The Three Ts of Virulence Evolution During Zoonotic Emergence

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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)

1. 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] and more potentially adaptive variants have since been reported [2]. 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 [3]. 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 [4]. 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 [5] and recognize that human populations impose novel, although often understood, selection pressures [6]. 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 [7,8].

Additionally, many experts studying infectious disease evolution are often quick to emphasize that we cannot predict how a specific pathogen will evolve [9]. This, however, 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 [10].

74 Theory predicts that pathogens may evolve towards optimal virulence and transmission rates due
75 to underlying constraints, but these predictions depend on nuances of pathogen biology, epidemic
76 stage, and host population structure [11,12]. It can, understandably, be frustrating when asking
77 how a pathogen will evolve to hear predictions that sound like contradictions and non-answers,
78 but this reflects the complicated realities of pathogen evolution. However, this real uncertainty
79 also seems to have created an environment where hope for simple answers means that
80 misinformation can spread.

81 On top of the inherent challenges of communicating complex scientific concepts,
82 researchers studying pathogen evolution must also play 'whack-a-mole' against a variety of
83 misconceptions that are wrong in different ways. Public concern sometimes skews towards
84 pathogens evolving to be hyper-virulent, hyper-transmissible superbugs [13]. Alternatively,
85 historical theories of evolution towards avirulence still pervade the public consciousness and
86 sometimes lead to the prediction that pathogens universally evolve to become less dangerous
87 [14]. In both directions, these misconceptions can lead to inappropriate public health policies.
88 However, the disjointed nature of combatting misconceptions as they arise has led to much of the
89 conversation on pathogen evolution in emerging zoonotic diseases being scattered across the
90 scientific literature and media. This can be compounded by the fact that researchers studying
91 pathogen evolution come from a variety of sub-disciplines and their work is often not well
92 integrated [15].

93 As pathogen evolution continues to be an important conversation in the current pandemic
94 of SARS-CoV-2 and is likely to again be important during future epidemics of emerging zoonotic
95 disease, this review aims to collect insights from the wealth of research on pathogen evolution to
96 provide a centralizing, conceptual understanding of the factors shaping the evolution of
97 transmission rate and virulence in epidemics of novel zoonotic disease. While we cannot
98 comprehensively discuss this vast literature, our aim is to provide a framework so that readers
99 understand the general principles of pathogen virulence and transmission evolution and can also
100 see how variations in the assumptions of these models based upon nuances of biology and
101 population structure can lead to deviations in their predictions. Because strong reviews of
102 virulence evolution exist elsewhere in the literature [4,12], our review focuses specifically on
103 virulence evolution in epidemics of novel zoonotic disease to focus on how general theory for
104 virulence evolution is altered by the specific characteristics of emerging zoonotic diseases and
105 shifting selection pressures during epidemics. Extending beyond the scope of any single
106 theoretical paper on this topic, we will discuss: (1) how do trade-offs between pathogen traits

107 constrain pathogen evolution?; (2) what predicts pathogen virulence at the spillover barrier?; (3)

108 why it is hard to predict how novel zoonotic pathogens will evolve?; and (4) how do optimal

109 strategies in populations with different epidemiological characteristics change over time during an

110 epidemic? Through this, we describe predictions for pathogen evolution during epidemics of

111 emerging zoonotic disease and how they can change depending on pathogen biology and host

112 population structure.

113

114 **2. The Three Ts Framework: Trade-offs, Transmission, and Time Scales**

115 The adaptive evolution of any trait depends on the presence of variation and the ability of

116 selection to act on that variation. It is clear that pathogens, particularly RNA viruses, can quickly

117 generate and maintain large amounts of variation [16]. At the start of an epidemic, selection on

118 these variants is weak compared to stochastic and demographic pressures, but gains strength as

119 the number of infections increase [10]. Selection on virulence during epidemics of emerging

120 zoonotic disease can be understood by considering the 'three Ts': trade-offs, transmission, and

121 time scales [7,17–19]. See Figure 1 for graphical summary.

