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COMMENTARY

Respiratory syncytial virus: enhanced understanding of the burden of disease and developments in active and passive immunisation

Bamford C[*1,2]
[1]Pathcare, East London, South Africa, [2]University of Cape Town, Cape Town, South Africa
*Corresponding author: colleen.bamford@pathcare.org

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Abstract
Respiratory syncytial virus (RSV) is a major cause of respiratory tract infection in infants and young children worldwide. Improvements in diagnostic testing have led to increased recognition of RSV infection in children in various settings as well as recognition of RSV as a significant cause of serious respiratory infections in older adults with underlying conditions. The burden of disease is significant with 33.0 million RSV-associated acute lower respiratory infection episodes globally in children younger than 5 years. Infants in the first 3 months of life bear the brunt of severe RSV disease. Recently a more effective and longer lasting monoclonal antibody targeting RSV F protein has been approved for use in infants, while maternal immunisation with a prefusion F protein–based (RSVpreF) vaccine provides effective protection against medically attended RSV-associated lower respiratory tract illness for infants during their first 3- 6 months of life. A number of other vaccines are in development that may offer protection for various age groups in the future.

Introduction

Respiratory syncytial virus (RSV) has been well known to clinicians for many years, having first been described in 1956. It has long been recognised as a highly infectious virus and is a major cause of respiratory tract infections including bronchiolitis, pneumonia and apnoea in infants and young children worldwide.

RSV is ubiquitous and most children are exposed within the first few years of life. The initial primary infection is the most severe, with infants under 6 months of age, especially premature babies, at risk for life threatening disease. Re-infections are common throughout early childhood, but generally become less severe with increasing age and number of infections. In older children and adults RSV infections chiefly affect the upper respiratory tract, but can also cause bronchitis, pneumonia and exacerbations of chronic obstructive pulmonary disease (COPD) and asthma. Older adults > 65 years are at increased risk of lower respiratory tract involvement.

To date no effective directed therapy for RSV infection exists and treatment remains supportive, primarily consisting of humidified oxygen.[1] Similarly, no preventive measures are available for most children, especially those in lower middle-income countries (LMICs).

Although RSV can be detected by variety of older laboratory methods, including viral culture, immunofluorescence, antigen detection and serology, the development and increasing availability of polymerase chain reaction (PCR) testing has greatly facilitated the rapid diagnosis of RSV infection. This has led to the increased recognition of RSV infection in children in various settings as well as recognition of RSV as a significant cause of serious respiratory infections in older adults with underlying chronic conditions, on a level approaching that of influenza.[2]

The objectives of this review are to highlight progress in the understanding of the burden of RSV disease and to the development of preventative strategies that aim to potentially reduce its impact.

Enhanced understanding of the burden of disease

Recent studies have provided more detailed updates on the burden of disease due to RSV. It is estimated that in 2019, there were 33.0 million RSV-associated acute lower respiratory infection episodes globally leading to 26 300 RSV-associated acute LRTI in-hospital deaths and 101 400 RSV-attributable overall deaths, in children younger than 5 years.[3] There were also an estimated 3.6 million -associated acute LRTI hospital admissions globally in the same year.

Infants aged 0-6 months account for 20% of acute episodes, 39% of hospital admissions and 51% of in-hospital deaths, whilst infants in the first 3 months of life bear the brunt of severe RSV disease.[3,4] The disease burden is also markedly skewed towards low or middle-income countries where more than 95% of acute LRTI episodes and more than 97% of in-hospital deaths occur.[3]

Relying on traditional hospital-based surveillance significantly underestimates RSV associated mortality. A community- based post-mortem study in Lusaka, Zambia among children 0-6 months showed that about two thirds of all RSV-associated deaths occurred in the community, and that RSV caused at least 2.8% of all infant deaths in this age group.[5]

Infants at highest risk include those born very prematurely or with underlying chronic predisposing conditions such as congenital heart or lung or neurological conditions.[6] In contrast, in LMICs most deaths occur in previously well infants.

RSV is also a common potentially under recognised cause of nosocomial LRTI infection. A recent global case series using an on-line RSV mortality registry showed that 20% of all deaths where information on site of acquisition was available, were nosocomial in origin.[7] This proportion was lower

in LMICs compared to wealthier countries, which given that the burden of nosocomial infection is generally recognised as being significantly higher in LMICs, may suggest under reporting.[8]

RSV is also associated with important long-term consequences, including recurrent LRTI, wheezing, asthma, and impaired lung function.[9,10]

Prevention of RSV infection

Passive immunisation for neonates

The first monoclonal antibody, paluvizumab, was licensed in 1998.[11] Given as a monthly intramuscular injection, it provides effective protection for high-risk neonates. More recently next generation monoclonal antibodies have been developed with more effective neutralising activity and a much longer half-life. Nirsevimab for example which targets the prefusion conformation of RSV F protein can be given as a single dose for the whole RSV season.[12] It was approved in UK and EU at the end of 2022 and in the USA in July 2023 for use in infants and young children on the basis of trials showing significant protection against medically attended RSV infection in otherwise healthy infants. The improved protection and easier logistics mean that nirsevimab and similar future monoclonal antibodies might now be a viable option for prophylaxis for most infants in HICs in their first RSV season, rather than being applicable only to very high-risk infants. Unfortunately, the cost of monoclonal antibodies means that these are not feasible for LMICs with the highest burden of disease.

