Respiratory syncytial virus: Common yet unknown

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Every year, millions of infants are infected by a little-known virus that is the most common cause of respiratory disease in children. Respiratory syncytial virus (RSV) (**Fig. 1**) causes a spectrum of respiratory illnesses in infants and young children that may lead to hospitalisations and a substantial number of outpatient visits, which result in a huge personal, economic and healthcare burden. Most hospitalisations happen in otherwise healthy infants born at term, demonstrating the need to protect all infants against RSV.

The World Health Organization estimates indicate that worldwide, RSV accounts for more than 60% of acute respiratory infections in children and more than 80% of acute respiratory infections in infants under 12 months of age. RSV is by far the most frequent cause of paediatric bronchiolitis and pneumonia, is a leading cause of hospitalisation in the first year of life and places a considerable burden on families and already-stretched healthcare systems[1].

Globally, in 2015, there were approximately 12 million episodes of RSV lower respiratory tract infections (LRTI), resulting in 2.3 million hospitalisations and 43,800 deaths in neonates and infants under 12 months of age, demonstrating the significant burden RSV causes in the first year of life[2]. In 2019, there were an estimated 33 million episodes of RSV-associated LRTI (such as bronchiolitis and pneumonia) in young children globally and 3.6 million RSV-associated acute LRTI hospital admissions (**Fig. 2**). These statistics, and many others like them, demonstrate that this common pathogen is a major public health concern[3]. The burden of disease caused by RSV is undoubtedly large, but is not fully described due to inconsistencies in surveillance, particularly in the outpatient setting.

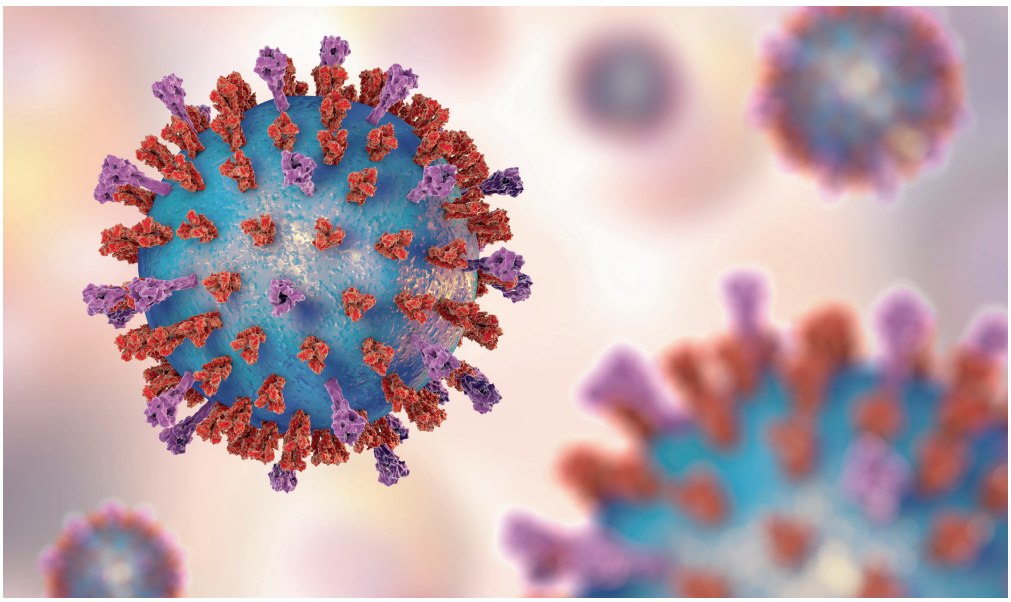

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Figure 1. An illustration of respiratory syncytial virus.

