Evolutionary consequences of delaying intervention for monkeypox

Since May, 2022, clusters of monkeypox infections have caused global concern. At present, this concern has been tempered by the fact that, even when uncontrolled, the number of infections is growing slowly, indicating a reproductive number (R) not much larger than unity. However, the effect of R on the probability of evolution might not be obvious. We suggest that, compared with zoonotic pathogens with large R values, those pathogens with R values just above 1, such as monkeypox virus, have a higher probability of evolution during the timeframe in which the number of cases remains low. Waiting until the number of cases is high would give monkeypox virus—or any emerging pathogen—the opportunity to adapt substantially to humans.

Population growth, ecological degradation, and climate change have increased the frequency of contact between humans and other animals, wild and domestic alike. The consequences include greater opportunities for pathogens to cross species barriers. Recent high-profile cases include Ebola virus (from bats), MERS coronavirus (bats or camels), SARS-CoV-1 and SARS-CoV-2 (bats), and monkeypox (rodents). After a zoonosis spills over into humans, subsequent evolution of the virus results in higher transmission, making control more difficult, and causing unpredictable changes in disease severity, as seen with different variants in the ongoing SARS-CoV-2 pandemic.

By definition, a zoonosis primarily infects non-humans. Any such pathogen is unlikely to be optimised for growth and transmission in humans, and substantial fitness increases are therefore possible. Retrospective phylogenetic analysis of the large Ebola outbreak from 2013 to 2016 revealed a small number of amino acid changes associated with increases in in-vitro growth in cell culture and transmission in the population.[1] The delta and omicron variants of SARS-CoV-2 contain extensive mutations, as illustrated in NextStrain,[2] and are associated with increases in effective R.[3] Similarly, the current monkeypox infections found both geographically and mutationally distant from the probable origin in Nigeria are consistent with adaptation by the pathogen for greater human-to-human transmission.[4]

These examples notwithstanding, gathering data on the evolution of newly emerging pathogens is challenging because it is harder to detect a small early-stage outbreak than a bigger later-stage outbreak. Advances in technologies such as wastewater sampling and the plummeting cost of sequencing pathogen genomes offer a promising way forward, but sampling still requires substantial public health resources. Is the use of these resources worth the effort?

Models provide a means to investigate this question by integrating pathogen epidemiological and evolutionary dynamics. Such models of emerging pathogens have focused on zoonoses with an initial human basic reproductive number (R_0) less than 1, where the initial cases give rise to stuttering chains of transmission ending in disease extinction, unless the pathogen evolves to increase R_0 above 1. In this scenario, the probability of evolution rescuing the pathogen from extinction increases enormously as R_0 approaches 1,[5] suggesting that particular attention should be paid to monitoring and controlling zoonoses with R_0 close to 1.

But what happens when R_0 exceeds 1? Monkeypox appears to be in this category, although only R, and not R_0, can be directly observed due to lingering cross-immunity against smallpox. The decline in this cross-immunity after the discontinuation of smallpox vaccination has led to an increase in the transmission of monkeypox since the 1970s.[6] Further adaptive evolution threatens to hamper control efforts through additional increases in R_0, changes in the route of transmission, or shifts to presymptomatic or asymptomatic transmission. For most emerging zoonotic infections, the primary

