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Unit No. 1

RESPIRATORY SYNCYTIAL VIRUS (RSV) – PUBLIC HEALTH IMPACT AND PREVENTION STRATEGIES

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ABSTRACT

Respiratory Syncytial Virus (RSV) is one of the most important respiratory pathogens that causes both upper and lower respiratory tract infections across all age groups. Worldwide, it is the leading cause of childhood hospitalisation, causing a significant health and economic burden. In young children, the first RSV infection may cause severe and possibly fatal bronchiolitis. RSV is also increasingly recognised to be a cause of severe lower respiratory tract infection in adults. It results in significant cardiorespiratory complications and mortality, especially in the frail and elderly and those with certain co-morbidities. Recurrent RSV infections are common throughout life as the immune response elicited by RSV is weak and short-lived. Therefore, prevention strategies including hand hygiene and monoclonal antibodies as prophylaxis are important. After several decades of research, there are now RSV vaccinations available for adults aged 60 years and above as well as for pregnant women to prevent severe RSV disease in infants through passive immunity.

Keywords: Respiratory syncytial virus, health impact, economic impact, prevention, vaccine

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INTRODUCTION

Overview of RSV, Seasonality, Clinical Manifestations

Human RSV was first isolated from chimpanzees in 1956.[1] It is a non-segmented, single-stranded enveloped RNA virus that belongs to the *Paramyxoviridae* family. A protein on the surface of the virus, which is named the F protein, causes cell membranes of two or more nearby cells to fuse and form a large cell structure called a syncytia. This is the structure from which RSV derives its name.[2]

Figure 1. Structure of the respiratory syncytial virus (RSV) virion. RSV is an enveloped virus with eight known structural proteins. The fusion protein (F), the attachment glycoprotein (G), and the small hydrophobic protein (SH) are located on the surface of the virion. The ssRNA genome and the remaining viral structural proteins, which are the matrix (M), the nucleocapsid (N), the RNA-dependent RNA polymerase (L), the phosphoprotein (P), and the M2 gene product M2-1, reside inside the envelope. The exact location of the M2 gene product M2-2 is currently unknown.

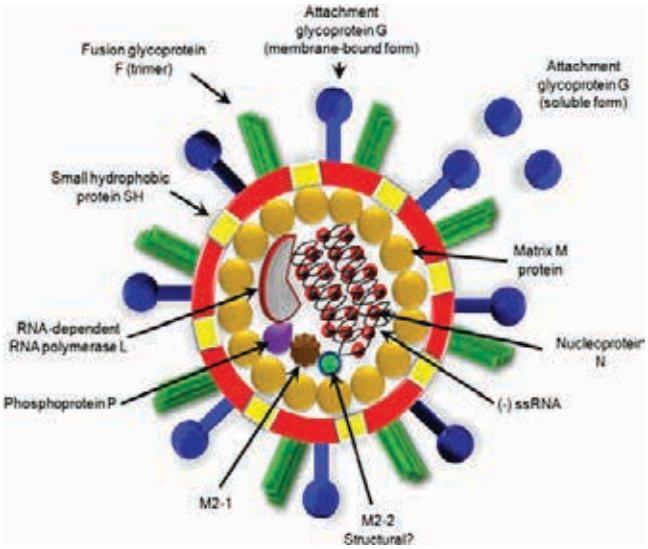

Figure obtained from González et al. Respiratory syncytial virus infection and immunity. Rev Med Virol. 2012 Jul;22(4):230-44.

In temperate regions, RSV infections generally increase during the colder season, from late autumn to spring, with a peak between mid-December and early February.[3] In tropical regions like Singapore, the patterns are less predictable, and RSV usually circulates throughout the year.[4] It is common to have multiple episodes of RSV infections throughout life as the immune response elicited by RSV is weak and short-lived.[5]

In most healthy older children and adults, RSV infection most often causes symptoms of the common cold, including runny nose, sore throat, cough, headache, fatigue, and low-grade fever. Wheezing may also occur in children with history of asthma.

