Can we eradicate viral pathogens?

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Abstract

The COVID-19 pandemic has led to a resurgence of the debate on whether host–parasite interactions should evolve towards avirulence. In this review, we first show that SARS-CoV-2 virulence is evolving, before explaining why some expect the mortality caused by the epidemic to converge towards that of human seasonal alphacoronaviruses. Leaning on existing theory, we then include viral evolution into the picture and discuss hypotheses explaining why the virulence has increased since the beginning of the pandemic. Finally, we mention some potential scenarios for the future.

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1 The hope of treatments and (RNA) vaccines

The popularisation of vaccination since the end of the XIXth century and the discovery of therapeutic drugs against bacterial, fungal, and protozoan infections in the early XXth century led to the hope that the burden caused by infectious diseases could be ended. This culminated in the 1960s with the infamous, but most likely apocryphal, quote from a surgeon general of the United States stating that it was "*time to close the book on infectious diseases*" (Spellberg and Taylor-Blake, 2013). The emergence or re-emergence of viral threats, starting with HIV but more recently with Ebola, Chikungunya, and Zika viruses in humans and foot-and-mouth-disease virus and begomoviruses in agricultural animals and plants, as well as the generalisation of drug resistance mutations, shattered this optimistic view. Furthermore, because of economic constraints, parasites always remained a major threat in many countries of the world.

Somehow paradoxically, the current COVID-19 pandemic is giving rise again to the hope of eradicating infectious diseases. This is largely motivated by the success in discovering, manufacturing, and implementing safe and efficient SARS-CoV-2 vaccines in less than a year. That some of the most widely-used of these vaccines rely on newer RNA technology further stimulates optimistic predictions. From a history of science perspective, the view traces back to Paul Ehrlich's "*magic bullet*" reference to highly-accurate therapies, since RNA vaccines can be designed to target specific motifs. Their production is also much more rapid than traditional protein-based vaccines. Their implementation is perhaps the only negative point, with a current necessity to store RNA vaccine doses at -80°C, which is prohibitively expensive in many healthcare settings.

Are RNA vaccines fundamentally changing the equation? Is the bold 1960's-era vision of eradicating diseases now within our grasp? Evolutionary biologists and ecologists can bring valuable insights based on decades of experience analysing how microbes adapt to anthropic

perturbations. In fact, the main reason why RNA vaccines were needed so rapidly is probably due to a virus spillover from an animal reservoir into the human population, a phenomenon that has been studied by evolutionary ecologists (Lloyd-Smith et al., 2009).

As illustrated by this special issue *Virus evolution on the mutualist - parasite continuum*, it is important to bear in mind that virus population have a huge diversity, a wide array of potential hosts, and that they are not always pathogenic. Furthermore, as also stressed by contributions in this issue, viruses evolve rapidly, implying that they can readily colonise new hosts or face changing environmental conditions. Importantly, by doing so, they modify the selective pressures that act on their evolution. In other words, public health policies should not be designed to target current viruses but rather evolving viruses and this is why our community has a role to play.

2 Defining 'pathogens' can be difficult

First, it is important to stress that the notion of pathogen is itself somehow loose (Méthot and Alizon, 2014). This is illustrated by the title of the special issue, itself inspired by an article from Paul W. Ewald (Ewald, 1987). Obviously, all parasites can harm their hosts, otherwise they would not be called as such. But the phenotype is the result of the parasite genotype, the host genotype, and the environment (Shapiro and Turner, 2018). For instance, some HCV mutations appear to only be detrimental when infecting human hosts with a specific mutation (Ansari et al., 2017). It is also evident that context matters. A classic example in humans is that coinfection by a flavivirus (GB virus C) or by herpesviruses (HHV-6 or HHV-7) can reduce HIV infection virulence (Virgin et al., 2009). In plants, infection by one virus species can protect against infection by those from another virus family, a phenomenon known as cross-protection (Ratcliff et al., 1999) that can also be interpreted as a priorinfection pattern in epidemiology (Sofonea et al., 2017). Even at the cellular level, viruses have been shown to compete for resources making virulence (or pathogenicity) difficult to define in a biologically diverse context (Turner and Chao, 2003; Alizon et al., 2013). From a more mundane perspective, it is unclear whether a current day 'pathogen' might be useful somehow in the future, *e.g.*, as a means to implement biological control of another parasite, or to yield genes beneficial for an applied use. Furthermore, we keep discovering new viruses. SARS-CoV-2 is of course an extremely deadly example, but many of these new viruses are only known through their DNA found in metagenomes. As illustrated by the study of Zhao et al. in this special issue, analysis of eukaryotic genome sequence data can be used to detect circular replication-associated protein-encoding single-stranded (CRESS) DNA viruses, thereby expanding discovery of previously-unknown virus diversity.

For simplicity, in the following sections we will focus on viruses that are more obviously deleterious to the host, so that virus pathogenicity is less questioned. Even here, the eradication question can be considered in a practical way (is eradication feasible?) and in an ethical way (should this eradication be attempted?).

3 Eradication requires will (and funding)

Regarding the practicality, biotechnology increasingly allows the generation of viruses *in vitro* based on their genomic sequence information alone.

