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Infectious disease

Trend of pathogens and respiratory co-infections in the province of Messina: from pediatric age to senescence

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Summary

Acute respiratory infections (ARI) are a leading cause of global morbidity and mortality and they're primarily caused by viruses such as rhinovirus, coronavirus, and respiratory syncytial virus (RSV), and to a lesser extent by bacteria like Streptococcus pneumoniae and Mycoplasma pneumoniae. The study examines the impact of COVID-19 control measures on the circulation of respiratory pathogens, indicating a reduction in infections during the pandemic period. A retrospective study was conducted on 1,286 patients at the "G. Martino" University Hospital of Messina to evaluate the prevalence of respiratory pathogens. The results showed that SARS-CoV-2, rhinovirus, and RSV are the most frequently isolated pathogens, with a clear seasonality from December to March. Co-infections were detected in 14.1% of cases, predominantly in young children. The study suggests the need for enhanced surveillance strategies to improve the management of respiratory infections and healthcare resources.

Introduction

Acute respiratory tract infections (ARI) are a leading cause of morbidity and mortality globally. They are responsible, particularly in the winter months, for the high number of accesses to the emergency department, hospital admissions, and the prescription of antibiotics [1].
According to the GBD (Global Burden of Disease, Injuries, Risk Factors Study) in 2019 globally, there were 17.2 billion cases of upper respiratory tract infections, with around 10,000 related deaths. It is the sixth leading cause of death for all ages and the main one among children under the age of 5 years old [2].
In the USA there are an estimated 180,000 cases of hospitalization every year with around 14,000 deaths in people over 65 years of age [2].
The causes can be viruses and bacteria and it isn't possible to estimate the real rate of these infections in the light of the purely clinical and non-laboratory diagnosis; nevertheless, according to recent estimates, respiratory infections caused by viruses are around 70% of bacterial ones are around 8%. In the context of viral etiology, according to the same data, *rhinovirus* and *coronavirus* would be responsible for 48% of all Acute Respiratory Failure [3].
In the bacteriological field, the percentage of ARI caused by bacterial agents ranges from 5% to 10%, and the most frequently recurring pathogens were: *Streptococcus pneumoniae, Streptococcus pyogenes, Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis, Mycoplasma pneumoniae and Chlamydia pneumoniae* [3].
In the previous season (2022-2023), the ERVISS surveillance network (Synthesis of European Surveillance on Respiratory Viruses) recorded respiratory diseases increase after the summer season, especially after September. In particular, the SARS-CoV-2 trend was characterized by an initial increase up to week 49, followed by a decrease that persists and the COVID-19 severe form has predominantly impacted individuals aged 65 and older. Regarding influenza, week 50 marked the start of the seasonal epidemic in European countries; both type A and type B influenza viruses have been detected, with a higher prevalence of A(H1N1) pdm09 virus in most countries. Unlike previous pathogens, *Respiratory Syncytial Virus* (*RSV)* activity began to increase around week 41, reaching a peak in week 50 followed by a decreasing trend and a greater impact among children aged between 0 and 4 years [4].
In Italy, in December 2023 it has been introduced a new integrated surveillance system (epidemiological and virological) called RespiVirNet represented the evolution of the Influnet and Influweb systems and has been launched to track and potentiate the isolation of viruses linked to influenza-like illnesses (ILIs, defined by the sudden and rapid onset of at least one general symptoms like fever or low-grade fever, malaise/exhaustion, headache, muscle pain and at least one of the respiratory symptoms such as cough, sore throat, labored breathing) and generally of all respiratory viruses. This system, based on general practitioners, pediatricians,

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and regional reference laboratories for respiratory viruses and coordinated by "Istituto Superiore di Sanità" (ISS) with the support of the Italian Ministry of Health, carried out dual surveillance, both epidemiological and the virological. In the latest Influnet report relating to the 2022-23 season, which is the period examined in our study, 27857 clinical samples were collected by the various laboratories with 22.4% (n= 6244) testing positive for the influenza virus (2% type A and 19.8% type B), 6.5% tested positive for SARS-CoV-2, and 21.8% for other respiratory viruses, mostly *RSV* (11.5%) and *Rhinovirus* (about 6%).

As of the time of this writing, the latest available RespiVirNet report is updated to the 4th of February 2024. Among 2781 samples received by laboratories connected to this network, 379 (13.6%) were found positive for *RSV*, 66 (2.3%) for SARS-CoV-2, and 95 (3.41%) for *Rhinoviruses*. Co-circulation of different respiratory viruses contributes to defining the incidence value of ILIs (8,53 cases for 1000 inhabitants); among them, the most prevalent ones were influenza viruses, RSV, SARS-CoV-2, and Rhinoviruses [5].

Every patient admitted to the ICU and/or subjected to ECMO, whose symptoms suggest a case of SARI or ARDS, must be reported via the notification form.

In particular, the definition of SARI (Severe Acute Respiratory Infection) provides hospitalized patient of any age with at least one respiratory sign or symptom (cough, sore throat, respiratory distress) present at the time of admission or in the 48 hours following admission to hospital and at least one systemic sign or symptom (fever or low-grade fever, headache, myalgia, general malaise) or deterioration of general conditions (asthenia, weight loss, anorexia or confusion and dizziness). The definition of ARDS, however, is based on the presence of hospitalized patient of any age with an inflammatory pulmonary syndrome, characterized by diffuse alveolar lesions and increased permeability of the pulmonary capillaries, with non-cardiac pulmonary edema, reduction of pulmonary compliance and bilateral pulmonary infiltrates spread to all segments, severe dyspnea, tachypnea, and cyanosis, despite the administration of oxygen [6].

