Abstract

There is increasing interest in the role that evolution may play in current and future pandemics, but there is often also considerable confusion about the actual evolutionary predictions. This may be, in part, due to a historical separation of evolutionary and medical fields, but there is a large, somewhat nuanced body of evidence-supported theory on the evolution of infectious disease. In this review, we synthesize this evolutionary theory in order to provide framework for clearer understanding of the key principles. Specifically, we discuss the selection acting on zoonotic pathogens’ transmission rates and virulence at spillover and during emergence. We explain how the direction and strength of selection during epidemics of emerging zoonotic disease can be understood by a three Ts framework: trade-offs, transmission, and time scales. Virulence and transmission rate may trade-off, but transmission rate is likely to be favored by selection early in emergence, particularly if maladapted zoonotic pathogens have ‘no-cost’ transmission rate improving mutations available to them. Additionally, the optimal virulence and transmission rates can shift with the time scale of the epidemic. Predicting pathogen evolution therefore depends on understanding both the trade-offs of transmission-improving mutations and the time scales of selection. (194/200)

Keywords: Trade-offs, Virulence, Transmission, Emerging Zoonotic Disease, Evolution

Introduction

Throughout the current global pandemic of Sars-CoV-2, we have seen a growing public fascination with the role of pathogen evolution during disease emergence. In May 2020, reports of a mutational variant (D614G) increasing in frequency sparked concern about virus evolution [1–3] and more potentially adaptive variants have since been reported [4–6]. These experiences with SARS-CoV-2 and with previous epidemics of other zoonotic diseases have clearly demonstrated the potential for pathogens to evolve during disease emergence [7]. Despite this importance, public conversations around pathogen evolution are often fraught with misunderstandings. To some extent, this is likely reflective of the historical separation of evolutionary and medical disciplines [8,9]. Beyond that, however, scientific communication around pathogen evolution is particularly tricky because the science to be communicated provides no clear answers to be packaged into simple explanations.
Experts studying infectious disease evolution understand that pathogens have the potential to rapidly adapt due to high population sizes, short generation times, and relatively high mutation rates [10] and recognize that human populations impose novel, although often understood, selection pressures [11]. At the same time, however, many experts are sometimes quick to express skepticism when public conversation is dominated by concern over pathogen evolution. This is partially because pathogen evolution is just one factor of many that collectively influence epidemic progression, so communication around its importance sits on a teetertotter of balancing a concern and attentiveness against a blinded focus on potential evolution over other factors shaping the epidemic [12,13].

Additionally, many experts studying infectious disease evolution are often quick to emphasize that we cannot predict how a specific pathogen will evolve [14]. However, this does not mean that we have absolutely no idea of how pathogens generally may evolve. We expect that pathogens will evolve in response to selection in human populations, but the speed at which they do depends critically on the availability of adaptive variation and the relative strength of selection compared to stochasticity, both of which relate to the number of infected individuals [15]. Theory predicts that pathogens may evolve towards optimal virulence and transmission rates due to underlying constraints, but these predictions depend on nuances of pathogen biology, epidemic stage, and host population structure [16,17]. It can, understandably, be frustrating when asking how a pathogen will evolve to hear predictions that sound like contradictions and non-answers, but this reflects the complicated realities of pathogen evolution. However, this real uncertainty also seems to have created an environment where hope for simple answers means that misinformation can spread.

On top of the inherent challenges of communicating complex scientific concepts, researchers studying pathogen evolution must also play ‘whack-a-mole’ against a variety of misconceptions that are wrong in different ways. Public concern sometimes skews towards pathogens evolving to be hyper-virulent, hyper-transmissible superbugs [18]. Alternatively, historical theories of evolution towards avirulence still pervade the public consciousness and sometimes lead to the prediction that pathogens universally evolve to become less dangerous [19]. In both directions, these misconceptions can lead to inappropriate public health policies. However, the disjointed nature of combatting misconceptions as they arise has led to much of the conversation on pathogen evolution in emerging zoonotic diseases being scattered across the scientific literature and media. This can be compounded by the fact that researchers studying
pathogen evolution come from a variety of sub-disciplines and their work is often not well integrated [20].

