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Trends in Immunology

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Opinion

Why are there so few (or so many) circulating coronaviruses?

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Despite vast diversity in non-human hosts and conspicuous recent spillover events, only a small number of coronaviruses have been observed to persist in human populations. This puzzling mismatch suggests substantial barriers to establishment. We detail hypotheses that might contribute to explain the low numbers of endemic coronaviruses, despite their considerable evolutionary and emergence potential. We assess possible explanations ranging from issues of ascertainment, historically lower opportunities for spillover, aspects of human demographic changes, and features of pathogen biology and pre-existing adaptive immunity to related viruses. We describe how successful emergent viral species must triangulate transmission, virulence, and host immunity to maintain circulation. Characterizing the factors that might shape the limits of viral persistence can delineate promising research directions to better understand the combinations of pathogens and contexts that are most likely to lead to spillover.

Highlights

Coronaviruses have emerged repeatedly in human history, indicating that exposure may be common.

Evidence suggests that the emergent coronaviruses have the capacity to infect a broad range of hosts, invade these via a variety of host cell receptors, evolve rapidly during the emergence process, and, in the case of the endemic coronaviruses, persistently circulate by avoiding sterilizing immunity.

From this, we hypothesize that a diverse set of emerging coronaviruses might be found within the human pathogen pool. However, only four endemic coronavirus species are known (HCoV-229E, -NL63, -OC43, and -HKU1), which exhibit limited genetic diversity within species.

The interaction between infection parameters such as transmission and virulence, and the pattern of immune crossprotection against existing endemic viruses, warrant further study to understand the trajectory of novel coronaviruses and to explain why so few can establish endemic transmission.

Emergent and endemic coronavirus diversity

Transmissible and pathogenic novel human coronavirus species have emerged three times since 2002 [severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1) 2002, Middle East respiratory syndrome (MERS) 2012, and SARS-CoV-2 2019]. Within species, rapid evolution has been observed, both in terms of the appearance of new variants after emergence (e.g., for SARS-CoV-2 [1]) and **immune escape** (see Glossary) for established **endemic coronavirus species** (e.g., human coronaviruses HCoV-229E and HCoV-OC43 [2,3]). Given this evidence of frequent **spillover**, rapid evolution, and the millennia of human history over which coronavirus diversity could have accumulated, one would expect a diverse abundance of coronaviruses in the human **pathogen pool**. However, only four endemic species are known to persist in human populations (HCoV-229E, -NL63, -OC43, and -HKU1), which harbor limited genetic diversity within species [4,5].

What could explain this apparent mismatch between the pace of emergence and the low diversity of endemic coronaviruses? The coronaviruses provide a timely example, but this pattern is not without precedent: frequent emergence is seen but without evidence of historical accumulation of a diverse endemic community for an array of pathogen groups (Box 1). We evaluate here the multiple factors that may govern the diversity of the endemic pathogen pool of a host, using coronaviruses as an example; we note in particular how population variation in immunity resulting from multi-pathogen dynamics might influence the prospects for pathogen emergence and persistence.

For a pathogen with emergence potential, barriers to becoming endemic may act at both the **reservoir-to-emergent** and **emergent-to-endemic** transitions (Figure 1A). Wildlife-infecting coronaviruses are rich in diversity, with ~50 classified species, and likely many more unassigned

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Box 1. The comparative context of coronavirus diversity

Approximately 20–30 viral families and 200–300 viral species are known to infect humans [27]. Comparing viral diversity across lower (e.g., serotype, genogroup, or strain) or higher (e.g., species or family) taxonomic levels is complicated by differences in taxonomy conventions. However, species level and intra-species diversity is low for some human viral groups. For example, most viral families have fewer than 10 known human viruses, of which not all have demonstrated stable transmission. This is compared with estimates that 1–2 million viral species may be circulating in mammals and birds alone [102], and >10 000 are thought to have the potential to infect humans [103]. Likewise, some non-viral pathogen groups are similar to coronaviruses in that evidence of recent emergence events does not correspond to high rates of endemism. In malaria, for example, two new species (*Plasmodium knowlesi* [104], and to a lesser extent *Plasmodium cynomolgi* [105–107]), have been observed to infect humans since the 1990s, but there are only four other long-known human malaria-causing parasite species [108,109]. Conversely, some pathogen groups exhibit high circulating diversity. Examples include enteroviruses, for which more than 100 serotypes are thought to co-circulate [77], and the Bunyaviridae, for which >40 human-infecting viruses have been described [27]. Bunyaviruses that are known to infect humans include a high number of species, but are often limited by the distribution of their arthropod vectors [110]. The high diversity of circulating enterovirus serotypes might be explained by the lack of cross-reactivity among enteroviruses lineages [77]; because immunity is highly specific for this group, many related viruses may be able to spread independently without being affected by immunity previously generated against other lineages. Characterizing the viral diversity of influenza virus, and others that evolve antigenically in response to immune pressure must account for the facts that, on the one hand, strains accumulate antigenic diversity rapidly via antigenic drift, but on the other hand, only a small fraction of that diversity of strains circulates at a given time [72].