Microorganisms' epidemiology and clinic

Adenovirus

More than 50 types of Adenoviruses are known to cause infections in humans. These viruses can affect different districts, such as the gastrointestinal (causing acute gastroenteritis) or ocular (causing conjunctivitis); when it affects the respiratory tree, the virus causes ILIs, up to and including bronchitis and pneumonia in severe cases. These infections occur with a seasonality most frequently in winter and spring, affecting the general population at every age group [7].

According to the RespiVirNet report 2024-14, Adenoviridae account for 6.1% of all identified ILIs not attributable to influenza viruses [8].

Human coronaviruses

As of today, seven human coronaviruses have been identified: four of them (229E, NL63, OC43, HKU1) cause an infection with symptoms ranging between the common cold and pneumonia/bronchiolitis; two of them (SARS-CoV-1 and SARS-CoV-2) are responsible for severe respiratory infections with very high transmissibility, and were responsible for the SARS epidemic in 2002-2004 and the COVID-19 pandemic in 2020-2023; the last one (MERS-CoV) causes respiratory ailments very similar to SARS, while transmissibility is influenced by interactions with diseased animals [9].

RespiVirNet 2023-2024 reports distinguish SARS-CoV-2 from other human coronaviruses: the prevalence of these, among the non-influenza viruses responsible for respiratory disorders, was quantified as 26.6% and 5.9%, respectively [8].

Human Metapneumovirus

The *Human Metapneumovirus* (HMPV) was discovered in 2001 and belongs to the *Pneumoviridae* family together with RSV. The symptoms caused by this virus are similar to those of other respiratory viruses, causing affections of the lower and upper respiratory tract, possibly leading to bronchitis or pneumonia. Its circulation is seasonal, occurring in winter and maintaining a detected infection rate until spring [10].

As reported in RespiVirNet's weekly report 2024-14, *Metapneumovirus* accounted for 6.9% of all 14,399 non-influenza respiratory virus identifications from week 2023-46 [8].

Rhinovirus

Rhinoviruses cause 30-35% of adult ILIs and represent the most common cause of Upper Respiratory Tract Infections (common colds), especially in school-age children, in whom 6-8 episodes may occur during the year. Nowadays more than 110 types of Rhinovirus have been identified with different antigenic properties and this great variety of viral antigens is responsible for the frequent recurrence of the infection. The most widespread transmission is via large airborne droplets, but transmission via small aerosolized particles has also been demonstrated. It is estimated that an infected patient is capable of infecting 75% of the members of a family or school group. Rhinovirus epidemics have been documented in indoor environments (such as schools, long-term care facilities, hospitals, neonatal healthcare facilities) and these pathogens are most active in the fall, spring, and summer, with an optimal temperature of 33°C (equal to that of the nasal mucosa) [11-14].

Influenza viruses

Seasonal influenza is a vaccine-preventable disease that each year infects approximately 10-30% of the European population and causes hundreds of thousands of hospitalizations across Europe.

Epidemics occur in the winter months in temperate locations and at different periods of the year in subtropical and tropical locations. Most influenza virus infections cause mild and self-limiting disease and around one-half of all infections occur with a fever. Older people, younger children, and those with chronic diseases have a greater risk of developing serious complications, such as pneumonia, myocarditis, and encephalitis that may result in death.

Four different types have been identified, all belonging to the *Orthomixoviridae* family:

- types A and B, responsible for classic flu symptoms;
- type C, usually asymptomatic;
- type D, whose possibility of infecting humans is not yet clear.

Influenza A viruses are further divided into subtypes based on molecular differences of the two surface glycoproteins (hemagglutinin and neuraminidase).

The typical influenza epidemiology arises from the marked tendency of influenza viruses to mutate (essentially with two mechanisms: antigenic drift and antigenic shift). This characteristic allows them to evade the host's immune response and therefore make the population more immunologically susceptible and for these reasons, the pathogens spread widely and rapidly.

These molecular variations are an important factor in the preparation of vaccines, whose composition must be updated every year, and, in this light, the surveillance activities are fundamental to selecting the specific strains to be included taking into account what has circulated in previous seasons.

According to the ECDC report the 2022/2023 influenza season marked the return of influenza virus activity at almost pre-pandemic levels in the EU/EEA countries. This season was characterized by an earlier start of the seasonal epidemic and an earlier peak in positivity compared to the four previous seasons [15-17].

Parainfluenza viruses

Parainfluenza viruses belong to the family *Paramyxoviridae* and they can infect terrestrial animals, aquatic mammals, birds, and some reptiles; they, also, include several viruses pathogenic to the human respiratory tract, similar in some aspects to influenza viruses. They differed from them in surface antigen characteristics and size. *Human parainfluenza viruses (hPIV)* are antigenically distinguished into 5 types: 1, 2, 3, 4A, and 4B. All of them cause respiratory infections in humans, although with different epidemiology and clinical picture [18]. *hPIV 1, 2*, and *3* are more prevalent than type *4*; in particular, *hPIV 1* and *2* are associated with "croup" (laryngotracheobronchitis) and upper and lower respiratory disease, while *hPIV 3* causes more bronchiolitis and pneumonia.

