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REVIEW

Respiratory viruses: new challenges for old enemies

Elio **Iovine** [1], Laura **Petrarca** [1], Maria Giulia **Conti** [1], Enrica **Mancino** [1], Fabrizio **Virgili** [1], Greta **Di Mattia** [1], Luigi **Matera** [1], Domenico Paolo **La Regina** [1], Alessandra **Pierangeli** [2], Fabio **Midulla** [1], Raffaella **Nenna** [1,*]

[*] **Correspondence to:**

raffaella.nenna@uniroma1.it. ORCID: https://orcid.org/0000-0001-8880-3462

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[1] Department of Maternal Infantile and Urological Sciences, Sapienza University of Rome, Rome, Italy

[2] Virology Laboratory, Department of Molecular Medicine, Sapienza University of Rome, Rome, Italy

ABSTRACT

The recent SARS-CoV2 pandemic has brought back to the attention of the scientific community the issue of respiratory viruses. In both the adult and pediatric population, respiratory viruses still represent an important cause of morbidity and mortality, representing the third leading cause of death among children under 5 years of age worldwide.

In this review we report the latest epidemiologic and clinical updates regarding respiratory viruses with a particular focus on the most important among them in pediatrics such as respiratory syncytial virus, rhinoviruses, enteroviruses, and adenoviruses, highlighting how and why the COVID-19 pandemic has changed the epidemiological panorama of respiratory viruses globally.

IMPACT STATEMENT: Respiratory viruses represent an important cause of morbidity and mortality. COVID-19 pandemic has changed the epidemiological panorama of respiratory viruses globally.

INTRODUCTION

The recent worldwide outbreak of the COVID-19 pandemic has once again brought the unsolved problem of respiratory viruses and related diseases to the attention of the scientific community. Although it is in the field of virology that modern medicine has reported some of its most important successes, with the eradication of smallpox in 1979 and the discovery of vaccines for many viral diseases, the COVID-19 pandemic has shown how unpredictable viruses are and how poorly understood are still the mechanisms behind the emergence of new genotypes and viral variants resulting in unpredictable outbreaks.

To date, as communicated by the Institute for Health Metrics and Evaluation, respiratory infections represent the fourth leading cause of burden of disease globally, only surpassed by cardiovascular diseases, cancers, and neonatal disorders; in particular, in Italy they represent the first cause of burden of disease among all infectious diseases (1).

In the pediatric population, respiratory infections have always been a major clinical concern. In fact, the global burden of disease study in 2016 included acute respiratory diseases as the third leading cause of death under the age of 5 world-

KEY WORDS

Respiratory viruses; influenza virus; children; respiratory syncytial virus; rhinovirus, respiratory enteroviruses; adenovirus.

wide, responsible for about 15 percent of under-five mortality and surpassed only by prematurity-related issues, also pointing out that they still represent the leading cause of death under the age of 5 in many developing countries (2).

To date, many viruses that can replicate within the respiratory tree resulting in respiratory symptoms have been isolated; influenza viruses, respiratory syncytial virus (RSV), rhinoviruses but also adenoviruses, coronaviruses, bocaviruses, enteroviruses, parainfluenza viruses and metapneumoviruses are just some of the respiratory viruses identified to date.

Through the years increasing knowledge has been acquired regarding the genetic and molecular characteristics of respiratory viruses, and even novel viruses have been isolated. Despite this, the clinical diagnosis of a viral infection remains difficult because of the overlapping symptoms of different viral diseases and of bacterial respiratory infections, causing inappropriate prescription of antibiotics with the increasing risk of antibiotic resistance (3).

In this review, we will report the latest updates about the epidemiology and characteristics of respiratory viruses, with a focus on those most commonly isolated in the pediatric population (influenza virus, respiratory syncytial virus, rhinoviruses, respiratory enteroviruses, and adenoviruses), highlighting how and why the COVID-19 pandemic has changed the epidemiological panorama of respiratory viruses globally.

INFLUENZA VIRUS

For many years the influenza virus has been considered the major cause of viral infections and of mortality and morbidity in all age groups being able to infect children as well as adults and elders (4). Globally, about 3-5 million severe influenza virus infections are estimated annually; these are responsible for about 300,000-650,000 deaths each year and account for about 13% of deaths caused by respiratory infection. In the pediatric population, the virus is also responsible for an important mortality rate, and it is estimated that among the countries with the highest mortality due to respiratory viruses, 10,000 to 100,000 deaths under age 5 are due to influenza virus (5).

