



Published in final edited form as:

Clin Chem. 2025 January 03; 71(1): 109–118. doi:10.1093/clinchem/hvae150.

Virus evolution in prolonged infections of immunocompromised individuals

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Abstract

Background: Many viruses can cause persistent infection and/or viral shedding in immunocompromised hosts. This is a well-described occurrence not only with SARS-CoV-2, but for many other viruses as well. Understanding how viruses evolve and mutate in these patients and the global impact of this phenomenon is critical as the immunocompromised population expands.

Content: In this review, we provide an overview of populations at risk for prolonged viral shedding, clinical manifestations of persistent viral infection, and methods of assessing viral evolution. We then review the literature on viral evolution in immunocompromised patients across an array of RNA viruses, including SARS-CoV-2, norovirus, influenza, and poliovirus, and discuss the global implications of persistent viral infections in these hosts.

Summary: There is significant evidence for accelerated viral evolution and accumulation of mutations in antigenic sites in immunocompromised hosts across many viral pathogens. However, the implications of this phenomenon are not clear; while there are rare reports of transmission of these variants, they have not clearly been shown to predict disease outbreaks or have significant global relevance. Emerging methods including wastewater monitoring may provide a more sophisticated understanding of the impact of variants that evolve in immunocompromised hosts on the wider host population.

Background

The prevalence of immunosuppression in US adults has more than doubled over the past ten years. The reasons for this are multifactorial, and include increases in the availability and prescription of immunosuppressive medications, record numbers of organ transplantations, and improved longevity of patients living with immunosuppressive conditions (1, 2). Immunosuppressed patients are uniquely susceptible to infection due to impaired host immune responses and pathogen clearance. Many infections that are typically brief and self-limited in immunocompetent hosts can cause prolonged and/or severe infection in the absence of a robust adaptive immune response. This is particularly true of viral pathogens.

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Conflicts of Interest

The authors have no conflicts of interest.

The phenomenon of prolonged viral infection and shedding in immunocompromised hosts is well-recognized and has been described across many different viruses, but none more so than SARS-CoV-2.

Over the course of the COVID-19 pandemic, there was an explosion of literature on prolonged infections in immunocompromised patients, with many reports describing accelerated intrahost viral evolution in these patients. Multiple case reports suggested acquisition of *de novo* intrahost mutations conferring increased ability to evade the host immune system (3-6). Indeed, one of the leading hypotheses explaining the origin of some variants of concern with large numbers of new mutations on emergence (including alpha and omicron) was that they had first originated in one or more immunocompromised hosts (7).

While the COVID-19 pandemic brought this topic to the fore, persistent viral infection and intrahost evolution in immunocompromised patients have long been of interest, and there is a wealth of data on this phenomenon in many other viruses, including influenza virus, norovirus, and poliovirus (8). Intrahost evolution in viruses that typically cause acute infections in immunocompetent hosts is best described in RNA viruses, whose short generation times and high mutational rates lead to large, diverse viral populations which can persist and evolve in the absence of effective host clearance, and which are the focus of this manuscript. The vast majority of emerging pathogens are viruses, and a virus is likely to be responsible for the next pandemic as well (9). As the number of immunocompromised people increases, an understanding of how viruses evolve in these hosts and how this evolution impacts the global host population is critical.

What is prolonged viral infection and how is this assessed?

Criteria for prolonged versus self-limited viral infection are not well-defined. This is partially because the duration of viral shedding in immunocompetent individuals can be challenging to rigorously define; for example, in SARS-CoV-2, the length of nucleic acid positivity ranges widely in the literature. Shedding is also affected by a variety of factors outside of the host's immunologic status, including immunizations and antiviral therapies. Site of sampling also matters; the duration of SARS-CoV-2 shedding varies widely between upper respiratory, lower respiratory, serum, and stool samples (10). Additionally, asymptomatic viral shedding and persistent symptomatic viral infection are not always distinguished, but likely have very different clinical and epidemiological implications.

These estimates are also affected by diagnostic method. The majority of studies across viruses use PCR-based diagnostics, which do not always have a predictable correlation with infectivity; in the minority of studies that also utilize viral culture, the duration of infectious viral shedding is significantly shorter (10, 11). The analytic sensitivity and quantitative reliability of PCR diagnostics also vary widely across platforms, and within the SARS-CoV-2 literature different cycle threshold cutoffs are used to define a negative test.