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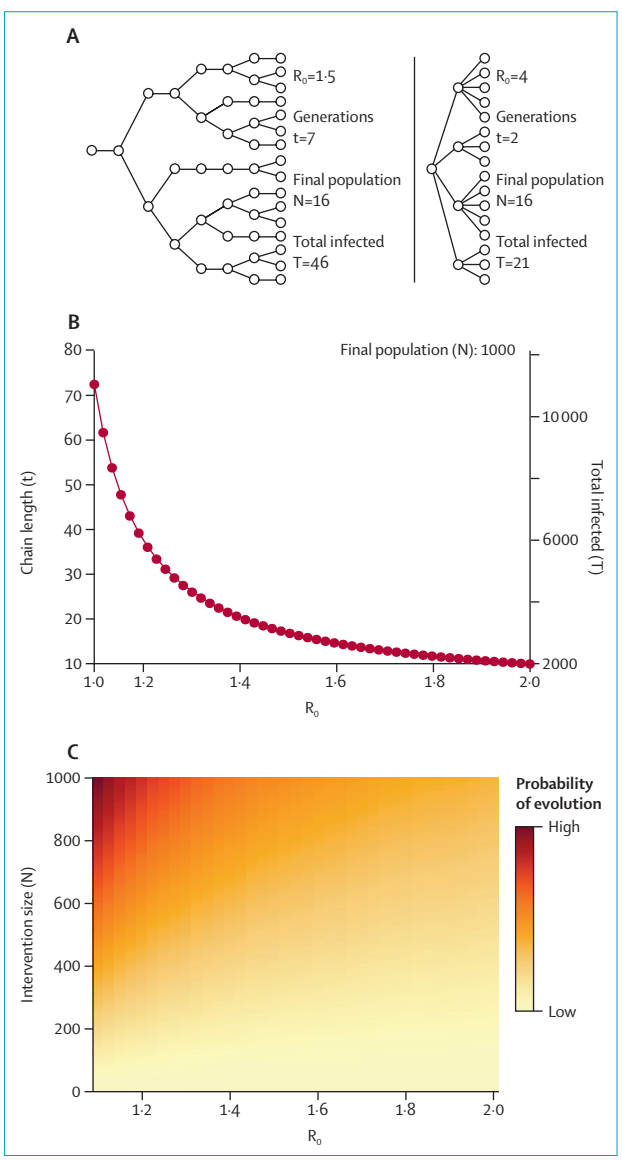

Figure: **R_0 affects a pathogen's evolutionary potential**
(A) When waiting until an epidemic affects N=16 people simultaneously, R_0=1.5 has longer chains of transmission affecting more individuals in total than R_0=4. (B) These patterns hold in general when waiting until N simultaneous infections, with lower R_0 being worse. (C) Evolution depends on mutations, which depend on the transmission chain length and total number of infected individuals, so, when waiting for a given N before intervening, lower R_0 has greater probability of evolving. R_0=basic reproductive number in humans before evolution.

constraint on adaptive evolution will be the availability of suitable mutations in the pathogen population, which increase as a function of time.

R_0 substantially affects the amount of time available for evolution before an epidemic reaches a critical size. A pathogen with a lower R_0 has both longer chains of transmission and a greater number of total infections before reaching a given number of simultaneous infections than a pathogen with higher R_0 (figure A). More generally, the length of the chain of transmission necessary to reach a threshold number of simultaneous infections (N) decreases with increasing R_0 as $\log_{R0}(N)$, and a qualitatively similar relationship exists between total infections and R_0 as $(R_0N–1)/(R_0–1)$ (figure 1B).

If substantial public health resources are deployed only toward pathogens that have achieved high visibility by infecting a large number of people (ie, a threshold number of infections), then we will miss a crucial window of opportunity to control low-R_0 emerging pathogens. Because time constrains evolution, lower R_0 (but still >1) pathogens have more opportunities to acquire advantageous mutations before an epidemic reaches a size at which the world becomes widely aware of the danger (figure 1C, top left corner).

For decades, monkeypox has been well known as an emerging infection with an R less than 1.[7] Now its R is probably higher, which could be the result either of evolution within the animal reservoir population or within humans. Regardless, now is the time—probably past the time—to put resources into controlling outbreaks before they grow larger and have time to evolve further. For the current outbreak of monkeypox virus, the rapid use of ring vaccination, where index cases, traced contacts (of the index case), and contacts of those contacts are all vaccinated with the licensed MVA-BN vaccine (known as imvanex), could help to ensure that this epidemic does not get out of control. This vaccine plus unlicensed monkeypox vaccines could be randomly tested for efficacy in ring vaccination. Such a vaccination strategy led to the eradication of smallpox and could be quite effective in the still-early phase of the monkeypox outbreak.

In general, our analysis from first principles highlights the benefits of rapid intervention even for mild emerging pathogens. In summary, just because a disease like monkeypox appears to be controllable does not mean it will stay controllable. Currently, monkeypox incidence is starting to decrease in Europe and North America. This reduction might be due to behavioural changes in at-risk populations and increased use of vaccines, but the epidemic is far from over and continued drive towards elimination is essential.[8] By reducing the chance of evolution, rapid and sustained intervention benefits not only local communities but also the world. That said, we considered the evolutionary implications of delaying intervention without addressing trade-offs that arise due to the inherent scarcity of public health resources. Future research might need to account for both factors to find a balance between minimising delay to prevent virus evolution and increasing delay to ensure optimal resource allocation.

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