In Europe in particular, the ECDC lists influenza as the leading infectious disease in terms of incidence and mortality, estimating the disease burden at 81.8 DALYs per 100,000 population (6).

This RNA virus of the *Orthomyxoviridae* family, thanks to its rapid antigenic variation, results in annual seasonal epidemics mainly during the winter months, in both the Southern and Northern hemispheres. The two main surface proteins, hemagglutinin, and neuraminidase, of which 18 and 11 antigenic variants are respectively known (7) undergo antigenic shift and antigenic drift mechanisms through which new viral strains originate every year (8). To date, 4 different types of influenza viruses have been identified: influenza A, B, C, and D, the last of which exclusively infects pigs (9). Of these, influenza A virus is the most frequently responsible for outbreaks during the annual influenza season. Type B influenza, on the other hand, is characterized by less variability than type A influenza and is therefore less frequent and responsible for minor epidemic outbreaks (10).

In the pediatric population, influenza viruses continue to be a major challenge being responsible for about 870,000 hospitalizations of children under the age of 5 worldwide (11) and a cause of concern because of the difficulty in predicting the emergence of new viral subtypes capable of leading to new pandemics as in the case of H1N1 in 2009, especially in light of the changed global viral ecosystem following the COVID-19 pandemic.

OTHER RESPIRATORY VIRUSES

While influenza virus represents a virus of major relevance in the context of respiratory viruses affecting all ages, it is only one of the isolated respiratory viruses. To date, at least 12 viruses belonging to different families, both DNA and RNA viruses, capable of causing respiratory infections, have been identified (12).

Among them, according to a CDC report, RSV, rhinoviruses, enteroviruses, and influenza virus are the most frequently isolated respiratory viruses in children with acute respiratory disease between 2016 and 2021, followed by parainfluenza virus 1-3, adenovirus and metapneumovirus (13).

RSV in particular is a major concern in pediatrics because of the potential severity of infection and the most affected age group (infants). To understand the relevance of the problem, in the pre-COVID-19 pandemic

era, there were an estimated 33 million RSV infections among children under 5 years of age, 3 to 4.5 million hospitalizations, and more than 100,000 annual deaths attributable to the virus with particular susceptibility of newborns and infants under 6 months of age (14).

The diagnosis of acute viral infections often remains based on clinical and epidemiological criteria, and a precise etiologic diagnosis is not always made. Distinguishing the type of infection and the virus involved on the basis of clinical and epidemiological data alone is not possible. In the absence of a precise etiological diagnosis, however, an opportunity is missed to implement isolation measures when necessary or to use appropriate antiviral drugs (15, 16).

The scale of the challenge is such that the implementation of virologic surveillance programs in the community and in the hospital and the establishment of national and international surveillance programs and incentivize etiologic research during acute respiratory infection can be an important step in the management of infections. These programs can now be carried out thanks to the introduction of new laboratory methods. In fact, more and more laboratories are adopting in addition to the real-time PCR assay, long used for isolation of viral samples, a nucleic acid amplification multiplex tests with specific respiratory panels. The use of these multiplexes allows a rapid simultaneous analysis of a single sample for multiple viral species, and a high concordance rate with real-time PCR results has been reported (17).

Thus, these multiplexes may provide an opportunity to facilitate and accelerate the diagnosis of viral infection. It has also been observed that these multiplex assays may sometimes appear more sensitive than traditional diagnostic methods and more frequently detect coinfections. However, the clinical relevance as well as the role of subclinical infections or viral persistence or reactivation remains unknown. Moreover, these systems are exclusively qualitative and not quantitative, and it is not possible to determine which virus among those isolated is the predominant and etiological cause of the acute respiratory syndrome. Likewise, it is not possible to date to establish a cut-off of clinical relevance (18).

Overcoming these problems and a rapid and certain virologic diagnosis could help to better understand respiratory viruses and their associated clinical syndromes with important clinical implications inside and outside the hospitals: limitation in the need for diagnostic tests, reduction in the use of inappropriate antibiotics, the possibility of appropriately prescribing antiviral drugs, or the possibility of building virologic prevention programs represent only some of the possible benefits (19). The greatest benefits are likely to be seen with a faster diagnosis and integration with other clinical and laboratory data (20).

