

Uncertain effects of the pandemic on respiratory viruses

Expanded genomic and clinical surveillance are needed to understand the spread of respiratory viruses

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The emergence and spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and subsequent mitigation measures have caused widespread social disruption. These disruptions have also affected community transmission of endemic diseases and the seasonal circulation patterns of other respiratory viruses. In both the Northern and Southern hemispheres, within-season influenza activity has been at historically low levels since 2020 (1, 2). Additionally, the circulation of human metapneumovirus, enterovirus, adenovirus, respiratory syncytial virus (RSV), and rhinovirus has been substantially reduced (3). These reductions in respiratory virus infections are linked to changes in health care-seeking behaviors and limited surveillance capacity, but mostly to the widespread implementation of non-pharmacological interventions (NPIs) to control SARS-CoV-2 transmission. How this will affect the transmission patterns of endemic respiratory viruses remains unknown.

NPIs such as face mask use, increased handwashing practices, social distancing, and restrictions of global mobility have been key measures in reducing circulation of other respiratory viruses. As NPIs are relaxed and vaccination programs increase to control SARS-CoV-2 infections, countries have started to report increases in activity and circulation of certain viruses, such as RSV and rhinoviruses, with atypical timing (3–6). It is unclear why similar trends of resurgence (off-seasonal increases) have not been observed so far in other respiratory viruses, such as influenza, following relaxation of NPI measures. Currently, questions remain as to what the downstream impact of the COVID-19 pandemic and our response to it will be on circulation patterns of endemic respiratory viruses.

What can be expected once this pandemic subsides and NPIs are lifted? If there is a reduction of population-level immunity, endemic respiratory viruses could resurge with atypical patterns and/or with high attack rates (higher risk of infection during a specific time period) owing to the large susceptible population. Current disruption in respiratory virus circulation could also lead to changes in their epidemiology—for example, changes in age distribution or disease severity. Moreover, it is unclear how many years it would take to reestablish regular seasonal patterns and whether new pandemic threats can be expected, especially considering the unpredictability of influenza virus evolution and the role of animal reservoirs (see the figure).

Modeling studies have started to explore the impact of an increase in population susceptibility due to minimal RSV and influenza virus infections in 2020–2021 on the magnitude of subsequent seasons (7). RSV is a common respiratory virus that often circulates during cold months in temperate countries, causing mostly mild disease in the general population but with a risk for severe disease in infants and the elderly. Contrary to influenza viruses, RSV has no known animal reservoir. Two main antigenic groups (A and B) present variability that may contribute to the ability of RSV to establish reinfections throughout a life span. Data from surveillance systems have recently identified off-season circulation of RSV in both Northern and Southern hemispheres, albeit of lower magnitude than in previously documented RSV seasons and despite some NPIs still in use. This increased circulation could have been driven by an increased susceptibility in the very young and waning of immunity among adults (5). Periodic circulation of RSV, even if limited, may minimize the pool of susceptible population in the long term and prevent large outbreaks in the future (6).

For influenza viruses, the overall modeling conclusions are less robust than for RSV (7). The rapid evolution and the dynamics of host immunity associated with influenza virus infections add further uncertainty and complexity to the modeling forecast. Although initial modeling analyses (7) help

illustrate broad scenarios of the possible impact of the COVID-19 pandemic on endemic respiratory diseases, they also highlight the gaps in data and knowledge on viral interference theories (which explain how an individual infected by a virus becomes resistant to infection by a second virus), environmental and temperature effects on virus seasonality, and the role of immunity in transmission at the population level.

Theoretically, in the case of influenza virus, limited community transmission, as documented in the last seasons, could present less opportunity for viral mutations (8) through antigenic drift (a process of gradual accumulation of mutations in the surface glycoproteins, or antigens, of the influenza virus). Overall, the lack of new mutation opportunities could limit the variability of circulating influenza viruses (9, 10). In turn, those viruses accumulating mutations could face limited antigenic selection due to a lower immunological pressure because there is a reduction in population-wide immunity, despite the increased influenza vaccination coverage observed in 2020 in various countries (11).

The pool of susceptible individuals could also change qualitatively, with children becoming especially vulnerable during future influenza epidemics if the rest of the population maintains cross-protection from infection with previous seasonal strains. The implication of this scenario is the possibility of future (larger) influenza seasonal outbreaks affecting clinically different subpopulations. Nonetheless, if more homogeneous populations of viruses are observed, disease could be controlled through well-matched vaccines. Conversely, reduced population-wide immunity could allow for the emergence of variant strains with pandemic potential, including those possibly introduced from other species. This is observed, for example, with H3N2v viruses, which are often detected during summertime in the US from exposure to swine in agricultural fairs (12). These variant strains mostly affect children because population immunity from other H3N2 circulating viruses may be controlling their spread among the adult population (13). Further research into the underlying mechanisms determining the epidemiological features of specific respiratory viruses that considers viral evolution, interactions among viruses, and between virus and host immunity is needed. This will help identify emerging pandemic threats as well as better prepare for the long-term management of future outbreaks and epidemics.