Thus, there is no agreed-upon definition of prolonged viral shedding, and a variety of cutoffs have been used in the literature ranging from 10 to >30 days of positivity.

Populations at risk

While immunocompromised patients are often discussed as a single entity, they represent a heterogeneous population with varying risk of prolonged viral infection. Control of viral infections depends on a complex interplay between the host immune response – including both innate and adaptive immunity – and the pathogen. For example, T cell immunity is known to be crucial for control of herpes viruses, and persistent active replication of cytomegalovirus (CMV) and Epstein Barr virus (EBV) can cause significant morbidity in post-transplant patients in whom the primary target of immune suppression is the T cell response (12, 13). T cells are also critical in mediating the host response to a variety of other viruses that typically cause more acute infection, including influenza, measles, dengue, and Zika. While T cells are likely important for control of SARS-CoV-2 infection as well, it is patients with deficiencies in B cell number and/or function who have emerged as the population at highest risk for prolonged SARS-CoV-2 (11). People living with AIDS, who have impairment in both T and B cell responses, also exhibit prolonged SARS-CoV-2 shedding, while patients with well-controlled HIV do not seem to have particularly increased risk (14). In line with this finding, patients with milder forms of immunosuppression (e.g. patients with solid malignancies on chemotherapy or those receiving corticosteroids) appear to have similar viral dynamics to patients with normal immune systems (15). There is also some evidence that risk factors for increased severity of SARS-CoV-2 such as age and certain comorbidities may also be predictive of prolonged infection, though this is likely at least partially mediated through the immunomodulatory effects of these conditions (16). Similarly, patients with B cell deficiencies are at highest risk for prolonged vaccine-derived poliovirus replication (8). For other commonly persistent viral infections such as norovirus, specific host risk factors remain unclear (17). Host-pathogen interaction is a dynamic process in which overly robust immune activation can often be more damaging than the pathogen itself; immunosuppressed patients may actually be protected from these types of maladaptive responses. Of course, this is a simplistic categorization, as different components of the immune response work in concert and cannot be understood separately. It is the net state of immunosuppression rather than any individual factor that is the key to understanding patient risk.

Clinical presentation

The clinical manifestations of prolonged viral infection vary widely depending on the host and pathogen, ranging from asymptomatic viral shedding to critical illness and death. The spectrum of prolonged viral infection is unknown as the existing literature is largely case reports, which tend to select for more severe clinical presentations; additionally, many of the larger studies of duration of viral shedding do not include descriptions of symptoms or clinical presentation. In SARS-CoV-2, several case reports of immunocompromised patients with prolonged viral shedding document severe respiratory illness requiring ICU-level care and ultimately leading to death (3, 18). However, many others detail few or minimal symptoms in patients with seemingly similar clinical characteristics (19, 20). Though other respiratory viruses are associated with significant morbidity and mortality in immunocompromised patients, studies have not shown a clear correlation between duration of viral shedding and severity of disease (21). Persistent adenoviral and noroviral infections

have also been associated with severe disease, though prolonged stool shedding is known to occur in asymptomatic individuals as well (22, 23). Similarly, while most documented cases of prolonged poliovirus infection have been in immunocompromised patients with paralytic poliomyelitis (24, 25), there are notable case reports of prolonged shedding in patients who were apparently asymptomatic (26, 27).

Viral evolution

RNA viruses have low-fidelity polymerases that, with the exception of coronaviruses, lack proofreading capabilities. They may therefore generate diverse populations by making many new mutations with each replication cycle. This diversity is in turn shaped by host selective pressures and random forces, such as genetic drift (28). Intrahost viral evolution is typically limited by rapid clearance and, in most infections, novel variants are present at a very low frequency (<10%). However, impaired immune responses allow for prolonged viral replication and the emergence of new mutations (Figure 1). One framework, proposed by Grenfell et al., hypothesizes that while immunologically normal hosts clear viral infections without issue, and profoundly immunocompromised patients do not exert significant pressure to select for fitter variants, those with moderate immunocompromise may be most likely to generate new viral variants. Their weakened immune systems allow for prolonged replication, but retain enough activity to exert selective pressure on the virus (Figure 2) (29). This hypothesis has largely been applied to RNA viruses; whether it holds true for DNA viruses which tend to evolve at much slower rates is unknown. While this hypothesis fits with much of the available data on viral evolution in immunocompromised hosts, the limited nature of this data and the relative rarity of these events leave many unanswered questions.