However, infants and young children under the age of two are at risk of lower respiratory tract infections, most commonly bronchiolitis. In fact, RSV is the most common cause of bronchiolitis.[6] This is characterised by rhinorrhoea followed by a dry, wheezy cough and tachypnoea. Bronchiolitis may be severe with signs of respiratory distress and may even be fatal.[7] Apnoea may also be observed in very young and premature infants.[3]

The frail and elderly, patients with chronic cardiopulmonary disease, and those who are immunocompromised are at risk of severe pneumonia and respiratory failure. A Hong Kong

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study reported that nearly 72 percent of the hospitalised adults with RSV have pneumonia, acute bronchitis, or exacerbation of underlying chronic obstructive pulmonary disease or asthma.[8] The incidence of hospitalisation among adults with RSV infections increases with age, with the highest rates among those aged 75 years and older.[9]

RSV BURDEN IN INFANTS AND YOUNG CHILDREN

RSV represents a significant disease burden in infants and young children globally. It is characterised by its seasonal nature (less so in our equatorial climate) and varying clinical severity, and has a profound impact on our social and healthcare systems.

The virus is highly infectious and spreads easily through respiratory droplets and contact with contaminated surfaces. Due to its infectious nature, it is the leading cause of childhood hospitalisation.[10] By the age of one, nearly 70 percent of children have been infected with RSV, and by the age of two, almost all children would have been exposed to the virus. Notably, approximately 36 percent of infants under the age of two have experienced at least two separate infections.[11,12]

Severe outcomes are mostly observed in infants with specific risk factors. These include those with incomplete airway development due to premature birth, pulmonary hypertension, airway hyper-reactivity, congenital heart disease, and immunocompromised states.[13] Additionally, acute lower respiratory infections and fatalities associated with RSV are more prevalent among infants living in developing countries compared to those in developed nations.[14]

In a study by Tam et al, the annual incidence of RSV among young children in Singapore was calculated using a statistical model. They reported 708 RSV-associated hospitalisations among children under six months old, translating to an incidence rate of 33.5 per 1,000 child-years. Among children aged 6-29 months, there were 1,096 RSV-associated hospitalisations, corresponding to an incidence rate of 13.2 per 1,000 child-years.[4]

RSV BURDEN IN OLDER ADULTS AND POPULATIONS AT RISK

Historically, RSV infection has been under-recognised in adults but in recent years it has gained recognition as a significant health threat in the elderly.

In the United States, among adults aged 65 years and older, an estimated 60,000 to 160,000 hospitalisations and approximately 6,000 to 10,000 deaths are linked to RSV annually.[15] Colosia et al reported that hospitalisation for RSV in older adults in the United States typically lasted 3-6 days. Of these patients, approximately 10-30 percent required intensive care admission, with 3-17 percent requiring mechanical ventilation.[16]

Earlier this year, in a cohort study of hospitalised adults aged 18 years and older across 20 US states between February 2022 to May 2023, Surie et al reported that RSV infection severity was similar to that of COVID-19 or influenza infection in unvaccinated patients, but significantly more severe than COVID-19 or influenza infection in vaccinated patients.[17]

A systematic literature review and meta-analysis by Savic et al provided critical insights into the impact of RSV infections among adults aged 60 years and older in high-income countries. "Attack rate" in epidemiology refers to the proportion of an at-risk population that contracts the disease during a specified time interval. The pooled estimates for RSV acute respiratory infection attack rate in this meta-analysis was 1.62 percent (95 percent confidence interval [CI]: 0.84-3.08), 0.15 percent (95 percent CI: 0.09-0.22) for hospitalisation attack rate, and 7.13 percent (95 percent CI: 5.40-9.36) for in-hospital case fatality rates. This would translate into approximately 5.2 million cases, 470,000 hospitalisations, and 33,000 in-hospital deaths in the year 2019.[18] These numbers underscore the substantial burden of RSV on older adults and highlight the significant risk of severe outcomes such as hospitalisations and deaths.

