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On the Relationship between Asymptomatic Infections and Diseases

Martin Zach[1]

1 Department of Analytic Philosophy, Institute of Philosophy of the Czech Academy of Sciences, Prague, Czechia. Email: zach@flu.cas.cz

Abstract

Many microbes responsible for infectious diseases are known to run an asymptomatic course in a significant portion of the population. By highlighting the conceptual complexities of host-microbe interactions, this paper elucidates the fact that while many infections remain asymptomatic, this does not necessarily mean that such infections are of no concern for health. The paper builds on the so-called damage-response framework and considers several developments required to gain a more comprehensive perspective on infections and their relationship to diseases. Irrespective of their (short-term) clinical manifestation, infections leave an imprint with consequences for health. Finally, these considerations regarding host-microbe interactions must be incorporated into policy decisions and public understanding of health if we hope to handle future pandemics such as Covid-19 better.

1. Introduction

Suppose you meet with a friend, who soon thereafter does not feel well. Your friend has a sore throat, coughs, feels weak, and has lost their sense of smell and taste. Since these are among the typical symptoms of Covid-19 caused by SARS-CoV-2, your friend undergoes a test for the pathogen. The result is positive. Because you may have been infected, you also take the test, which also comes out positive. Yet you feel perfectly fine and never develop any symptoms.

An immediate question suggests itself. Do you have the disease called Covid-19 if you are infected but do not have symptoms? This hints at a more general question concerning the relationship between an infection, a disease, and symptoms. Philosophers of medicine have long debated the nature of diseases by proposing various accounts in the form of a set of criteria, each necessary and together sufficient. Such accounts are then tested against a wide array of examples judged to be examples of disease and non-disease conditions (see Reiss and Ankeny 2016; Murphy 2020 for an overview; see also Lemoine 2013, forthcoming 2024; Sholl 2015; Fuller 2018 for a critical discussion of the particular philosophical approach). An example of such philosophical debate on diseases, which includes asymptomatic infections, is provided by Alex Broadbent (2014). It is generally believed that possessing a set of criteria that determine whether something is an instance of a disease

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may have practical consequences (but see, for example, Hesslow 1993 for a dissenting voice). Whether someone is regarded as having a disease often comes with certain personal and societal privileges as well as limitations, such as entitlement to treatment and reimbursement (Amoretti and Lalumera 2020).

Let us now return to the original example: you are infected with SARS-CoV-2 yet feel perfectly fine. What might this mean for you in the long run? Once again, this hints at a more general issue: what the outcomes of a variety of infections are beyond the acute (a)symptomatic phase. Until recently, this question has not gained wide traction—to the detriment of patients. To concern oneself merely with the acute phase, including the issue of whether asymptomatic infection can, on some definition, count as disease, might miss an opportunity to recognize far wider and diverse categories of outcomes of infections, which have important ramifications and direct relevance for public health.

It is precisely this *latter question* regarding the long-term impact of infections—as opposed to the former question regarding definition of disease—that I discuss in this paper. While such an endeavor is no longer about the quest to define disease (the usual obsession of philosophers of medicine), there is nevertheless ample opportunity for philosophers interested in the investigation of the nature of biological phenomena and its conceptualization. After all, how we conceptualize things influences how we approach problems, as well as our very capacity to identify existing problems. Conceptual complexities become apparent as soon as one starts considering the nature of host-microbe interactions. Following an outline of the damage-response framework introduced by Liise-anne Pirofski and Arturo Casadevall (2002) in section 2, I shed light on why and how the framework needs be expanded (section 3). Such additional considerations further highlight the point that, irrespective of their (short-term) clinical manifestation, infections leave an imprint, with consequences for health. As a result, these considerations are relevant to policymakers and public understanding of health (section 4).

2. Exposure, Infection, and Disease: The Damage-Response Framework

The conceptual distinction between exposure, infection, and disease is part and parcel of immunology and microbiology. Exposure to a pathogen does not necessarily lead to the establishment of an infection, and an infection does not necessarily result in disease. Following Pirofski and Casadevall (2002), exposure can be defined as denoting the theoretical risk of, or actual contact with a microbe; infection as the acquisition of a microbe; and disease as the nature and extent of damage to the host that "can result from microscopic, macroscopic, clinically apparent, or clinically unapparent events" (2002, 630). Additionally, "disease only becomes apparent when host damage reaches a certain threshold" (2002, 630). More specifically, "infection only results in disease when the host-microbe interaction produces sufficient damage to disrupt normal homeostasis and/or to become clinically apparent" (2002, 631).