122 In terms of **trade-offs**, theory has often assumed, and empirical data has increasingly

123 shown us, that many pathogen traits, like transmission rate and virulence, **trade-off** with each

124 other [12,17,20,21] (See Table 1). The **trade-off** theory is important because it explains how

125 different intermediate virulence, transmission, and recovery rates can be optimal for a pathogen

126 due to constraints between these key traits [12,17,21]. In terms of **transmission**, emerging

127 zoonotic pathogens typically do not have histories of selection in human populations and thus are

128 likely to be maladapted for human-to-human transmission [22]. This maladaptation potentially

129 means that emerging zoonotic pathogens may initially have 'no-cost' mutations available that

130 improve transmission rate without impacting traits like virulence [18]. In these cases, emerging

131 diseases can be selected to increase their **transmission rates** with no, or potentially

132 counterintuitive, impacts on virulence [18]. Finally, **time scale** matters since, even with trade-offs

133 between virulence and transmission rate, transmission rate improvements continue to be the most

134 important selection pressure at the start of an epidemic because the relative strength of selection

135 on transmission rate and virulence shifts as the density of susceptible hosts changes during an

136 epidemic [19,23]. This effect further alters a number of theoretical predictions that are classically

137 evaluated at equilibrium for how different host, pathogen, and epidemiological factors shape

138 selection on pathogen traits. Therefore, a pathogen's optimum strategy changes over **time** during

139 an epidemic under a wide array of conditions. We will discuss each of these in detail below.
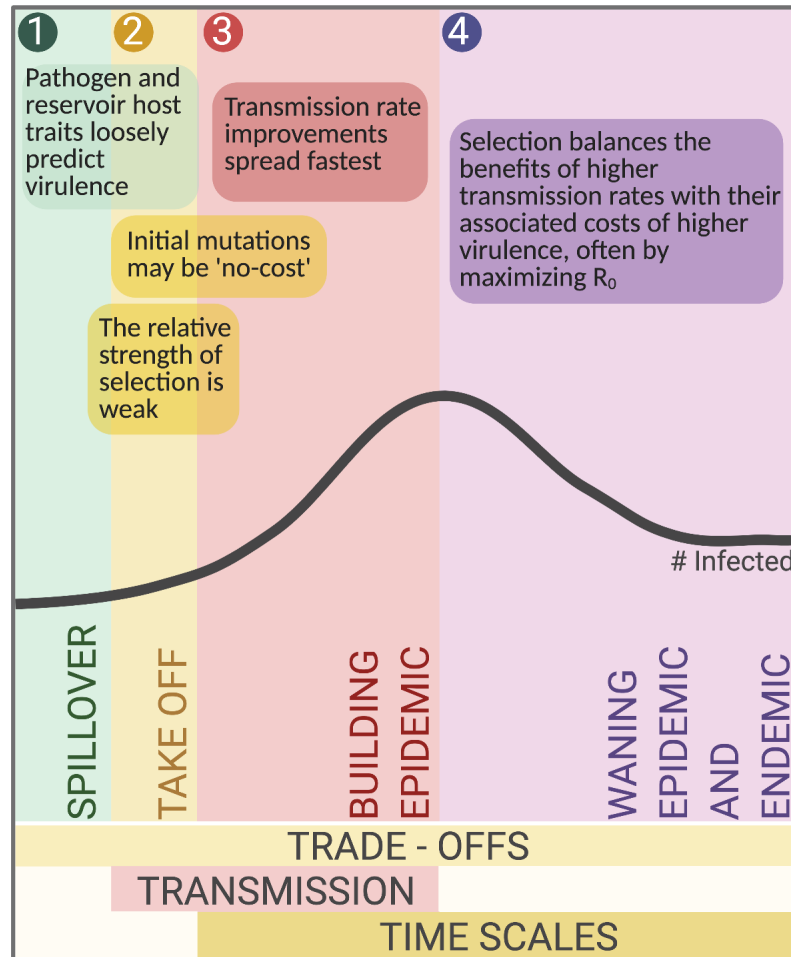
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Figure 1: The Three Ts of Virulence Evolution During Zoonotic Emergence. Trade-offs between virulence and transmission rate determine pathogen fitness at every point during an epidemic, regulating pathogen fitness at the spillover barrier and shaping selection as the epidemic progresses. Early in the epidemic, however, individual transmission rate improving mutations may be 'costless' and not have trade-offs. Improvements in transmission rate are the most important selection pressure during epidemic take-off and building phases, though selection is weak at take-off. Finally, the time scale of the epidemic shifts the pathogen's optimal virulence and transmission rate strategies as the density of susceptible hosts changes. Created with Biorender.com

3. How do trade-offs between pathogen traits constrain pathogen evolution?

Evolutionary biologists have long been interested in why pathogens harm their hosts, or cause virulence (Figure 2) [24]. Based on the assumption that host damage was detrimental to parasite fitness, early ideas predicted that all parasites should evolve towards avirulence [4,14]. 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 [17]. Trade-offs between these traits would mean that low virulence would come at a cost of low transmission rate or fast recovery and