As pathogen evolution continues to be an important conversation in the current pandemic of SARS-CoV-2 and is likely to again be important during future epidemics of emerging zoonotic disease, this review aims to collect insights from the wealth of research on pathogen evolution to provide a centralizing, conceptual understanding of the factors shaping the evolution of transmission rate and virulence in epidemics of novel zoonotic disease. While we cannot comprehensively discuss this vast literature, our aim is to provide a framework so that readers understand the general principles of pathogen virulence and transmission evolution and can also see how variations in the assumptions of these models based upon nuances of biology and population structure can lead to deviations in their predictions. We will discuss: (1) how a pathogen's evolutionarily stable (long term 'optimal') strategy depends on trade-off shape; (2) what predicts pathogen virulence at the spillover barrier; (3) why selection favors transmission rate improvements in maladapted zoonotic pathogens; and (4) how selection changes over time during epidemics. Through this, we describe predictions for pathogen evolution during epidemics of emerging zoonotic disease and how they can change depending on pathogen biology and host population structure.

The Three Ts Framework: Trade-offs, Transmission, and Time Scales

The adaptive evolution of any trait depends on the presence of variation and the ability of selection to act on that variation. It is clear that pathogens, particularly RNA viruses, can quickly generate and maintain large amounts of variation [21]. At the start of an epidemic, selection on these variants is weak compared to stochastic and demographic pressures, but gains strength as the number of infections increase [15]. Selection on virulence during epidemics of emerging zoonotic disease can be understood by considering the ‘three Ts’: trade-offs, transmission, and time scales [12,22–24]. See Figure 1 for graphical summary.

In terms of trade-offs, theory has often assumed, and empirical data has increasingly shown us, that many pathogen traits, like transmission rate and virulence, trade-off with each other [17,22,25,26] (See Table 1). The trade-off theory is important because it explains how different intermediate virulence, transmission, and recovery rates can be optimal for a pathogen due to constraints between these key traits [17,22,26]. In terms of transmission, emerging zoonotic pathogens typically do not have histories of selection in human populations and thus are likely to be maladapted for human-to-human transmission [27]. In theory, this maladaptation
means that emerging zoonotic pathogens may initially have ‘no-cost’ mutations available that improve transmission rate without impacting traits like virulence [23]. In these cases, emerging diseases can be selected to increase their transmission rates with no, or potentially counterintuitive, impacts on virulence [23]. Finally, time scale matters since, even with trade-offs between virulence and transmission rate, transmission rate improvements continue to be the most important selection pressure at the start of an epidemic because the relative strength of selection on transmission rate and virulence shifts as the density of susceptible hosts changes during an epidemic [24,28]. Therefore, the pathogen’s optimum strategy changes over time during an epidemic. We will discuss each of these in detail below.
Evolutionary biologists have long been interested in why pathogens harm their hosts, or cause virulence (See Box 1) [29]. Based on the assumption that host damage was detrimental to parasite fitness, early ideas predicted that all parasites should evolve towards avirulence [19,30]. This was considered the ‘conventional wisdom’ until the 1980s, when foundational papers began to appreciate that virulence might be linked to other parasite traits like transmission or recovery rates and therefore could have an evolutionary optimum [22]. Trade-offs between these traits would mean that low virulence would come at a cost of low transmission rate or fast recovery and...
that avirulence would therefore hinder parasite fitness. This virulence and transmission trade-off is now fundamental to our theories on pathogen evolution.

Theory on the virulence and transmission trade-off typically suggests that virulence and transmission rate are both functions of the within-host exploitation or replication rate [17,30]. Because faster replicating pathogens generate larger population sizes, they increase their transmission rate while causing more host damage [17,26]. Damage increases host mortality, thereby decreasing the host’s infectious period and providing a shorter window for the infected host to contact susceptible hosts [22]. In short, faster within-host replication increases the likelihood of infection upon contact while decreasing the overall duration of infection [22,26]. Under the trade-off hypothesis, parasites are therefore selected for exploitation rates that balance virulence and transmission rate [17,22,26].

Transmission rate and virulence do not necessarily need to trade off through the within-host exploitation rate for selection to balance the two traits. A virulence-recovery trade-off can occur if low replication rates make pathogens easier to clear such that lower virulence trades off with faster recovery rates [22]. Alternatively, a transmission-recovery trade-off can occur if the immune response is activated in a density dependent manner so that high replication rates have high transmission rates, but fast recovery [31]. A sickness behavior-transmission trade-off may result if faster replication rates make the host feel sick and isolate themselves so that high replication leads to a higher probability of infection upon contact, but fewer contacts [32]. Finally, the virulence and transmission trade-off does not necessarily depend on changes to the within-host replication rate if symptoms themselves are needed for transmission [33].

