heuristic to make judgments about an uncertain object, event, or process. For example, what is the probability that object x belongs to set A? Tversky and Kahneman [47] have demonstrated that when people use the representativeness heuristic to make these judgments, they estimate the subjective probability of x belonging to set A by using the perceived similarity of x to the other objects in set A as the probability. The perceived similarity is the extent to which x resembles the other objects in set A, either in "essential characteristics to its parent population" or "reflects the salient features of the process by which it is generated." If the perceived similarity is high, the probability estimate is high. If the perceived similarity is low, the probability estimate is low. Extensive study of the representativeness heuristic has identified many systematic errors in intuitive

likelihood estimates, including a central finding of pervasive insensitivity to sample size [81], and base-rate neglect (Example 2).

In an epidemic context, the representativeness heuristic can have enormous importance. Individuals, including experts, may use the representativeness of the individuals they interact with and their personal social network, instead of accurate probability estimates, to produce false conclusions about the prevalence, contact risk, and morbidity of a disease.

2. *Base-Rate Neglect.* Experimental psychology has demonstrated that people tend to ignore prior probabilities, or base rates, when making probability judgments about uncertain events, particularly when presented with individuating information [1, 7, 46]. Vaccination is an important example where base rate neglect can affect the spread of disease. For example, in determining whether individuals will vaccinate or not, rational actor models may use Bayes Theorem to estimate the probability of having an adverse reaction (A) given a vaccination (V),

$$P(A|V) = \frac{P(V|A)P(A)}{P(V)} = \frac{P(V|A)P(A)}{P(V|A)P(A) + P(V|A^c)P(A^c)}$$

where $P(A|V)$ equals the probability of an adverse reaction given vaccination, and $P(V|A)$ is the probability of having been vaccinated given an adverse reaction. These are multiplied by the prior probabilities, or base rate $P(A)/P(V)$. When base rates are excluded, the inverse probabilities are equated,

$$P(A|V) = P(V|A)$$

Media attention typically focuses on the person who had an adverse reaction after receiving a vaccine. In the presence of this individuating information, individuals may ignore base rates or see them as irrelevant. As a result, overestimation of the likelihood of an adverse reaction, and undervaccination of the public, may occur.

3. *Hyperbolic Discounting.* Individual's discount rates are often inconsistent across time spans, tending toward far greater impatience in the short run [57]. This is relevant when modeling diseases that have long incubation periods or for which the risk of infection changes over long periods.
4. *Conditional Expected Utility (or the Illusion of Control).* Individuals frequently overweigh how much their own actions matter when estimating the probability of an outcome [58]. Thus, while proper hygiene may reduce the probability of contracting a disease, it is possible that individuals will systematically overstate their own control over disease outcomes.

These are just a few selected departures from the rational actor model that explain some of the systematic ways in which people fail to make optimal decisions or maximize their expected utility. Future models must incorporate the psychology of

risk [35] and take account of behavioral aspects that might influence the spread of disease.

6.3 ANTIBIOTIC RESISTANCE, BEHAVIOR, AND MATHEMATICAL MODELING

6.3.1 Why an integrated approach?

Ecologically the dynamics of bacterial pathogens are complicated by the fact that they are embedded in the microbiome. Thus, these pathogens must compete with other species of microorganism—some of which are closely related-both directly, for resources, and indirectly, as the hosts immune response alters the ecological landscape. The ecology of the environment, including agricultural practices, may also affect disease dynamics by promoting increased resistance or the long-distance spread of certain pathogens. Epidemiologically many bacterial pathogens can be difficult to track as they do not always cause disease. Thus, individuals can remain colonized and infectious without ever experiencing clinical symptoms, making it difficult to understand the transmission pathways of a disease. In addition, the mechanisms by which colonized individuals progress to disease are not well understood. However, the ecology and epidemiology are also affected by individual/institutional behavioral decisions. For instance, there is a strong link between increased antibiotic use and resistance [6, 78]; thus, individual decisions on antibiotic usage strongly influence the rate that resistance will emerge and spread. Prescription rates for antibiotics are shaped by patients' expectations for antibiotic therapy, and studies show that physicians often prescribe based on their beliefs about what patients expect [22, 66, 73], even though doctors are actually not particularly good at divining patients' expectations [66]. This communication gap leads to injudicious use of antibiotics. On the other side of the prescription decision, patients often will not complete a course of antibiotic therapy, which can allow for the development of resistance. Transmission of antibiotic resistance is also affected by contact networks, which are age dependent [65], as well as the effectiveness of interventions. Infection control in hospitals is one of the primary interventions aimed at reducing the spread of resistance. Even so, hospitals may base their level of investment in infection control on the amount other hospitals that share the same population invest in infection control [76]. At the individual level, rates of hand-washing compliance, which is seen as paramount in reducing the probability of transmission within the hospital, have been notoriously difficult to increase [38, 82].