149 that avirulence would therefore hinder parasite fitness. This virulence and transmission trade-off

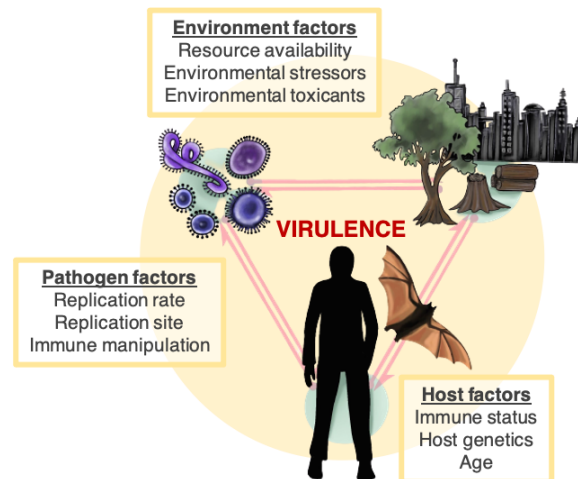150 is now fundamental to our theories on pathogen evolution.

151

Figure 2: Disease Triangle of Virulence

152   Theory on the virulence and transmission trade-off typically suggests that virulence and

153 transmission rate are both functions of the within-host exploitation or replication rate [4,12].

154 Because faster replicating pathogens generate larger population sizes, they increase their

155 transmission rate while causing more host damage [12,21]. Damage increases host mortality,

156 thereby decreasing the host's infectious period and providing a shorter window for the infected

157 host to contact susceptible hosts [17]. In short, faster within-host replication increases the

158 likelihood of infection upon contact while decreasing the overall duration of infection [17,21].

159 Under the trade-off hypothesis, parasites are therefore selected for exploitation rates that balance

160 virulence and transmission rate [12,17,21].

161   Transmission rate and virulence do not necessarily need to trade off through the within-

162 host exploitation rate for selection to balance the two traits. A virulence-recovery trade-off can

163 occur if low replication rates make pathogens easier to clear such that lower virulence trades off

164 with faster recovery rates [17]. Alternatively, a transmission-recovery trade-off can occur if the

165 immune response is activated in a density dependent manner so that high replication rates have

166 high transmission rates, but fast recovery [25]. A sickness behavior-transmission trade-off may

167 result if faster replication rates make the host feel sick and isolate themselves so that high

168 replication leads to a higher probability of infection upon contact, but fewer contacts [26]. Finally,

169 the virulence and transmission trade-off does not necessarily depend on changes to the within-

170 host replication rate if symptoms themselves are needed for transmission [27].

171   In simple host-parasite models, pathogens are selected to maximize the epidemiological

172   R_0 (i.e. the number of secondary infections that a parasite produces during its infectious period in

173   an entirely susceptible population) [17] (but see [28,29]). The virulence-transmission trade-off

174   predicts that these two traits are positively correlated, but the shape of this relationship is critical

175   to the predictions of evolutionary theory [17,21]. When the trade-off is linear, pathogens evolve

176   maximum virulence; but when the trade-off is saturating (such that virulence is acceleratingly

177   costly in terms of transmission rate), pathogens will evolve towards an intermediate virulence

178   [4,17]. Given the centrality of the trade-off hypothesis to our understanding of virulence, it is

179   noticeable that there are a number of empirical studies that have found support for the core idea

180   (See Table 1, Rows 1-2) [20].