Many older studies of viral genomics are based on Sanger sequencing, which is laborious, time-intensive, and lacks the depth of coverage needed to characterize intrahost variants. Next-generation sequencing (NGS) platforms were introduced in 2005, and allow for high throughput sequencing through massively parallel reads. NGS itself has evolved considerably since its introduction, and is capable of producing millions of parallel reads at the high coverage necessary to confidently call single nucleotide polymorphisms (SNPs) present at even low frequencies relative to a reference genome (30, 31). Understanding the frequency of these variants is key to understanding intrahost viral diversity. There are different NGS approaches depending on desired output. Traditionally, single gene or amplicon-based sequencing, which amplifies only a selected portion of the viral genome, has been utilized to identify specific mutations of interest (e.g., drug-resistance mutations). Increasingly, whole viral genome sequencing (WGS) is being utilized as this method becomes less expensive, and as genes of interest may be unknown or distributed across the viral genome. WGS has wider applications in the study of viral diversity and evolution, and has been utilized in many of the studies cited in this review to identify novel variants, describe phylogenetically important sites, and study intra-host evolution (30, 31).

There are many challenges and pitfalls unique to viral NGS; one of the most critical is the accuracy of variant calling at low mutational frequencies. Difficulties identifying rare variants can also present barriers to epistatic analysis, which is crucial for understanding

genetic evolution. There are a variety of available tools utilizing error models to distinguish between low-frequency variants and sequencing errors that improve confidence (32). Recombination, the process by which multiple viral genomes exchange genetic segments, is also a key mechanism of viral genetic change. Recombinants can be challenging to reconstruct with the short reads typical of most NGS platforms, but in recent years a number of statistical strategies have been applied to overcome this problem (33).

Using this information to understand viral evolution on both an intrahost and global scale is challenging due to the vast complexity of both host and viral factors that shape this process. There are a variety of models that estimate different processes, including comparing nucleotide divergence across populations or calculating the ratio of non-synonymous to synonymous substitutions (dN/dS), which can be used to infer positive or purifying selection (Figure 3) (34-36). There are pitfalls to each of these methods; for example, some viruses have a predilection for certain types of nucleotide substitutions over others, and there is variability in the rates of nucleotide substitution across different viral sites. It can be challenging to calculate within-host evolutionary rates for viruses that cause acute infections and for which longitudinal data is rarely available, though methods have recently been developed to overcome this limitation (37). The timescale over which evolution is being assessed is also critical; purifying selection acts slowly, and viruses may appear to evolve faster when analyzed over shorter intervals than when assessed over longer periods (38, 39).

Patterns of virus evolution in prolonged infection

Early in the pandemic, many case reports and small case series documented the rapid emergence of new mutations in immunocompromised hosts with prolonged SARS-CoV-2 infection (3-5). The majority of these intrahost mutations were in the spike protein, which facilitates viral entry into host cells and is the target of both infection- and vaccine-induced antibody response. Several mutations that emerged in immunocompromised patients were noted to also be present in variants of concern, raising suspicion that immunocompromised hosts might be a source of these variants (40, 41). Many of these mutations developed under the selective pressure of convalescent plasma and/or monoclonal antibody treatments, which can select for resistant variants in hosts who do not clear the virus following treatment (3, 42). At least one study documented transmission of a viral strain with novel mutations (6). However, these reports were limited by their small sample size and selection bias, and most were documented prior to the emergence of the dominant omicron variant and even prior to vaccines or more effective antiviral treatments.

Since that time, a few large-scale prospective studies in the post-omicron era have examined the same question. A single-center prospective study of 56 immunocompromised and 184 non-immunocompromised patients found that patients with severe immunocompromise had a higher number of new mutations in spike vs. their immunocompetent counterparts. Patients with severe immunocompromise were also more likely to develop mutations associated with monoclonal antibody resistance (15). We recently published a multicenter prospective study of 150 immunocompromised patients; only a minority exhibited prolonged viral replication by PCR, and even fewer (only 8%) were positive by culture for ≥ 21 days. There were very few shared *de novo* mutations arising in this patient population; the most common

shared mutation was associated with monoclonal antibody resistance and almost all patients with this mutation had received monoclonal antibody treatment. Resistance to other antiviral therapies was rare. Overall, we did not find evidence for accelerated viral evolution in our cohort (11).