Glossary

Antigenic drift: evolution, often rapid, of the genetic sequence encoding a pathogen antigen driven by host antibodies against the original sequence.
Cross-reactivity: an adaptive immune response raised against an antigen from one pathogen which recognizes and may be protective against another.
Emergent-to-endemic transition: following emergence, the process of attaining sustained and widespread transmission such that the pathogen establishes itself as endemic in a host population.
Endemic coronavirus species: also referred to as 'common-cold' coronaviruses, HCoV-229E, -NL63, -OC43, and -HKU1 are globally distributed, regularly observed, directly transmitted acute viral species hat infect humans.
Epistasis: interaction of different genes within the genome such that the overall effect of a mutation in one gene (e.g., a mutation that may allow immune escape) is dependent on other genes (e.g., that are associated with viral replication).
Immune escape: the ability of new pathogen genotypes to avoid existing immunity.
Original antigenic sin: a characteristic of the immune system where the response to the original virus infection affects, and often reduces the effectiveness of the antibody response to a second, related virus infection.
Pathogen pool: the collection of pathogens regularly circulating in a host population.
Reservoir: a non-human host for a pathogen.
Reservoir-to-emergent transition: following spillover, the process of initial emergence and spread of a new pathogen in a host population.
Spillover: exposure to the pathogen pool of an animal reservoir resulting in a new pathogen entering the human population.

or unobserved lineages that infect a broad range of mammalian hosts [6]. A subset of this diversity – the four endemic human coronaviruses – are thought to have entered human populations between 50 and 700 years ago (Figure 1B) and are observed as common respiratory infections globally [7–11]. The endemic species are distantly related and may have emerged from different **reservoirs**, or in some cases via different intermediate hosts, suggesting that, for coronaviruses, there might be multiple pathways to becoming endemic, although this remains conjectural.

In recent years there have been several emergent coronaviruses. SARS-CoV emerged in 2002–2004 and infected >8000 people across 30 countries [12]. To date, MERS has infected >2000 people across 27 countries and has repeatedly emerged and become extinct in human populations [13]. SARS-CoV-2 has infected >150 million humans globally since emerging in 2019 [14]. Supporting a broad host competency, SARS-CoV-2 has also infected a broad range of hosts, including various carnivores, bats, non-human primates, and rodents [15–17], and is likely capable of infecting many more [18] (Figure 1C). Other historical emergences may have gone undocumented [19–21].

A range of possible hypotheses might contribute to explaining why the evolution and emergence of coronaviruses – via different pathways – are commonly observed, but with limited species and intraspecies diversity. We first summarize evidence suggesting that difficulties in detecting viral species are alone unlikely to explain this mismatch. Next, multiple lines of evidence suggest that barriers to spillover, or limits to host competency, are unlikely to explain the observed pattern of coronavirus diversity. This motivates the exploration of the downstream processes by which emergent viruses (post-spillover) can become, or fail to become, persistent endemic pathogens. We conclude by noting the urgency for achieving a better understanding of the role that cross-pathogen immunity plays in enabling pathogen emergence, and spotlight future empirical work that might yield insight in this area.

Hypothesis 1: limits of coronavirus detection

A first potential explanation for the apparent mismatch between coronavirus emergence and endemism rates might simply be underestimated endemic viral diversity. For instance, many previous studies on endemic coronaviruses have occurred in wealthy, high-latitude nations [22–26], suggesting a general bias in viral discovery [27]. In addition, although existing surveillance efforts