In simple host-parasite models, pathogens are selected to maximize the epidemiological \( R_0 \) (i.e. the number of secondary infections that a parasite produces during its infectious period in an entirely susceptible population) [22] (but see [34,35]). The virulence-transmission trade-off predicts that these two traits are positively correlated, but the shape of this relationship is critical to the predictions of evolutionary theory [22,26]. When the trade-off is linear, pathogens evolve maximum virulence; but when the trade-off is saturating (such that virulence is accelerately costly in terms of transmission rate), pathogens will evolve towards an intermediate virulence [22,30]. Given the centrality of the trade-off hypothesis to our understanding of virulence, it is noticeable that there are an increasing number of empirical studies that have found support for the core idea (See Table 1) [25].
Box 1. Defining virulence, transmission rate, and R0

In the virulence and transmission trade-off theory, virulence is strictly defined at the additional rate of mortality due to infection. This notably differs from definitions used in other fields like plant pathology, where virulence refers to the range of host genotypes that a pathogen can infect, or microbiology, where virulence often refers to specific virulence factors [36]. Virulence in the trade-off theory is therefore a product of host, pathogen, and environmental traits that together affect the additional mortality rate of infected individuals (Figure 2).

In the virulence and transmission trade-off theory, virulence trades off with the transmission rate (or $\beta$), which is a product of the probability of infection upon contact and the contact rate between individuals in the population.

Together, the transmission rate and the duration of infectiousness (the inverse of virulence) determine the pathogen’s $R_0$, or the number of secondary infections that a parasite produces during its infectious period in an entirely susceptible population. $R_0$ is therefore a metric of parasite fitness that is analogous to the lifetime reproductive success of the infection.

| Table 1. Empirical tests of virulence evolution theory |
|-----------------|-----------------------------------------------|
| **System**      | **Results**                                   |
| **The virulence and transmission trade-off** |                                               |
| *Oryctolagus cuniculus*/ Myxoma virus [22] | $R_0$ was maximized at an intermediate virulence that had slower recovery and mortality rates |
| *Mus musculus*/ *Plasmodium chabaudi* [37] | Virulence and transmission stage density are both positively correlated with replication rate |
| *Homo sapiens*/ *Plasmodium falciparum* [38] | Parasite fitness peaks at intermediate virulence values with higher parasite replication and lower mortality |
| *Daphnia magna*/ *Pasteuria ramosa* [39] | Transmission stage production peaked at intermediate virulence |
| *Homo sapiens*/ HIV-1 [40] | $R_0$ peaks at intermediate viral set point load and virulence |

Figure 2: Disease Triangle of Virulence
| Parasite | Host | Relationship
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<tr>
<td>Danaus plexippus / Ophryocystis elektroscirha [41]</td>
<td>Parasite lifetime fitness peaks at intermediate replication rates</td>
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<tr>
<td>Gallus gallus domesticus / Marek’s disease virus [42]</td>
<td>$R_0$ peaks at intermediate virulence</td>
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<tr>
<td>Brassica rapa / Cauliflower mosaic virus [43]</td>
<td>Virulence and transmission rate show a positive, saturating relationship, but not replication rate</td>
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<tr>
<td>Haemorhous mexicanu / Mycoplasma gallisepticum [44]</td>
<td>Virulence increases with parasite replication rate in isolates before, but not after host resistance evolution</td>
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<tr>
<td>Haemorhous mexicanu / Mycoplasma gallisepticum [33]</td>
<td>$R_0$ peaks at intermediate virulence, even when the relationship between transmission rate and virulence is not dependent on replication rate</td>
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<tr>
<td>Meta-analysis of multiple systems [25]</td>
<td>Strong evidence of increasing relationships between virulence and replication and between transmission rate and replication</td>
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**Transient virulence evolution depending on susceptible host density**

- **Escherichia coli / bacteriophage lambda [45]**
  Virulent, lytic phage is strongly favored by competition at the start of an epidemic, but latent virus outcompetes it as the epidemic progresses

**Virulence evolution in spatially structured populations**

- **Escherichia coli / T4 coliphage [46]**
  Prudent strategies dominate with spatially restricted migration, while virulent dominate with global migration

- **Plodia interpunctella / granulosis virus [47]**
  Spatial structure selects for less infective, more prudent virus