Norovirus is among the most common and prolonged infections in immunocompromised hosts, and chronically infected patients can shed the virus for years after infection. Multiple small retrospective studies have found that these patients harbor genetically distinct viral populations with accumulation of mutations at antigenic sites; this is in contrast to patients with self-limited infection, who tend to have very little inter- or intra-host diversity due to tight transmission bottlenecks and rapid viral clearance (43, 44). Multiple studies in chronically infected individuals have shown increased numbers of mutations with evidence of positive selection in antigenic sites of the capsid, which is responsible for viral entry and targeted by neutralizing antibodies(45). These mutations have been associated with immune escape. Multiple studies have also shown high degrees of genetic diversity within the chronically infected patient, both in and across sampling timepoints, suggesting that this diversity promotes prolonged replication by providing more opportunities for viral adaptation, selection of fitter variants, and host immune escape (43, 46).

While poliovirus has been nearly eradicated from the global population, prolonged infections have been described in recipients of the live, attenuated trivalent oral poliovirus vaccine (OPV). OPV has been the mainstay of the polio eradication campaign in lower and middle income countries due to its low cost and ease of administration. In immunocompetent hosts, OPV strains replicate in the GI tract for a brief period and are cleared over 2-6 weeks; however, immunocompromised patients may continue to exhibit viral replication long after this period (47). These vaccine-derived strains have unstable genomes with high rates of spontaneous mutations, can circulate widely, and occasionally revert to neurovirulent variants. Vaccine-derived polioviruses (VDPVs) are defined as variants that exhibit >1% nucleotide divergence from OPV in the VP1 gene from serotypes 1 and 3, or >0.6% divergence from serotype 2. VDPVs can be categorized into 2 classes, circulating (cVDPVs), associated with outbreaks in underimmunized communities, and immunodeficiency-associated (iVDPV), which have largely been studied in patients with primary – predominantly humoral – immunodeficiencies, some of whom have shed virus for many years (24, 25, 27, 48, 49).

Analysis of iVDPVs has primarily shown accelerated evolution with evidence of positive selection, including mutations in antigenic sites and more common reversion to neurovirulent strains, compared to cVDPVs in undervaccinated communities, which typically do not demonstrate strong evidence of positive selection (24, 50-52). Antigenic site mutations have been associated with decreased neutralizing capacity and immune escape (53). However, some analyses of patients with profound immunocompromise have shown no evidence of accelerated evolution or mutations in antigenic sites, perhaps owing to lack of immune pressure on the virus and in line with the Grenfell hypothesis (29, 54). Similarly, rubella virus vaccine can rarely cause persistent infection in patients with primary immunodeficiencies (known as iVDRV); these vaccine-derived strains have also been noted

to have accelerated viral evolution and evidence of positive selection with significant divergence from the parent vaccine strain (55).

As in many other respiratory viruses, long-term shedding of influenza has been reported in immunocompromised hosts (21). Emergence of antiviral resistance following antiviral therapy in these patients is well-documented, but influenza has a propensity to develop resistance to antiviral agents, and this has been observed in immunocompetent hosts as well (56-59). Case reports utilizing sequencing of serial samples in persistently infected patients have shown increased viral diversity and evolutionary rates concentrated in the surface proteins hemagglutinin (HA) and neuraminidase (NA), which are also the most common sites of *de novo* mutations globally (37, 60). In one study examining evolutionary patterns in immunocompromised hosts, the same mutations were noted to arise in multiple patients (and indeed within multiple subpopulations within the same patient, where various mutational combinations were noted to compete) (61).

Global impact

Infections in immunocompromised patients have been hypothesized to play a role in the emergence of new, circulating viral variants. While difficult to test, this is an attractive hypothesis, as novel variants often have large numbers of new mutations on emergence without obvious phylogenetic intermediates, and multi-mutational events have been identified in immunocompromised hosts across an array of viruses.

