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Reflections

On modes of disease transmission and the hidden shape of pandemics: A review of *Asymptomatic* by Joshua Weitz

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Abstract

The importance of asymptomatic transmission was a key discovery in our efforts to study and intervene in the COVID-19 pandemic. In *Asymptomatic* (Johns Hopkins University Press, 2024), Joshua Weitz uses this aspect of SARS-CoV-2 natural history to discuss many counterintuitive characteristics of the pandemic. In this essay, I engage the arguments in the book, and discuss why asymptomatic transmission is such a critical dimension of the study of infectious diseases. I explore ideas contained within *Asymptomatic* and connect them to related issues in evolutionary virology and disease ecology, including epistemic uncertainty and the evolution of virulence. Furthermore, I comment on the broader messages in the text, including the gap between scientific knowledge and social understanding.

Keywords: asymptomatic transmission; COVID-19; epidemiology; virus evolution; science; society

Introduction

In December 2019, the earliest transmission events of a then uncharacterized virus, SARS-CoV-2, were taking place in the Hubei province of China. This was the start of what would be one of the largest pandemics in human history, killing millions worldwide, and forever shaping many corners of our lives: our approach to public health, the economy, our political identity, and countless other dimensions of modern life.

Shortly thereafter, an impressive collective scientific response helped develop a vaccine and popularize public health practices. In recent years, communities of experts related to the pandemic have rarely huddled in pursuit of a comprehensive postmortem on what the hell happened. Some of this can be attributed to political and social distractions that have stymied attempts at a proper reflection. But many of the reasons for society's reluctance to fully debrief are due to "COVID-fatigue," a residual social trauma from the era that has made the pandemic exhausting to think and talk about.

Joshua Weitz's *Asymptomatic* was released in this weary conversational landscape. At just over 200 pages, it is a relatively concise summary of some of the most important issues that arose during the COVID-19 pandemic. Weitz's book is abold attempt at a synthesis, and he uses an important theme: the asymptomatic transmission features of SARS-CoV-2 natural history. Using this instrument, Weitz gives us a work that will surely be remembered as a modern classic on topics related to epidemics, and a shining example of how one need not sacrifice technical rigor for social relevance.

Other books on COVID-19 have done meaningful work in explaining the legal issues that intersect with the pandemic (Witt 2020), or taking on the complexities that underlie the origins and manifestations of the pandemic (Christakis 2020; Scarpino 2020). Unlike these other works, Weitz's text was not released during the pandemic, but in a time (fall 2024) that can be described as post-pandemic. Also, unlike any major text on the topic, Weitz focuses on a specific feature of SARS-CoV-2 biology. Weitz explains the aims of the project (Chapter 5: "Testing as a Form of Pandemic Mitigation'):

'This book's premise has been that asymptomatic spread is a double-edged sword: a silent or mild outcome for some that can lead, inadvertently, to far greater numbers of severe cases for the population as a whole."

While asymptomatic transmission is not the only unique thing about SARS-CoV-2, it does serve as a hub for many aspects that made the pandemic so disruptive and confounding.

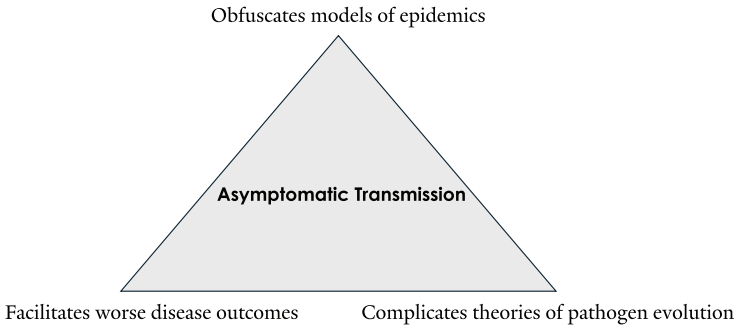

Figure 1. A schematic depicting three of the many ways that asymptomatic transmission influences important aspects of disease ecology and evolution. Asymptomatic transmission can lead one to underestimate the explosiveness of an outbreak, thereby throwing off our model predictions. Furthermore, because asymptomatic carriers can serve as inconspicuous links that can transmit pathogens, they can make outcomes much worse than a hypothetical pandemic that is exclusively symptomatic. Lastly, asymptomatic transmission subverts deterministic theories on how pathogen virulence should evolve. Refer to main text for more discussion.

Pernicious consequences

"Asymptomatic transmission" can be defined as a state where an infected individual displays no specific, observable signatures of illness but can nonetheless transmit disease to another host. And it is a deceptively rich notion. We know that sneezing and coughing are standard symptoms for many respiratory infections, but the line can be thin between very light symptoms and enough symptoms to qualify as being truly symptomatic. Further, the biological roots of asymptomatic transmission remain mostly a mystery, the likely stew of several forces including virus type and host characteristics.