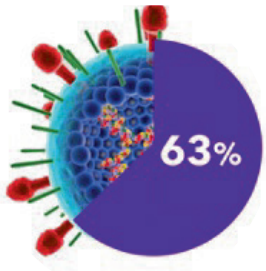
RSV has been recognized as a global health priority and at Sanofi, a company with a known commitment to advancing science in vaccines and preventative solutions, we demonstrate our determination to help tackle this public health need with our extensive pipeline, which includes several candidates for the prevention of RSV.

TRANSMISSIBILITY AND PUBLIC HEALTH CONCERNS

RSV is a common respiratory pathogen that causes disease throughout life, particularly in the early years and especially in infants under 12 months of age. Different modes of transmission are possible, with the most recurrent being through inoculation of the nasopharyngeal or conjunctival mucosa with respiratory secretions from infectious individuals[1]. Infection from respiratory secretions involves close or direct contact with large droplets or fomites. The virus can survive for up to 6 hours on hard surfaces and for several hours on fomites, it remains viable for 90 minutes on rubber gloves and 20 minutes on the surface of the skin. The prolonged potential for the virus to survive highlights the need for non-pharmaceutical interventions to reduce the transmission, such as handwashing and contact precautions to limit the spread of infection. The incubation period ranges from two to eight days and individuals can shed the virus for up to three weeks[1].

RSV is highly contagious and transmissible, with a mean Ro of 4.5, meaning that one infected subject can spread the virus to 4.5 other individuals[4]. RSV circulates with ease, particularly in locations in which infants are in close proximity to others, such as daycare settings or with siblings and family who may be mildly infected or asymptomatic.

Previous infection with RSV does not convey persistent



of acute respiratory infections in infants worldwide are due to RSV

Figure 2. Infection rate of respiratory syncytial virus (RSV)[1,2] and acute respiratory infections due to RSV[1,4].

immunity, even in the presence of significant antibody levels. Consequently, subsequent infection is common, and can recur within the same viral season across all age groups[1]. Long-term immunity to the virus does not develop and as a result, children and adults can be reinfected throughout life, although their risk of hospitalisation decreases significantly with age. The first episodes of infection (typically during the first two years of life) tend to be the most severe because of limited immunologic protection, smaller airway size and the structural and functioning features of the developing respiratory tract in younger age groups[1].

RSV infection is extremely common and is the most frequent cause of respiratory disease in children, with up to 90% of infections occurring before a child reaches its second birthday (**Fig. 3**). Around 75% of babies will be infected with RSV before their first birthday. For many, infection causes mild upper respiratory tract illness that resembles the common cold, but in up to 40% of infected children the disease progresses to an LRTI such as bronchiolitis or pneumonia[2]. It is estimated that 50–90% of hospitalisations for bronchiolitis in infants and up to 40% of hospitalisations for pneumonias in children are caused by RSV[5].

Pneumonia is a more commonly known name for an infection in one or both lungs. Bronchiolitis is a term used to describe a process of inflammation in the smallest airways of the lungs and is commonly caused by RSV. This inflammation causes swelling and increased production of mucus that can block the airways and make it harder for the baby to breathe. Infants under 12 months of age have the smallest aperture airways and this leaves them especially vulnerable to severe disease that may require hospitalisation.

Certain high-risk groups are more prone to develop severe RSV and to be hospitalised due to RSV LRTI. They include infants born prematurely (8% of newborns in the United Kingdom), babies with congenital heart disease or chronic lung disease and newborns with a low birth weight. Some other factors can have an impact on the severity of the RSV infection, including winter births, exposure to tobacco smoke and malnutrition[6].

Although babies in high-risk groups are more likely to end up hospitalised due to an RSV LRTI, the majority of hospitalised babies are born at term and have no pre-existing medical conditions[6]. Premature babies account for 19% of the total RSV cost burden in the United Kingdom, whilst the RSV cost burden for babies born at term is 4 times higher[7].