While case reports of patients with prolonged SARS-CoV-2 have identified the emergence of mutations that were later seen in variants of concern, larger scale studies have not confirmed these findings. In our cohort, while patients with very prolonged infections lasting >2 months accumulated mutations concentrated in the spike, these were largely distinct from mutations in the global population and we did not find evidence that even very prolonged infections predicted future variants of concern (11). However, immunocompromised hosts remain a plausible source for the omicron variant of SARS-CoV-2, whose abrupt emergence in 2021 with >30 new mutations in spike alone has continued to puzzle the scientific community. For example, the highly divergent BA.2.86 omicron subvariant itself had >30 new spike mutations compared to its predecessor BA.2, several of which have also been identified in immunocompromised hosts, though the temporal relationship remains unclear (11).

Limited data exist examining the impact of influenza mutations that develop in immunocompromised hosts on the global host population. There is a single case report of prolonged influenza shedding in an immunocompromised child who developed antigenic drift that mimicked that of viral strains circulating in the community at the time. This report was published prior to the use of oseltamivir, and details on genetic sequencing were not provided (62). Mutations that develop in antigenic sites, especially in hemagglutinin (HA), have also been shown to reach high frequency globally, though it is unclear if mutations in immunocompromised patients predict global mutations or if similar evolutionary patterns occur within and across hosts (61). A large-scale study of consensus HA sequences over several years found that immune status had no significant impact on positive selection;

immunologically naïve patients were as likely as experienced patients to harbor viruses with mutations causing antigenic change. This study used age as a proxy for immune status and was conducted in patients with acute infection, so it is not a perfect correlate for immunocompromised hosts, but suggests a more limited role for individual immune pressure in generating new antigenic variants (63).

Norovirus is characterized by global outbreaks associated with the emergence of novel variants. However, significant diversity is not typically seen during an outbreak season, and thus the source of these novel variants is unclear; many animals harbor norovirus strains, but there has never been a documented case of zoonotic transmission, and thus intrahost evolution in humans is thought to be the source of novel variants (64). Genetically distinct viral populations have been identified in patients with prolonged norovirus infection and have been posited as a source of new pathogenic variants (44, 46). There is controversy about whether these patients shed infectious virus due to challenges of available viral culture models, but chronic viral shedding has been identified as a source of at least one disease outbreak (65).

In line with the above, a proposed mathematical model assessing how prolonged viral replication in immunocompromised hosts impacts emergence of new viral strains was developed, relying on nucleotide substitution rates to measure the relative contribution of different subpopulations to epidemiologic viral evolution. Using data from patients with prolonged norovirus infections, this model showed that immunocompromised hosts did not contribute significantly to overall evolutionary rates of norovirus due to the rarity of these prolonged infections compared to the high prevalence of norovirus infections in the general population (66). Thus, while these patients are a logical source of novel pathogenic viral variants, there is very little evidence to support this hypothesis.

Despite 149 reported cases of iVDPV as of 2020, many involving extremely prolonged viral shedding, none has been clearly associated with an outbreak (48, 67). While there are individual case reports of iVDPV with reversion to neurovirulence years after initial infection, there are also case reports of very prolonged replication (up to 28 years) in apparently asymptomatic individuals (68, 69). Poliovirus in the general population is associated with tight transmission bottlenecks limiting genetic diversity; while transmission dynamics of iVDPV are unknown, perhaps these tight bottlenecks (in addition to herd immunity) explain the lack of clear community spread despite many identified cases of prolonged shedding (70).

Ebolaviruses, a group of hemorrhagic fever viruses, have caused many outbreaks in sub-Saharan Africa since their discovery in 1976. Ebolaviruses can persist in immune privileged sites of survivors, including semen and probably breast milk and vaginal secretions, for months to years after recovery from illness (71-73). Most Ebola virus outbreaks are thought to be due to individual zoonotic spillover events. However, phylodynamic analysis of a 2021 outbreak in Guinea found significantly fewer mutations in the viral genome responsible for the outbreak than would be expected from sustained host-to-host transmission in the 6 years since the previous outbreak. Phylogenetic analysis placed the 2021 virus as a single cluster along with the Ebola virus responsible for a 2013-2016 outbreak in West

Africa, predominantly from Guinea in 2014; this outbreak was linked to a survivor with prolonged infectious viral shedding for >500 days (presumably from an immune privileged site) who had no known immunocompromise (74, 75). The 2021 outbreak genome also contained the A82V mutation, which arose during the prior outbreak and is associated with increased transmission in humans. Based on this analysis, the source of the 2021 outbreak was likely persistent viral shedding in a survivor of the previous epidemic rather than a new transmission event (74, 76). Similar analysis from a 2021 outbreak in Democratic Republic of Congo also linked that outbreak to a prior outbreak in 2018-2020, rather than to a spillover event (77).