A recent meta-analysis showed in almost all the high-quality studies that rapid virologic diagnosis resulted in a reduction in the length of hospitalizations, a reduction in the use of chest radiography, and an increase in the appropriate use of Oseltamivir in influenza virus-positive patients. In contrast, a smaller effect was observed on antibiotic use, duration of antibiotic therapy, and number of hospitalizations (21, 22).

Respiratory syncytial virus

RSV is a single-stranded RNA virus with negative polarity. Classified until 2016 as part of the family *Paramyxoviridae*, it was recently reclassified and included within a newly formed family, the *Pneumoviridae* (23). Recognized in 1956, it was so called because of its ability to form host cell syncytia when placed in culture. RSV is a capsular envelope-coated virus whose genome encodes for 11 proteins, of which the fusion protein F and the attachment glycoprotein G are the major ones. Based on the variability of the G protein, the virus is divided into the two subgroups A and B and with respect to sequencing the second half of the hypervariable region of the G protein into different genotypes. (24, 25). The two viral subgroups circulate simultaneously during epidemic periods so that multiple genotypes of subtype A and B may circulate simultaneously in the same epidemic season with not yet fully elucidated clinical relapses, thus explaining the short-lasting genotype-specific immunity (26).

The virus represents a major concern in pediatrics being responsible for more than 20% of acute lower respiratory tract infections in the first 5 years of life (27, 28). It is estimated that about 70% of infants will be infected with RSV in the first year of life, more than 20% will develop symptoms, about 2% will be hospitalized, and about 2% of these will require invasive respiratory care (29).

Moreover, the virus represents a ubiquitous virus of all ages, particularly for patients older than 65 years. In this age group, RSV infection is burdened with a high

mortality rate, especially in immunocompromised or fragile patients (30).

Moreover, the acute infection is not the only factor determining its health and economic burden. Growing evidence supports the association between RSV infection in early life and the development of preschool wheezing and in some cases, over the years, with the development of asthma. However, it is unclear to date whether there is a causal relationship between RSV infection and the development of wheezing and asthma or whether genetic and anatomical factors of the subject, in themselves predisposing for preschool wheezing and asthma, may also facilitate RSV infection in early life (31). In this regard, the fact that it is to date possible to isolate the different virus genotypes has made it possible to hypothesize that the genetic diversity between the various genotypes may in part allow the recognition of disease endotypes and more accurately predict the severity of acute infection and eventually the likelihood of developing wheezing or asthma in the future. For example, some studies have shown a tendency for the RSV-A NA1 to affect younger infants and cause more severe infection than the emerging RSV-A ON1. On the other hand, infants hospitalized for bronchiolitis in whom RSV-B was isolated had a greater number of risk factors for asthma (family history of asthma, eosinophilia) (32). Underlying these differences could be a different immune response elicited by the virus, with mainly activation of the IFN I/III system in the case of RSV-A NA1 infection, which would allow better control of viral replication but could contribute to worsening the acute disease, or with a reduced IFN but rather Th2-oriented immune response in the case of RSV-B or RSV-A ON1 infections, which are responsible for milder acute infections but are associated with a higher risk of respiratory sequelae (33). In any case, immune and viral factors together contribute to disease severity, as shown by the recent progressive increase over the years in the severity of RSV-A ON1 infections probably as a result of the increasing number of amino acid substitutions in the second hypervariable region of the G protein resulting in increased virulence or in facilitation of immune escape (34).

Rhinovirus

The rhinoviruses were the only viruses belonging to the genus of rhinovirus until 2008, when they were reclassified within the genus of enterovirus, of the family of *Picornaviridae* (35). It is a single-stranded positive polarity RNA similar to that of the other enteroviruses so that recent molecular assays have verified the similarity between the genotypes of some serotypes such as Rhinovirus 87 and Enterovirus D68 recognizing them as a single genetic identity now classified as Enterovirus D68 (36).

To date, more than 160 viral genotypes have been recognized and grouped into 3 species: Rhinovirus A, B and C, the last of which was only recognized in 2006 (37).

The presence of such a high number of genotypes and the fact that 20 to 30 genotypes are usually circulating during an epidemic season explains why the rhinoviruses infections and the common cold can recur frequently during a season and over a lifetime.