At the dawn of the germ theory of disease, it was generally thought that microbes are pathogenic—that they directly cause disease by virtue of their intrinsic properties. However, at the beginning of the twentieth century, it became obvious that this view required rethinking. It was discovered that many of these microbes do not cause clinically apparent disease in most of their hosts. Perhaps the best-known example was the identification of

Mary Mallon, commonly known by the derogatory nickname "Typhoid Mary," as a carrier of *Salmonella typhi,* the causative agent of typhoid fever (Leavitt 1992). While working as a cook, Mallon unknowingly infected dozens of people over the course of several years, some of whom died. Yet she herself experienced no symptoms and was thought to remain healthy. Such a condition is now well known and the phenomenon of *asymptomaticity* is, in fact, very common across pathogens. To give but a few additional examples, consider, for instance, the fact that the vast majority of people infected with the poliovirus do not display symptoms; polio is a rather rare outcome of infection, affecting less than 1% of infected individuals (CDC 2022). A similar pattern is also true of *Mycobacterium tuberculosis* infection, which gives rise to tuberculosis in about 5–10% of infected individuals (Olive and Sassetti 2018). Although the estimates of asymptomatic SARS-CoV-2 infection differ (but it seems safe to assume at least 20% of the cases are asymptomatic) (Meyerowitz et al. 2021), the fact remains that SARS-CoV-2 is a recent addition to a long list of pathogens that do not induce clinically apparent disease in all infected individuals.

Additionally, it was discovered that some microbial species, including bacterial, viral, and fungal, are in fact beneficial to their hosts, constituting their microbiome. Yet the distinction between good and bad microbes could not stand, for it was soon realized that there are different ways in which a microbe can coexist with a host: for example, as pathobionts, the "good" ones can turn "bad." Finally, it was understood that pathogenicity is a complex and dynamic relation between the host and the microbe (Méthot and Alizon 2014), meaning that host damage occurs not only because of something the microbe does but also because of what the individual host response to the microbe does, which is context-dependent and may change in time. While some host-microbe interactions are on average more prone to result in host damage, this is also due to the pathogen-induced damage and host-induced damage, rather than merely the reflection of the intrinsic properties of the microbe.

According to Pirofski and Casadevall (2002), the relevant outcome of such host-microbe interaction is the extent of damage imposed on the host, summarized by the damage-response framework.[1] *Such a framework shifts focus from the question of when someone is merely infected versus diseased to the question of what the outcome of an infection is.* One of the outcomes can be a state of latency, which brings about some damage but not enough to result in clinically apparent disease. A prime example is the HIV infection, which leads to damage but remains symptom-free for many years (the latent stage) before progressing to AIDS in most but not all individuals (the disease stage). Opportunistic microbes are also thought to be commonly present in the latent state, with the potential to result in overt disease in situations of immune impairment. Another possible outcome of an infection is the state of colonization in which alteration of host homeostasis and damage may occur but not of sufficient quantity or quality to result in clinically apparent disease. This can be contrasted with latency, which can be discerned from colonization by the temporal and damage considerations: colonization is usually transient and progressively increases the damage burden. Finally, the outcome can also be the state of commensalism, which denotes host-microbe interactions in which microbes that are usually acquired early in life, and inhabit the host throughout its life, are associated with no damage. In fact,

[1] To be more precise, one should also include in the framework the physiological stress imposed on the host due to the infection, and the respective stress responses (see, for example, Soares, Teixeira, and Moita 2017).

commensals have been shown to play several important and protective roles (Rakoff-Nahoum et al. 2004).

However, all these states, including commensalism, can, under a variety of conditions, at some point, cross the damage threshold and give rise to clinically apparent disease (see Pirofski and Casadevall 2002, Figure 1, for a schematic depiction of all the states and their relationship). Distinguishing these dynamic states based on the resulting damage in clinical practice is dependent on the available technology that can detect said damage.