- **Escherichia coli / bacteriophage lambda [48]**
  Latent, prudent virus outcompetes lytic, virulent virus in spatially structured populations

**Virulence evolution with environmental transmission**

- **HeLa cells / vesicular stomatitis virus [49]**
  There is a trade-off between transmission rate and the formation of environmentally persistent particles

- **BHK cells / vesicular stomatitis virus [50]**
  There is a trade-off between viral fecundity and the formation of environmentally persistent particles

- **Homo sapiens / respiratory tract pathogens [51]**
  Respiratory pathogens that survive longer in the environment are more virulent

**Virulence and transmission trade-offs acting at spillover**

As we have outlined, theory on the virulence and transmission trade-off is based upon the idea that pathogens will be selected towards an optimal level of virulence within the host populations to which they are adapted [17]. Recently emerged zoonotic diseases do not have this evolutionary history with human populations and are therefore highly unlikely to be at their evolutionary optimum when they first emerge [27,52]. However, emerging pathogens may still be regulated by an underlying virulence and transmission trade-off. In meta-analyses of recently emerged viral zoonoses, excessively high virulence is associated with a lower $R_0$ [27,53,54] and this negative association supports the theoretical prediction that high virulence impedes pathogen
fitness. Theory also predicts a cost to excessively low virulence, an effect that is not supported in these analyses [22,27]. However, this could easily result from discovery bias because we are unlikely to notice low-$R_0$ zoonoses that cause only a few infections and have low virulence [16]. As such, there is little evidence to not expect emerging diseases to be governed by trade-offs once they emerge into human populations.

**What predicts the virulence and transmission of zoonotic pathogens when they first infect humans?**

Emerging zoonoses vary widely in their virulence and transmission rates, but there are key reservoir host characteristics that are associated with the pathogen’s phenotype in humans [27,53,55]. In particular, meta-analyses of recently emerged viral zoonoses have supported phylogenetic trends in zoonotic potential [27]. The phylogenetic distance between a pathogen’s reservoir host and novel host predicts the pathogen’s probability of being zoonotic [55], virulence [27,56], and $R_0$ [27,53]. Mammalian hosts closely related to humans (e.g. primates) harbor zoonoses associated with lower human mortality and higher $R_0$, while more distantly related hosts (most notably, bats) harbor highly virulent zoonoses that appear to be relatively maladapted for human-to-human transmission [27,57]. These phylogenetic trends can be understood if pathogens from distantly related reservoir hosts have evolved replication strategies adapted to their reservoir host’s more dissimilar immunology, physiology, and ecology [27,52].

Importantly, these variations in pathogen virulence upon emergence reflect evolutionary histories within non-human reservoir hosts and demonstrate that emerging zoonotic diseases are not likely to be well adapted to human populations [27,52]. Reservoir host and pathogen traits can suggest what phenotypes a pathogen may have upon emergence, but do not tell us where these starting point phenotypes are relative to a pathogen’s ‘ideal’ phenotypes in humans, since each pathogen will have a different evolutionary optimum depending on the nuances of its biology in the new host [14].

**Do we expect to see adaptive evolution of transmission and virulence in recently emerged diseases?**

Because emerging zoonotic diseases are maladapted to human populations, we certainly expect for there to be selection for improved pathogen fitness. However, this does not necessarily mean that there will be adaptive evolution [15,18]. A key tenant of evolutionary theory is that selection must act through a background of stochasticity and drift to result in adaptive evolution.
Small population sizes mean that both stochasticity and drift are relatively strong, and therefore the inevitably small population of infected individuals at the start of an epidemic means that stochasticity and drift are likely to overwhelm selection and determine the spread of mutants [59]. Additionally, the existence of founder effects during epidemic range expansions results in spatial stochasticity analogous to genetic drift [60]. Thus, founder effects and variation in transmission due to host behavior and stochasticity likely determine the fate of mutants at the start of epidemics [15].

Additionally, adaptive evolution in acute, respiratory pathogens may be constrained by the small bottleneck sizes of transmission events [61,62]. Short infectious periods and small bottlenecks mean that it is less likely for a pathogen to have enough time within a host to generate adaptive mutations and select on those variants strongly enough for them to reach the high frequencies needed to transmit through tight bottlenecks [61]. This can impede adaptive evolution at the population level [63]. All of these stochastic factors can overwhelm selection, especially at the start of an epidemic. However, as the population size of infected individuals increases or if there are mutations of large enough effect size, the balance between selection and stochasticity may shift towards selection and result in adaptive evolution.