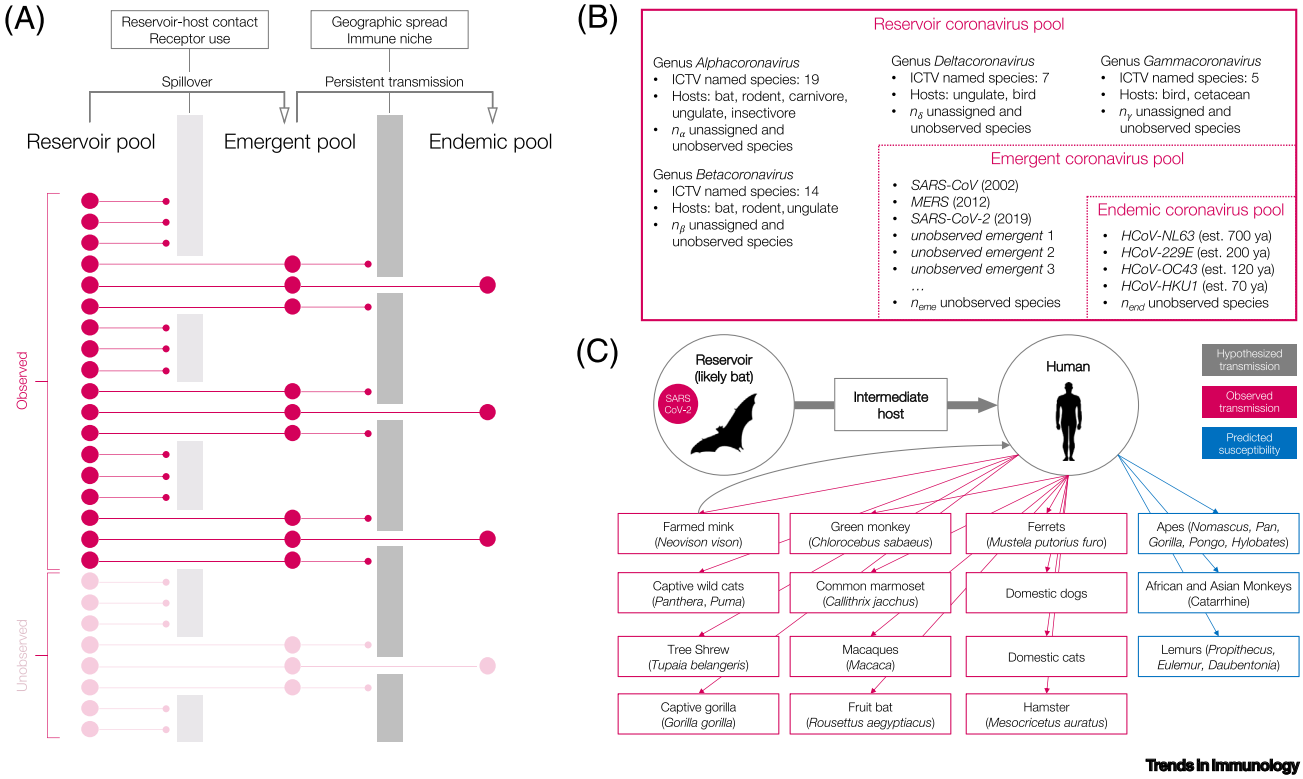

Figure 1. Coronaviruses and the pathway to endemism. (A) In this schematic, a subset of pathogens in the diverse reservoir pool enters the emergent pool via spillover, and a subset of emergent pathogens attain sufficiently stable transmission to enter the pool of persistently circulating endemic pathogens. Owing to incomplete sampling, a fraction of each pool remains unobserved (lighter colors). (B) Depicted are the reservoir, emergent, and endemic pools for coronaviruses, and again a fraction of each remains unobserved. Classification follows the International Committee on Taxonomy of Viruses (ICTV) [6]. (C) Spillover and cross-species transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from a likely bat reservoir, to a possible intermediate host, to humans, and then to secondary human–animal transmission. Bats have been hypothesized to be unusually prolific hosts for pathogens [111], but many other hosts are also noted (including non-human primates, wild and domestic carnivores, and ungulates). Note that human–mink–human transmission is suspected from fur farms, and susceptibility based on angiotensin-converting enzyme 2 (ACE2) receptor sequence variation was predicted, but unconfirmed, for some non-human primates [15–18]. Abbreviation: est. *n ya, established n years ago; MERS, Middle East respiratory syndrome.*

identified SARS-CoV-1, MERS, and SARS-CoV-2 soon after their emergence, it is less likely that the timely observation of an endemic virus that is not associated with severe clinical manifestations will occur. However, there is evidence that the rate of viral discovery has slowed, suggesting that current estimates likely capture the broad scale of endemic viral diversity [27,28]. Further, gaps in surveillance likely comprise missing emergent as well as endemic pathogens. For example, emergent pathogen diversity may be underestimated due to the paucity of viral and immunological surveillance in populations where the incursion of humans into previously forested areas is occurring (see hypothesis 2 below). It seems unlikely that global sampling efforts systematically over-detect transient emergence events and also under-detect common pathogens; thus, the rarity of endemic events relative to the frequency of emergence is not likely to be solely an issue of ascertainment.

Hypothesis 2: nonlinear rates of coronavirus spillover in human history

Another explanation may be that viral spillover could have recently accelerated. If the context of human-zoonotic pathogen transmission in the past few decades is substantially different from previous periods in human history, the currently limited endemic pathogen pool might simply reflect historical lower rates of pathogen emergence compared with those seen currently

(Figure 2A, Key figure). Notable emergence events, including Zika, Ebola, and influenza H1N1 viruses [29], have occurred often in the past few decades and have been tied to a nonlinear increase in the rate of anthropogenic disruptions of natural systems [30–32]. Alternatively, historical spillovers may have occurred frequently, but perhaps remained local, because of a much lower scale of travel relative to current rates [33].

However, epidemics associated with zoonoses going back hundreds of years provide ample evidence of historical spillovers that pre-date the scale of extractive behavior and human contact seen today. The 1918 influenza virus pandemic, as well as many large-scale epidemics in the pre-industrial world (e.g., smallpox [34], measles [35], and others; e.g., the plague [36,37]) indicate that sufficient human connectivity for pathogen spread at large spatial scales has long been present. Indeed, although air-traffic enabled SARS-CoV and SARS-CoV-2 global spread, data indicating the establishment of some endemic coronaviruses hundreds of years ago [9] show that consistent coronavirus spread was possible prior to the rates of (air) travel seen in the recent past.