Parainfluenza viruses are ubiquitous, and they can infect adults, but the most affect children, in whom the virus results in more severe symptomatology (bronchiolitis, bronchitis, pneumonia). hPIVs, particularly serotype 3, are, after respiratory syncytial virus, the second cause of lower respiratory tract infections in newborns and infants [19, 20]. Forty-one percent of croup cases were associated with these viruses [19]; especially hPIV 1 and hPIV 2 (in lower percentage than type 1) were the most involved. Infection occurs early in life, and serologic data indicate that 50% of one-year-old children and 90% at 5 years have protective antibodies to hPIV 3, 75% to hPIV 1, 60% to hPIV 2, and 50% to hPIV 4 [18, 19]. The seasonality of infections differs according to serotype: hPIV 1 and 2 cause epidemics during autumn and winter; however, episodes of overlapping epidemics caused by the hPIV 1 and hPIV 2 subtypes are possible; hPIV 3 cause sporadic infections throughout the year with a peak in spring; hPIV 4 is present throughout the year but is infrequent and doesn't cause relevant symptoms. Clinically, parainfluenza viruses result in a broad spectrum of lower and upper respiratory tract symptoms: croup, bronchitis, and bronchiolitis were the most common symptoms in children, in addition to cases of coryza, otitis, and pneumonia. In non-immunocompromised adults, on the other hand, parainfluenza viruses lead to simple colds or rhinolaryngitis.

Chlamydia pneumoniae

This intracellular bacterium is a recognized cause of community-acquired pneumonia [21] and it has also been documented in patients with cystic fibrosis [22]. Recent studies have also linked *C. pneumoniae* to bronchitis and asthma [23]. Higher rates of infection were recorded in children compared to adults [24].

The spread of *C. pneumoniae* occurs through direct contact with an airborne transmission or indirectly through fomites [25].

There is currently a resurgence of *C. pneumoniae* infections, after an initial reduction in rates recorded during the SARS-CoV-2 pandemic [26].

Much *C. pneumoniae* infections go unrecognized because they typically manifest as upper respiratory tract infections, often with mild or no symptoms. There isn't typically a discernible seasonal pattern, and outbreaks tend to occur predominantly in crowded environments such as college residence halls and long-term care settings.

Bordetella pertussis and parapertussis

These pathogens cause respectively parapertussis and pertussis (whooping cough), which are highly infectious bacterial diseases involving the respiratory tract whose symptoms are like those of the common cold, including sneezing, runny nose, low-grade fever, and cough with different clinical evolution. Parapertussis is characterized by mild signs and symptoms.

Pertussis, notifiable in Italy, is characterized by epidemic cycles recurring every 2-5 years and represents a public health threat, given its re-emergence despite high vaccination coverage (94% in Italy among children of 24 months old in September 2022) [27, 28].

This resurgence may be attributed to several factors such as improved diagnosis methods, genetic changes in circulating BP, and increased bacterial circulation among adolescents and adults related to the waning of vaccine-induced immunity. Adolescents and adults are a reservoir for BP and the source of infection to unvaccinated newborns [29].

Furthermore, naïve children represent the most vulnerable group; in fact, literature detected the highest rates of morbidity and complications, such as hospitalization and intensive care unit (ICU) admissions and, consequently mortality. On the other hand, adolescents and adults tend to have a prolonged illness characterized by cough but without other severe symptoms [30].

The greatest disease burden was observed in the paediatric population, linked to the non-immunization or incomplete immunization during the first month of age. In fact, in California, during the 2010 outbreak, the highest rates of disease and hospitalization occurred in infants < 6 months old [28, 31]; in the UK, during the 2011-2012 outbreak, the highest incidence and mortality occurred in infants < 3 months old [32].

The pertussis incidence rate in the Italian population aged ≥ 5 years old reported by the ECDC in 2018 was 6.75 per 100,000 in the 5-14 age group and 0.28 per 100,000 in the ≥ 15 age group. In newborns and infants, *Bordetella pertussis* can cause or complicate bronchiolitis; in particular, bronchiolitis-associated morbidity and mortality are higher with concomitant *B. pertussis* infection. However, to date, the pertussis mortality rate in this age group is likely underestimated [33].

According to the systematic review by Macina et al., some comorbidities might increase the risk of developing pertussis. Three studies showed pertussis can lead to increased exacerbations of chronic conditions/illnesses and associated hospitalizations, although one study showed a reduction in the effects of chronic bronchitis. Previous pertussis seemed to contribute to the increased likelihood of developing some respiratory conditions like asthma, and conversely, people with asthma or COPD are at increased risk of severe pertussis requiring further interventions [34].

History of prematurity and an age of less than 3 months emerged as risk factors for the development of fatal pertussis [35].

Mycoplasma pneumoniae

Mycoplasma pneumoniae is a common cause of respiratory tract infections, representing community-acquired pneumonia as the major disease-related burden. Infections occur year-round in many different climates worldwide, with epidemics every few years.

The periodic occurrence of epidemics is due to many factors, including the decline of herd immunity or the introduction of new subtypes into the population. The most recent outbreak occurred in late 2019 and early 2020 simultaneously in several countries, predominantly in Europe and Asia. According to previous data the interval between *M. pneumoniae* epidemics in Europe was about 1-3 years.

In 2020 the introduction of non-pharmaceutical interventions (NPIs) against COVID-19 resulted in an abrupt ending of these epidemics and a marked decline in *M. pneumoniae* detection worldwide. In detail, there was a significant reduction in the incidence of *M. pneumoniae* from the pre-pandemic period to the first year after the implementation of NPIs (from 8.61% in 2017-20 to 1.69% in 2020-21), with similar values to the other respiratory pathogens incidence. This value decreased significantly in the second year (0.70%, in 2021-22), when other respiratory pathogens re-emerged as an indicator of community transmission [26].