In adults, underlying medical conditions associated with an increased risk of severe RSV infection include pulmonary diseases such as chronic obstructive pulmonary disease and asthma; cardiovascular diseases such as congestive cardiac failure and coronary artery disease; moderate to severe immunocompromised states; and diabetes mellitus. Other factors associated with an increased risk of severe RSV infection include elderly age of 60 years and older, frailty, residence in a nursing home, or similar long-term care facilities.[9]

COMPLICATIONS OF RSV COMPARED WITH INFLUENZA IN OLDER ADULTS

Among older adults, RSV causes significant morbidity and mortality, comparable to influenza. Outbreaks observed in long-term care facilities have brought about an increased awareness of this.[19]

A landmark study by Falsey et al in 2005 evaluated respiratory illnesses in healthy adults aged 65 years and older and high-risk adults with chronic cardiopulmonary diseases over four consecutive winters from 1999 to 2003. It reported a similar number of RSV and influenza infections in these populations. Additionally, it also found that individuals with RSV and influenza had similar rates of intensive care stays (15 percent vs 12 percent) and mortality (8 percent vs 7 percent), respectively.[20]

Closer to home, Zhang et al conducted a retrospective cohort study in Beijing, China, comparing the characteristics and outcomes of hospitalised adults with RSV and influenza A infection. The authors found that the percentage of patients more than 60 years of age was significantly greater in the RSV cohort than in the influenza A cohort. Interestingly, fever

and cough were less prevalent among RSV cases, yet there was a higher incidence of pneumonia and cardiovascular complications such as arrhythmia, myocarditis, and decompensated cardiac failure in the RSV-infected cohort.[21]

One of the largest retrospective studies in this area was published in 2019. It looked at hospitalised adults aged 60 years and older who had either RSV or influenza infection. Similar to previous studies, the authors observed that the patients with RSV infection had a higher odds ratio for pneumonia, exacerbation of chronic obstructive pulmonary disease, hospital stay of more than a week, admission to intensive care unit, and higher mortality within one year of admission compared to influenza infection.[22]

UNDERESTIMATION OF RSV IN ADULTS

RSV infections in older adults are underdiagnosed and the true prevalence and impact may be underestimated for several reasons.[23]

Firstly, there is poor awareness amongst both healthcare providers and the general public about RSV as a significant cause of respiratory illness in adults, compared to its well-recognised impact in children.

Secondly, diagnostic testing for RSV in adults is not routine and is usually only performed in severe or hospitalised cases. Among adults, nasal swab PCR also has poorer diagnostic sensitivity, likely due to milder symptoms and hence lower viral loads in nasal secretions.

Many countries also lack comprehensive surveillance systems specifically targeting RSV infections in adults. As a result, the true prevalence and burden of RSV-related illnesses in older adults may not be fully captured by existing public health data.

ECONOMIC IMPACT OF RSV

Beyond the acute infection itself, the longer-term effects of RSV also place a high burden on both inpatient and outpatient healthcare resources, such as multiple visits for recurrent post-infectious wheeze or exacerbation of pre-existing illnesses, especially that of cardiopulmonary conditions.

A systematic review by Zhang et al reported an estimated global cost of €4.82 billion of RSV-related ARI, accounting for 0.7 percent of the global healthcare expenditure in 2017.[24]

In the paediatric setting, the economic burden of RSV is well-recognised. Infected children have significantly more outpatient visits to their primary healthcare provider and tend to see a specialist more often. Hospital admission rates and ICU utilisation rates for inpatients are also higher in RSV patients.[25]

A study of Italian paediatric database records between 2010 to 2018 reported direct healthcare costs per patient-year to be ten times (€3,605 vs €344) higher in RSV patients than in the general population.[26] In Singapore's context, Tam et al estimated healthcare expenditure linked to medically-attended RSV disease to be SGD 5.7 million (approximately USD 4.3 million) based on 2014 prices.[4]

In the adult setting, the economic impact is not as well-documented. However, in a US claims database analysis by Amand et al, the difference between the adjusted mean annual costs of the RSV and non-RSV controls was the highest in elderly aged >65 years old.[27] Expenditures are also higher among RSV-infected adults with comorbidities than those without in both the inpatient and outpatient setting.[28]

PREVENTION STRATEGIES

RSV is transmitted primarily via large droplets from close contacts. The virus can remain stable for a few hours on hard surfaces, hence transmission can also occur by self-inoculation after touching contaminated surfaces. Because of this, regular hand hygiene and mask-wearing are the mainstay of prevention strategies, aside from immunisation.