Maladapted emerging zoonotic pathogens can evolve in unexpected ways

There are many ways that emerging zoonotic pathogens can adapt to human hosts and the foremost is to improve their $R_0$ [64]. Classic trade-off theory assumes that $R_0$ should be maximized at intermediate virulence and transmission rates if these traits have tight, positive, and saturating correlations. However, these tight correlations assume that the pathogen is already relatively adapted to its host such that all potential adaptive mutations (for higher transmission rate or lower virulence) have costs (of higher virulence or lower transmission rate, respectively). This is unlikely to be the case for emerging zoonotic pathogens [27].

The concept of Pareto fronts describes scenarios where phenotypes can be in the region of sub-optimal phenotype space below the trade-off front (See Figure 3) [65]. The trade-off front (or Pareto front) separates these accessible, maladapted phenotype combinations from impossible, ideal phenotypes [65,66]. At the Pareto front, the two phenotypes trade-off with each other. Below the Pareto front, however, improvements in one trait may not affect the other trait as simple adaptations can be made before costs are incurred. Because they lack any evolutionary history with humans, emerging zoonotic diseases are unlikely have fixed all available ‘no-cost’ adaptations and thus likely have phenotypes below Pareto fronts. Applied to virulence evolution,
this means that recently emerged diseases, even if broadly regulated by trade-offs, may select for no-cost improvements in transmission rate that do not affect their virulence (See Figure 3a) [23]. This means that we cannot predict how any individual mutation improving transmission rate will affect virulence in a maladapted pathogen that starts below the Pareto front.

![Conceptual Diagram of the Pareto front between virulence and transmission rate. Possible phenotypes can be selected to improve the transmission rate along any pathway within the accessible phenotype space. Since each pathogen's function determining their virulence and transmission rate trade-off varies, we cannot know where a hypothetical phenotype sits below the Pareto front. Selection for improved transmission rate can therefore involve decreases, no changes, or increases in virulence depending on the pathogen's starting point and mutational availability.](image)

**Figure 3a.** Conceptual Diagram of the Pareto front between virulence and transmission rate. Possible phenotypes can be selected to improve the transmission rate along any pathway within the accessible phenotype space. Since each pathogen’s function determining their virulence and transmission rate trade-off varies, we cannot know where a hypothetical phenotype sits below the Pareto front. Selection for improved transmission rate can therefore involve decreases, no changes, or increases in virulence depending on the pathogen’s starting point and mutational availability.

![Recently emerged viral zoonoses follow a Pareto front of virulence and R0 where R0 seems to be maximized at intermediate case fatality rates within viral families. Data is from a published dataset of recently emerged viral zoonoses from mammalian hosts [27].](image)

**Figure 3b.** Recently emerged viral zoonoses follow a Pareto front of virulence and R0 where R0 seems to be maximized at intermediate case fatality rates within viral families. Data is from a published dataset of recently emerged viral zoonoses from mammalian hosts [27]. Each dot represents an individual epidemic of a viral zoonosis. Approximate R0 is classified from 1 (no human-to-human transmission) to 4 (endemic transmission) [64]. Dots represent potted residuals from linear models of CFR and approximate R0 including virus family and citation count as factors. Plots were made with ‘ggplot2’. See supplement for code.

**Selection on virulence and transmission rate during epidemics**

While early adaptations may be costless, trade-offs between pathogen traits are likely to regulate evolution once these initial ‘no-cost’ mutations have been exhausted. We’ve discussed how variations in trade-off shape can lead to different optimal transmission rates and virulence for different pathogens [17,22,26], but the optimal values of these rates can also depend on host and parasite epidemiological characteristics [17,30]. Classic models examine the long term evolutionary outcome at equilibrium [67]. Selection on virulence and transmission rates during the
Start of an epidemic can be explored by using models that do not assume equilibrium [23,24,28,68]. These models allow for the existence of multiple simultaneous mutants so that the competitive fitness of each can be assessed over shifting epidemiological conditions in time. They show that strategies with higher transmission rates and virulence can be selected during epidemic growth stages, despite $R_0$ optimized (intermediate virulence) strategies dominating at endemic equilibrium [24,28]. This is because strategies with higher transmission rates spread fastest at the start of the epidemic when the density of susceptible hosts is high [24,28].