SYMPTOMS RANGE FROM MILD TO SEVERE

The manifestations of RSV can vary widely in severity, depending on the child's age, comorbidities, environmental exposures and history of previous infections. Typically, the infection starts with signs and symptoms of mucosal inflammation and irritation of the upper respiratory tract (blocked, runny nose, and sneezing). Symptoms can evolve to include the lower respiratory tract, manifested by cough, and greater effort breathing as accessory respiratory muscles are recruited to overcome the increased resistance of obstructed airways[1]. Children affected by RSV-associated bronchiolitis in early life may be more at risk of developing asthma during childhood and to suffer from long-term wheezing and reduced lung function[1]. Although among children the impact of RSV is much greater than that of influenza, the virus is much less known outside healthcare circles.

Christine is a mother of two. Both of her babies were healthy and born at full term and both suffered with RSV infections: "When I had my children, I wish I had general information about RSV, the warning signs and prevention. You really don't know what you don't know. If you aren't aware of RSV and how it can seriously affect your baby, you really wouldn't know what to look out for. Education and keeping an open dialogue between parents and their health care provider are just so important."

PREDICTABLE EPIDEMICS

Studies[8] have found that the seasonality of RSV in temperate climates is largely stable over time, with most countries experiencing a distinct peak in RSV cases in the winter.

Temperate countries in the northern hemisphere generally experience the start of the RSV season between September and January (median start of epidemics consistently occurred in December or January and ended in February or March) and those in the southern hemisphere between March and June, closely aligned with colder temperatures[8]. The seasonality

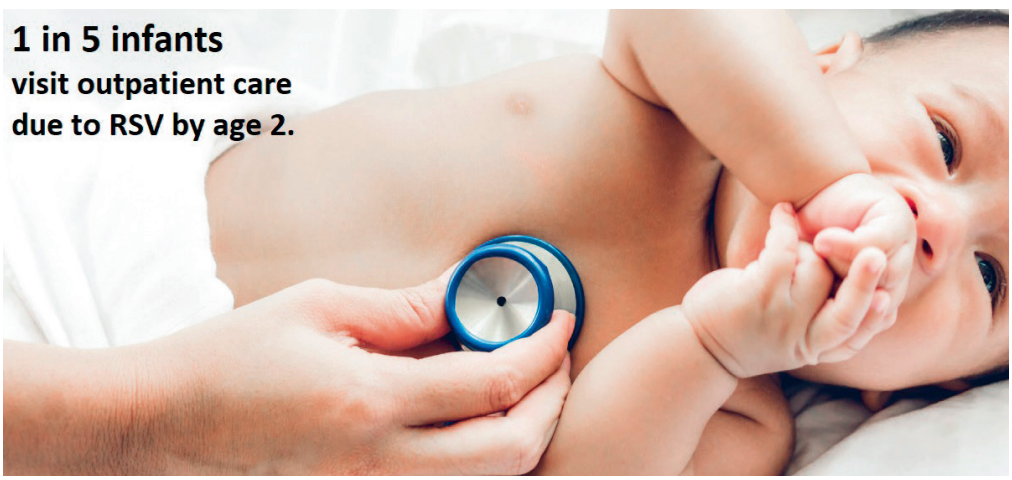


Figure 3. Infection with respiratory syncytial virus (RSV) is extremely common, with up to 90% of infections occurring before a child reaches its second birthday.

Barbara Lacassagne

Figure 4. Respiratory syncytial virus remains the leading cause of hospitalizations in all infants and young children.

of RSV in (sub)tropical climates appears less consistent, with some studies indicating that the peak of RSV epidemics is closely aligned with the rainy season; while others have found increased RSV activity with higher temperatures[8]. Additionally, studies have explored the impact of RSV subtype dominance on seasonality, but the association between an RSV A- or B-dominant season and the timing of epidemics remains unclear[8]. In Europe, most countries showed stable seasonality both nationally and comparatively, with all epidemics in the Netherlands, Spain and Portugal starting in December and a median epidemic duration of 10 or 11 weeks[8].