Respiratory syncytial virus

Respiratory syncytial virus is a RNA virus and, until today, two subtypes are recognized, A and B: the first most related to more severe infections and the second one prevalent in pediatric age (10). RSV infection is typically seasonal, with viral circulation typically occurring in the winter period, peaking between December and February [36].

RSV infection generally causes a mild disease, but the severity of the clinical manifestations varies considerably based on age. The most severe forms of the disease are associated with the pediatric age and occur in children under five years of age (especially in infants younger than six months), adults aged 65 years and older and individuals with specific comorbidities [37].

RSV represents the second cause of death globally after malaria, the first cause of death among respiratory infections and the first cause of hospitalization in children under one year of age [38].

Premature infants or those born close to RSV season and/or with bronchopulmonary dysplasia or congenital heart disease have the highest risk of developing severe acute RSV and related lower respiratory tract infection (LRTI) [39]. Natural infection provides short-lasting immunity, so cases of reinfection are common, particularly those of the upper respiratory tract [40].

Nowadays there are no specific therapies for the treatment of serious RSV infections and the only authorized drug (ribavirin) is complex to manage due to safety issues of use [41].

Therefore, the treatment of severe forms of LRTI is more often limited to symptomatic therapies and supportive measures (hydration and oxygen); a fundamental role is played by primary prevention, given by hygienic-behavioral measures, such as the correct application of hand hygiene, sanitization, social distancing, and the use of monoclonal Abs such as Palivizumab (SYNAGIS) and Nirsevimab (BEYFORTUS) [42]. The first one was the only weapon available for the prevention of RSV infections until the end of 2022, but its indications were limited to children under 24 months of age who had certain conditions that exposed them to a high risk of severe RSV disease (such as ≤ 35 weeks of gestational age and with age < 6 months at the start of the seasonal RSV epidemic; age < 2 years treated in the last 6 months for broncho-pulmonary dysplasia; age < 2 years with hemodynamically significant congenital heart disease) [43].

Furthermore, one dose of Palivizumab provides protection that lasts approximately 1 month, making up to 5 doses of the drug necessary per season, with evident problems of complete adherence to the prescribed regimen and costs. The use of this monoclonal antibody for the protection of all newborns therefore clashes with insoluble organizational and economic problems [44].

In February 2023, a new monoclonal antibody, Nirsevimab (Beyfortus), was definitively approved by the European Medical Agency (EMA), which has advantages such as a long half-life (protection demonstrated for at least 5 months) and a schedule that involves a single administration (increased compliance). This medication is recommended for all infants younger than 8 months and born during – or at the beginning of – their first RSV season (typically fall to spring) and for some infants aged 8 to 19 months who are at high risk for severe RSV (severely immunocompromised or entering the second RSV season) [45].

Thanks to the availability of Nirsevimab, a universal prevention strategy for RSV diseases appears possible through administration to all cohorts of newborns in the October-March epidemic period, before hospital discharge and the catch-up of non-immunized newborns in the April-September period [46].

Another possible future preventive strategy could be the active immunization, using two prefusion F protein-based recombinant vaccines recently approved by the EMA to prevent LRTI in subjects over 60 years of age [47, 48].

The first authorized preparation (June 2023) (RSVPreF3 OA) is an adjuvanted RSV vaccine containing recombinant respiratory syncytial virus F glycoprotein stabilized in the pre-fusion conformation (RSVPreF3) as the antigenic component. From data in the literature, it emerged that single administration of the vaccine shows a satisfactory safety profile, with an efficacy of approximately 94.1% against severe RSV-related lower respiratory tract disease and 71.7% against RSV-related acute respiratory infection, regardless of RSV subtype and the presence of underlying coexisting conditions [47].

The second authorized preparation (EMA August 2023) is a bivalent vaccine, containing balanced quantities of stabilized prefusion (preF) antigens derived from the two primary subgroups of RSV (RSV A and RSV B), which demonstrated 67% effectiveness in reducing the likelihood of developing RSV-associated lower respiratory tract disease (LRTD) among older adults with two or more symptoms and 86% in reducing the risk of RSV-associated LRTD among individuals with three or more symptoms [48].

This vaccine could be also indicated in mothers during pregnancy (between weeks 24 and 36 of gestation) to protect their children from LRTI (from birth to 6 months of age) [49].

In the final weeks of 2022, the circulation of respiratory syncytial virus (RSV) in the EU intensified, with transmission rates increasing in all population groups and an earlier onset than the usual one [50].

Several EU countries have reported high circulation of RSV and an increase in the number of severe acute respiratory infections (SARI) due to it [50].

Given the growing circulation of RSV and the shortage of available weapons, the ECDC has identified the implementation of surveillance and monitoring systems as one of its priority objectives wherever possible.]. In particular, the specific objectives of the study were to evaluate the circulation of respiratory pathogens in our reality which required hospitalization or access to the emergency/urgency system [50]; we hypothesized that the pandemic period made an important contribution to the epidemiology of respiratory pathogens and we would like to evaluate it.