181

Table 1. Empirical tests of virulence evolution theory	
Key Finding	**Key Empirical Evidence (Selected Papers)**
Virulence and transmission rate are positively correlated through replication rate	*Mus musculus / Plasmodium chabaudi* [30] ; *Homo sapiens / Plasmodium falciparum* [31] ; *Daphnia magna / Pasteuria ramosa* [32] ; *Homo sapiens /* HIV-1 [33] ; *Danaus plexippus / Ophryocystis elektroscirrha* [34] ; Meta-analysis of multiple systems [20]
Positive trait correlations saturate so that R_0 peaks at intermediate virulence	*Oryctolagus cuniculus /* Myxoma virus [17] (virulence-recovery rate); *Homo sapiens / Plasmodium falciparum* [31] (virulence-transmission rate) ; *Daphnia magna / Pasteuria ramosa* [32] (virulence rate-transmission rate) ; *Homo sapiens /* HIV-1 [33] (virulence rate-transmission rate), *Danaus plexippus / Ophryocystis elektroscirrha* [34] (virulence-transmission rate), *Gallus gallus domesticus /* Marek's disease virus [35] (virulence-transmission rate), *Haemorhous mexicanu / Mycoplasma gallisepticum* [27] (virulence-transmission rate)
High susceptible density at the start of an epidemic selects for higher virulence	*Escherichia coli* / bacteriophage lambda [36]
Structured host populations select for less transmissible, prudent strategies	*Escherichia coli* / T4 coliphage [37] ; *Plodia interpunctella* / granulosis virus [38] ; *Escherichia coli* / bacteriophage lambda [39]
High virulence can trade-off with decreased host movement	*Danaus plexippus / Ophryocystis elektroscirrha [40] ; Haemorhous mexicanu / Mycoplasma gallisepticum [41] ; Paramecium caudatum / Holospora undulata* [42]
Virulence evolves in natural epidemics of emerging disease	*Haemorhous mexicanu / Mycoplasma gallisepticum* [43,44] (Less virulent strains spread fastest because of movement-virulence trade-offs and then are replaced by higher virulence strains. When hosts start evolving resistance, virulence continues to

	increase through increased symptom severity rather than through replication rate) *Oryctolagus cuniculus /* Myxoma virus [45] (Lower virulence quickly evolves from extremely high virulence introduction strains. When hosts start evolving resistance, virulence starts to increase) *Corvus brachyrhynchos /* West Nile Virus [46] (A mutation conferring high virulence in American crows was positively selected, though this may have been a result of selection in another bird or vector species)

182

4. What predicts virulence and transmission rate at spillover?

4(a). Virulence and transmission trade-offs act 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 [12]. 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 [22,47]. 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 [22,48,49] 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 [17,22]. 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 [11]. As such, there is little evidence to not expect emerging diseases to be governed by trade-offs once they emerge into human populations.

4(b). Virulence and transmission rates of zoonotic pathogens reflect evolutionary histories with their reservoir hosts

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 [22,48,50]. In particular, meta-analyses of recently emerged viral zoonoses have supported phylogenetic trends in zoonotic potential [22]. The phylogenetic distance between a pathogen's reservoir host and novel host predicts the pathogen's probability of being zoonotic [50], virulence [22,51], and R_0 [22,48]. 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

208   (most notably, bats) harbor highly virulent zoonoses that appear to be relatively maladapted for

209   human-to-human transmission [22,52]. These phylogenetic trends can be understood if

210   pathogens from distantly related reservoir hosts have evolved replication strategies adapted to

211   their reservoir host's more dissimilar immunology, physiology, and ecology [22,47].

212   Importantly, these variations in pathogen virulence upon emergence reflect evolutionary

213   histories within non-human reservoir hosts and demonstrate that emerging zoonotic diseases are

214   not likely to be well adapted to human populations [22,47]. Reservoir host and pathogen traits can

215   suggest what phenotypes a pathogen may have upon emergence, but do not tell us where these

216   starting point phenotypes are relative to a pathogen's 'ideal' phenotypes in humans, since each

217   pathogen will have a different evolutionary optimum depending on the nuances of its biology in

218   the new host [9]. Because we cannot know where an emerging pathogen's starting point

219   phenotypes are relative to its optimal phenotypes, we cannot precisely predict the direction of

220   selection on virulence or transmission rate.

221

222   **5. Why is it difficult to predict how a novel zoonotic pathogen will evolve when it spills**

223   **over into humans?**

224   **5(a). Stochastic effects in small populations can overwhelm selection**

225   Because emerging zoonotic diseases are maladapted to human populations, we certainly

226   expect for selection to favor improved pathogen fitness. However, this does not necessarily mean

227   that pathogens will adaptively evolve [10,13]. A key tenant of evolutionary theory is that selection

228   must act through a background of stochasticity and drift to result in adaptive evolution [53]. Small

229   population sizes mean that both stochasticity and drift are relatively strong, and therefore the

230   inevitably small population of infected individuals at the start of an epidemic means that

231   stochasticity and drift are likely to overwhelm selection and determine the spread of mutants [53].

232   Additionally, the existence of founder effects during epidemic range expansions results in spatial

233   stochasticity analogous to genetic drift [54]. Thus, founder effects and variation in transmission

234   due to host behavior and stochasticity likely determine the fate of mutants at the start of epidemics

235   [10].