Key figure

Possible hypotheses to explain the limits of endemic viral diversity

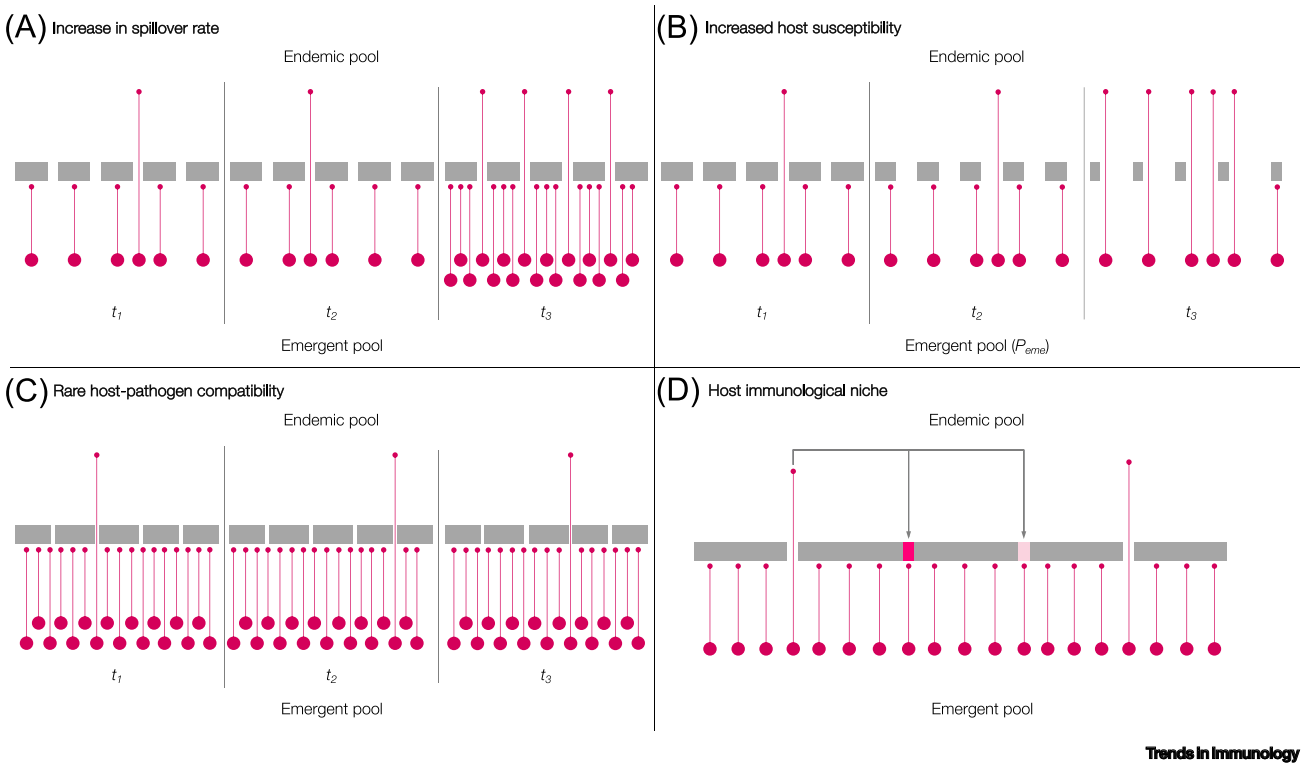

Figure 2. (A) An increase in spillover over time leads to the movement of more pathogens (shown as pink circles) from the emergent pool to the endemic pool. The filters or barriers to establishment as an endemic pathogen (shown as a gray bar with gaps) are constant; in other words the probability of an emergent pathogen being established remains fixed over time. (B) Host susceptibility increases over time such that a greater proportion of emergent pathogens can exploit widening gaps in immunity. (C) Emergent pathogens are numerous and diverse but the probability of establishment is small owing to narrow requirements for host and pathogen factors that are compatible with persistent transmission. (D) Opportunities for viral emergence depend on previously established pathogens that block or partially block immune niches or gaps via cross-reactive immune responses (e.g., for coronaviruses [84]).

In the past two decades, coronaviruses have emerged more than once per decade. Even if earlier times were less favorable for viral emergence, a lower rate maintained over the many thousands of years of pre-modern history would still have resulted in many emerging viruses [19,21]. If these emerging viruses persisted, even at low rates, there would be many endemic coronaviruses around today. As a result, lower spillover rates and lower travel rates in the past do not seem to fully explain why only a small number of coronaviruses are endemic in the present day.

Hypothesis 3: host susceptibility to coronavirus infection and changing human populations

Another dramatic change in recent decades has been the rapid increase in the average age of human populations owing to increased lifespan and declining birth rates [38]. All else equal, novel spillover pathogens are more likely to encounter older human hosts. Populations with a higher number of older individuals might be more susceptible to pathogen colonization for two reasons. First, because of **original antigenic sin**, the immune response to a novel pathogen could be modulated by previous exposure to other, often related, pathogens [39]. During the first challenge with a pathogen-specific antigen, memory B cell responses are generated. Upon subsequent host infection with other pathogens bearing **cross-reactive** antigens, naïve B cells may be less able to develop new, more specific memory responses to these cross-reactive antigens compared to the first antigen from the first encounter. From the host perspective, these responses might be less effective in preventing infection or onward transmission relative to *de novo* priming responses. From the pathogen perspective, novel pathogens are likely to encounter heterogeneous host immunity, with adaptive and innate immune responses varying depending on factors such as host age, geography, and historical exposure to other infections (e.g., influenza virus [40]). Second, for instance in humans and mouse model systems, as the host ages, immunosenescence has been associated with depletion of naïve B and T cells capable of recognizing new pathogens; this in turn can lower the defense barrier against pathogen colonization and/or onward transmission (Figure 2B) [41].