SARS-CoV-2 was not the first (and will not be the last) newsworthy pathogen where asymptomatic transmission is a feature. What, then, makes it so important as to warrant being the focus of a book about the COVID-19 pandemic? We can briefly summarize three ways (of many) that asymptomatic transmission creates obstacles for the sciences of epidemiology and evolutionary virology. We organize them as follows: asymptomatic transmission facilitated worse outcomes at the population level, complicated existing models of virus evolution, and obfuscated mathematical models of disease (Fig. 1). Note that some of these ideas arose from my engagement with the content of *Asymptomatic*, and not directly from its pages.

At the population scale, asymptomatic transmission leads to worse outcomes

The existence of asymptomatic transmission had a counterintuitive effect on the pandemic: studies have shown that an intermediate proportion of asymptomatic transmitters can lead to worse outcomes at the population scale than a scenario where everyone was either asymptomatic or symptomatic (Park et al. 2023). The particulars of why this is so may require some algebra and calculus, but the broader reasons can easily be explained by a few characteristics of asymptomatic transmission outlined in Chapter 3 ("Asymptomatic Transmission Leads to Many More Fatalities"). Weitz explains:

"Individuals who feel fine are unlikely to need a day off. They go out to work, visit friends and family, and are more likely to let their guard down when around others. Why should someone who feels fine need to wear a mask when around others?"

That is, people with no symptoms were understandably less likely to participate in the strict public health practices (e.g. frequent testing, masks, and social distancing) necessary to stymie a growing disease. Tragically, those asymptomatic carriers of SARS-CoV-2 shed virus at a level largely indistinguishable from their symptomatic counterparts (Kissler et al. 2021). Because of this, those less likely to participate in public health behavioral practices are also very likely to infect others, often doing so without ever being aware of their positive infection status. Weitz punctuates this point:

"Ultimately, people who were asymptomatically infected became silent links in growing chains that led to more than 1 million deaths in the United States alone."

Asymptomatic transmission complicates theories of virus evolution

Weitz does not mince words and uses space efficiently. Because of this (and knowledge of the author's vast expertise), one can guess that there are several topics related to asymptomatic transmission that were left on the cutting room floor. Here, we will consider one idea not covered in the pages *Asymptomatic*: how the transmission route of SARS-CoV-2 influences our perspective on canonical theories of virus evolution.

One dominant model of infectious disease is called "the evolution of virulence." Virulence has many technical definitions but can be more casually described as increased harm to a host resulting from parasite infection. The evolution of virulence theory posits that there is a relationship between how virulent a pathogen can evolve to become and its propensity for transmission (Lenski 1988; Bull 1994; Ewald 1995). Transmission can be defined as the ability to successfully transmit a viral infection from one host to another. The evolution of virulence proposes that how sick a virus makes a host—its virulence—can be limited by whether that virulence level influences the odds of effective transmission.

The evolution of virulence serves as a useful example of how tradeoffs and constraints manifest in adaptive evolution. And it benefits from a copious amount of evidence in support of it. That said, the theory can suffer from oversimplifying the evolutionary forces that craft disease symptoms. Furthermore, some have questioned the tradeoff model in the evolution of virulence (Ebert and Bull 2003), and mathematical studies suggest that evidence for any relationship between virulence and transmission are highly idiosyncratic, driven by certain natural histories of disease (Surasinghe et al. 2024).

The asymptomatic route of transmission poses specific challenges for the evolution of virulence. In asymptomatic transmission, symptoms are often decoupled from odds of transmissibility.

Asymptomatic carriers are effective transmitters, and they can transmit viruses that lead to symptoms and death in other individuals. Because of this, it is naïve to impose a theoretical expectation for how SARS-CoV-2 should evolve to be more or less virulent with respect to contagiousness. In many cases, the severity of illness caused by the virus was unrelated to its success in spreading from host to host. More generally, SARS-CoV-2 evolution was a deeply peculiar phenomenon, with multiple constraints and contingencies, many driven by the biology of the host–virus interaction. These sorts of questions were amplified by the evolution of variants of interest and variants of concern. This encouraged genomic epidemiologists to reconsider how genotypic changes translated into phenotypic differences, specifically with regard to how SARS-CoV-2 mutations influence vaccine efficacy (Grubaugh and Cobey 2021).