236   Additionally, adaptive evolution in acute, respiratory pathogens may be constrained by the

237   small bottleneck sizes of transmission events [55]. Short infectious periods and small bottlenecks

238   mean that it is less likely for a pathogen to have enough time within a host to generate adaptive

239   mutations and select on those variants strongly enough for them to reach the high frequencies

240   needed to transmit through tight bottlenecks [55]. This can impede adaptive evolution at the

241 population level [56]. All of these stochastic factors can overwhelm selection, especially at the

242 start of an epidemic. However, as the population size of infected individuals increases or if there

243 are mutations of large enough effect size, the balance between selection and stochasticity may

244 shift towards selection and result in adaptive evolution.

245

246 **5(b). Maladapted emerging zoonotic pathogens can evolve in unexpected ways**

247 There are many ways that emerging zoonotic pathogens can adapt to human hosts and

248 the foremost is to improve their R_0 [57]. Classic trade-off theory assumes that R_0 should be

249 maximized at intermediate virulence and transmission rates if these traits have tight, positive, and

250 saturating correlations. However, these tight correlations assume that the pathogen is already

251 relatively adapted to its host such that all potential adaptive mutations (for higher transmission

252 rate or lower virulence) have costs (of higher virulence or lower transmission rate, respectively).

253 This is unlikely to be the case for emerging zoonotic pathogens [22].

254 The concept of Pareto fronts describes scenarios where phenotypes can be in the region

255 of sub-optimal phenotype space below the trade-off front (See Figure 3) [58]. The trade-off front

256 (or Pareto front) separates these accessible, maladapted phenotype combinations from

257 impossible, ideal phenotypes [58,59]. At the Pareto front, the two phenotypes trade-off with each

258 other. Below the Pareto front, however, improvements in one trait may not affect the other trait as

259 simple adaptations can be made before costs are incurred. Therefore, Pareto fronts determine

260 which phenotype combinations are possible, and selection acts upon these possible phenotypes

261 to move them towards more selectively advantageous regions.

262 Because they lack any evolutionary history with humans, emerging zoonotic diseases are

263 unlikely have fixed all available 'no-cost' adaptations and thus likely have phenotypes below

264 Pareto fronts (See Figure 4). Applied to virulence evolution, this means that zoonotic diseases

265 emerging with lower than optimal transmission rates or higher than optimal virulence may initially

266 select for no-cost improvements even if their 'optimal' phenotype is regulated by trade-offs (See

267 Figure 3) [18]. This means that, in addition to not being able to precisely predict the direction of

268 selection because we do not know where a pathogen's starting point phenotypes sit relative to

269 their optimal phenotypes, we also cannot predict how any individual mutation improving

