Dissecting Pandemic-Prone Viral Families

Volume 1: The Picornaviridae

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Contents

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Introduction

Among the approximately 2 dozen families of viruses that have the capacity to infect humans, roughly 25% of these families have pandemic potential (Figure 1). Specifically, this capacity is conferred by their ability to be transmitted via the respiratory route.[1] Devising response plans for each of these 6 viral families — *Adenoviridae*, *Coronaviridae*, *Paramyxoviridae*, *Picornaviridae*, *Pneumoviridae*, and *Orthomyxoviridae* — is essential for pandemic preparedness.

Response to the COVID-19 pandemic triggered the implementation of various nonpharmaceutical interventions (NPIs) (eg, closures, teleworking, physical distancing, masking, etc.). These mitigation measures were intended to block transmission of SARS-CoV-2, the virus that causes COVID-19, between people. Indeed, and as anticipated, masking and physical distancing diminished the spread of SARS-CoV-2, as well as most respiratory pathogens, viral and bacterial alike, around the world. There were well-documented transmission drops of viruses in the families *Adenoviridae*, *Coronaviridae*, *Paramyxoviridae*, *Pneumoviridae*, and *Orthomyxoviridae*.[2]

Notably, however, the NPIs put in place to slow the spread of SARS-CoV-2 — which belongs to the *Coronaviridae* family — did not suppress the spread of key viruses in the *Picornaviridae* family as markedly as they did these other 5 families. Because of this, *Picornaviridae* — which includes rhinoviruses and enteroviruses — raises particular concern. Both the Johns Hopkins Center for Health Security and the National Institute of Allergy and Infectious Diseases (NIAID) have independently identified *Picornaviridae* as one of the key viral families posing a future pandemic threat.[3]

Individuals can be infected with *Picornaviridae* viruses through various transmission routes, including respiratory, fecal-oral, and contact with fomites and conjunctival and skin secretions. Infections with these viruses can cause a wide spectrum of illness. Many viruses of this family perennially cause a tremendous burden of disease that includes severe manifestations such as pneumonia, encephalitis, and meningitis; readily mutate to avoid immunity from prior infection; have virtually no medical countermeasures available; and are environmentally hardy. Often, infected individuals with minimally symptomatic disease can perform their activities of daily living while contagious to others. There is real concern that an uncharacterized member of this family may emerge with the ability to cause widespread severe disease or that a previously identified member with concerning features may acquire the ability to spread more widely.

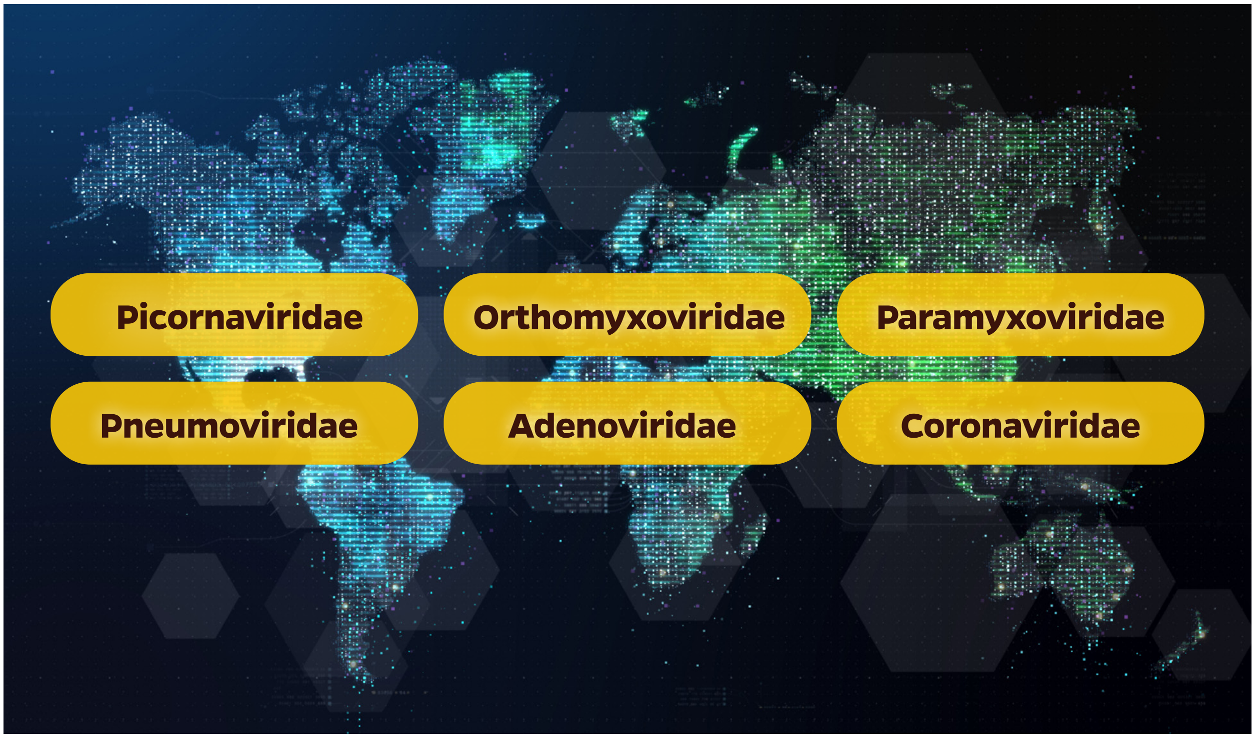
The early response to a future pandemic involving respiratory transmissible viruses is likely to include the targeted use of various NPIs. Given the pandemic potential of the *Picornaviridae*, the comparative diminished impact of COVID-era NPI measures in slowing the rate of transmission of key viruses in this family is striking. If evidence already shows that current NPIs have less impact on the *Picornaviridae*, then planning for the response to that viral family needs to adapt and be strengthened accordingly.