In the United States, United Kingdom, France and Germany, RSV infection is a clearly identified winter virus, usually occurring within the period between October and March. Whilst the timeframe can vary slightly from year to year, it has been historically accepted that this five-month duration is the RSV season[9]. The predictable seasonality of RSV infection was impacted by the non-pharmaceutical interventions implemented during the early peaks of COVID-19. During the course of the pandemic, interventions such as wearing masks, physical distancing, lockdowns (including the closure of high transmission settings such as daycare and schools) and increased handwashing, limited the circulation of respiratory pathogens. Indeed, the prevalence of respiratory pathogens other than SARS-CoV-2 decreased significantly during this time[10]. Although the seasonality of RSV circulation continues to be disrupted in some regions, the pattern of predictable epidemics is beginning to return, with peaks occurring during the winter months in temperate regions and predominantly affecting children under the age of one.

Having a better understanding of RSV epidemics is important to ensure the optimal timing of prevention and control measures and is relevant because previous generalizations regarding the seasonality of influenza infection have resulted in suboptimal vaccination strategies, which would be especially problematic in the case of RSV where the administration of a prophylaxis is often more time sensitive. As such, increased awareness of the timing of RSV epidemics ensures that optimal levels of protection are achieved in a maximally effective manner. In addition, better knowledge of the timing of RSV activity will allow health care providers to better prepare and manage limited resources, which are often stretched in the winter months, in an efficient manner.

The most effective tool for deeper insight into the seasonality of RSV is widespread viral surveillance. Although some surveillance systems are in place these are not always consistently rolled out, especially in primary care settings.

A LEAD CAUSE OF HOSPITALISATION

In high-income countries, RSV is the leading cause of hospitalisation in children. In the United Kingdom, RSV-attributable disease is estimated to result in between 20,000 and 30,000 hospitalisations every year[11], which is significantly higher than for influenza (**Fig. 4**). The majority of hospitalisations are infants who were previously healthy and were born at term. The pattern is replicated across other high-income countries. For example, in France, RSV causes on average, 45,000 hospitalisations per year, of which 69% are in infants under 12 months of age, which represents nearly 30% of hospitalisations in this age group[12].

Studies conducted in the United States have shown that in infants under the age of 1, the rate of hospitalisation per 100,000 is more than 10 times higher for RSV than for influenza and even this may be an underestimation (**Fig. 5**)[14].

RSV-RTI caused between 4,131 and 34,996 bed days annually in Scotland, England, the Netherlands, Finland, Denmark and Norway, and 2,817 bed days annually in the Veneto region of Italy. Between 70% (Norway) and 89% (the Netherlands) of these bed days were in infants <1 year. After accounting for country population statistics, RSV-RTIs were associated with 9.9 to 21.2 bed days per 1,000 children under 5 years annually, 40.3 to 91.2 bed days per 1,000 infants aged <1 year annually, and 1.1 to 7.1 bed days per 1,000 children aged 1–4 years[13]. Compared to hospital admissions for other respiratory tract infections, the annual number of bed days for RSV-RTI admission was 1.5–3.5 times higher in children under 5 years of age across the countries[13].

The average length of stay in a hospital for a child with a respiratory tract illness is between two and four days[13], which can have a considerable impact on both healthcare resources and family life.

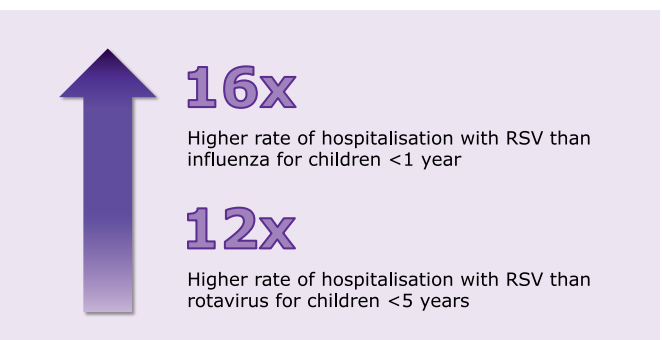


Figure 5. Rate of hospitalisation[14] with respiratory syncytial virus (RSV) versus other viruses in the United States from 1993 to 2008. Rotavirus-associated hospitalization and emergency department costs and rotavirus vaccine programme impact[15] in the United States 2003 to 2009.