Usage of antibiotics is also likely to be subject to feedbacks as in other diseases (i.e., people are likely to respond to the prevalence of resistance by changing their usage patterns). A central example is methicillin-resistant *S. aureus* (MRSA), a multiply resistant pathogen that is a scourge of hospitals and has become resistant to nearly every known antibiotic. An October 2007 report estimated that MRSA killed more people annually than HIV [54]. This finding led to an enormous surge in interest in MRSA that then waned exponentially toward baseline levels over time

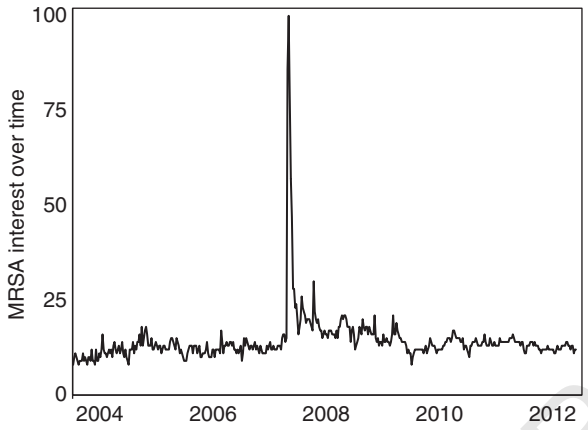

FIGURE 6.1 Data are searches on Google for how often MRSA was entered as a search term relative to the total search volume across the world. The horizontal axis of the main graph represents time (starting from 2004) and the vertical is how often a term is searched for relative to the total number of searches, globally. Data Source: Google Trends (www.google.com/trends).

(see Fig. 6.1). The surge and decline in MRSA interest raises important questions. What sort of impact does such a surge in concern about a resistant bacterial pathogen that is increasing in frequency have on the transmission of that pathogen and the usage of antibiotics? Along with the primary article were numerous reports discussing ways to mitigate transmission, including efforts to change behavior in places such as locker-rooms. What sort of lasting effect did this have? Do these types of behavioral changes explain why rates of MRSA have largely stagnated (or even gone down) in recent years [53], or is its stagnation the result of primarily ecological factors? These are important open questions. Addressing them adequately will require integrated approaches that encompass the roles of economics, sociology (network dynamics), the psychology of risk, computer science, and the ecology and epidemiology of disease.

Over the past several decades, significant advances have been made in understanding disease transmission, individual behavior, and social structures. For instance, one of the biggest advances in the area of epidemic modeling is use of Bayesian inference in conjunction with Markov chain Monte Carlo methods to impute unobserved data [23]. This methodology has been used to estimate epidemic trees of bacterial pathogens where many of the infections may be asymptomatic and thus unobserved [24, 56]. Nonetheless, much of the research has remained "balkanized" with few of the advances within each discipline spreading to others. This is particularly unfortunate in that understanding the complex interplay between behavior, transmission, and disease evolution requires an approach synthesizing insights from each discipline. For instance, exploring how the announcement of an emerging disease affects the future transmission of that disease requires an understanding of how people respond to different types of information, how the information and

associated emotions such as fear of the disease spread, and how the resulting behavioral responses (e.g., fear-driven self isolation, long-range flight) alter social contact patterns, treatment seeking (or refusing) behavior, and the transmission of the disease.

Adding to the complexity of the problem, these behavioral responses and their effects unfold against a backdrop of evolving pathogens that may change based on transmission itself. For example, ecological evidence and theory suggest that when drug-resistant pathogens first emerge they may be more virulent than drug-sensitive pathogens [16, 19, 20, 25, 51, 72, 79, 86]. At the same time, awareness of this increased virulence can change individuals' behavior (improved hygiene, increased hospital visitation, modification of contact networks, etc.). These individual behavioral adaptations can in turn alter the future ecological and evolutionary trajectory of the pathogen, to an extent as great as, if not greater than, the changes in the pathogens intrinsic virulence.