Intuitively, these results can be explained as: an infected host during the early stages of an epidemic encounters mostly susceptible hosts, so strains with higher transmission rates will have faster population growth rates since they have shorter generation times than strains with higher $R_0$ (but lower transmission rates) that produce more secondary infections more slowly over a longer infectious period. Therefore, improvements in transmission rate are the most important at the start of an epidemic and can be selected for even if they have shorter infectious periods because of increased virulence. This also demonstrates that the high density of susceptible hosts early in epidemics crucially influences selection [17,23,24,28].

**Selection on virulence and transmission rate with multiple infection**

Classic virulence evolution trade-off theory also assumes that each infection is caused by only one parasite strain so that hosts are not co-infected by different parasites or by multiple genotypes of one parasite. However, multiple infection by different genotypes is likely to be common [69] and can result in altered selection on virulence due to within-host competition for resources [70]. Whether multiple infection selects for higher or lower virulence, however, can depend on the specific mechanisms of pathogen competition and virulence [71,72]. Clearly, the probability of being multiply infected will depend on the prevalence of infection and thus vary over the course of the epidemic [73]. Thus, any selection effects on virulence due to multiple infection will be weak at the start of epidemic and increase with the number of infected individuals.

**Selection on virulence and transmission rate in structured populations**

Classic virulence evolution trade-off theory assumes that transmission happens randomly in a homogeneously mixing population [17]. However, natural populations almost always have heterogeneous mixing patterns due to spatial structure and social networks [74,75]. In these structured populations, transmission occurs more often between neighboring individuals and those in social groups. This can lead to ‘self-shading’ where highly infectious strains rapidly
deplete their local susceptible populations and compete for available hosts with related strains [74,76]. Thus, structured host populations select for lower pathogen infectivity and virulence at endemic equilibrium. However, the high availability of susceptible hosts at the start of an epidemic is likely to reduce the impact of self-shading and, moreover, pathogens need to have higher transmission rates to seed an epidemic in a spatially structured population than in a well-mixed one [77]. Before equilibrium, the invasion front of a spatially structured epidemic also has a high local supply of susceptible hosts, which leads to a dynamic where virulent, high transmission rate strains are selected at the invasion front and then are succeeded by more prudent strategies as the local dynamics approach equilibrium [78,79]. Overall, then, it is possible that structure in host populations temporarily selects for higher virulence while the epidemic is spreading through mostly susceptible populations. However, if there are also trade-offs where high virulence impedes host movement, then the spatial front of the epidemic might instead have lower virulence [80]. As such, it is unclear how population structure and movement overall will select emerging pathogens during different parts of the epidemic.

Selection on virulence and transmission rate with environmental transmission

Classic virulence evolution trade-off theory assumes that pathogens only transmit by direct contact between hosts. However, many pathogens also transmit through the environment [81–84]. The ‘curse of the pharaoh' hypothesis suggested that parasites could have higher virulence if they transmitted through the environment because transmission would not be linked to the host’s infectious period [81]. The conditions under which the ‘curse of the pharaoh' holds can be complex, but models show that environmental transmission can select for higher virulence strategies at equilibrium if hosts can be multiply infected or transmit after death [83,85,86]. However, propagule survival in spatially structured populations may actually increase self-shading and select for even lower virulence [84]. During the epidemic stage, however, environmental transmission can select for high virulence during the epidemic stage under broader conditions because environmentally transmitting high virulence strategies have higher population growth rates [24,82]. However, these dynamics shift if there are trade-offs associated with making environmentally persistent particles [87,88] and some empirical studies have shown that adaptations to increase environmental persistence can require more host resources or impede attachment to host cells [49].

Selection on virulence and transmission rate with antigenic escape
Finally, classic virulence evolution trade-off theory assumes that recovered hosts are fully immune such that host immunity does not wane and pathogens do not evolve to escape such immunity. However, some, but not all, viral pathogens exhibit antigenic evolution to escape neutralizing antibodies conferred by previous infections or vaccines [89,90]. We will not fully explore selection for antigenic escape here, but note that selection for antigenic or vaccine escape evolution is significantly slower and less efficient than for drug resistance—likely due to differences in the timing and breadth of within-host selection pressures [63,89]. When antigenic escape occurs, however, it means that recovered individuals are newly susceptible to evolved strains and essentially ‘resets’ the timescale of an epidemic by replenishing the density of susceptible hosts. This effect can select for more acute, highly transmissible and virulent pathogens [23,91]. However, mutations conferring antigenic escape likely trade-off with other pathogen traits like receptor binding avidity and expression, so trade-offs may constrain the possible virulence and transmission rate phenotypes for such mutants [92].

