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Editorial

Respiratory Syncytial Virus and influenza infections in adults: more in common than meets the eye



Infecciones por virus respiratorio sincitial y gripe en adultos: más en común de lo que parece

Respiratory infections are the leading cause of consultation in primary care and one of the most important causes of hospital admission, maintaining a strong association with the epidemiology of the main respiratory viruses of an epidemic nature.^{1,2}

The viruses responsible for these infections could be classified from a clinical-epidemiological point of view into classic or *major* viruses (influenza virus, respiratory syncytial virus [RSV] and rhinovirus) and *minor* viruses (parainfluenza, adenovirus, coronavirus 229E), and among them others of relatively more recent discovery (metapneumovirus, bocavirus, coronaviruses HKU1, OC43 and NL63, and some respiratory enteroviruses, notably E68). The new human coronavirus SARS-CoV-2 responsible for the COVID-19 disease has now been added to this list as another major virus. All of them fit the clinical-microbiological canon “a virus responsible for different diseases; the same disease caused by different viruses”.³

Influenza sometimes occurs in the form of pandemics in which the genetic rearrangement between animal viruses and other human viruses gives rise to a genetic constellation in the virus that allows its replication in an efficient, sustained and continuous manner in human hosts, which are characteristics that define a pandemic virus. Therefore, from a global One Health concept, influenza should be considered as an intermittently emerging anthroozoonosis. From the pandemic emergence of a new influenza virus, adaptive evolutionary mutations of the pandemic ancestors occur that cause minor variants of viruses of the same subtype, responsible for seasonal autumn/winter epidemics.

RSV, named in reference to the giant cells (syncytia) it causes in cell culture, was isolated for the first time in 1956 from a chimpanzee suffering from a respiratory infection.⁴ It is a typically human virus of which there are two antigenic types (A and B) with similar clinical features, and although since its discovery it has been associated with significant infant morbidity and mortality, especially in underdeveloped countries (5), subsequent epidemiological studies suggest that the clinical impact of RSV in certain adult populations may approach that of seasonal influenza.^{5–7} Seasonal RSV epidemics generally begin before influenza epidemics and although the epidemic peaks of maximum incidence do not usually coincide, there are usually several months of overlap in the circulation of both

viruses.⁸ For a long time, RSV has lacked an epidemic surveillance system similar to the one for influenza, and the absence of data has not allowed RSV to be clearly perceived as “a global pathogen in an aging world”.⁹ It is necessary, as with influenza, to adopt a similar nomenclature based on the molecular analysis of different clades to obtain a clearer idea of its behavior.^{10,11}

That typical seasonal epidemic presentation of influenza and RSV has been repeated year after year in a similar way until the outbreak of the COVID-19 pandemic. The tremendous social restrictions and other non-pharmacological measures (NPM) caused important epidemic alterations in the epidemic presentation of some of the respiratory viruses, notably influenza and RSV, which some authors had anticipated.¹² This phenomenon meant that in the 2020–2021 season there were hardly any cases of influenza in the world, with the exception of some countries such as China or India, and that the epidemiology of RSV suffered a notable temporal alteration, with epidemic waves being recorded in the spring and summer months, and a greater average age range of the affected child population without an increase in severity. As the NPM were replaced by a systematic vaccination for the entire population, the epidemic normality of RSV and influenza was recovered, with some exceptional events being observed in the latter. Thus, in the 2021–22 season, two waves of influenza clearly caused by the same subtype A (H3N2) occurred for the first time in many countries, including Spain, separated by an interval of four to five weeks. This resulted in a flu season being much longer, with even summer hospitalisations although with less epidemic intensity and total fewer hospitalisations. The 2022–2023 flu epidemic (third post-pandemic) also had two separate waves, the first being produced by subtype A (H3N2) and the second by influenza B of the Victoria lineage and to a lesser extent subtype A (H1N1), both of them causing also being responsible for a higher incidence of Flu-like-illness in children and adolescents.

Every pandemic leaves some lessons that can only be correctly assessed years later. The influenza A pandemic that took place in 2009 definitively established viral diagnosis by PCR in hospitals. This gradually evolved and developed in the following years until multiplex PCRs were available to detect several types of respiratory microorganisms, and their use became popular in most Spanish hospitals.¹³

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The COVID-19 pandemic has also had its effects and lessons. Thus, one of the most notable post-pandemic socio-health effects has been the rediscovery of the viruses responsible for respiratory diseases for society in general and for health workers in particular. Both pandemics have ensured that the majority of microbiology laboratories in Spanish hospitals today have the technical and material resources to apply these techniques efficiently to the routine virological diagnosis of respiratory pathology.