As Ebola therapies improve and the mortality rate declines, there will be more long-term survivors with the potential to serve as reservoirs for future outbreaks. While the role of immunocompromised hosts in persistent Ebola viral shedding is unclear, there are suggestions that partial immunity – for example, as conferred by therapeutics later found to be minimally effective – may predispose patients to persistent infection and viral reactivation (78, 79). Similarly, while there are only rare case reports of measles viral persistence in immunocompromised hosts, measles viral RNA can persist for months in immune cells, urine, and respiratory secretions of immunocompetent patients (80). How viral RNA persistence in immune-privileged sites might affect the global host population is unknown, but warrants further study as we enter an era of increased disease outbreak.

Conclusions and future directions

The phenomenon of prolonged viral shedding and infection in immunocompromised hosts has been shown across a diverse array of viruses, and these patients may exhibit accelerated intrahost viral evolution and mutation accumulation in antigenic sites. However, the global impact of this phenomenon remains unclear despite many studies attempting to elucidate this problem. In the most widely studied virus, SARS-CoV-2, there is some evidence that variants of concern- for example, omicron subvariants BA.1 and BA.2.86 – may have originated in an immunocompromised host, but in other studied viruses there is sparse evidence that immunocompromised hosts serve as a reservoir for outbreak strains or viral variants that go on to have global importance. If these hosts do serve as reservoirs, they seem likely to be a relatively rare source of outbreaks. However, this body of literature is hampered by small sample sizes, inconsistent methodologies, and selection bias, and larger scale prospective studies are needed.

Many studies of persistent viral infection in immunocompromised hosts have suggested that these patients should be prospectively surveilled and targeted for aggressive antiviral treatments in attempts to eliminate them as potential reservoirs. While this is a reasonable approach from a clinical and perhaps local public health perspective, whether this would have any impact on the global viral ecosystem is unclear. Additionally, the best approach to surveillance is not clear, as the risk profile varies according to the virus in question, and for many viruses we do not have a sophisticated understanding of patient risk factors. Targeted antiviral treatment of these patients is also fraught, as they are more likely to have persistent infection despite antiviral therapies and therefore to develop drug resistance mutations.

Wastewater monitoring is increasingly being used to monitor infection dynamics as our understanding of the stool microbiome, and specifically the stool virome, expands; this approach allows for rapid viral detection and assessment on a much wider scale at lower cost, and may allow for identification of patients with prolonged viral shedding more easily than conventional surveillance strategies. In SARS-CoV-2, cryptic wastewater lineages with high rates of non-synonymous mutations in spike protein have been documented, mimicking patterns seen in immunocompromised hosts, and some studies have suggested a single host origin of cryptic lineages (81). Some of these mutations have gone on to be prevalent globally. Further studies are needed to determine the origin of these cryptic lineages, but wastewater surveillance is a powerful tool in the viral evolution arsenal that is still being developed.

In conclusion, while there is ample evidence that immunocompromised patients can exhibit prolonged viral infection and accelerated intra-host viral evolution, the implications of this are not clear. Documented transmission events from patients with persistent viral shedding are rarely reported, and despite significant investigation, these intra-host variants have not clearly been shown to be important on the global scale. Study of this phenomenon is challenging as these infections are comparatively rare events that can be difficult to assess in the large-scale, prospective manner needed to make any definitive conclusions. As the number of patients with immunocompromise expands in the coming years, innovative approaches to study this problem are urgently needed.

Acknowledgements

Biorender was used to generate the figures. Work on this topic in the authors' laboratory is supported in part by a Burroughs Wellcome Fund Investigator in the Pathogenesis of Infectious Diseases Award and NIAID R01 AI148371 (both to ASL).