270 transmission rate will affect virulence in a maladapted pathogen that starts below the Pareto front.
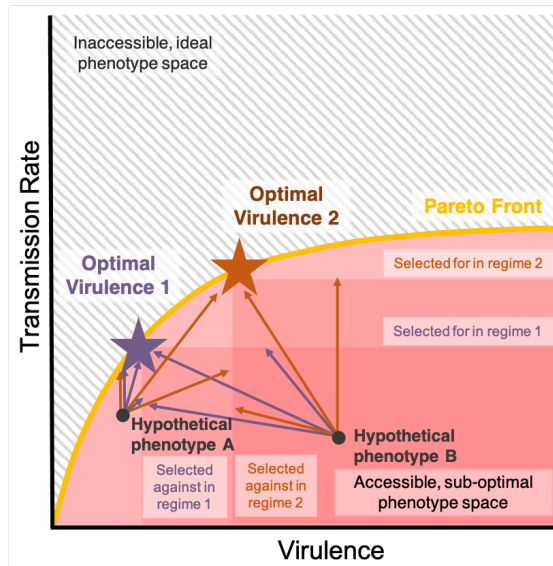
Figure 3. Conceptual diagram of the Pareto front between virulence and transmission rate. A Pareto front between virulence and transmission rate defines a region of accessible phenotype space. Theory determines where the 'optimal strategy' sits on the Pareto front to determine which regions of this phenotype space are selectively advantaged or disadvantaged. Phenotype combinations far from the Pareto front may technically be possible but would be highly selectively disadvantaged and likely to go extinct. Possible phenotypes can move towards their optimal strategy along any pathway within the accessible phenotype space. However, we cannot know where a hypothetical phenotype sits below its individual 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.
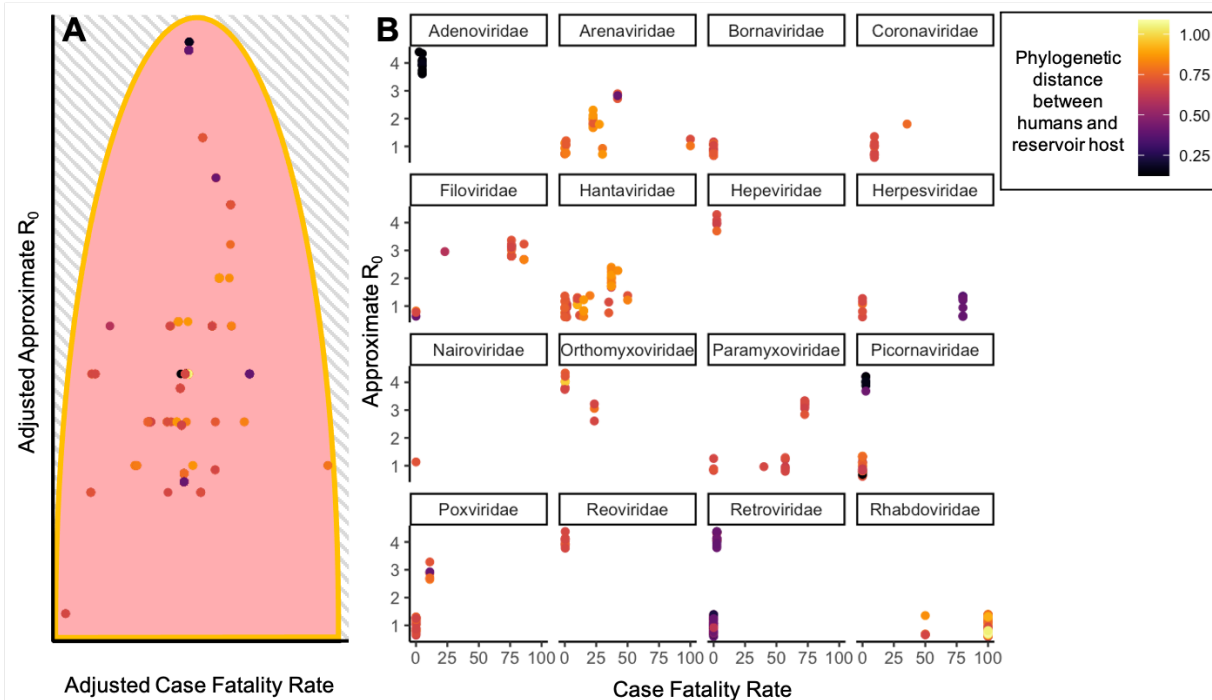
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Figure 4. Recently emerged viral zoonoses loosely follow a Pareto front of virulence and R_0 where R_0 seems to be maximized at intermediate case fatality rates within viral families. Data is from a dataset published in 2019 of recently emerged viral zoonoses from mammalian hosts [22]. Approximate R_0 is classified from 1 (no human-to-human transmission) to 4 (endemic transmission). In figure 4A, dots represent plotted residuals from linear models of CFR and approximate R_0 including virus family as a factor. By regressing out virus family, we somewhat control for the variation in trade-off shape for each virus and can make general observations across the dataset. Each dot therefore represents the virulence and R_0 of an individual epidemic of viral zoonosis scaled by virus family. In figure 4B, CFR and Approximate R_0 are directly plotted and separated by virus family so that the non-aggregated trends could be seen within virus families. In both panels, dots are colored by the phylogenetic distance between humans and the reservoir host. Plots were made with 'ggplot2'. See supplement for code.

6. How does a pathogen's optimal transmission rate and virulence depend on epidemiological characteristics and change over time?

While we cannot predict exactly where the virulence and transmission rate of an emerging zoonotic disease sit relative to its Pareto front and thus also cannot predict whether fitness-improving mutations necessarily have costs, evolutionary epidemiology theory can tell us how different epidemiological characteristics shift which regions of the possible phenotype space are selectively advantageous. Additionally, while novel zoonotic pathogens sitting far below their Pareto front may initially have costless fitness-improving mutations, their evolution will be increasingly constrained by trade-offs as their fitness improves and they approach their Pareto front.