Individuals with chronic diseases associated with different immunological states, as well as immunosuppressed individuals, are increasingly prevalent (e.g., because of treatments associated with chemotherapy or owing to HIV-1 infection). The presence of these groups within populations might modify the context of viral emergence by altering immune system functioning and changing the evolutionary selection pressure for mutations associated with transmission or immune escape, as suggested for SARS-CoV-2 [42]. However, various confounding factors could limit the effects of ill, immunosenescent, or immunosuppressed individuals. For example, as in the case of hunters, there might be an association between a given occupation and exposure to a potential spillover – the latter remaining constant regardless of overall demographic trends [43]; this in turn might contribute to minimizing age-related differences in the observed immune responses to pathogens. Nevertheless, although the scale of influence remains uncertain, shifting demographics may have relevant implications for immune patterns at the population level, potentially altering environments for viral emergence.

Hypothesis 4: pathogen-driven limits to endemic infection

Host preference and receptor binding

If contact between two host species occurs, a first requirement for viral spillover is the ability of the virus to invade cells in the new host. A second requirement is the ability to overcome host innate immune defenses such as the secretion of type I interferon (IFN) from immune cells [44,45] to impair completion of a viral replication cycle within the new host. Could these requirements for host–pathogen compatibility explain the limited number of endemic coronavirus species in human populations? (Figure 2C). Many lines of evidence suggest that this is unlikely. Coronaviruses

have repeatedly demonstrated the ability to cross the species barrier and replicate successfully; for example, betacoronavirus 1 can replicate in dogs, humans, and numerous ungulate species [46]. In addition, SARS-CoV-2 spillback to pets such as dogs [17], farmed minks [47], and tigers and lions in zoos [48] is unsurprising given the broad host potential for the virus, as evidenced from analyses on the structure of the SARS-CoV-2 receptor-binding domain and its potential to bind to mammalian host cell receptors [49]. In addition, broad and overlapping host ranges may allow genome recombination among viral lineages, which can further diversify the pathogen pool [50,51].

The coronaviruses known to infect humans are relatively phylogenetically distant [9], suggesting that there is no evolutionarily rare, 'special' feature that is necessary to invade human populations. They also use an array of different receptors: MERS-CoV uses dipeptidyl peptidase 4 (DPP4, a ubiquitous cell-surface protease [46]); HCoV-NL63, SARS-CoV-1, and SARS-CoV-2 use angiotensin-converting enzyme 2 (ACE2); HCoV-OC43 and -HKU1 bind to 9-*O*-acetylated sialic acids [52]; and HCoV-229E uses aminopeptidase N [53]. These receptors have in common that they are widely expressed in human cells, and tend to be evolutionarily conserved among hosts [18,54].

Together, the evidence for considerable host promiscuity among coronaviruses, and the wide range of origins for different coronaviruses infecting humans, suggest that host species boundaries pertaining to receptor binding, cellular tropism, evasion of innate immunity, and replication are not the only limiting factors for coronavirus spillover. If the virus can also successfully complete a replicative cycle in host cells (further discussed under hypothesis 5) the next set of barriers to viral emergence include how viral replication translates into host survival and host-to-host transmission.

Suitable transmission virulence

An ability to successfully invade and replicate in new host cells is still not sufficient to ensure that a virus can successfully persist. It must also achieve sustained onward transmission (Figure 2C). This implies that the virus possesses a set of adaptations that are necessary not only to invade and transmit (e.g., present in droplets exhaled by the host) but also to avoid killing the host too swiftly either from damage inflicted by the virus or from a robust immune reaction [55]. Of note, early morbidity and mortality with a potential to curtail transmission were characteristic of SARS-CoV-1 infections in humans; indeed, early symptomatic presentation was an important feature for the successful containment of this pathogen [56]. By contrast, SARS-CoV-2-associated morbidity and mortality in humans seem to occur after much of the transmission has occurred [57]. This suggests that a wide range of transmission and virulence features are possible among coronaviruses.

The number of new infections per infected individual in a completely susceptible population, R_0, provides one lens to understand the trade-offs between loss of hosts due to mortality and rate of transmission. R_0, also termed the net reproductive value, is defined by the rate of transmission (β) that reflects the rate of increase of infectious individuals, divided by the rates of loss via recovery (γ) or via mortality (μ_1): $R_0 = \beta/(\gamma + \mu_1)$ [55]. For an emergent pathogen to be established $R_0 > 1$ is required, and high values of μ_1 will tend to reduce R_0. Because human coronavirus infections are predominantly respiratory (despite being predominantly enteric in animal reservoirs [58]), and disruption of the lung can be rapidly fatal, high virulence may be a particular barrier to coronavirus emergence in human hosts. Indeed, endemic coronaviruses are minimally virulent (i.e., have little effect on mortality or on symptoms that are sufficient to curtail transmission), thus contributing to an R_0 estimated to oscillate between 1.7 and 2.2 [59], which enables persistence of the viruses in

the population. Of the emergent coronaviruses, R_0 has been estimated to be in the range 0.8–1.3 for MERS [60] and between 2–3 for SARS-CoV-1 [61]; these magnitudes, together with their relatively short durations of infectiousness but high virulence, may be in part what has restricted the spread of these two emergent pathogens. However, with an R_0 of 2–3, as well as considerable asymptomatic transmission, SARS-CoV-2 has established itself broadly [62]. Furthermore, this magnitude of transmission and duration of infection are such that susceptible host numbers are unlikely to rapidly decrease in frequency. The loss of susceptibles can constitute another potential barrier for emergent pathogens, especially for those that are highly transmissible, because the pathogen may become extinct by chance, when available susceptible hosts become rare after the first wave of infection [63].