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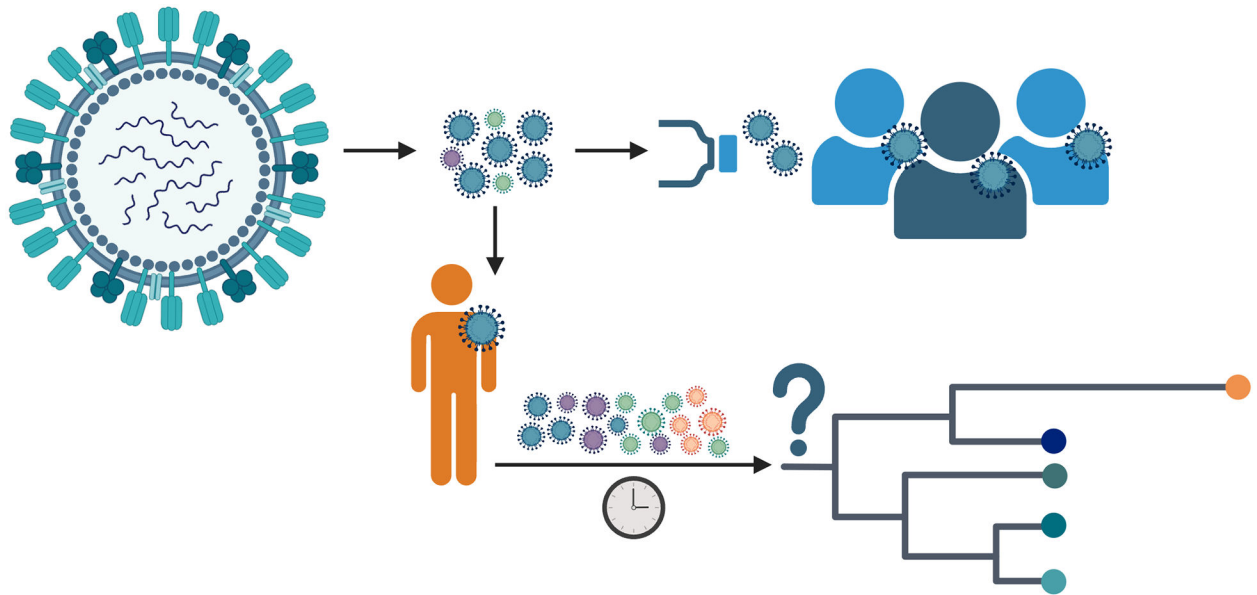


Figure 1.

Patterns of viral evolution and transmission. While RNA viruses generate diverse populations through error-prone replication cycles, diversity is limited by tight transmission bottlenecks and rapid host clearance in the general population (top panel). In immunocompromised hosts, lack of sufficient immune response allows for prolonged viral replication and accumulation of mutations over time. These viral variants may then be transmitted to other hosts and become important on the global scale (bottom panel). Sequence variants are represented by virus icons of varying colors as well as the tips (circles) of the phylogenetic tree schematic.