Thus, evolutionary epidemiology theory based upon the virulence and transmission trade-off can tell us what scenarios might select for different pathogen virulence and transmission rates. However, evolutionary epidemiology theory on the virulence and transmission trade-off is perhaps more nuanced than commonly appreciated. We've discussed how variations in trade-off shape can lead to different optimal phenotypes for different pathogens [12,17,21], but the optimal values of these rates can also depend on host and parasite epidemiological characteristics and change over time in an epidemic [4,12]. While saturating virulence and transmission rate trade-offs generally predict that intermediate virulence and transmission rate is optimal, certain epidemiological characteristics can bias a system towards selecting for higher transmission rate or less virulence depending on the relative selective importance of either trait. Below, we will discuss several bodies of theory that explore how different epidemiolocal characteristics effect optimal virulence and transmission rate, specifically focusing on those where the effect of the epidemiological characteristic being explored varies depending on the time scale of the epidemic. There are also several additional sections in the supplement on these effects in systems with multiple infection, environmental transmission ('curse of the pharaoh'), and antigenic escape (Supplemental Materials. S6(a), S6(b), S6(c), and Table S1).

6(a). Selection favors high transmission rates when susceptible density is high at the start of an epidemic

Classic models for virulence evolution examine long term evolutionary outcomes at equilibrium [60]. Selection on virulence and transmission rates during the start of an epidemic can be explored by using models that do not assume equilibrium [18,19,23,61,62]. These models allow for the existence of multiple simultaneous mutants so that the competitive fitness of each

307 can be assessed over shifting epidemiological conditions in time. They show that strains with

308 higher transmission rates and virulence can be selected during epidemic growth stages, despite

309 R_0 optimized (intermediate virulence) strains dominating at endemic equilibrium [19,23]. This is

310 because strains with higher transmission rates spread fastest at the start of the epidemic when

311 the density of susceptible hosts is high [19,23].

312   Intuitively, these results can be explained as: an infected host during the early stages of

313 an epidemic encounters mostly susceptible hosts, so strains with higher transmission rates will

314 have faster growth rates since they have shorter serial intervals (or infection generation times)

315 than strains with higher R_0 (but lower transmission rates) that produce more secondary infections

316 over a longer infectious period but more slowly. For a simplified numeric example, a strain that

317 has an infectious period of 2 days and infects 50% of its 2 contacts per day in an entirely

318 susceptible population will only produce 2 new infections, but will double every 2 days.

319 Comparatively, a strain that has an infectious period of 5 days and infects 40% of its 2 contacts

320 per day in an entirely susceptible population will produce 4 new infections, but only double every

321 2.5 days. Thus, the higher transmission rate strain can spread faster while susceptible host

322 densities are high during epidemic growth stages, but the R_0 optimized strain can outcompete it

323 when susceptible density is low at endemic equilibrium because it produces a larger number of

324 infections over its longer infectious period. Therefore, improvements in transmission rate are the

325 most important at the start of an epidemic and can be selected for even if they have shorter

326 infectious periods due to increased virulence. This also demonstrates that the high density of

327 susceptible hosts early in epidemics crucially influences selection [12,18,19,23].

328

329 **6(c). Structured host populations select for prudent strategies at equilibrium, but**

330 **transiently select for virulent strategies at the epidemic front**

331   Classic virulence evolution trade-off theory assumes that transmission happens randomly

332 in a homogeneously mixing population [12]. However, natural populations almost always have

333 heterogeneous mixing patterns due to spatial structure and social networks [63,64]. In these

334 structured populations, transmission occurs more often between neighboring individuals and

335 those in social groups. This can lead to 'self-shading' where highly infectious strains rapidly

336 deplete their local susceptible populations and compete for available hosts with related strains

337 [63,65]. Thus, structured host populations select for lower pathogen infectivity and virulence at

338 endemic equilibrium. However, the high availability of susceptible hosts at the start of an epidemic

339 is likely to reduce the impact of self-shading and, moreover, pathogens need to have higher