Asymptomatic does not directly address erroneous predictions for virus evolution during the COVID-19 pandemic. To briefly explain the evolution of virulence (a complicated idea) in a book meant for the public would be too ambitious, especially when Weitz covers so many other topics. But that I am able to connect themes from the book to contemporary issues in virus evolution is a strength and a testament to the generative potential of *Asymptomatic*: it implores all who study viruses to think more carefully about the theoretical pillars of our fields.

Asymptomatic transmission obfuscates models of disease

The asymptomatic feature of SARS-CoV-2 dynamics had implications for how we modeled and counted infections, and undermined simplistic explanations for what was happening. Furthermore, the COVID-19 pandemic highlighted how imprecision from experts had serious consequences. One set of egregious miscalculations lived in a model created by the Institute for Health Metrics and Evaluation (IHME) (Jewell, Lewnard, and Jewell 2020; IHME COVID-19 Forecasting Team 2021). Weitz describes its pitfalls in Chapter 1 (It was Never "Just the Flu"):

"It turns out that the IHME model was worse than useless–it was dangerously wrong, providing what appeared to be legitimate cover for an anti-scientific response to a rapidly spreading epidemic."

The IHME model suffered from several flaws, including an allegiance to classical concepts like Farr's Law, which proposes a symmetrical rise and fall of infectious disease over the course of an outbreak (Bregman and Langmuir 1990). But many of the sins of the IHME model, and several others, can be attributed to the asymptomatic nature of many transmission events. That so many people spreading disease did not suffer from symptoms helps explain the manner through which SARS-CoV-2 spread early in thepandemic.

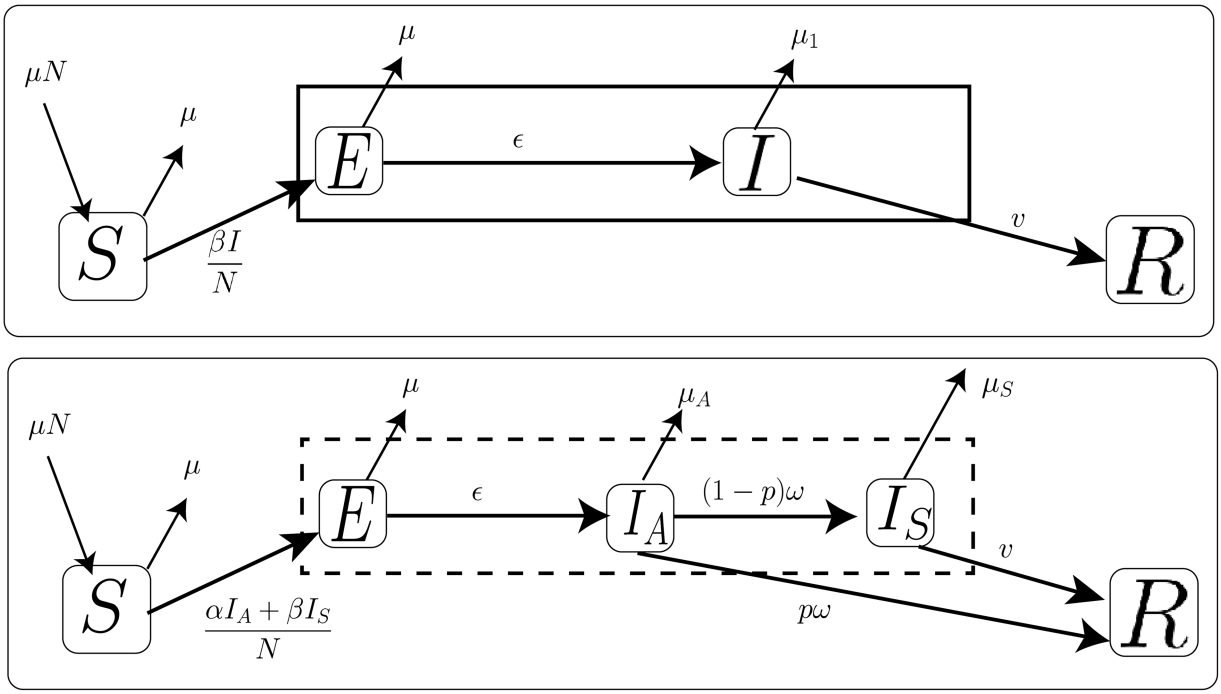

Figure 2. Epistemic uncertainty in disease modeling related to asymptomatic transmission. As is standard in elementary mathematical epidemiology, [S] corresponds to the population of individuals susceptible to infectious disease. The [E] compartment corresponds to those who have been exposed to disease but have not yet become fully infected. [I] component corresponds to those fully infected (and infectious), and [R] component those that have recovered (often with immunity). The top model structure assumes that all exposed individuals can become infected individuals and can be characterized by a single compartment, [I]. The lower model, however, disaggregates the [I] compartment into symptomatic [I_S] and an asymptomatic [I_A] sub-compartments (dashed-placeholder box). Greek letters correspond to parameter values that compute the flow of individuals in and out of the model, and between compartments. As described in the identifiability problem, these two mathematical model structures for a pandemic virus can lead to similar disease dynamics, depending on parameter choices (Eisenberg, Robertson, and Tien 2013). Note: these particular models are modified based on prior work, where relevant parameter values and other details can be found (Surasinghe et al. 2024). Those interested in general explanations of mathematical models should consult comprehensive texts on related topics (Otto and Day 2011; Weitz 2016).