Things get even more complicated with regard to the following two aspects. First, the connection between damage and symptoms is not always straightforward since the damage can be masked. Second, the impact of infections on health outcomes goes beyond the concerns with (acute) damage. In the next section these two issues are discussed in some detail. While both are broadly consistent with the damage-response framework, they imply that the consideration of additional nuances regarding host-microbe interactions would significantly enrich the framework, and allow a more comprehensive understanding of host-microbe interactions and the development of more adequate policies.

3. Concerns beyond the Damage-Response Framework

3.1 Infections: Damage but No Symptoms

One puzzling observation concerns the fact that the relationship between damage and clinically apparent symptoms is not straightforward. For example, while hypoxemia in Covid-19 caused by damage to the lung tissue often manifests itself in shortness of breath, some individuals suffer from severe hypoxemia with no such apparent manifestation, a state called silent hypoxemia (Swenson, Ruoss, and Swenson 2021). This constitutes a case in which there is profound damage and loss of function, yet such damage does not correlate in time with clinically apparent disease.

In other cases, there may be a significant damage to the host that does not result in a loss of function due to an efficient compensation mechanism such as tissue renewal or tissue repair. Infections that cause damage but are compensated enough to prevent major disruptions of physiological functions also remain asymptomatic (Medzhitov, Schneider, and Soares 2012). For example, an increase in erythropoiesis is a compensatory mechanism that protects against hemolytic microbes, such as *Plasmodium falciparum,* the causative agent of malaria.[2] However, compensation also does not come for free, as maintaining primary function is achieved at the expense of other, less crucial functions, which can be

[2] More generally, to survive infections, organisms employ disease tolerance—that is, the capacity to withstand the negative effects of pathogens and immunopathology without affecting the pathogen load (Schneider and Ayres 2008; Soares, Teixeira, and Moita 2017; Ayres 2020; see also Zach and Greslehner 2022 for a philosophical discussion). Janelle Ayres calls for shifting attention from the question of "how we fight infections" to "how we survive infections" (see, for example, her TEDx talk "Ending the Arms Race with Infectious Diseases," Ayres 2016). The former question relates to strategies aimed at eliminating pathogens, whereas the latter (disease tolerance) consists in preventing and fixing the damage due to the pathogen and immunopathology. Such a change in perspective on infectious diseases promises to potentially lead to the development of new kinds of treatments that, among other things, would not drive, for example, antibiotic resistance since disease tolerance is not expected to exert the same selective pressure on the pathogens. It is also worth noting that while morbidity and mortality are often thought to result from an impairment in the capacity to clear a given pathogen, they can also result from the failure of disease tolerance (Medzhitov, Schneider, and Soares 2012)—something the immunological community at large is still struggling to appreciate fully (Schneider 2021).

detrimental to the host over time. Thus, even the very process of *effective* damage and tissue repair takes its toll on the organism over time.

3.2 Infections and Sequelae

Infections may exhibit a complicated relationship with some ensuing diseases. Infectious agents may *trigger* pathological processes—that is to say, they may act as an inciting stimulus, triggering a self-perpetuating process of disease driven by factors other than the inciting stimulus, which may be no longer present in the organism. Establishing the causal relationship can be tricky since the onset of a symptomatic disease may not temporally coincide with the infection. Infections may also *drive* and maintain pathology. For example, a variety of infections, especially viral infections, have been associated with the onset of autoimmune diseases, either as triggers or drivers of the disease via a range of different mechanisms (Sollid and Jabri 2013; Sollid 2022), but also of cancers (Weinberg 2014) and other conditions. Importantly, such infections can run an asymptomatic course.

Many infectious agents are now known to cause sequelae and chronic disability: post-polio, which appears anywhere between 15 and 40 years after the initial polio subsides (CDC 2022), post-Ebola, post-flu, and post-acute sequelae of Covid-19, to name just a few examples from dozens of known sequelae of viral infections (Choutka et al. 2022; Griffin 2022). Bacterial infections are no exception. A mechanistic illustration is provided by the work of Denise Morais da Fonseca and colleagues (2015): following the clearance of gastrointestinal infection with *Yersinia pseudotuberculosis,* microbes that are part of the normal microflora of infected mice will start acting as chronic pathogens. As a result, the tissue is remodeled in such a way that it gives rise to immune dysfunction. Thus, a previously cleared infection can have long-term and cumulative effects, resulting in a persistent impairing of the mucosal immune functions. Detrimental effects are not necessarily limited to the local tissue context in which the original insult caused disruption but can have distant manifestations in other organs, such as inflammation in the brain following the disruption of the epithelial barrier in the gut or lung (Akdis 2021). Overall, however, long-term effects and sequelae of many endemic respiratory and gastrointestinal infections that affect modern societies and high-density urban neighborhoods remain understudied.