340   transmission rates to seed an epidemic in a spatially structured population than in a well-mixed
341   one [66]. Before equilibrium, the invasion front of a spatially structured epidemic also has a high
342   local supply of susceptible hosts, which leads to a dynamic where virulent, high transmission rate
343   strains are selected at the invasion front and then are succeeded by more prudent strategies as
344   the local dynamics approach equilibrium [67,68]. Overall, then, it is possible that structure in host
345   populations temporarily selects for higher virulence while the epidemic is spreading through
346   mostly susceptible populations. However, if there are also trade-offs where high virulence
347   impedes host movement, then the spatial front of the epidemic might instead have lower virulence
348   [69]. As such, it is unclear how population structure and movement overall will select emerging
349   pathogens during different parts of the epidemic.
350
351   **6(f). How might public health measures shape selection on virulence and transmission**
352   **rate?**
353   The question of whether public health measures can purposely or inadvertently drive
354   pathogen evolution naturally arises when discussing virulence evolution. Public health measures
355   intentionally driving the evolution of virulence may be unrealistic in emerging zoonotic diseases
356   because, as we have discussed, virulence evolution is very difficult to fully predict [9]. However,
357   we can gain insight into how public health measures can inadvertently select on virulence. Non-
358   pharmaceutical public health interventions for epidemics primarily aim to decrease transmission
359   and therefore either stop the epidemic or slow it until vaccines and treatments can be developed.
360   This decreases the total number of infected individuals, which will have the greatest impact on
361   the total mortality burden of any epidemic [7]. This also limits the evolutionary potential of the
362   pathogen by limiting the number of cases and therefore the strength of selection and opportunities
363   for mutation [7]. However, some of these interventions may also contribute to the selection acting
364   on the pathogen [7,9]. , decreased travel and extra-household contacts should alter the spatial
365   and social structure of the population to make a more structured transmission network, which
366   might prevent low transmission rate pathogens from spreading initially [63,66]. Second,
367   quarantine of symptomatic individuals may select for decreased or altered symptoms, which could
368   select for lower virulence if symptoms are linked to virulence [71]. Third, increased environmental
369   sanitation decreases environmental transmission, thus potentially selecting for lower pathogen
370   virulence under the 'curse of the pharaoh' hypothesis [70] (See Supplementary Material S6(b)).
371   Finally, vaccines can sometimes create selection pressures on pathogens with potential
372   evolutionary impacts to consider [72] (See Supplementary Material S6(c)).

373   While the most human mortality will be prevented by simply preventing transmission,
374   considering the effects of control measures on pathogen evolution can, in principle, lead to better
375   epidemic management [7]. Understanding host population characteristics creating strong
376   selection for high transmission rate strategies could help distribute public health effort if there are
377   limited resources [7]. However, a key point is that weak epidemic control measures that allow for
378   extended transmission in humans increase the evolutionary potential of zoonotic pathogens
379   because they allow for stronger selection and more mutations [7]. Thus, the best evolutionary
380   management practice for an epidemic of a zoonotic infectious disease would be to suppress
381   transmission using strong, rapid public health interventions.

382

383   **7. Conclusion**

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

389   The slightly more complicated answer is that, while we cannot predict how any specific
390   pathogen will evolve, we do know how selection is expected to generally act on emerging zoonotic
391   diseases and how different assumptions affect these predictions. We know that novel zoonotic
392   pathogens emerge into the human population maladapted to human hosts [22,50]. Generally, we
393   expect that virulence and transmission rate trade-off, leading to selection towards intermediate
394   values of both [17]. However, we also know that a maladapted zoonotic pathogen's virulence and
395   transmission phenotypes may start below the Pareto front, so selection for higher transmission
396   rates can have decoupled effects on virulence [18]. Our theory also says that, with trade-offs, the
397   optimal balance between virulence and transmission rate shifts depending on the time scale of
398   the epidemic and different epidemiological and population characteristics [17,18].

399   All of these uncertainties make virulence evolution an academically interesting topic with
400   a rich body of theory surrounding it, but no universal predictions [9]. Unfortunately, any sort of
401   evolutionary prediction depends on a good understanding of how the phenotypes that the
402   pathogen emerges with compare to their 'optimal' phenotypes in human populations; what fitness
403   improving mutations the pathogen has available to it and what their associated trade-offs are; and
404   how host population structure and epidemiological characteristics will shape the selection
405   pressures on the pathogen. These data are exceptionally difficult to quickly gather. However,

406   despite our inability to conclusively predict how a pathogen will evolve, we do know that we can

407   prevent it from doing so by implementing strong, rapid public health measures that suppress

408   transmission early on since this will decrease the evolutionary potential of such pathogens while

409   also decreasing the total mortality burden by limiting the number of people infected.

410

415

416   **Author Contributions**

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

418

419   **Data Availability**

420   No novel data is used in this manuscript; data used is publicly available as online Supplementary

421   Material from [22]. The annotated R script used for analysis is provided in the supplement.

422

429

430   **Competing Interests**

431   We declare no competing interests.

432

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