To examine this challenge, the Johns Hopkins Center for Health Security undertook a project with the specific aim of understanding the course of *Picornaviridae* during the COVID response, the underlying causes for lack of suppression during the pandemic, and the implications for pandemic preparedness against this viral family.

Methods

The methodology of this project included an in-depth literature review and subject matter expert interviews. The literature review involved searching the PubMed database for papers related to detection of *Picornaviridae* and its constituent members (ie, enteroviruses, rhinoviruses, echoviruses, parechoviruses) during the COVID-19 pandemic. Interviews were conducted with 6 subject matter experts, some of whom were authors of key papers identified in the literature review.

Figure 1: The 6 pandemic potential viral families



The State of Play of Respiratory Viruses During the COVID-19 Pandemic

Once NPI measures were initiated and practiced by the population in response to the widespread circulation of SARS-CoV-2, there were immediate and significant reductions in most other circulating respiratory viruses except *Picornaviridae*, which are spread by respiratory transmission but also through direct contact with certain body fluids, fomites, or ingestion. For example, the COVID-19 pandemic began amid a brisk influenza season, which was abruptly truncated.[4] This phenomenon extended to all respiratory viruses, except for *Picornaviridae*, as well as to any pathogen transmitted between people via respiratory and enteric routes, including group A streptococcus and norovirus.

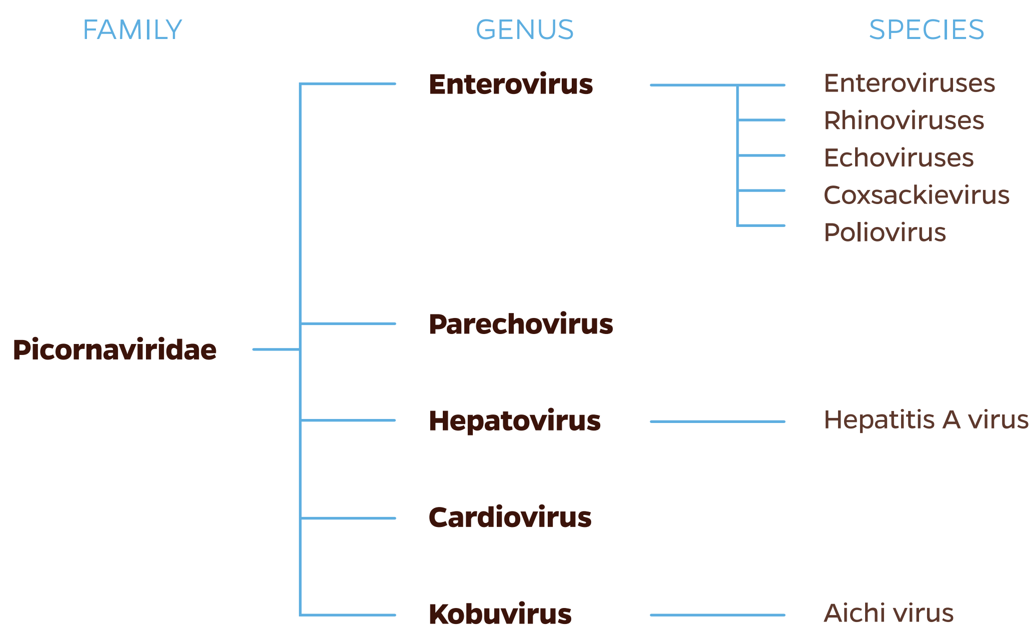
These changes in pathogen dynamics were driven primarily by a lack of physical interaction. There also may have been a component of viral interference, defined as the ability of one virus to hamper the ability of another virus to replicate. Multiple studies show SARS-CoV-2 has the capacity to interfere with other respiratory viruses.[5]