Another layer of complexity stems from the realization that while most host-microbe interactions on average favor either an acute or a chronic (latent or persistent) course of infection, they cannot always be neatly categorized in this way since many “acute” microbes can be retained by the host in whole or in part (Goulding et al. 2007). Such persistence includes cases in which patients exhibit clinical recovery and no longer harbor detectable levels of the infectious microbe in question, other than some of its remnants such as (full-length) viral RNA and other antigens (Griffin 2022). Although persistence may have some beneficial effects, it is also associated with a number of detrimental outcomes, including the late onset or exacerbation of some (progressive) diseases such as cardiac dysfunction or asthma (Griffin 2022).

3.3 Infections and Modulation

Infections can also modulate a wide range of host features, having a long-term effect on host susceptibility to various conditions. Depending on the particular condition and context, such modulations can have beneficial or detrimental effects. These modulatory changes occur either during or after an infection.

Most commonly, an active acute infection triggers a particular type of immune response aimed at a specific microbe, which modulates the response against another kind of microbe. This is why certain coinfections, such as infection with influenza virus followed by a pneumonia-inducing bacteria, are associated with severe morbidity and mortality (Eberl 2016).[3]

Chronic infections also modulate responses. A prime example are helminth infections (Maizels and McSorley 2016): for example, mice infected with *Trichuris muris,* an intestinal nematode worm, induce regulatory T cells, which are protective against damage but also contribute to immunosuppression and eventually to the development of cancer (Hayes et al. 2017). Furthermore, in both acute and chronic conditions, the establishment of adaptive and innate immune memory modulates responses to subsequent challenges and has both beneficial and harmful effects (Netea et al. 2020; Divangahi et al. 2020). For example, cross-reactive memory T cells can have a protective effect but they can also lead to immunopathology (Welsh and Selin 2002).

Following the resolution of an influenza virus infection, changes in alveolar macrophages contribute to the prolonged establishment of an immunosuppressive environment in the lungs, with consequences for responses to secondary infections (Didierlaurent et al. 2008; see also Snelgrove, Godlee, and Hussell 2011 for additional considerations). Relatedly, studies have shown that various changes occur in a subclinical manner after an infection is resolved, constituting a so-called post-resolution phase (Goulding et al. 2007; Motwani et al. 2017; Feehan and Gilroy 2019). Such changes also highlight the fact that infections leave a long-term imprint in the form of a change to the physiology of the tissue. The altered state of a tissue due to an infection influences the outcome of a later infection, with some sequences of certain infections having a beneficial effect on a later response and other sequences exhibiting harmful effects (Goulding et al. 2007; Hussell 2016; Jenkins and Allen 2021). In addition to the particular sequence of infections, the timing also matters. For example, there appears to be an association between early-life asymptomatic viral infections and an increased susceptibility to later-life respiratory infections (De Steenhuijsen Piters et al. 2022). The tissue changes due to infections also impact a host of noninfectious conditions (Naik and Fuchs 2022), including tissue transplants (Sachs 2003).

In summary, while rooted in the damage-response framework, the emerging view on host-microbe interactions is greatly enriched by considering a wider array of phenomena, many of which exhibit a (more) complicated relationship to damage. Overall, irrespective of their (short-term) clinical manifestation, infections leave a long-lasting mark on the host, with consequences for health.

[3] Alternatively, the explanation may lie in triggering pathways that afford disease tolerance to one kind of microbe, which are incompatible with disease tolerance to another kind of microbe (Medzhitov, Schneider, and Soares 2012).

4. Implications for Policymakers and Public Understanding of Health Impacts

The preceding considerations reveal some of the conceptual complexities underlying host-microbe interactions with respect to diseases. However, much of the reporting and science communication, and many policies, do not reflect these complexities.