Like RSV, rhinovirus also affects all ages from newborns to the elderly with clinical manifestations varying from the common cold to sinusitis, otitis media or lower respiratory tract infection with bronchiolitis, pneumonia and wheezing (38). It also represents an important cause of asthma, chronic obstructive pulmonary disease, and cystic fibrosis bronchopulmonary exacerbations (39, 40). In the pediatric population, the virus is a frequent cause of bronchiolitis, being responsible for about 20% of cases (41).

Although several studies have shown a lower severity of rhinovirus bronchiolitis compared with RSV bronchiolitis with a shorter length of stay and lower clinical score, (42, 43) it has also been reported that rhinovirus infection is associated with long-term sequelae and in particular an increased risk of asthma (44, 45). This risk may be partly explained by the fact that the virus appears to alter the epithelial barrier by disrupting the integrity of tight junctions during viral replication thereby increasing epithelial permeability and facilitating contact with airborne allergens (46). Furthermore, it has been hypothesized that immunological factors may also determine the increased risk of asthma. Indeed, some studies have identified in infants with rhinovirus bronchiolitis a polarization of the T2 immune response associated with other atopic markers such as eosinophilia and increased IgE and low activation of the interferon (INF) system (47-49). Likewise, it is not yet possible to discriminate whether rhinovirus bronchiolitis contributes to the development of asthma or represents itself a marker of genetic susceptibility to atopy (50).

Respiratory enteroviruses

The *Picornaviridae* family also includes other viral species besides rhinoviruses namely Enterovirus species A-L, belonging to the genus Enterovirus (51). The name derives from the tropism of some of them for the gastro-intestinal system; these viruses are all characterized by a single-stranded RNA genome with positive polarity and all of them lack an envelope.

Among the known enterovirus species, Enteroviruses A-D are the only ones that infect humans with very different clinical presentations. Indeed, infections mostly run mildly with fever, rhinitis, pharyngitis, and in some infants with vomiting or diarrhea but some viral species have demonstrated a marked tropism for the central nervous system following systemic dissemination with possible encephalitis, meningitis, or flaccid paralysis as well as sepsis, myocarditis, and pericarditis (52, 53). Indeed the 15 genera of entroviruses currently known include those formerly classified as Polioviruses, Coxachieviruses A and B, and Echoviruses.

Among respiratory viruses, Enterovirus D-68 represents the emerging serotype of greatest interest and concern. First isolated in 1962 in California, this virus has been the cause over the past decade of large outbreaks in America and Europe with biannual peaks in 2014, 2016, and 2018 (54, 55).

This serotype initially considered to cause mild to moderate respiratory symptoms has recently been identified as a cause of severe asthma exacerbations and severe acute respiratory disease, sometimes complicated by neurological symptoms, in particularly by a severe acute flaccid myelitis (56). Respiratory symptoms mainly affect the pediatric population with symptoms ranging from common cold to cough to wheezing and respiratory distress with the need for respiratory support, especially in individuals with a history of asthma or wheezing (57).

A study conducted in Sweden in 2016 showed increased circulation of the virus during that epidemic season and greater severity of the virus compared to other enteroviruses with increased need for hospitalization and medication, both in children above and below 5 years of age (58). During the 2014 United States outbreak, the clinical symptoms appeared to be even more severe with 59% of hospitalized patients requiring intensive care unit admission and often invasive or noninvasive ventilation (57).

The following epidemic seasons appear to have been clinically milder but the true incidence of EV-D68 infection may be underestimated due to the inability of standard diagnostic panels to discriminate between rhinovirus and EV-D68.

Today, after the reduction in the detection of respiratory viruses during the 2020 epidemic season because of the COVID-19 pandemic restrictions, the incidence of the virus appears to have increased again with similar levels of isolation as in 2018 and higher than in 2017 and 2019 with concomitant increase in the number of children visited in emergency departments for acute respiratory symptoms and asthma exacerbations (59). In this regard, given the virulence of the virus and its associated neurological complications and given the possible immunological changes in the population because of measures to contain COVID-19 infection, a careful surveillance will be necessary in the near future.

Adenovirus

Human adenoviruses (AdV) are a group of viruses responsible for a wide and broad range of symptoms involving multiple organs and systems. Of these viruses belonging to the mastadenovirus genus of the *Adenoviridae* family, more than 50 serotypes classified into 7 species are known to date, all characterized by a double-stranded DNA genome (60).