Vaccination

Development of RSV vaccines has been hampered by the negative experience of vaccine enhanced disease that was associated with the 1960s formalin- inactivated viral vaccine.[13] RSV naïve recipients of this vaccine experienced more severe disease on subsequent RSV infection through a process of antibody dependent enhancement, associated with the development of poorly neutralising antibodies and a T Helper Type 2 biased T cell response.[14]

A further complicating factor has been that immunity to RSV following natural infection is incomplete with re-infection occurring throughout life. To date neither the underlying immune response nor the correlates of protection to RSV infection are fully understood. However, cell mediated immunity, mucosal IgA and neutralising antibodies are all recognised to be associated with protection.[6]

Greater understanding of the epitopes targeted by highly neutralising antibodies in general and success in stabilising the prefusion conformation of F protein particularly has led to a recent explosion of focused vaccine development, with over 30 vaccine candidates in clinical development including a number in advanced or recently reported phase 3 clinical trials. A variety of vaccine types, including subunit, particle-based, live attenuated, recombinant vector, chimeric and nucleic acid vaccines are being tested, targeting mainly prefusion F antigen but also other antigens such as RSV G protein involved in initial viral attachment.[6]

To avoid vaccine enhanced disease RSV naïve infants will need a vaccine that generates potent neutralising antibodies, whereas older infants > 6 months and children can potentially receive a variety of vaccines that boost immunity after primary infection, including live attenuated vaccines.[6] Vaccines for pregnant women such as protein- based subunit vaccines generate protective antibodies that can be transferred to the fetus, a sort of natural delivery of passive immunisation. A recently reported Phase 3 trial in pregnant women using a single dose of a bivalent RSV prefusion F protein–based (RSVpreF) vaccine showed significant protection against medically attended RSV-associated lower respiratory tract illness for infants during their first 3- 6 months of life.[15] The only currently licensed RSV vaccines are in fact two preF subunit vaccines recently licensed for use in adults > 60 years of age based on high vaccine efficacy rates reported in recent trials in this population.[16,17]

The rapid progress in RSV vaccine development is likely to continue in the next few years and there are hopes that effective RSV vaccines may be on the horizon. Nucleic acid or mRNA vaccines in particular have advanced quickly to late phase trials, buoyed by the success of COVID mRNA vaccines, which was in turn built on knowledge previously acquired in RSV vaccine development.[6]

Considerable work is going into preparatory studies at country or regional level that could assist in introducing and maximising benefit from future maternal vaccination and neonatal monoclonal antibody programs.[18] Access and affordability will be critical for LMICs or under resourced areas, and methods to reduce costs could be beneficial. For example, RSV causes seasonal outbreaks in the majority of countries away from the equator, including 75% of 52 LMIC countries studied.[19] Infants are at greatest risk of hospital admission for RSV if born 1-2 months before peak RSV activity. In countries with a seasonal disease pattern, seasonal use of maternal vaccines given only for the months shortly before and during the RSV season could prevent more cases of disease per dose administered, and therefore be more cost effective and feasible than year-round administration.[19]

Following an adequate maternal immune response, efficient transfer of these antibodies across the placenta is required for successful maternal immunization. Since the most abundant immunoglobulin, IgG1, mainly crosses the placenta in the last 4 weeks of pregnancy, preterm infants may receive inadequate antibodies. In addition, maternal factors, such as hypergammaglobulinaemia, HIV infection and placental malaria may impair transplacental transfer of antibodies. Unfortunately, all these conditions are more common in LMICs, and are not necessarily reversed by treatment of the underlying maternal condition and could impact on future maternal vaccination programs.[20]

Unexpected adverse events can derail vaccines even at late stages of development. A trial of a GlaxoSmithKline preF RSV vaccine in pregnant women was halted in 2022 because of higher rates of preterm delivery in the vaccine arm.[21] No safety concerns were identified in the Pfizer study of a similar target vaccine recently reported.[15] However, in that study the rate of preterm delivery before 37 weeks was higher in the vaccine group than in the placebo group (5.7% versus 4.9%) although this was not statistically significant given the relatively small numbers.

This all suggests that further studies will be needed to confirm effectiveness and safety of future potential vaccines, and to determine how to implement them in different age groups and different epidemiological settings. Passive immunisation whether via monoclonal antibodies or maternal vaccination or a combination thereof will likely delay first episodes of RSV infection. How a potential delay will affect the severity of subsequent RSV infection is not entirely clear, while determining the optimal timing for active vaccination of infants following an initial period of protection via passive immunisation is also unclear.

Conclusion

In summary whilst there are still many unknowns in the methods for the prevention of RSV disease, there is excitement that there is potential “light at the end of the tunnel” or that this is the” beginning of the end” for this pathogen that casts such a heavy burden on vulnerable children and older adults.[22] There is much work to be done to facilitate rapid uptake of new preventative methods in LMICs as soon as possible.[23]

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