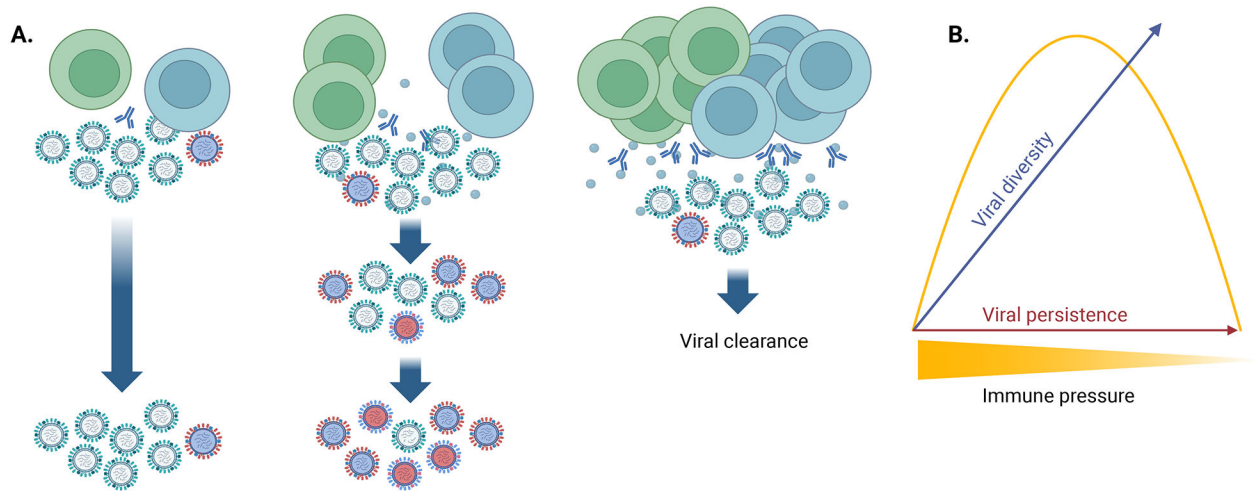


Figure 2.

Immune control of viral replication and the Grenfell hypothesis. Patients with profound immunodeficiency are unable to clear viral infection, but also do not exert meaningful immunologic pressure (e.g., antibody icons) on the virus to select for fitter viral variants (virus icons of varying colors, left); patients with normal immune systems clear viral infection and do not allow for prolonged replication (right); patients with moderate immunocompromise are unable to clear virus but also exert sufficient selective pressure on the virus and produce diverse viral populations (center).

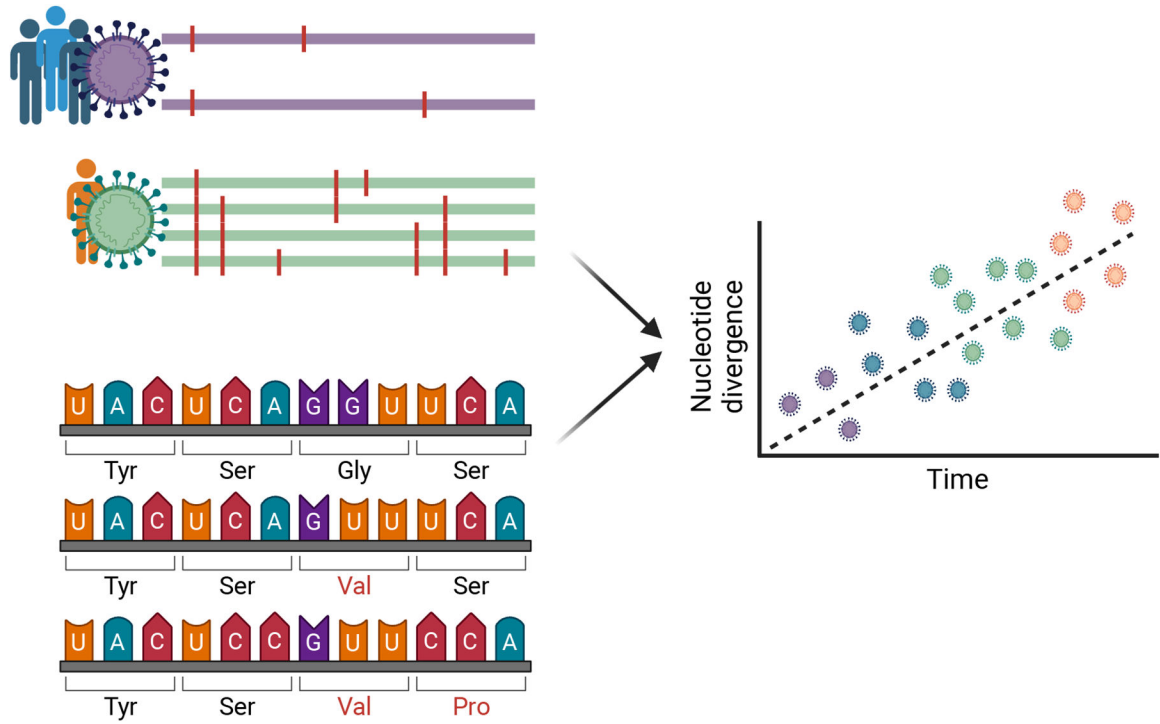


Figure 3.

Methods of assessing viral evolution. Whole genome viral sequencing can be used to assess mutational rates for the general population vs. in immunocompromised hosts (top panel, vertical lines indicate mutations), calculate the ratio of non-synonymous to synonymous mutations (dN/dS, bottom panel), and capture nucleotide divergence over time (right panel, virus icons of varying colors indicate new sequence variants).