Methods

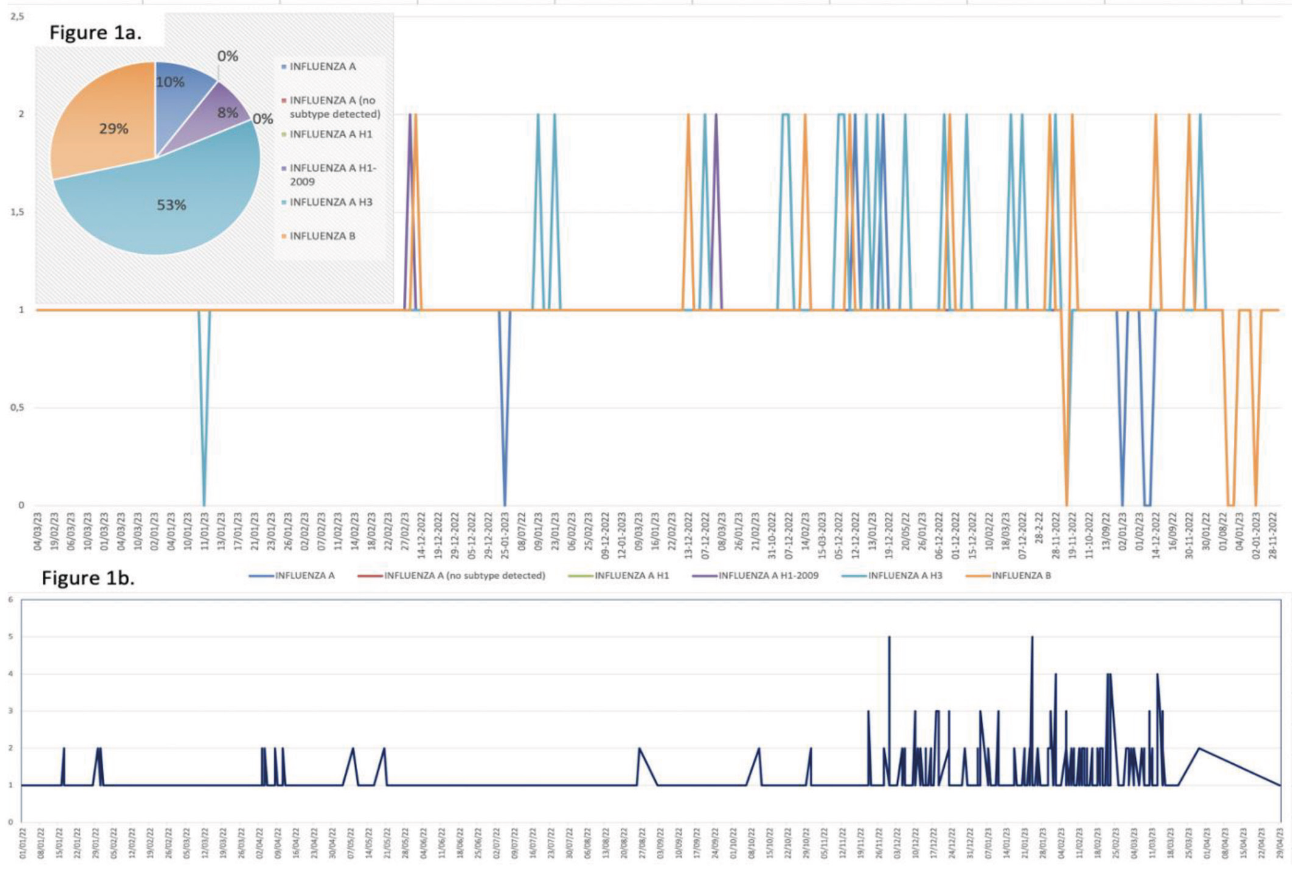
A retrospective and monocentric study was conducted, thanks to the collaboration between the Hospital Hygiene Unit and the Microbiology Unit of the University Hospital "G. Martino" of Messina; this study analyzed the prevalence of the various respiratory pathogens found in a cohort of 1286 patients belonging to the several units of our hospital from January 2022 to May 2023 and who carried out a nasopharyngeal swab subsequently analyzed using FilmArray (Biofire RP2.1 by Biomerieux which detects the presence of 19 viruses (*Adenovirus, Coronavirus HKU1, Coronavirus NL63, Coronavirus 229E, Coronavirus OC43, Human Metapneumovirus, Human Rhinovirus/Enterovirus, Influenza A, Influenza A/H1, Influenza A/H1-2009, Influenza A/H3, Influenza B, Parainfluenza 1, Parainfluenza 2, Parainfluenza 3, Parainfluenza 4, Respiratory Syncytial Virus*, SARS-CoV-2 (2019-nCoV), MERS-CoV) and 4 bacteria (*Bordetella pertussis*, *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae*, *Bordetella parapertussis*). This test allowed the qualitative detection of the nucleic acid of viruses and bacteria in nasopharyngeal swab samples; it is an integrated platform that combines automated sample preparation, total nucleic acid extraction with nested multiplex PCR and reverse transcriptase PCR, and automatic detection of amplified targets. The FilmArray test used in this study has a sensitivity of 95% and a specificity of 98% for detecting respiratory pathogens and we choose it for this reason respect to other methods.

Inclusion criteria: participants were included if they met the following criteria: they were 18 years or older, undergoing nasopharyngeal swabs, and were able and willing to provide informed consent.

We choice the FilmArray (Biofire RP2.1 by Biomerieux) platform for pathogen detection because it enables simplified test ordering, faster turnaround times, and increased accuracy by minimizing manual data entry.