This transmission cessation of many respiratory viruses continued for approximately 2 years during the COVID-19 pandemic. The suppression of influenza was such that a major subtype of influenza B likely was driven to extinction, as was a clade of influenza A.[6]

In contrast to the near cessation of other respiratory virus transmissions, viruses of the *Enterovirus* genus of *Picornaviridae*—which include rhinoviruses and typically are not distinguished on many molecular diagnostic platforms—were consistently detected throughout the pandemic. Detection was at higher rates than other respiratory viruses (though lower than prior seasonal rates, presumably due to an incomplete viral interference effect of SARS-CoV-2 on rhinovirus/enterovirus circulation or recalcitrance to COVID-19 measures). This was a worldwide phenomenon.[7]

These were not all benign viruses, as evidenced by the fact that during the pandemic, the Centers for Diseases Control and Prevention (CDC) issued a health alert in July 2022 in response to clusters of neonatal and infant infections with another member of *Picornaviridae*, parechovirus (PeV), specifically PeV-A3. Meningitis was one of the presentations of PeV-A3.[8]

Figure 2: Key genera and members of the *Picornaviridae* family



Rhinoviruses: Underappreciated Burden of Severe Disease

Rhinoviruses fall under the *Enterovirus* genus within *Picornaviridae* but were for many years assigned to their own genus.[9] While rhinoviruses are well known as ubiquitous viruses that are a major cause of the common cold, their potential to cause severe disease in some is grossly underappreciated. In addition, the economic toll of rhinoviruses, in terms of absenteeism and lower productivity, is well-established.[10]

Rhinoviruses have been shown to be the most common viral cause of admission to pediatric intensive care units (PICUs), with rhinovirus C the major driver. Rhinoviruses are also the most common identified cause of community-acquired pneumonia in adults,[11] 29%–39% of which may be severe as scored by the Pneumonia Severity Index (PSI).[12] During the COVID-19 pandemic, one study of 7 emergency departments revealed that more than 44% of children who tested positive for rhinovirus/enterovirus were admitted to the hospital.[7] Control of rhinoviruses *today* would alleviate a significant burden on the healthcare sector and create adeptness if a more severe variant were to emerge or evolve with the capacity to cause severe disease at a higher rate.

Given the potential severity of rhinoviruses and the overall burden they cause, government and industry have underrecognized and underinvested in this challenge, compared to other viruses. Notably, in the past, a lack of diagnostic tests has obscured the role of rhinoviruses in severe disease, but the widespread availability of respiratory molecular diagnostic tests is now far better illuminating the role of rhinoviruses in serious illness.

Enteroviruses: A Varied Spectrum of Illness with Ability to Cause Severe Disease

The *Enterovirus* genus of *Picornaviridae* comprises numerous ubiquitous and varied viruses. This genus includes the lettered enteroviruses (A-D), echoviruses, coxsackieviruses, polioviruses, and, as mentioned, rhinoviruses. They are responsible for a wide range of clinical illness ranging from encephalitis, meningitis, and paralysis on one end of the spectrum and viral exanthems (rashes), such as hand-foot-and-mouth disease (HFMD), upper respiratory infections, and gastroenteritis on the other. This group of viruses has well-known associations with severe disease.