How might public health measures shape selection on virulence and transmission rate?

The question of whether public health measures can purposely or inadvertently drive pathogen evolution naturally arises when discussing virulence evolution. Public health measures intentionally driving the evolution of virulence may be unrealistic in emerging zoonotic diseases because, as we have discussed, virulence evolution is very difficult to fully predict [14]. However, we can gain insight into how public health measures can inadvertently select on virulence. Non-pharmaceutical public health interventions for epidemics primarily aim to decrease transmission and therefore either stop the epidemic or slow it until vaccines and treatments can be developed [93]. This decreases the total number of infected individuals, which will have the greatest impact on the total mortality burden of any epidemic [12]. This also limits the evolutionary potential of the pathogen by limiting the number of cases and therefore the strength of selection and opportunities for mutation [12]. However, some of these interventions may also contribute to the selection acting on the pathogen [12,14]. First, increased environmental sanitation decreases environmental transmission, thus potentially selecting for lower pathogen virulence under the ‘curse of the pharaoh’ hypothesis [82]. Second, decreased travel and extra-household contacts should alter the spatial and social structure of the population to make a more structured transmission network [74]. Third, quarantine of symptomatic individuals may select for decreased or altered symptoms [94]. Finally, vaccines can sometimes create selection pressures on pathogens with potential evolutionary impacts to consider [95].
While the most human mortality will be prevented by simply preventing transmission, considering the effects of control measures on pathogen evolution can, in principle, lead to better epidemic management [12]. Understanding host population characteristics creating strong selection for high transmission rate strategies could help distribute public health effort if there are limited resources [12]. However, a key point is that weak epidemic control measures that allow for extended transmission in humans increase the evolutionary potential of zoonotic pathogens because they allow for stronger selection and more mutations [12]. Thus, the best evolutionary management practice for an epidemic of a zoonotic infectious disease would be to suppress transmission using strong, rapid public health interventions.

Conclusion

In the face of the extraordinarily stressful circumstances of a global pandemic, we all understandably want simple answers for what will happen next and how the pathogen will evolve. Unfortunately, the simplest answer is that we cannot predict the evolution of any specific novel zoonotic pathogen. Its virulence and transmission rate may trade-off; it may be selected to increase its transmission rate; and the dynamics of selection may change with time.

The slightly more complicated answer is that, while we cannot predict how any specific pathogen will evolve, we do know how selection is expected to generally act on emerging zoonotic diseases and how different assumptions affect these predictions. We know that novel zoonotic pathogens emerge into the human population maladapted to human hosts [27,55]. Generally, we expect that virulence and transmission rate trade-off, leading to selection towards intermediate values of both [22]. However, we also know that a maladapted zoonotic pathogen’s virulence and transmission phenotypes may start below the Pareto front, so selection for higher transmission rates can have decoupled effects on virulence [23]. Our theory also says that, even with trade-offs, the optimal balance between virulence and transmission rate shifts depending on the time scale of the epidemic and different epidemiological and population characteristics [22,23].

All of these uncertainties make virulence evolution an academically interesting topic with a rich body of theory surrounding it, but no universal predictions [14]. Unfortunately, any sort of evolutionary prediction depends on a good understanding of how the phenotypes that the pathogen emerges with compare to their ‘optimal’ phenotypes in human populations; what fitness improving mutations the pathogen has available to it and what their associated trade-offs are; and how host population structure and epidemiological characteristics will shape the selection pressures on the pathogen. This data is exceptionally difficult to quickly gather. However, despite
our inability to conclusively predict how a pathogen will evolve, we do know that we can prevent it from doing so by implementing strong, rapid public health measures that suppress transmission early on since this will decrease the evolutionary potential of such pathogens while also decreasing the total mortality burden by limiting the number of people infected.

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Author Contributions

All authors researched and edited the paper. EV and MB conceptualized and wrote the paper.

Data Availability

No novel data is used in this manuscript; data used is publicly available as online Supplementary Material from [27]. The annotated R script used for analysis is provided in the supplement.

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Competing Interests

We declare no competing interests.

References