In this sense, one of the main problems for clinicians and infectious disease specialists in clinical practice is to know when to suspect, and subsequently rule out as accurately as possible, the possible viral aetiology of a respiratory condition. Paediatricians or infectious disease specialists can often rule out a viral condition from a bacterial one, but going further requires the help of a microbiological diagnosis. That is why the massive use of PCR for the diagnosis of COVID-19 in severe hospitalised cases was one of the first weapons available in the early moments of the pandemic, and the laboratories that were able to use homemade PCRs against SARS-CoV-2 were in better clinical condition to manage their patients. As the pandemic situation evolved and COVID-19 lost part of its prominence, there was a growing need for a correct and rapid aetiological diagnosis in severe respiratory conditions. At the same time, the rapid diagnostic tests by capillary immunochromatography (home test) went from being authorised to being sold to the general public and being massively used by non-diagnostic professionals, while also expanding their diagnostic capacity to COVID-19 and influenza simultaneously in the same test, initially excluding RSV. As discussed at the XXV Congress of SEIMC (Spanish Society of Infectious Diseases and Clinical Microbiology) –first in-person post-pandemic–, for the second time in the history of microbiological diagnosis (after the diagnosis of HIV with alternative samples to serum), this went from point of care to home testing, when the patient arrives at their health centre with a microbiological pre-diagnosis of SARS-CoV-2 or influenza already carried out and known by the patient themselves. On the other hand, virological diagnosis is key in a world where antimicrobial resistance is a major international threat. The use of rapid molecular diagnostics has demonstrated a great potential to improve both the management of pneumonia patients and the stewardship of antibiotics.

In this volume of Infectious Diseases and Clinical Microbiology, Losa Martín et al.¹⁴ present a retrospective, observational study of cohorts of adult patients diagnosed with RSV or influenza virus infection during the winter of 2018–19 in years prior to the pandemic. Their findings illustrate and confirm the importance and severity of infection by both respiratory viruses, pointing out few differences in the morbidity of both. Influenza virus infections have been identified for years as an important cause of morbidity and mortality at the age extremes of life – children and the elderly. However, mortality in influenza is usually concentrated in the older population and in those individuals who have chronic underlying diseases that significantly compromise their health. Among these, diabetes, chronic liver disease or kidney disease stand out for their importance, but above all of them are cardiovascular pathologies that suffer serious decompensation during the clinical course of influenza and lead in a significant number of cases to the death of the patient. In contrast, RSV has clearly and traditionally been identified as an important cause of severe illness and hospitalisation, especially in infants and children under two years of age. However, studies such as the one published in this issue and others^{5–7,14,15} emphasise that the importance and severity of RSV infections requiring hospitalisation are comparable to or of greater severity than those of influenza in hospitalised adults.¹⁶

One of the pioneering prospective articles in drawing attention to the consequences of RSV infection in adults⁶ established that in the group of hospitalised patients, 10.6% of them were due to pneumonia, 11.4% due to chronic obstructive pulmonary disease,

5.4% due to congestive heart failure and 7.2% due to asthma. It thus demonstrated that RSV infection is an important disease in the elderly and high-risk adults, with a disease burden similar to that of seasonal influenza in a segment of the US population in which flu vaccination coverage is high, pointing out the absence of specific antiviral therapy for RSV and no vaccine for its prophylaxis, therapeutic and prophylactic tools that do exist for influenza. RSV is increasingly recognised as an important cause of severe respiratory disease in older adults. In the United States, an estimated 60,000–160,000 RSV-associated hospitalisations and 6,000–10,000 RSV-associated deaths occur each year among adults aged ≥ 65 years.¹⁶

In Spain, there are few clinical studies on the outcomes of influenza in hospitalised patients and even fewer in adult patients with severe RSV disease.¹⁵ The work of Losa Martín et al. confirms what has been pointed out in this regard in different publications from other countries.^{5–7,14,15} The severity of RSV infections in hospitalised adults is similar to that of seasonal influenza. However, some clarifications should be made regarding this statement, as the patients in the RSV-infected cohort were more vulnerable due to more pre-existing comorbidities than influenza patients. Among them, a greater association of severe RSV infection was found among cancer patients, patients with non-ischaemic heart disease, patients on immunosuppressive treatment or those with greater dependence for basic activities of daily living. For this reason, it seems that the virulence of the influenza virus for adults is greater than that of RSV, as the former requires fewer vulnerability factors for adults to be hospitalised due to severe illness. Although RSV infection results in fewer visits to the health centre than for influenza healthcare use by high-risk adults has been found to be similar for the two viruses.^{5,16}

Influenza is often described as a mild illness, and in most cases it is. However, the fact that it spreads so widely and in a short space of time, generally five to six weeks at its maximum incidence rates, makes the disease burden very important, evident and with serious consequences, as demonstrated in the cited article. On the other hand, the epidemic waves of RSV and influenza overlap at some point in their annual epidemic evolution. The RSV epidemic usually begins before the flu epidemic and lasts from November to March, decreasing thereafter, although cases of RSV infection are detected or diagnosed throughout the year.¹⁷ This means that without specific diagnostic tools for RSV, hospitalised cases can be confused with flu cases, especially when only clinical definitions of the disease are used and the epidemic period corresponds mostly to influenza. The virological diagnosis in these cases is key since there are specific treatments for influenza (oseltamivir, baloxavir, etc.), but there are none for RSV.