Meningitis

Group B enteroviruses are the most common cause of viral meningitis. Though this is typically a benign condition, in virtually all cases it merits emergency department evaluation and observational admission to the hospital. Hospitalization is usually coupled to multiple diagnostic tests, including invasive procedures such as lumbar puncture and empiric antibiotics, until bacterial meningitis is ruled out.

Encephalitis and EV-A71

Encephalitis is one of the most severe manifestations of any infectious disease because of its attendant high morbidity and mortality. Enteroviruses are the cause of a significant proportion of viral encephalitis cases, and many different enteroviruses have this capacity.

A particular enterovirus with the potential to cause severe encephalitis is EV-A71. This virus was responsible for outbreaks in Taiwan that prompted significant public health actions. The first large outbreak in Taiwan occurred in 1998, with 78 recorded pediatric deaths. In a 2000–2001 outbreak, more than 20 children died from EV-A71 infection, followed by another severe outbreak in 2012.[13] Taiwan has developed many surveillance systems and countermeasures for this virus; however, with no vaccines or treatments, the disease continues to spread with devastating consequences, including deaths and school closures. Other countries with recent notable outbreaks of EV-A71 include Australia, Cambodia, China, Japan, Malaysia, Singapore, South Korea, Thailand, and Vietnam.[14]

Acute flaccid myelitis (AFM)/Acute flaccid paralysis (AFP) and EV-D68

The most notorious enterovirus capable of causing paralytic symptoms is, of course, poliovirus, a member of the species *Enterovirus C*. Polioviruses are currently deemed a public health emergency of international concern (PHEIC) by the World Health Organization (WHO) and command a high degree of public health resources to complete eradication efforts. However, polioviruses are joined in their symptomatology by several polio-mimics: most notable is EV-D68.

EV-D68 circulates every year, with seasonal peaks in late summer and fall. In 2014, a widespread outbreak in the United States and Canada affected more than 2,000 people, mainly children, causing severe respiratory infection, a spike in acute flaccid myelitis (AFM) and acute flaccid paralysis (AFP) cases, and the deaths of at least 14 children. Children with respiratory-related comorbidities faced a higher threat of severe infection; however, severe cases were also seen in generally healthy children. This virus continued to cause a flurry of AFM cases biennially (likely due to a buildup of a cohort of susceptible individuals) until interrupted by the COVID-19 pandemic.[15] There is concern that EV-D68 or another related virus may be able to cause AFM/AFP in a higher percentage of the infected, ceasing to be a rare phenomenon but one that causes paralysis in higher numbers.

Echoviruses and Severe Disease

In May 2023, a report of severe and fatal disease in neonates attributable to echovirus 11 (E-11) prompted French public health authorities to issue an alert. WHO soon followed suit, listing 4 other European Union countries (Croatia, Italy, Spain, Sweden) and the United Kingdom as reporting severe disease from E-11.[16] Though not observed in France or elsewhere prior to June 2022, E-11 has been continuously detected and causing severe disease since then.

Parechoviruses: Common Childhood Pathogens with Various Clinical Manifestations

Parechovirus is another significant genus of *Picornaviridae*. This group was recently reclassified out of the *Enterovirus* genus because of significant virological differences from enteroviruses.[17] These viruses cause a spectrum of illness ranging from undifferentiated fever to meningitis and encephalitis.

As mentioned earlier and attesting to their resiliency, CDC issued a message via its Health Alert Network (HAN) in July 2022 — during the COVID-19 pandemic — in response to reports from healthcare providers in multiple states of meningitis cases in neonates and young infants attributed to parechovirus A3 (PeV-A3).[8]

Kobuviruses: Human Aichi virus (AiV)

A member of the *Kobuvirus* genus of *Picornaviridae*, Aichi virus A (AiV-A1), primarily causes mild gastroenteritis in humans. In immunocompromised hosts, however, the virus can cause multiorgan infection, including hepatitis.[18]