Setting aside for the moment the ethics of such engineering, we note that treatment availability is not enough to guarantee eradication at a population level (at the individual level, several treatments or vaccines do achieve this goal). As illustrated with SARS-CoV-2, although vaccines decrease the probability to be reinfected, their main efficacy is against severe disease (Creech et al., 2021). Even with an infection-blocking vaccine, implementation and surveillance require

original approaches, as illustrated in the (successful) case of variola virus (smallpox disease) elimination (Henderson, 2011). Conversely, for HPV, safe and efficient vaccines have been implemented for over a decade and the most oncogenic types (HPV16 and HPV18) are nowhere near extinction at a worldwide scale (de Martel et al., 2017). Recent results from the UK reporting that HPV vaccination decreased cervical cancer risk by 72 to 94% in women above 30-years old that were vaccinated at age 12 or 13 (Falcaro et al., 2021) confirm that vaccine efficacy is not to blame; rather, the lack of funding and of political will seem to be the main factors.

The contrasting cases of HPV and variola virus demonstrate the biological and economical limitations of vaccination. These shortcomings are also visible in the terminology and the distinction between control, disease elimination, infection elimination, and eradication. In the case of the ongoing pandemic, some countries have so far succeeded in greatly reducing SARS-CoV-2 infections; the development of treatments leads to the hope of eliminating the disease (COVID-19), but most countries mainly focus on controlling the infection. Eradication currently seems unrealistic given the vaccine efficiency in blocking infections and the possibility for presence in animal reservoirs, which could differentially impact virus evolution. For instance, differences in host-cell receptors can drive divergence among influenza virus lineages as they adapt *in vitro* Barnard et al.. The host itself is only part of the equation and for an ssRNA plant virus the habitat in which these plants are located also shapes evolutionary dynamics Peláez et al..

4 Viruses evolve

Under-appreciating virus evolution jeopardizes the promise and success of eradication programs. Similarly, before evolution of generalised drug resistance, the World Health Organisation was aiming for eradication of malaria *Plasmodium* parasites (Molyneux et al., 2004). In a virus example, the main concern in poliovirus eradication is that epidemics are now caused by evolutionary reversion of the oral vaccine strains, illustrating unwarranted (long-term) effects of eradication policies (Famulare et al., 2018).

Theory in evolutionary ecology tells us a lot about population extinctions. For instance, the closer a population approaches extinction, the stronger the selective pressure for 'evolutionary rescue' (Gonzalez et al., 2013). If we transpose this to viruses, the more likely an eradication policy is to succeed, the more we should beware of an evolutionary (phenotypic) response in the pathogen. This evolution response can manifest itself in several ways. The most common one is virus resistance to the intervention, which means that we lose a treatment. Unfortunately, as demonstrated in the case of Marek's disease virus (MDV) in poultry farming (Read et al., 2015), vaccination may exert selection that favours more virulent viral strains. Fortunately, such evolutionary response is less frequent for prophylactic vaccines, i.e., administered before infection, than for curative treatments given to infected hosts because in the former case the population within-host diversity remains limited (Kennedy and Read, 2017). A potential worry, however, is that treatments targeting more-virulent strains can lead to the correlated evolution of both increased resistance and virulence (Alizon, 2020).

Interestingly, the evolution of pathogen resistance issues that are faced by clinicians in hospital are also evidenced in parasites of bacterial populations. For instance, the study by Common et al. (2020) in this special issue shows how bacteria have evolved a diversity of defence mechanisms, which select for bacteriophage ability to evolve counter-resistance.

5 Not a call for inaction

The threat of virus evolution should in no way serve as an excuse for inaction. First, the potential risks need to be assessed. Second, it is important to mitigate these risks as much as possible. Again, the SARS-CoV-2 pandemic raised these questions in a particularly acute way. The development of RNA vaccines was undoubtedly fast and, when they were first implemented at the end of 2020, clinical studies had somehow limited overview on potential complications (which happened to be as rare as suggested by the initial results). However, the very high fatality rate of the infection (at least 10 times that of seasonal influenza) combined with its massive spread clearly outweighed the uncertainty risk. Furthermore, as pointed out by Alizon and Sofonea in their review in this issue, SARS-CoV-2 virulence has increased since the beginning of the epidemic in the absence of vaccination, showing that inaction does not guarantee virus evolution will improve the situation.

One possibility of action is to devise 'evolution-proof' treatments. It can be debated whether these can ever truly exist because, as in the case of anti-microbial peptides which were initially thought to be extremely robust to the evolution of resistance (Perron et al., 2006), microbes may always find their way. However, the fact remains that anticipating an evolutionary response should help to slow it down. For instance, at the Jacques Monod conference associated with this special issue, we learned how genetic engineering can radically decrease the aforementioned risk of reversion in the polio vaccine (Yeh et al., 2020).

Evolutionary biologists have much to contribute to the elaboration of eradication, elimination, or control strategies. However, when it comes to human health, we should also bear in mind that this is not as simple as writing an opinion piece in a society journal. In our special issue, Froissart and Brives use the example of phage therapy to stress how our community needs to navigate and interact with regulation of medicines, so that promising new therapies actually have an impact.

The ongoing pandemic has led to the realisation that mutations can generate 'variants' directly responsible for national lock-downs and reduced global travel. This is perhaps one of the strongest illustrations of the importance of virus evolution in recent history. We also know that public health policies will act as a selective pressure on viruses. This should by no means be a call for inaction. However, it is vital to monitor phenotypic evolution (Kennedy and Read, 2020) and to be at least one step ahead of viruses when implementing any type of control strategy.

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