There is a term used in the philosophy of science, epistemic uncertainty, which describes a lack of statistical information or knowledge, often manifesting in the modeling process (Hüllermeier and Waegeman 2021). This defines much of the experience of COVID-19, where epistemic uncertainty distorted our perception of disease dynamics.

We provide an example of how this may manifest in Fig. 2. Here we observe two schematics of mathematical models for an infectious disease. In both settings, there is an "exposed" [E] category that captures the flow of disease before a person is fully infectious. But the two different model structures can lead to similar dynamics under certain parameter combinations, a flaw that statisticians refer to as the identifiability problem (Cortez and Weitz 2013; Eisenberg, Robertson, and Tien 2013). Notably, both of these model structures have been used to describe SARS-CoV-2 transmission dynamics in different highly cited studies (<350 citations), both published during 2020 (Carcione et al. 2020; Mwalili et al. 2020).

The error of engineering an incorrect model can be akin to an honest mistake. Because complex biological systems can be difficult to grasp, researchers should not (necessarily) be faulted for building models that do not describe the real-world. But during a global pandemic, these errors can have life and death consequences. *Asymptomatic* emphasizes how the asymptomatic transmission feature, which may appear like a subtle detail in a mathematical model, is the product of unique pathophysiology, and it has profound implications for many aspects of COVID-19 dynamics.

I emphasize that the three areas mentioned earlier (shown in Fig. 1) are neither exhaustive nor the only ways to categorize the many challenges fostered by asymptomatic transmission. For example, how asymptomatic transmission specifically frustrates interventions could quality as its own main category. I have chosen one such categorization for discussion purposes.

The COVID-19 synthesis that we deserve

Weitz is a leader in the greater fields of quantitative virology, and an author of seminal technical texts on related areas (Weitz 2016, 2024). Because of this, we should not be surprised by his mastery of the vagaries of clinical statistics and virus pathophysiology. But *Asymptomatic* thrives in both its technical depth and its topical breadth. With sagacity, Weitz highlights that the defining problems of the COVID-19 pandemic were not solely about the molecular tricks that RNA viruses use to survive, or the immunological roots of the asymptomatic route of transmission. Rather, Weitz recognizes that communication was a major problem during the pandemic: society suffered from broken communication pipelines between public health professions, basic scientists, policy makers, and the citizen–scientist public.

Among his focuses in Part II of the book ("Preparing for Pandemics to Come") include communication models for relaying details of risk to the public. In Chapter 4 ("Respecting the Public: Putting Data into their Hands"), Weitz states:

"…COVID-19 has revealed fundamental inadequacies in the link between rigorous epidemic research, the assessment of uncertainty, and the communication of accurate information to the public at large."

He spends a lot of time in this area, even highlighting an underappreciated barrier to communicating science during a pandemic: that the pace at which relevant scientific information is generated is far different than the pace in which scientific products are typically produced and evaluated. These are important cultural insights that I was pleasantly surprised to see explored with such depth, given the technical acuity of the first half of the book.

Consistent with Weitz's emphasis on public health messaging, *Asymptomatic* is very readable, and I suspect the lessons will be interpretable by nonexperts. Surely aspects can be challenging for even epidemiologists to grasp on first pass, but Weitz does an impressive job of explaining complicated concepts like sensitivity/specificity, herd immunity, and the basics of epidemiological modeling.

The importance of *Asymptomatic* resides in how it succeeds in multiple challenging ambitions. It is both an exemplar of accessible science communication and is the rigorous COVID-19 synthesis that we all deserved. And it casts a light on dubious practices within science and society that the pandemic revealed.

In its many triumphs, *Asymptomatic* provides a dose of caffeine for our COVID-19 fatigue. The reader emerges alert, emboldened with a nuanced understanding of one of the greatest pandemics in human history, and prepared to defend a scientific process that is increasingly in peril due to misinformation and disinformation.

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Data availability

No new data appear in this manuscript. For the models discussed in the text, relevant data and code can be found in the cited technical papers.

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