In this sense, Losa Martín et al. point out how severe hospitalised adult cases of RSV had a later diagnosis than those of influenza from the beginning of the symptoms of both. This justifies and underpins the need to establish a broad, timely and reliable aetiological diagnosis of severe respiratory infection that requires close collaboration between infectious disease doctors and the microbiology laboratory from the moment a patient with the clinical characteristics described in the article arrives at the hospital. Although the seasonal influenza epidemic is in full evolution, an infection by RSV, rhinovirus or other respiratory viruses in an adult patient cannot be ruled out, based on epidemiological or clinical data, since their seasonal epidemic waves often overlap and only subtle details of the clinical symptoms differentiate one from the other, thus compromising the patient's treatment and hospital care. As the authors of the article point out, one in five cases in which a microbiological diagnosis was requested were caused by RSV instead of influenza, which reinforces the importance of the previous reflections.

The clinical and analytical findings of cases of adults with infections requiring hospitalisation due to RSV or influenza have many

more similarities than differences. In fact, only the fever observed more frequently in patients with influenza, and the greater presence of rhonchi, leukocytosis ($\geq 11,000$ cells/ μ l) or superinfection by *S. aureus* in cases of RSV, reached statistical significance in the exhaustive list of symptoms and analytical parameters described in Losa's article. The quantitative differences between patients hospitalised for influenza and RSV make statistical significance difficult in many of the parameters and symptoms considered. Prospective studies of several seasons are needed so that the balance of severity between RSV and influenza is adequately weighed.

On the other hand, it is important to point out that the possibilities of vaccination or immunisation against both viruses are diametrically different. While for influenza there are different types of vaccines and national and regional recommendations for implementation through campaigns in autumn,¹⁸ for RSV there is nothing similar, since until 2023 there was no authorised vaccine against RSV available. Although data on vaccination percentages by specific age groups are not provided, in Losa's article among the global data collected from patients hospitalised for influenza or RSV, it is striking that flu vaccine coverage is 10 points below the Spanish coverage for that age group, and more than 20 points below 75%, the percentage recommended by the WHO for that population group. This should make us reflect on the urgent need for improvements in this aspect to limit the burden of serious illness due to seasonal influenza. Although the flu vaccine has suboptimal effectiveness against influenza infection, its effectiveness linked to the strains included in the vaccine when there is no antigenic mismatch is high enough to prevent serious events and mortality.¹⁸ The historical underestimation of the severity of influenza disease and the lack of strength of the recommendation by healthcare professionals are mainly responsible for the differences in coverage in population groups in which it is necessary to insist on its administration. This does not occur for vaccination against pneumococcus in which the coverage percentages, without being optimal, are between 10 and 11 points higher than those for influenza. The fact that the frequency of flu vaccination is annual, forces us to insist even more on the strength and consistency of the recommendation by nurses and doctors. In not too distant years, the effectiveness of the influenza vaccine was evaluated using a methodology based on the negative test, ignoring the fact that the main objective of influenza vaccination is not to prevent mild or moderate infection but rather serious cases and their consequences. Although there is general agreement on the need to have more effective vaccines against influenza, it must be remembered that vaccination is the most effective measure to prevent influenza and for its overall preventive performance to be optimal, its coverage must be increased to the maximum.

Probably none of the current vaccines or passive immunisation measures confer total or permanent protection against RSV,¹⁹ a virus that has developed a panoply of biological strategies to evade the host's immune response, infecting and making most people sick at some point in their lives. Therefore, having protection windows, even if they are only temporary, through vaccines or passive immunisation with specific monoclonal antibodies, at key moments in life such as childhood or old age, can have a tremendous impact on the burden of disease on public healthcare.

Finally, and as has already been referred to by Falsey⁶ and Walsh,¹⁹ understanding the need for busy practitioners to make treatment decisions on the basis of clinical grounds, it must be maintained that “everything that looks like “the flu” in the winter is

not”. Rapid, sensitive and specific viral diagnostic tests might help augment intuition. Clinical-microbiological collaboration from a patient's first contact with the health system will contribute to adequate clinical management and a more precise knowledge of the epidemiology of both infections. RSV and influenza infections in adults have more in common than meets the eye.

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