Explanations for *Picornaviridae* Viral Persistence During COVID-19 Pandemic

The most probable explanation for why certain *Picornaviridae* viruses were recalcitrant to NPIs during the COVID-19 pandemic likely has a virological explanation. SARS-CoV-2, like many other respiratory viruses, possesses an envelope, but *Picornaviridae* do not have an envelope. This fatty outer shell facilitates easier cellular egress by allowing virus particles, or virions, to take advantage of existing cellular secretory pathways. However, envelopes also confer a higher degree of fragility in environmental conditions where virions are susceptible to quicker desiccation compared with viruses that do not possess envelopes. Envelopes also make fomite-based transmission less efficient and, therefore, less likely. Such a discrepancy is so well-established that disinfectant specifications differ for nonenveloped viruses because of their environmental hardiness.[19] Their lack of envelopes likely allowed members of the *Picornaviridae* family to persist and skirt the widespread use of NPIs during the pandemic.

Medical Countermeasures for *Picornaviridae*

Only 2 medical countermeasures (MCMs) have been developed and licensed for use against any of the *Picornaviridae*: the hepatitis A vaccine and the poliovirus vaccines. It has been nearly 30 years since the Food and Drug Administration (FDA) approved the hepatitis A vaccine, representing the second of the 2 extant *Picornaviridae* MCMs.

As such, there are effectively zero MCMs of any type — antivirals, monoclonal antibodies, or vaccines — for the pandemic-prone members of this viral family. While the availability of vaccines against hepatitis A and poliovirus are not alone sufficiently robust or broad-based to be able to forestall a disruptive outbreak from this viral family, neither hepatitis A nor poliovirus currently pose a new pandemic risk, due in large part to the predominant fecal-oral mode of transmission. Diagnostic tests are available for many of the most important *Picornaviridae*, typically as part of respiratory viral panels performed for hospitalized patients, and there are point-of-care diagnostic tests available for some viruses in this family. There are no at-home tests for any *Picornaviridae*.[17]

Antiviral therapy, in the form of an antiviral agent called pleconaril, failed to garner FDA approval due to side effects not thought to outweigh benefit from a mild illness such as the common cold, as well as concern regarding management of drug-drug interactions.[17]

The mainstay of therapy for *Picornaviridae* is supportive. Mixed data exist on the use of zinc for symptomatic relief.[20] There has also been, like with SARS-CoV-2, some data on the prophylactic use of intranasal interferon as a preventative measure.[21]

Implications for NPIs

If a pandemic or disruptive outbreak of a *Picornaviridae* virus were to occur today, there would be no antiviral therapy, no monoclonal antibody, no vaccine, and no home test to mitigate consequences. If severe disease occurred at high rates due to the emergence or evolution of a member of this viral family, there would be no immediate or simple way to forestall high levels of morbidity, mortality, and stress on the healthcare system.

In such a circumstance, NPIs—including indoor masking, handwashing, and targeted physical distancing—would likely be recommended. However, as the COVID-19 pandemic illustrated, the ability of such interventions to slow the spread of disease for many members of this viral family would be compromised by biology. NPIs that would possibly blunt respiratory transmission would not be sufficient or targeted enough to block fecal-oral, fomite, or secretion pathways of spread, all of which are strong features of different members of *Picornaviridae*. COVID-19 NPIs initially often included some consideration of surface and fomite transmission but these were correctly jettisoned when found not to have a significant impact on transmission of the enveloped SARS-CoV-2.

In the event of a fomite/surface-based outbreak, supplementary interventions will need to be implemented. First, however, various techniques for what amounts to surface disinfection will require study for their efficacy and safety, including determining the potential value of using ultraviolet and high-energy light devices. If found effective, sufficient attention will need to be directed to implementation procedures, cost effectiveness, and public communication strategies to encourage use. The public perception of the measures taken to interrupt surface and fomite transmission is that they are of no value or "hygiene theater," so there will need to be dedicated efforts to reverse those perceptions if such measures are found in studies to be valuable in slowing the transmission of a *Picornaviridae* pandemic.

These issues are further analyzed in the complementary white paper, titled *Infectious Disease Emergencies Caused by Fomite-Transmitted Pathogens: A Challenge for COVID-Era Nonpharmaceutical Interventions (NPIs)*, published as Annex A in this report.