Although the similar scale of R_0 across all these exemplars hints that there might be biological constraints on transmission (β), evidence of rapid transmission within other reservoirs (e.g., pigs [64,65]) suggests that this is not necessarily the case for all coronavirus infections. Overall, it is difficult to characterize the degree to which this combination of pathogen features presents an important barrier to coronavirus spillover. Among the coronaviruses that have emerged over the past two decades, one (SARS-CoV-2) has had the right combination of features for establishment. This suggests that obtaining the right combination of pathogen features is not an insuperable barrier.

Hypothesis 5: host immunological niche and limits to establishment

Successful emergent pathogens must persistently evade innate and adaptive immunity to establish endemically. Some aspects of coronavirus biology in reservoir hosts may have contributed to the preadaptation of SARS-CoV-2 to evading human innate immunity. For instance, sequence analysis indicates that SARS-CoV-2 and its closest relatives have the lowest CpG dinucleotide rates among all known bat and human coronaviruses, which has been hypothesized to result from selection within particular bat host species or tissues. This low CpG content has been suggested to be a factor that might facilitate human innate immune system evasion by SARS-CoV-2 because CpG-rich sequences, which are relatively rare in the human genome, are targeted by the innate immune system [66,67]. Moreover, similar historical selection of the virus in non-human hosts may have resulted in the ability of SARS-CoV2 to evade IFN pathways within replicative cell cycles, as evidenced from *in vitro* infection experiments using epithelial cell lines [68]. Presumably, not all spillover viruses have this capacity. Indeed, humans living near caves harboring bats – known reservoirs of non-human SARS-CoV-related viruses – were found to be seropositive but without evidence of continued circulation of those non-human coronaviruses; this in turn indicated that some spillovers do not achieve onward transmission [20]. Likewise, the recent detection of porcine deltacoronavirus (PDCoV) in three children in Haiti further suggests that there may be independent coronavirus spillovers [69].

Beyond innate immunity, a distinctive feature of adaptive immunity is the highly specific targeting of pathogens to which the host has been previously exposed – the principle of immunological memory. This feature might make adaptive immunity initially negligible to novel pathogens, while placing strong selective pressure on endemic pathogens, as evidenced from **antigenic drift** [70,71]. Antibodies that can neutralize circulating viruses based on their current configuration can drive the spread of variants that are able to escape, or partially escape, this immunity [72]. Well-characterized for influenza virus, similar processes have been reported for endemic coronaviruses [2]. Changes that enhance immune escape can also increase receptor binding in influenza viruses [70] and coronaviruses [3,73], thus increasing the challenge for achieving effective host immune defenses.

However, **cross-reactivity** is also a signature of adaptive immunity: an adaptive immune response raised against one pathogen may be protective against another (Figure 2D). For example, reduced endemic coronavirus infections in human populations have been associated with prior influenza virus infection [74], and rhinovirus infections in human bronchial epithelial cells can block SARS-CoV-2 replication [75]; this suggests that prior infection with another pathogen might reduce the colonization and/or establishment of an emergent coronavirus. Pathogens can thus compete with each other for host invasion, limiting the prospects for emergence: early growth of spillover pathogens will no longer be governed by R_0 but by $R_0 \times S$, where S constitutes the fraction of the population that is left susceptible by the competing species (Figure 3) [55]. Indeed, the barrier to monkeypox spillover created by cross-protective immunity associated with smallpox vaccination is a remarkable example of this phenomenon: recent cohorts of human hosts not receiving smallpox vaccination lack this barrier, such that the frequency of monkeypox spillover into these human cohorts is currently increasing over time [76]. Conversely, the absence of cross-protective immunity removes this possible immune barrier to spillover: this may also potentially constitute one explanation for the rich strain diversity that is observed among enteroviruses in humans (Box 1) [77] (also assuming limited behavioral interactions) [78].

The issue of cross-protective immunity may also provide another angle on why the number of endemic coronaviruses is currently four: competition between species can also influence the