The clinical symptoms caused by these viruses are very broad, and different serotypes demonstrate different tissue tropism and therefore different clinical manifestations of variable severity. The respiratory system is most frequently involved with infections with a predominantly moderate course involving the upper and lower airways, but the clinical phenotype also depends on the characteristics of the host and the viral serotype involved (61). Gastrointestinal tract infections, conjunctivitis and, especially in immunocompromised patients, hepatitis, pancreatitis, or meningoencephalitis are also possible as a result of virus dissemination (62).

From a respiratory perspective, adenoviruses are responsible for about 5% of acute respiratory infections in the pediatric population including bronchiolitis and pneumonia, and several deaths have been reported among both immunocompetent and immunocompromised children following Adenovirus pneumonia (63, 64). The infection also appears to cause long-term

complications such as bronchiectasis, bronchiolitis obliterans, or Swyer-James syndrome (65).

The most frequent serotypes involved in respiratory infections of children are AdV1-2 and 7, with serotypes 1 and 7 accounting for more than 50 percent of the serotypes globally identified although the epidemiology of the virus varies widely depending on the considered geographic region (60). Clinical severity also appears to change with serotype: for example, AdV-7 appears to be apparently more virulent than the other serotypes and responsible for fatal pneumonia among immunocompetent patients (66).

Moreover, in 2007 a life-threatening form of AdV-14 pneumonia emerged in the United States. In the early months of that year, more than 140 cases were confirmed in several states in the United States. Of these 24 required intensive care unit admission and 9 patients died (67).

Although representing a widespread virus among respiratory viruses, adenoviruses have recently gained interest in the scientific community for their possible etiologic role in the development of severe hepatitis of unknown etiology. In fact, the World Health Organization reported in the first half of 2022 the outbreaking of a new form of hepatitis, negative for the most common infectious agents causing hepatitis, in previously healthy children aged 1 month to 16 years (68). More than 500 cases of these hepatitis were reported in an ECDC report; 404 of these were tested for adenovirus, and more than 50 percent of those tested were positive. When subtyping was possible, serotype 41 was the most frequently detected (69). To date, it is considered unlikely a direct virus-induced liver damage, as demonstrated by histological findings, but rather it is speculated that viral and immune factors and perhaps either COVID infection or COVID period immunity changes related together with adenovirus infection may represent the cause of this new hepatitis (69).

WHAT'S NEW

To date, the global respiratory virus scenario has been radically changed since the outbreak of the COVID-19 pandemic. The first SARS-CoV-2 outbreak was described in Wuhan, China, in December 2019. Since then, the virus has spread across the 5 continents, and the World Health Organizatoin (WHO) declared the pandemic on March 11, 2020 (70).

The COVID-19 pandemic dramatically demonstrated the unpredictability of the virus behavior and how poorly we still know about them, but it also provided an opportunity to better understand them and the impact that the emergence of a new virus and/or the implementation of specific infection preventive non-pharmacological interventions (NPIs) can have on a complex viral ecosystem.

Several virologists and epidemiologists have referred to the implementation of NPIs on a global scale as a large-scale natural experiment involving many respiratory viruses, and they predicted that this experiment could have increased our knowledge regarding virus transmission and the behavior of seasonal viruses and their impact on chronic diseases.

A strict lockdown in the early 2020 in many states around the world along with the implementation of NPIs such as careful handwashing with appropriate soaps or the use of face masks have not only contributed to containing SARS-CoV-2 infection but have also changed the epidemiology of the most common respiratory viruses globally among both adult and pediatric populations. For example, as reported by the WHO the influenza virus almost disappeared globally in the 2020-2021 epidemic season in both the Northern and Southern hemisphere precisely during the implementation of the tightest prevention strategies of viral contagion (71, 72). Influenza virus circulation was not the only one to change during the pandemic period. A recent single-center study showed that during the 2020-2021 epidemic season the number of hospitalizations for acute respiratory tract infections were reduced by more than 80 percent compared with the same pre-pandemic period, and also that respiratory viruses were isolated more infrequently during that epidemic season, and thus the circulation of all respiratory viruses and RSV in particular was reduced, with the only exception of rhinovirus (73). However, the same phenomenon was not observed during the subsequent epidemic season. With the relaxation of NPIs and the cessation of lockdown in the winter of 2021-2022, there was an unexpected increase in respiratory diseases in the pediatric population and in particular RSV bronchiolitis. In contrast to previous years, hospitalizations began to in-

crease in the second half of October 2021 with a peak in early November 2021 and thus much earlier than in previous epidemic seasons during which the highest number of infections was recorded in the northern hemisphere between December and February. It is also interesting to note that during that season there was an opposite trend between the number of RSV and COVID-19 infections that increased as the number of RSV infections decreased (74) (**Infobox 1**).