The evolution of SARS-CoV-2 and the appearance of variants threatening the effectiveness of newly authorized vaccines have underlined the importance and limitations of genomic surveillance networks globally.

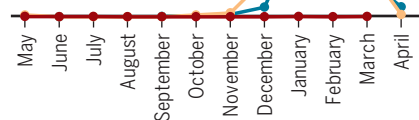
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Patterns of respiratory virus infections

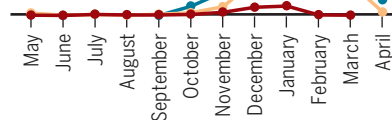
During the pandemic, circulation patterns of respiratory viruses other than severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been disrupted. This could mean a future shift in the epidemiology of respiratory diseases, potential for new epidemic threats, or larger outbreaks than previously observed. It is also unknown how long it will take for seasonal circulation patterns to return to prepandemic levels. Graphs illustrate trends in detection of respiratory viruses. Data are from respiratory illness surveillance in participating sites of the Global Influenza Hospital Surveillance Network (14).

— 2018–2019 — 2019–2020 — 2020–2021

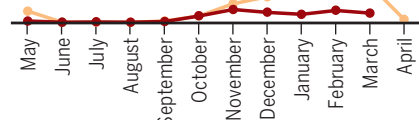
Influenza virus



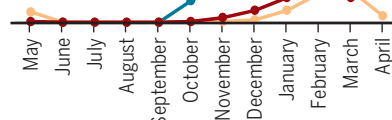
Respiratory syncytial virus



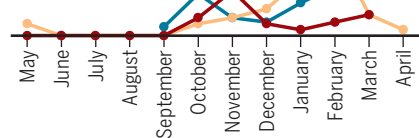
Rhinovirus



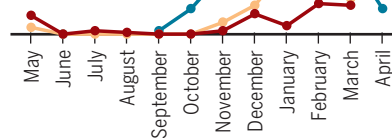
Metapneumovirus



Parainfluenza virus



Human coronaviruses (excluding SARS-CoV-2)



The uncertainty in future scenarios for other respiratory viruses in the post-COVID-19 period, including possible surges off-season and changes in clinical burden distribution, raises the need for an improved and comprehensive approach to respiratory disease and viral genomic surveillance. Widespread virus genomic surveillance embedded as part of national disease surveillance efforts and with links to clinical and epidemiological data could not only help monitor evolution but also identify those changes in strains associated with increased disease severity or vaccine breakthrough. It could improve current and new vaccine targets by refining vaccine strain selection against COVID-19 and influenza.

The COVID-19 pandemic has exposed the extent to which countries are still ill-prepared to monitor the emergence of new viruses, to assess their potential public health risk and the effectiveness of public health responses. The World Health Organization's Global Influenza Surveillance and Response

System (GISRS) network, though providing much needed surveillance coverage, has limited linkages to clinical data, and global hospital-based surveillance networks once heavily supported by the US Centers for Disease Control and Prevention have suffered from disinvestments in recent years. Ensuring effective and real-time data sharing, expanding geographical coverage, and integrating genomic data of identified viruses with clinical data will require dedicated financing mechanisms and a stronger scientific collaboration between diagnostic and pharmaceutical companies, public health authorities, and academic institutions.

The Global Influenza Hospital Surveillance Network (GIHSN) has provided a proof of concept for the expansion of current systems (14). This public-private partnership initiative was built 8 years ago to improve surveillance of influenza viruses and covers more than 100 hospitals across over 20 countries. Centers are asked to identify episodes of severe acute respiratory illness among hospital-

ized patients, testing primarily for influenza virus but covering other selected respiratory viruses, such as SARS-CoV-2, as resources allow. The network then ensures that virus whole-genome sequencing data are linked to epidemiologic and clinical data. The genomic sequences are uploaded into GISAID, a global data-sharing platform that has become the largest database of SARS-CoV-2 genomic data (15). These initiatives aim to provide flexibility to collaborating stakeholders, creating a solid infrastructure for expanded respiratory disease surveillance.

The vision of a global surveillance network for respiratory viruses, bringing together key players (multilateral and bilateral organizations, local governments, foundations, civil society, academia, and industry) with a common mission and roadmap, could ground an efficient global pandemic preparedness framework. Public and private resources could empower initiatives such as GISRS or the Coalition for Epidemic Preparedness Innovations (CEPI) in supporting governments and academic centers to maintain a sustainable surveillance and research platform to respond to public health agendas and promote preparedness. Currently, the emergency response to COVID-19 is a global priority, but preparation for future threats by building on existent global networks, fostering synergies, and expanding collaborations among a more inclusive stakeholder population should not be overlooked. ■

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