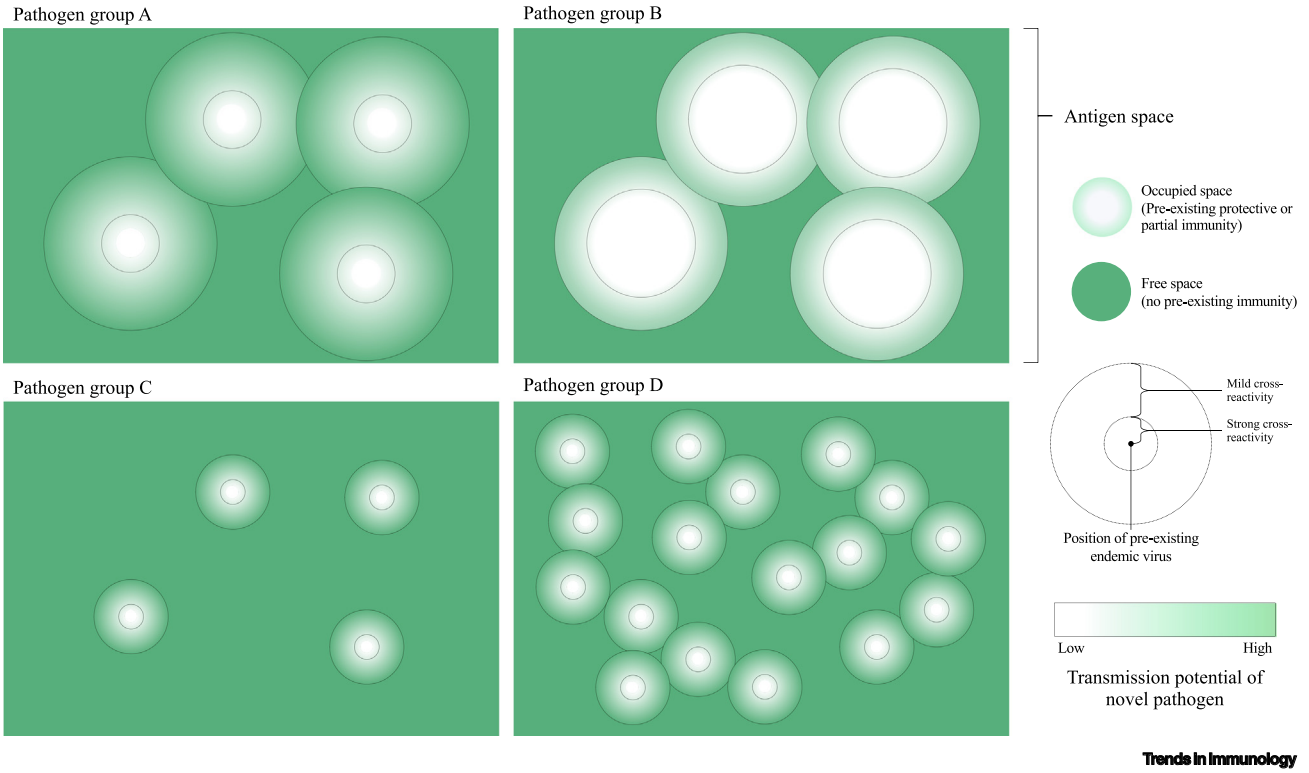

Figure 3. The landscape of variable immune responses against coronaviruses and the concept of 'free antigen space'. 'Antigenic space' can be represented in 2D [112]. Above, a large proportion of possible antigenic phenotypes are within areas of antigenic space featuring some degree of cross-reactivity to existing endemic pathogens. The potential for transmission (e.g., in terms of R_0) of a novel pathogen situated near an existing pathogen can vary from low (white) to high (green), and the proportion of 'occupied' space where transmission is strongly reduced can vary from small (group A) to large (group B). Below, for different pathogen groups, each existing pathogen generates an immune response that occupies a smaller proportion of antigenic space, either because of more specific immunity or a larger possible antigenic space. As a result, a greater proportion of antigenic space is 'free' (group C) or more pathogens can occupy the antigenic space without much overlap (group D).

species that coexist. Specifically, if cross-protection is broadly symmetrical, then, among those coronaviruses eliciting overlapping crossprotection, the virus with the highest R_0 may exclude all the other coronaviruses, including spillover species [79], resulting in a single endemic viral lineage. If differences in R_0 are minor (as suggested for coronaviruses [59]), then persistent co-circulation among host populations may depend on how coexisting species avoid sharing a given immunological niche – for example, by evolving away from existing cross-protective immunity – or on how they tolerate sharing the immunological niche – for example, by shifting infection to a different time of year or to a different age group [22].

Immunity against coronaviruses is suggested to be relatively short (e.g., reinfection has been often observed at 12 months for endemic human coronaviruses from multi-decade longitudinal studies) [80–82]. In addition, immunity against endemic coronaviruses can be cross-reactive, and (based on analyzing the time-series for cases of coexisting species [59], in conjunction with systems serology approaches identifying convalescent plasma viral neutralization capacity [83]) can be to some extent cross-protective [2,84]. If the immune response elicited by each virus reduces viral growth more than it does for other competing viruses, then coexistence may ensue – assuming similar R_0 magnitudes. In addition, differences in R_0 might be offset by differences in susceptibility to cross-reactive immunity; specifically, a lineage that is less transmissible but is able to avoid cross-reactive immunity, might harbor an advantage over other lineages subjected to cross-reactive immunity. Moreover, slight differences in seasonal patterns of transmission, associated with small heterogeneities in climate dependencies [85,86], might enable coexistence; for example, by enabling multi-annual cycles where pairs of viruses exhibiting the highest cross-reactivity might reach their maximum incidence in different years. For HCoV-229E and -NL63, this pattern was suggested in time-series studies of human endemic coronaviruses undertaken in Scotland [22], Sweden [23], and Michigan [25]. For larger differences in R_0, differences in the duration and specificity of immune reactions against different viruses might enable partitioning of the immunological niche across human age ranges [87]. However, to date, this remains highly conjectural for human coronaviruses and warrants further investigation [22–26,88–90].