***Infobox 1**. Hypothesis on the unseasonal RSV epidemiology.*

- COVID-19 restrictive measures
- Decline in population immunity
- Increase in the susceptible population (immunity debt)
- Viral interference:

→ Competition between SARS-CoV-2 and other respiratory viruses

→ Innate antiviral response induced by viruses

The past two years have thus allowed us to make some observations about the behavior of respiratory viruses in the pediatric population and to make some hypothesis and draw some conclusions about what we have observed.

First, it was understood that the implementation of hygiene and social distancing measures can be effective in reducing the circulation of multiple respiratory viruses simultaneously even though some viruses may be more resistant as in the case of rhinovirus. It has been hypothesized that rhinovirus may behave differently from other viral species due to some of its characteristics that make it more resistant to hygienic containment measures: 1) the absence of a lipid envelope would make it more resistant to soaps and lipophilic solutions; 2) a compact icosahedral virion structure would make it more stable on surfaces; and the fact that it could be spread, unlike other viruses, by aerosols of 4-5 micrometers would make it more contagious (75) (**Infobox 2**).

***Infobox 2**. Rhinovirus has some features that make it more resistant to hygienic containment measures.*

- The absence of a lipid envelope would make it more resistant to soaps and lipophilic solutions
- The compact icosahedral structure of the virion make it more stable on surfaces
- It is small and can be spread by aerosols of 4-5 micrometers
- It causes mild symptoms that are often overlooked

Furthermore, it was understood that the viral ecosystem should always be considered in its entirety and in regard to its interaction with the immune system. The earlier and more violent re-emergence of respiratory viruses after the relaxation of containment measures could in fact represent a consequence of the increased susceptibility of the population to viral infection following the decline of population immunity and thus represent the immunological debt to be paid after a period of immune isolation.

Finally, the observation of the increase in the number of SARS-CoV2 infections as the number of RSV infections declined has allowed us to speculate that the already known viral interference phenomenon may have played an important role in virus transmission and susceptibility. Already in the past, epidemiological and experimental studies have emphasized the possibility that in specific ecological niches virus-virus interaction has the potential to trigger immunological mechanisms capable of influencing individual and population risk of infection so that a first infection may prevent superinfection by a second virus through activation of the immune system and in particular the INF system (76).

In this regard, it has been hypothesized that Sars-CoV2 and particularly the Omicron variant contributed to the reduced RSV circulation explaining the early interruption of RSV spread among newborns and infants in winter 2021 (77).

This yet incompletely understood mechanism of viral interference, together with the inability to predict the actual impact that infection containment measures have had at the immune and epidemiological scale, make it difficult to date to predict how respiratory viruses will behave in the near future and whether new viral variants might be selected.

This unpredictability is, for example, evidenced by recently acquired data about the course of the influenza season in Australia during the summer of 2022 and in Europe during the winter of 2022-2023. In Australia, the peak of infections occurred in mid-June, earlier than observed in previous epidemic seasons but its length was short, and the clinical severity was mild (78). Also, in Italy the influenza epidemic peak occurred earlier than in any other epidemic season in the past 10 years with the highest number of infections during the first days of December. Interestingly, in contrast to Australia, the recorded incidence was also the highest of the past 10 years, and the most affected age group was children under 4 years old (79).

It is important, therefore, that the knowledge that the scientific community has always had about the seasonality of respiratory infections be considered with caution in the future, especially in the light of the new viral ecosystem that could represent an opportunity for the emergence of new viruses and variants. In this global context, a careful epidemiological surveillance of respiratory infections may be the only strategy for a prompt intervention (**Infobox 3**).

***Infobox 3**. Conclusions.*

- Respiratory infections continue to account for a significant burden on the health system
- The knowledge we have always had about seasonality of respiratory infections must be consider with caution in the future
- The viral ecosystem, altered in the last two years could be breeding ground for new viruses and/or variants
- Careful surveillance of respiratory infections can allow for rapid action

COMPLIANCE WITH ETHICAL STANDARDS

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Ethical approval

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N/A.

Animal studies

N/A.

Data sharing and data accessibility

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Publication ethics

Plagiarism

All original studies are cited as appropriate.

Data falsification and fabrication

All the data correspond to the real.

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