Policy Recommendations

The biological properties of *Picornaviridae* viruses, their transmission patterns and spread despite the use of NPIs during the COVID-19 pandemic, and their potential for disease severity that is now increasingly recognized with new diagnostic tools, all give rise to 4 major policy recommendations detailed below.

1. **Medical Countermeasure Development**

   The dearth of MCMs for this viral family throughout the history of modern medicine cannot be understated. The COVID-19 pandemic increased recognition of the potential for widespread mild illness to cause significant social and economic impacts. Yet *Picornaviridae* members' disruptive nature and potential to cause serious disease year after year have resulted in comparatively very little research and development around MCMs. This should change. The focus of the MCMs should be on decreasing symptomatology, decreasing contagiousness, and preventing severe disease.

   Concerted efforts should begin to develop at least 2 antivirals with distinct mechanisms of action (to anticipate the possibility of drug resistance) that are effective against each of the major groups of viruses in this family: enteroviruses, rhinoviruses, echoviruses, and parechoviruses. Coupled to this should be a monoclonal antibody effort aimed at targeting durably conserved areas of the viral structures with the aim of decreasing hospitalization rates. Vaccine development should proceed in a similar fashion. Home tests and more point-of-care diagnostics also should be developed, which would have salutary effects on seasonal disease and inappropriate antibiotic prescribing.

   Government(s) should initiate and incentivize the research and development process with respect to the pandemic potential of the *Picornaviridae* family, since the private sector has shown it is unlikely to initiate this process on its own. Still, private sector companies will be key to developing and manufacturing the products that come out of this process. There exist sizable and potentially lucrative markets for companies that generate products that counter the seasonal impact of these viruses, and efforts should be conceived with this fact in mind to take advantage of economies of scale.

2. **More Adept Clinical Care**

   Picornaviridae viruses are an underappreciated cause of severe disease. As a major cause of adult pneumonia, pediatric admission, meningitis, encephalitis, and AFM/AFP, this viral family exacts a considerable toll on humans. Clinical care improvements will help confer stronger preparedness for a future potential pandemic caused by a member of this viral family. While MCM development will assist in achieving this task, initiating studies of the severe manifestations of *Picornaviridae* infections will contribute. Also important is developing understanding of risk factors for severe disease, immunologic pathways activated, and best supportive care practices, and studies in these areas should be pursued alongside an MCM research agenda.

3. **Enhanced Surveillance**

   Because this viral group is ubiquitous and causes countless infections every day, it is critical to understand when shifts in the viral ecology are occurring. One way to do this is to encourage all jurisdictions to implement enhanced reporting to CDC when any severe clinical manifestation of this viral family is documented. Clinical event-based reporting should be supplemented by routine sequencing of isolates — from a wide variety of clinical syndromes and geographic locations — to develop situational awareness of viral strain behavior and to rapidly detect evolutionary changes in the viral family that could have human health consequences.

   Public health authorities could also establish formal mechanisms for the reporting of data generated through the routine use of respiratory viral panels in clinical care settings to help them stay apprised of the relative proportions of various respiratory viruses in their area. CDC currently collects such data on various other respiratory viruses via the National Respiratory and Enteric Virus Surveillance System (NREVSS) but does not include any members of *Picornaviridae*, with the exceptions of hepatitis A and poliovirus (via other reporting mechanisms).[22] Wastewater surveillance also could be expanded to track the prevalence of various epidemiologically significant viral family members, including PeV-A3, EV-D68, E-11, and EV-A71.

4. **Fomite-Based NPI Planning**

   Because of the intransigence of this viral family to ordinary respiratory virus NPIs, academia and public health agencies should develop a formal research agenda to determine how to augment NPIs. A focus of study should be on public spaces where many are exposed to surfaces, such as schools, workplaces, and transportation vehicles and hubs. In addition, research should assess how various forms of hospital disinfection could be extrapolated to civilian settings, as well as examine novel technologies such as ultraviolet C (UV-C) lighting, high-energy visible (HEV) lighting, and antimicrobial surfaces.

Conclusion

The *Picornaviridae* family demonstrated formidability throughout the COVID-19 pandemic while other viral families fell away in the wake of public health interventions. Several policy and investment decisions would greatly improve pandemic preparedness for this viral family.