The data were collected in a structured database. The qualitative data were expressed as absolute and relative frequencies, while the quantitative data were expressed as mean, minimum, maximum, and standard deviation values. The results were stratified according to age, gender, and the number of possibly coexisting pathogens. Furthermore, the temporal trend of the various pathogens in the years under examination was analyzed. Statistical analysis was conducted using Stata software. The

Fig. 1. Seasonality and trend in the number of infections by month for Influenza viruses (Fig. 1a) and RSV (Fig. 1b).



number of co-infections was investigated by stratifying the sample by age and sex. Seasonal trends of each pathogen were also evaluated. Statistical differences in the prevalence of positive samples among pediatric, adult, and elderly patients were assessed."

Results

Our sample consisted of 1286 individuals, aged between 1 month and 99 years (mean age 52.45 ± SD 30.89). The sample was predominantly male (53.92%).

The most frequently isolated pathogens were:

- SARS-CoV-2 (13.76%), is more frequent in males aged between 1 and 17 years;
- Human Rhinovirus (11.35%), is more frequent in males aged between 0 and 16 years;
- RSV (9.10%), is more frequent in patients aged between 0 and 14 years, with equal distribution between genders.

The seasonal trend of each pathogen was also evaluated. For two of the most frequently found pathogens in our sample, *Human Rhinovirus* and *RSV*, the typical seasonality of respiratory viruses was observed, with the highest number of cases occurring from December to March. The trend observed in previous years was also confirmed for SARS-CoV-2.

The infection trends over the two years were analyzed, as shown in Figure 1.

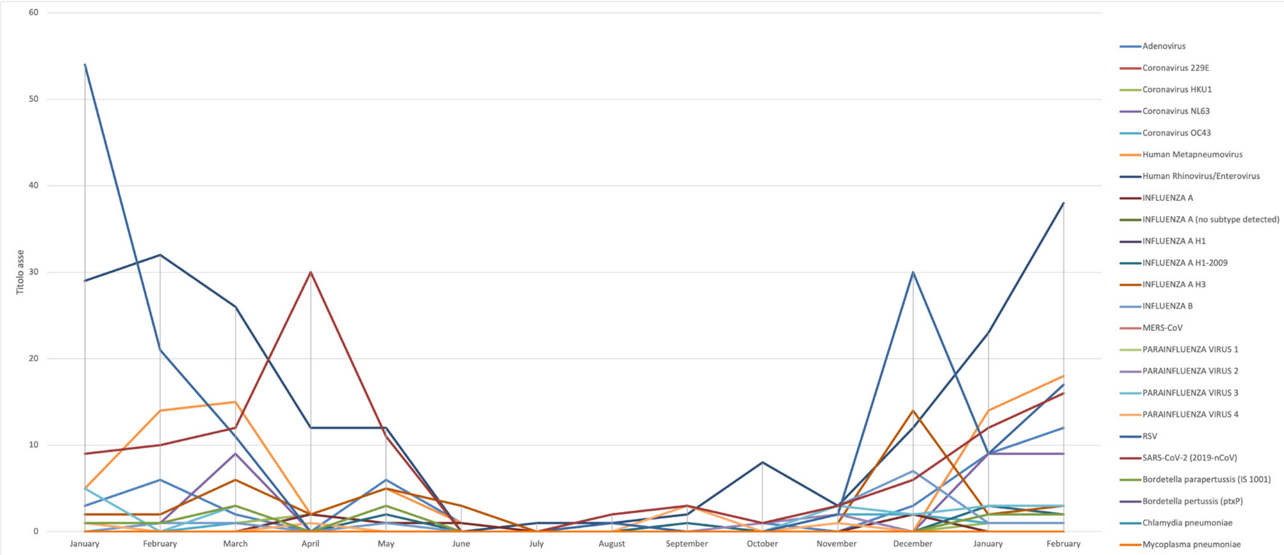
The use of masks and the implementation of isolation and prevention measures to avoid the spread of SARS-CoV-2 led to a reduction in the number of infections.

We also evaluated the presence of statistical differences in the prevalence of positive samples among pediatric, adult, and elderly patients. Significant statistical differences were found (p value = 0.001), with higher prevalence of SARS-CoV-2 in elderly and pediatric patients, and higher prevalence of RSV only in pediatric groups (Tab. I).

Tab. I. Respiratory virus prevalence by age groups.

Age groups	SARS-CoV-2	RSV	Rhinovirus	p value
< 14 years old	5,06%	82,26%	63,52%	0.001
15-64 years old	38,20%	4,84%	20,13%	
>64 years old	56,74%	12,90%	16,35%	

Fig. 2. Seasonality and trend in the number of infections by months for all respiratory pathogens investigated.