In the face of so much complexity, mathematical and computational models are extremely valuable research and policy tools. They can help strip away extraneous detail, revealing the core generators of complex dynamics. They can offer predictions, forecast the effectiveness of interventions, and even prioritize empirical research [31, 84]. This is particularly important as individual behavior is a significant driver of the emergence and spread of antibacterial resistance. While there are more than 260 million prescriptions written for antibiotics annually, it has been estimated that as much as 60% of antibiotic use is inappropriate or unwarranted [78]. Inappropriate antimicrobial use is the result of individual behavior on the part of both patients and physicians (who prescribe antibiotics). Overuse of antibiotics accelerates the emergence and the transmission of antibiotic resistance in the population, and in some cases (e.g., carbapenem-resistant enterococci) all known antibiotics may soon be exhausted. All of this makes antibiotic resistance, and the diverse behaviors driving it, a particularly timely area for integrated modeling.

6.3.2 The role of symptomology

One important area of modeling bacterial pathogens that can be instructive in devising new policy options is how symptoms (or lack thereof) of infection affect behavior and disease spread. While clinical symptoms are a clear signal to which an individual can respond (stay at home, go to the doctor, etc.) or to which others can respond (e.g., avoid unnecessary contact or sharing of food), many bacterial pathogens can also colonize people for long periods of time. These asymptomatic infections allow individuals to go about their daily routine unfettered. This has the potential to greatly impact the dynamics of disease. To capture behavior appropriately, models of bacterial resistance should account for infection status, distinguishing between (1) clinically ill, (2) asymptomatic, and (3) well individuals.

1. *The clinically ill.* Clinically diseased individuals can have multiple behavioral responses, but the most important include increased probability of contact with the healthcare system and decreased contact with large parts of their "normal" network. These two factors can either increase spread or decrease it, depending

on the protective response of infected individuals and others in their network. For instance, an individual that goes to the hospital could spread the disease more widely than they would have had they only maintained normal contact patterns. In the modern European history of smallpox, for example, half of all transmissions took place in hospitals [30, 61].

2. *The Asymptomatically Infected.* This category of individuals is often ignored or subsumed in the infected class in determining transmission patterns, particularly in bacterial resistance [77], but can in fact be more influential than individuals expressing symptoms. An infection can be asymptomatic at the beginning of its natural history (due to genetic or immune factors for example), or at the end, after the resolution of symptoms (spontaneously or therapeutically) without clearance of the pathogen. Asymptomatic infection can be momentous as exemplified by Typhoid Mary, who remained infectious for typhoid throughout her life despite never becoming symptomatic. This phenomenon has been recognized as a problem for enteric diseases such as cholera [50] and should also be included in models of bacterial pathogens. The behavior of asymptomatically infected individuals depends as well on awareness of their status. As seen with HIV, people may act very differently if they know they are infectious [80], all of which invites integrated modeling.
3. *"Well" individuals*. Uninfected individuals can also respond to disease, of course. The "worried well," as they are sometimes called, have been known to adopt extreme behaviors of prevention, such as self-sequestration (e.g., locking oneself in the basement), and spatial flight. Both can be very consequential for disease spread and can be driven by contagious fear, the extreme forms of which qualify as a mass sociogenic illness [8]. This behavior at its extreme can inundate emergency departments, which may be understaffed due to absenteeism among "worried well" health care personnel, degrading vaccination programs, delaying care for the truly ill, and hampering other control measures. In sum, fear contagion among the perfectly well can sharply inflate the demand for emergency resources while at the same time depressing the supply, a vicious spiral to be sure. Worried well are also likely to overuse antibiotics, making them more susceptible to infection. In addition, every individual that takes antibiotics produces some resistant bacteria, though this does not necessarily mean pathogenic bacteria. Still, the use of antibiotics will produce some resistant bacteria (at least transiently). These resistant bacteria are transmitted to other individuals, or are excreted from the body and enter the environment, spreading resistant genes to other bacteria, including pathogenic ones.

6.4 CONCLUSION

Understanding the interaction of epidemiological, evolutionary, and behavioral factors is crucial if we are to design innovative public health strategies against bacterial pathogens. Such strategies can significantly improve the health and well-being of

millions in the United States and internationally. Understanding of this multifaceted problem requires an integrated approach that incorporates insights from multiple disciplines, and focuses on specific pathogens as bacterial pathogens can have very different routes of transmission (airborne vs. environmental vs. person-to-person) as well as different networks (community vs. hospital) and different ecological niches (gut vs. skin). Future models of antibacterial resistance must also take account of human behavior, taking particular care to develop behavioral considerations for different disease classifications of individuals, specifically addressing how asymptomatically infected individuals behave relative to sick individuals and how this might impact the dynamics of the disease. Cross-discipline cooperation that can incorporate the particulars of a disease into models that include social structure and behavior are more likely to provide useful policy recommendations.

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