BURDEN BEYOND THE HOSPITAL

RSV places a significant burden on outpatient care. The true impact of the virus in the community is hard to quantify with precision because of low rates of viral testing outside the hospital setting. Nevertheless, in the United Kingdom alone there were an estimated 450,000 general practitioner appointments per year attributable to RSV[7]. These appointments translate not only into pressure on healthcare systems already stretched during winter, but also loss in productivity because of caretaking responsibilities.

Based on data for 2019, the RAND Corporation estimates that the annual healthcare costs and productivity losses to the United Kingdom economy resulting from RSV in children younger than five years of age totalled approximately £80 million (in 2020–2021 price terms), equivalent to a mean total cost per child under five years presenting to the National Health Service with RSV of £97.

Approximately 80% (nearly £65 million) of the total annual cost is attributable to direct healthcare costs (for example, hospital admissions and outpatient attendances). However, more than £14 million is due to productivity losses and about £1.5 million to parents/carers' out of pocket costs[7]. Equally important is the significant emotional impact of illness and hospitalisation on parents and caregivers.

In addition to hospitalisation and broader healthcare costs, there is a potential impact from RSV on long-term health and quality of life. Respiratory issues can persist for an extended period after the RSV infection has resolved, manifesting as wheezing or coughing. While the evidence suggests a possible link between RSV in childhood and later development of other health issues (such as asthma), the level of risk and the most at-risk groups are not clear from the reviewed literature[7].

For some conditions, such as asthma, estimates of the effect of RSV on morbidity varied across studies and age groups. An international review from 2016 notes that recurrent wheezing may be up to three times higher for children with a history of RSV disease than children with no RSV history[7].

Evidence from studies in Sweden also suggests a link between RSV in early years and childhood asthma, suggesting that the risk is nearly 22 times higher at 13 months follow-up, 5 times higher at 13 years follow-up, and 4 times higher at 18 years[7].

Unfortunately, RSV can be fatal in some cases. It is estimated that an average of 33 children under five years old die from RSV in the UK each year[7].

TREATMENT AND PREVENTION

There is no effective specific drug treatment for RSV and as a result, the mainstay of management for infants with RSV bronchiolitis is supportive care. This may range from symptomatic relief with over-the-counter medication, to supportive care in hospital with nasal suctioning and nebulized supplemental oxygen, intravenous fluids or invasive ventilation[17].

Criteria for hospitalisation may include low oxygen saturation (<90-92%), moderate-to-severe respiratory distress, dehydration and involuntary pauses in breathing[16].

Infants hospitalized with RSV bronchiolitis often have decreased nutritional intake due to fever, respiratory distress and fast breathing, and may need fluid and nutritional support. This may mean that babies with severe RSV require fluid or nutritional support either through a nasogastric tube or intravenously[1]. There is no evidence to support the use of bronchodilators, corticosteroids, chest physiotherapy, antibiotics or antivirals[16].

Most infants who are hospitalised with disease caused by RSV were previously healthy and were not born prematurely[6]. This makes predicting which infants will be most severely affected challenging and leaves the majority of the infant population unprotected against the virus. The development of prevention strategies against RSV for all infants entering their first RSV season constitutes a large unmet medical need.

RSV IN CONTEXT

RSV is a relatively unknown pathogen that causes significant annual healthcare disruption and results in more hospitalisations than any other cause in infants. Awareness amongst healthcare practitioners and the public is crucial, as is the availability of preventatives and therapeutics. The unpredictability with which this virus causes severe disease and hospitalisation means that interventions must be broad and cover the entire population of infants who are at risk every winter.

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