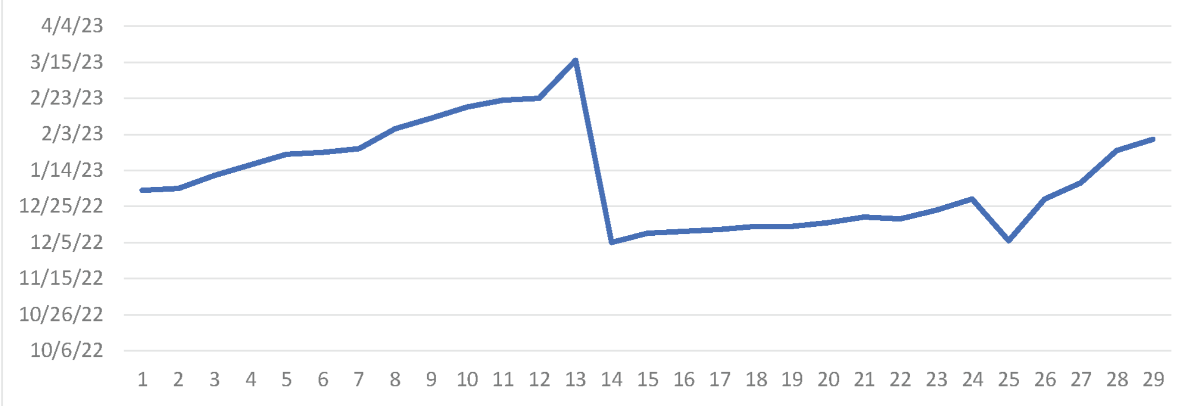


The highest percentage of RSV infections was found in the winter period, with an early peak in November (Figs. 1b, 2).
Another data to highlight was the presence of a high prevalence for some bacteria such as *Bordetella parapertussis*, especially in children under 2 years of age (66.67%). No detection of *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* was found with an emerging role of *RSV* infection in determining cases of bronchiolitis and pneumonia.
In 14.1% of cases, co-infections were found, predominantly affecting both sexes in the 0-4-year age group. Notably, two patients had five pathogens isolated simultaneously. Furthermore, the number of co-infections was investigated by stratifying the sample by age and sex. From the analysis of the data, it can be seen that the highest percentage of co-infections was detected in the male sex and the age period between 1 and 4 years (mean age = 2.65 ± 2.5 SD; 66% male sex).
The temporal trend of co-infections was also analyzed, with a major peak recorded from November 2022 to March 2023 (see Fig. 3). We detected a value of about 14% of coinfection, especially in pediatric patients (0-4 years); the most frequent coinfection were SARS-CoV-2, RSV, and Rhinovirus.

Discussion

In agreement with national data, our analyses have revealed a greater circulation of the Respiratory Syncytial Virus [5, 11-14]. In our study RSV was the most frequently isolated virus after SARS-CoV-2, influenza A H1N1 virus, and rhinoviruses. Viral and bacterial co-infections were observed in 14.1% of cases, predominantly in children aged 0-4 years. Further studies are needed to understand the interaction between different pathogens and their impact on disease severity." However, these data confirm some recent studies, according to a recent systematic review of the literature in which the authors found 35-40% of pediatric subjects affected. The role of viral-coinfections remained unclear in the severity of RSV-associated respiratory diseases, but several systematic reviews suggested that there isn't an association between disease severity and viral co-infections [51].
In our study, among the epidemiological characteristics, a greater prevalence emerged in the male sex as reported by other authors [52, 53]. However, other studies in the literature have reported a higher prevalence in females [54]. Other epidemiological factors investigated were age and seasonality. The greater prevalence was detected in younger patients, confirming available national data about an higher prevalence in patients under 5 years of age, especially in the presence of comorbidities (*i.e.* bronchopulmonary dysplasia and congenital heart disease, low birth weight) and/or risk factors (preterm birth, artificial breastfeeding, *etc*.). However, older adults and people living with underlying diseases are known to be at a higher risk of respiratory infections, RSV and flu [55]. The peak of the RSV in November that we detected correlates with a recent systematic review of the literature, showing an early temporal peak in December [56].
We found higher values of detection for SARS-CoV-2 in elderly and pediatric patients and for RSV only in pediatric ones ($p < 0.001$), confirming data of a recent systematic review [57].
Another important result of our study is the use of FILMARRAY as a diagnostic tool to facilitates patient management and guide clinical decisions. It has been demonstrated that its use improves the clinical outcome, reducing the use of antibiotics and ICU admission [58]. Another study using this method showed a concordance

Fig. 3. Temporal trend of coinfections.



in defining an early RSV peak in November in the pediatric analyzed population [59]. Furthermore, the resumption of seasonality for RSV indicates how the precautionary measures used have had a major impact on the circulation of RSV and how the application of barrier measures is fundamental in the management of airborne microorganism outbreaks and epidemics [60-67].

RSV detections are less frequent during periods of high influenza activity and RSV incidence may peak 1-2 months earlier [68]. Dynamics such as these make it more difficult to reliably predict the epidemiological trends of ARIs and ILIs. A recent effort in this direction has been set up by the ECDC, with the launch of RespiCast, a platform for real-time forecasts of respiratory disease activity and burden [69].

Although it doesn't focus specifically on RSV, the forecasts provided by this system may help public health workers in drafting an effective prevention campaign.

The coronavirus disease 2019 (COVID-19) pandemic has drastically disrupted the epidemiology of Respiratory Syncytial Virus (RSV) respiratory tract infections in children. Proposed mechanisms include decreased viral immunity in vulnerable age groups caused by the prolonged lack of RSV circulation early in the pandemic, potential SARS-CoV-2-induced immune dysregulation, viral interactions between SARS-CoV-2 and RSV, and modifications in health-seeking behaviors as well as health systems factors [70].

The compilation of precise epidemiological data is also made difficult by a surveillance system against RSV that still needs work. Several European countries still only rely on estimates regarding the burden and incidence of infection [71].

One study examined Belgium's RSV surveillance network and highlighted its inability to accurately predict the epidemiological circulation of the virus. Systems to detect the hospital burden of RSV infections are suggested, with more sentinel hospitals and collection of the treated patients are suggested [71].