The evidence of seasonal offsets [22], antigenic drift [2,91], and cross-neutralizing antibodies [24,84,92,93] among endemic coronaviruses is consistent with evolutionary pressure acting on endemic coronaviruses as a result of competition among themselves (Figure 3). That endemic coronaviruses are not entirely offset temporally or antigenically (indicating that opportunities for competition continue) suggests that there might be an upper limit to the degree to which antigenic variation and immune escape can occur, while other aspects of viral fitness are maintained (**epistasis**). This remains an important open question that is closely related to the issue of which combined circumstances might have created an opportunity for SARS-CoV2 spillover into humans in late 2019. Perhaps it was simply a case of bad luck – the random local extinction of an endemic coronavirus [22] could have created a local, temporary gap in immunity at the place where spillover occurred. It may have occurred by chance: events in the evolutionary history of the virus in the nonhuman reservoir could have led to the antigenic profile of SARS-CoV-2 being such that it evaded existing cross-neutralizing immunity in human populations. Indeed, although antibody cross-reactivity between endemic coronaviruses and SARS-CoV-2 is often detected in human populations [94], no effect on hospitalization has been identified [95], suggesting that existing antibodies might not be protective against severe disease. Similarly, memory T cells in humans without prior exposure to SARS-CoV-2 do cross-react with the virus [96], but there is little evidence that this has slowed the spread of the pandemic [97]; furthermore, cross-reactivity does not seem to be inevitable because T cell responses to endemic coronaviruses do not cross-react with MERS [98]. Overall, multiple lines of evidence suggest

opportunities for immune-driven competition among coronaviruses. This competition might act to filter out potential emergent viruses that, unlike successful emergent species (e.g., SARS-CoV-2), occupy an immunological niche for which strong protective cross-reactivity is already common in the population.

Concluding remarks

The existence of four coronavirus species endemic to the human population seems to be a small number compared with the three spillovers that have been observed in the past two decades. Assuming that this is not simply an issue of ascertainment (hypothesis 1) or of greatly changed recent geodemographic conditions (hypotheses 2 and 3), the answer to the question of why there so few coronavirus species endemic to human populations must lie at the intersection of at least three factors: transmission, virulence, and any existing immune cross-reactivity elicited from other coronaviruses. Indeed, to successfully emerge, a new species must thread the needle in terms of virulence and transmission, while also successfully evading existing immunity in the human population.

Of note, techniques for measuring population-level heterogeneity in immunity are rapidly advancing [99,100]. Combined with expanding synthetic biology approaches (e.g., constructing a spectrum of potential coronavirus spike domains), such data might yield insight into the potential viral spillover events that the immune system might successfully keep at bay. Conversely, it may also be possible to assess vulnerabilities, such as gaps in human immunity around other non-human coronaviruses with the potential to emerge (see Outstanding questions). In turn, these data could assist in identifying locations and specific viral lineages for which increased surveillance efforts or pre-emptive vaccine development could be considered. Collectively, such information may be valuable in assessing the SARS-CoV-2 pandemic and any future putative coronavirus spillover/pandemic events; it may also allow better dissection of the relevance and applicability of the five hypotheses presented in this opinion article.

More broadly, this discussion is relevant to fundamental questions in viral biology, such as why only ~200–300 viral species infect humans, out of the large number that are circulating; also, a pressing question concerns why some subgroups of human viruses (e.g., the enteroviruses) are largely diverse, whereas others (e.g., respiratory syncytial virus, RSV), are more restricted (Box 1 and see Outstanding questions). Broadening the comparative context of these analyses might also inform questions in viral ecology. These include examining the role of environmental context in enhancing viral diversity (e.g., a shared wetland habitat can act as a reservoir for influenza virus transmission among waterbirds [101]) and the role of tissue tropism (e.g., the different limits to immunity and pathogen tolerance in the gut versus the lung). Lastly, the non-pharmaceutical interventions that were deployed globally in 2020–2021 may yield additional and fascinating information regarding the coexistence and persistence of endemic coronaviruses in humans.

Outstanding questions

What proportion of coronavirus lineages in the reservoir pool are at a position in antigenic space that is occupied by cross-reactivity to an existing human endemic coronavirus?

Before emergence, can we identify existing wildlife coronaviruses that are (i) able to avoid protective cross-reactivity from endemic coronaviruses, and (ii) have transmission and virulence parameters that permit persistent circulation in human populations?

Why are human coronavirus infections respiratory (at least predominantly) whereas most major animal coronavirus infections are enteric (e.g., swine, canine, and feline CoVs) or pneumoenteric (bovine CoV)? Given the greater fragility of the lung in comparison to the gut, how do tissue tropism and virulence interact to shape emergence potential? Do viral groups infecting different tissue systems have different patterns of species or intraspecies diversity?

Comparing across viral groups, do groups for which immunity against existing pathogens occupies a smaller proportion of antigenic space have more diverse endemic pathogen pools (i.e., do endemic viruses cast narrower cross-reactivity shadows for some groups)?

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Declaration of interests

None are declared.

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