RSV vaccine development commenced in the 1960s with an unsuccessful formalin-inactivated RSV vaccine. This vaccine induced a severe lung inflammatory response, including two fatal cases, when RSV-naïve infants encountered natural RSV infection after vaccination. This phenomenon, known as vaccine-associated enhanced respiratory disease, became a significant concern and impeded the subsequent progress of alternative RSV vaccine development.[10]

For many years, RSV prophylaxis was limited to passive immunisation with monoclonal antibodies such as Palivizumab and Nirsevimab, which are approved for infants at risk of severe RSV infections. In the last decade, advances in our understanding of RSV structure have led to a rapid expansion of RSV vaccine candidates.[29]

The RSV virion surface consists of three integral proteins – a receptor attachment glycoprotein, a fusion (F) glycoprotein, and a small hydrophobic protein.[30] The F protein is a key target for vaccine development because it plays a critical role in viral fusion and entry into host cells. There are two major epitopes found on the F protein. Vaccines that stimulate the immune system to produce neutralising antibodies against these epitopes block fusion of the viral and host cellular membranes.[31,32]

In May 2023, the United States Food and Drug Administration approved the first RSV vaccines (Arexvy, an adjuvanted RSVPreF3 vaccine and Abrysvo, a non-adjuvanted bivalent RSVpreF vaccine) for prevention of lower respiratory tract disease (LRTD) in adults aged 60 years and older.[33] Efficacy of one dose of RSV vaccine in preventing RSV-associated LRTD ranges from 74.5 to 84.4 percent and in preventing medically attended RSV-associated LRTD ranges from 77.5 to 81 percent.[34,35] However, due to their sample size, the studies did not have enough statistical power to estimate the vaccines' efficacy

against important severe outcomes such as hospitalisation, severe illness requiring respiratory support or death.[33]

During the trials, both vaccines were generally well tolerated with satisfactory safety outcomes. There were, however, a few post-vaccination inflammatory neurological events, including Guillain-Barré syndrome (GBS) and acute disseminated encephalomyelitis. Subsequently in May 2024 it was reported that vaccination-associated GBS was indeed more frequent than the expected background rates.[36]

After reviewing the available data, the US Advisory Committee on Immunization Practices (ACIP) determined that the benefits of RSV vaccination for adults aged 60 years and older outweighed the potential risks. Hence, RSV vaccination is currently advised for individuals aged 60 years and older and should involve informed and shared clinical decision-making with the patient.[37]

The bivalent RSVpreF vaccine has been studied in pregnant women at 24 through to 36 weeks' gestation, as infants could benefit from passive immunity via placental transfer of maternal antibodies. It has been shown to effectively reduce medically-attended severe RSV-associated LRTD in infants up to six months old, with no safety concerns identified.[38] ACIP therefore recommended one dose of bivalent RSVpreF vaccine administration for pregnant women at 32-36 weeks of gestation in the United States during RSV peak season occurring between September to January.[39]

CONCLUSION

RSV is highly infectious and circulates in Singapore throughout the year. It is a common cause of both upper and lower respiratory tract infections in all ages, with young children and elderly being the most vulnerable. While RSV is well-recognised as a cause of paediatric respiratory infections, there is a need for increased awareness of its significance in the adult population. Severe RSV-associated LRTD may require mechanical ventilation and can possibly result in death, especially in patients with underlying risk factors such as prematurity, cardiopulmonary conditions and immunocompromised states. Prevention strategies including vaccinations are crucial in reducing transmission rates and severity of illness. This will in turn result in reduced healthcare expenditures related to the virus.

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LEARNING POINTS

- **RSV is a common and important respiratory pathogen that could result in upper and respiratory tract infections. It primarily affects young children, causing significant morbidity and mortality. In recent years, it has been recognised as a cause of severe lower respiratory tract disease in older adults and patients with chronic cardiopulmonary disease or conditions causing immunocompromised state.**
- **Among older adults, RSV infections carry a similar burden of illness and mortality as influenza. The incidence of hospitalisation due to RSV infections increases with age, with the highest rates among those aged 75 years and older.**
- **There are currently RSV vaccines that are approved for use in adults aged 60 years and older. Vaccinations reduce the incidence of symptomatic infection and LRTD.**