As stated previously, the recent approval of vaccines against RSV opens up new scenarios for its prevention. Protection from RSV in newborns will be provided by the administration of the vaccine in pregnant women or by the inoculation of monoclonal antibodies into the child. This approach was tested in a Luxembourg study, where Nirsevimab was administered to 84% of those born between October 2023 and January 2024. The monoclonal antibody was found to be statistically significantly associated with a reduction in hospitalizations, hospital length of stay, and an increase in the mean age of RSV-related cases [72]. In light of these premises, it will be necessary to formulate a new approach that takes into account the peculiarities of each patient group to make the most advantageous choice from an economic and social point of view.

The potential use of one of the two vaccines against RSV during pregnancy clashes with the vaccination hesitancy wall of this population which is very doubtful and sensitive to this topic.

A recent systematic review showed that the source of vaccination information (specialized healthcare worker, family doctor, mass media, non-professionals) is among the main determinants of vaccination hesitancy in pregnant women [73]. The role of the healthcare workers thus becomes increasingly crucial in communicating and responding to patients' doubts, taking care not to downplay their concerns.

Another population that will greatly benefit from the introduction of an effective vaccine is the immunocompromised. RSV was shown to be the fourth most prevalent microorganism in a study investigating transplanted subjects presenting respiratory symptoms [74]. More specifically, patients who had received a hematopoietic stem cell transplant acquired the infection in the nosocomial environment in 50% of cases, a significantly higher percentage than the general population; solid organ transplant recipients, on the other hand, had an incidence of RSV infection of 6-16% [75].

Limitations of the study: one major limitation of our study is its single-center design, which may limit the generalizability of the findings. Additionally, the exclusive use of molecular diagnostics may underestimate the true co-infection rates. Furthermore, the impact of the COVID-19 pandemic on the ARI trend could limit

the results of this study. Moreover, potential biases in Data Collection and Analysis could be discussed.
The COVID-19 pandemic significantly altered the patterns of respiratory infections due to several factors such as lockdowns, social distancing, mask-wearing, changes in healthcare-seeking behavior, and healthcare system priorities. These changes likely led to an underreporting or delay in diagnosing ARIs (Acute Respiratory Infections) and RSV (Respiratory Syncytial Virus) cases during peak pandemic periods. There is also the potential for biases related to immune interactions between SARS-CoV-2 and other viruses (such as RSV), which may have led to atypical patterns of coinfections and viral suppression. The potential immune dysregulation caused by SARS-CoV-2 infection could also have skewed data, leading to inconsistent results that do not align with pre-pandemic trends. A single-center study may not fully capture the diverse epidemiological dynamics of RSV and ARI trends across different geographical locations or healthcare settings. This limitation affects the generalizability of the findings and creates a bias towards the specific population and setting studied. Solely relying on molecular diagnostics (like PCR) can result in biases, as it might underestimate the true rates of viral and bacterial co-infections due to variations in test sensitivity and specificity. Diagnostic methodologies may also differ across studies, affecting the consistency of results and comparisons. Age, gender, seasonality, and comorbidities were identified as influential epidemiological factors. However, there is variability in findings across different studies - for instance, discrepancies in the prevalence of RSV between male and female subjects or the specific age groups most affected. This variability might reflect underlying biases in study design, population demographics, or other unmeasured confounding factors. Changes in health-seeking behavior during the pandemic and modifications in healthcare delivery (*e.g.*, telemedicine vs. in-person visits) could have influenced the detection and reporting rates of RSV and ARIs. Such systemic changes may introduce biases in the dataset, particularly in the assessment of disease burden and the effectiveness of preventive measures.

Conclusions

Although national and European data show an increase in the virus's circulation level, only a small number of subjects with acute respiratory symptoms were tested for RSV. A growing body of evidence demonstrated that perfecting the surveillance system would certainly guarantee a more correct characterization of the epidemiology, contributing to the more appropriate use of medical and pharmacological resources. In most European countries, RSV is not a mandatory reportable disease. However, in 2018 the World Health Organization deemed it appropriate to activate a surveillance system for cases of RSV infection, with particular attention to children under 2 years of age and patients requiring hospitalization, to improve the microbiological diagnosis criteria and precisely outline the characteristics of seasonality, risk groups and spread of the infection.
A significant proportion of studies are likely to underestimate the incidence of RSV infection in older adults, although the effect size is unclear and there is also potential for overestimation. Well-designed studies, together with increased testing for RSV in patients with ARI in clinical practice, are required to accurately capture both the burden of RSV and the potential public health impact of vaccines [76].
Our study sheds light on the burden of RSV-related infections on our local reality. Although the general population was examined, it is the youngest children who are most affected by RSV. As highlighted by data in the literature, our study confirms an early RSV peak in November. The winter seasonality of the disease revealed by the study also argues for more preventive care for those born in this period. The role of viral co-infections in which RSV is involved should be further investigated [77-82].
Our study highlights the need for enhanced surveillance strategies for respiratory infections. We recommend more rigorous preventive measures, such as influenza vaccination and improved hygiene practices.

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Informed consent statement

Informed consent was obtained from all subjects involved in the study.

Conflicts of interest statement

The authors declare no conflicts of interest.

Authors' contributions

For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used: Conceptualization, CG and RS; methodology, CG; software, CG; validation, all authors; formal analysis, all authors; investigation, GG, CG, RS; resources, GG, CG, RS; data curation, GG, CG, RS; writing-original draft preparation, GG, CG, RS; writing-review and editing, GG, CG, RS; visualization, GG, CG, RS; supervision, GG, CG, RS; project administration, GG, CG, RS; funding acquisition, no one. All authors have read and agreed to the published version of the manuscript.

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