Consider, for example, media reports covering the 2001 outbreak of *Bacillus anthracis,* the causative agent of anthrax. In those reports, while the term "exposure" denoted a situation in which an individual harbored *B. anthracis* without clinical manifestation of anthrax, the term "infection" was used to refer to those who manifested anthrax (Pirofski and Casadevall 2002). The use of these terms is misleading. Similarly, during the Covid-19 pandemic, many of the complexities seem to have been treated in a confusing manner, brushed away by various stakeholders responsible for shaping public opinion, or replaced with intuitive yet not universally valid generalizations.

Much of the early communication during the Covid-19 pandemic was inspired by epidemiological modeling. While a variety of models were used, including, for example, agent-based models (Maziarz and Zach 2020, 2021), much of the attention was put on SIR compartmental models (and the corresponding key concepts—susceptible, infected, and recovered) and on "flattening the curve" since hospitalization and death rates were alarming. While SIR and other such models are an essential tool, the communication should not have stopped at these simple concepts, especially as the pandemic progressed and it became clear—as many feared, based on studies on related pathogens such as SARS-CoV and MERS-CoV, as well as other pathogens—that many individuals suffer from sequelae, colloquially known as long Covid.[4] What is worse is that "it continues to be overlooked by decision makers, who still present the costs and benefits of COVID-19 containment in terms of data on cases, hospitalizations and deaths alone" (Spinney 2022, 385). However, it should never have been forgotten that "pandemics disable people" (Spinney 2022). Even if infection with SARS-CoV-2 turns out to be a relatively weak risk factor for developing various sequelae, we can expect to see lots of downstream disease in years to come because of how many people have been infected and reinfected. Put otherwise, the impact of and the policies adopted throughout a pandemic such as Covid-19 should not be evaluated merely in terms of their impact on immediate considerations of life span but also on health span.

Indeed, as noted before, an oversimplified take on the host-microbe interactions overshadows many effects on health arising from infections and perpetuates the false narrative that survivors necessarily recover fully and bounce back to their original health. Furthermore, it relates to the popular yet obscure and wrong idea that an infection, should you survive it, is good for you as it helps to *strengthen* your immunity (Zach and Greslehner 2023). Such an idea may also be summarized in the simple slogan: "A little disease is good for you." This is taken to mean that a host affected by an infection that does not lead to clinically apparent disease, or leads only to mildly symptomatic disease, reaps the benefits of attaining protection against severe disease on second encounter. In fact, there is a debate in the literature along those lines: for example, it has been suggested that persistent or recurrent infection with the causative agent of malaria, in cases in which it is controlled but

[4] Here, we may want to distinguish between what is colloquially called long Covid, characterized by lingering or late onset of some symptoms, and another kind of sequela that presents itself as a risk factor for developing a variety of other complications and diseases, such as cardiovascular or metabolic diseases, among others (Altmann et al. 2023).

not entirely eliminated, provides protection against severe disease (Doolan, Dobaño, and Baird 2009). However, the outcomes of these so-called asymptomatic infections, despite providing protection against severe malaria, result in other detrimental health outcomes, such as impaired cognitive function, increased susceptibility to bacterial infections, and complications in pregnancies, which is why some suggest that all malaria infections may require treatment, irrespective of their clinical presentation (Chen et al. 2016). Relatedly, a low dose of an infectious agent is commonly thought to be better for the host than a large dose, and a repeated low dose is thought merely to stimulate the immune system, thus building up immunity without the detrimental effects of severe disease associated with large doses. To realize that this is, if nothing else, not generally valid, consider a study in which rabbits sequentially infected with five low doses of *Mycobacterium tuberculosis* exhibited greater lung pathology than rabbits infected with a single large dose equivalent to those five (Urbanowski et al. 2018). Immunology, the place where "intuition goes to die" (Yong 2020), much like biology in general, is full of such exceptions, rather than strict universal rules.

Overall, the damage-response framework, and extensions of such a framework, are what bring us a step closer to obtaining a more comprehensive understanding of host-microbe interactions and their impact on host health. In addition to empirical data, we need conceptual innovations in the form of comprehensive frameworks to correct existing communication strategies and policies and to develop new ones that may help us better prepare for—or even prevent—future emergencies.

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