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Annex A

Infectious Disease Emergencies Caused by Fomite-Transmitted Pathogens: A Challenge for COVID-Era Nonpharmaceutical Interventions (NPIs)

The COVID-19 pandemic provided a major opportunity to understand the impact of nonpharmaceutical interventions (NPIs) on the transmission and spread of various pathogens. Attention to the differential impact of these measures provides important information regarding their relative efficacy against disparate pathogens.

Modes of Transmission

Humans can be infected by pathogens in a wide variety of manners. Routes range from (non-exhaustively) animal or insect transmission, respiratory/airborne transmission, sexual contact, congenital transmission, fecal-oral transmission, person-to-person contact, or contact with blood or other body fluids. For each mode of transmission, different mechanisms can decrease transmission efficacy of the pathogen, often through recommended behavior changes. For example, the use of tick repellent can reduce the risk of tickborne disease transmission. For many means of transmission, human-to-human contact is key, and, therefore, physical distancing — to the extent practiced — will diminish the spread of a wide variety of pathogens that transmit through varied forms of contact (eg, sexual, blood-body fluid, and respiratory).

COVID-19 NPIs

The NPIs that were chiefly used and recommended throughout the COVID-19 pandemic included physical distancing, mask wearing, and handwashing. Such NPIs were variably successful depending on adherence by the population and the virology of SARS-CoV-2 (as more contagious variants required higher levels of adherence), but their biological plausibility and efficacy were demonstrated for a virus such as SARS-CoV-2.

In addition to hampering transmission of SARS-CoV-2, COVID-19 NPIs also had a cascading impact on other viruses with similar modes of transmission, typically via the respiratory route, and on those that spread through close human-to-human contact. Multiple viruses — and some respiratory-borne bacteria — experienced plummeting case numbers, including influenza and RSV. Some viral branches were even rendered extinct.

Fomite Transmission as an Exception

As detailed in the Johns Hopkins Center for Health Security report, *Dissecting Pandemic-Prone Viral Families – Volume 1: The Picornaviridae*, a notable exception to the constrained transmission of pathogens due to COVID-19 NPI implementation were members of the *Picornaviridae* family: namely rhinoviruses, enteroviruses, echoviruses, and paraechoviruses.

What likely underlies the phenomenon of these viruses' recalcitrant transmission characteristics is that the physical structure of this viral family — their nonenveloped status —facilitates greater viability in the environment, leading to more efficient fomite transmission. While these viruses are transmitted in other manners — such as direct contact, fecal-oral contact, and the respiratory route — the proportion transmitted via fomites was sufficiently high enough to be repeatedly noticed as a relatively aberrant pattern in multiple areas of the world during the quietude of respiratory virus circulation during the COVID-19 pandemic.

Varied Technologies Exist

The mainstay of preventing fomite-based transmission is *active* hand hygiene and surface cleaning with various disinfecting products. However, there exist multiple *passive* disinfecting technologies such as ultraviolet-C (UVC) light, high-energy visible (HEV) light, and antimicrobial-coated surfaces.

Consumer and nonhospital marketing of these technologies occurred during the COVID-19 pandemic. Some airports, schools, and other venues implemented their use.

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The *Picornaviridae* are a pandemic-prone viral family and have sizable seasonal impact causing billions of dollars of economic losses, thousands upon thousands of hospitalizations, and many deaths. The implication is that, in the event of an outbreak, epidemic, or pandemic caused by a pathogen that is efficiently spread via fomites and surfaces, simply implementing a suite of COVID-era NPI measures is not likely to be sufficient.

Thus, the systematic development of an NPI plan to be widely executed in the event of an infectious disease emergency precipitated by an efficient fomite- or surface-transmitting pathogen should be a priority. To this end, the development and study of NPIs directed specifically at fomite-transmitted nonenveloped viruses for use in public areas should be pursued. Settings include schools, transportation centers, shopping centers, and offices. Many of these NPIs already are used regularly to varying degrees in healthcare facilities and congregate settings such as cruise ships; some were trialed briefly during the COVID-19 pandemic.

A research agenda — as well as implementation and cost-effectiveness studies in public settings — should be prioritized to augment pandemic preparedness and possibly decrease these pathogens' seasonal and congregate spread.

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