Narrative Review
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RSV Lower Respiratory Tract Illness in Infants of Low- and Middle-income Countries

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Abstract
This review addresses differences in respiratory syncytial virus (RSV) lower respiratory tract illness (LRTI) between industrialized and developing countries and provides observations associated with the dissimilar consequences of viral infection in both environments. RSV LRTI is an important cause of morbidity and mortality in infants worldwide. Its burden is highest in developing countries, where most hospitalizations and mortality occur. Palivizumab has been approved for disease prevention in premature infants in numerous countries but its cost and requirement for several doses hampers its routine use. The significant gap between low- and high-income countries in mortality rates stresses the need to identify specific risk factors for RSV LRTI prevention in different populations. **Conclusion.** RSV LTRI continues to be a serious problem for industrialised and developing countries, although mortality occurs preferentially in the latter. Several vaccines and monoclonal antibodies to prevent severe disease are advancing steadily in late phase trials. The next decade may witness a change in the landscape of RSV infections in young infants.

Key Words: RSV ▪ Global Burden ▪ Developed Countries ▪ Risk Factors.

Introduction

Lower respiratory tract infections (LRTI) are the main cause of morbidity and mortality in infants and young children between 1 month and 5 years of age (1). Respiratory syncytial virus (RSV) is the most frequent cause of LRTI in infants, associated with 33.8 million new episodes of RSV LRTI every year worldwide, and an incidence in developing countries doubling that of industrialised nations. Worldwide, RSV is associated with about 28% of all LRTI episodes and 13-22% of al LRTI mortality in young children (2).

In 2005, 3.4 million children developed severe episodes of RSV LRTI requiring hospital admission, particularly in infants younger than 6 months. Global mortality is estimated to range between 66,000 and 199,000 deaths per year; 99% of these deaths occur in developing countries (3). Conversely, RSV LRTI deaths in industrialized countries are infrequent and affect high-risk infants with chronic lung, heart, or neuromuscular disease, children with Down's syndrome and those born prematurely (4) (200 deaths per year in children between 0–59 months vs 47,800–74,300 deaths in developing countries) (2).

Acute RSV bronchiolitis is a seasonal disease, typically starting in late fall until early spring, with a winter peak. Infection is often mild and presents with symptoms that mimic a common cold, but can progress to display tachypnea, wheezing, and crackles, in the most severe cases leading to respiratory failure and/or death. In addition to deaths at medical institutions, in developing countries approximately half of all RSV deaths in infants and young children occur at home (5). Risk factors for home death in this population associate with environmental and social variables including precarious household conditions, crowding, incom-

plete vaccination for age, no breastfeeding, and prematurity (6, 7). In addition to acute disease, infants who experience severe RSV LRTI early in life are more prone to develop wheezing during early childhood, and may have increased rates of airways hyperreactivity and asthma later on (8-11). Therefore, preventing severe RSV LRTI may impact the global burden of paediatric wheezing. New vaccines and monoclonal antibodies (mAb) against RSV are promising strategies to reduce the burden of acute and long-term illness associated with the virus.

The aim of this review is to address disparities in RSV LTRI burden and disease outcome between industrialised and developing countries.

Severe Disease Worldwide

The incidence of severe RSV LTRI differs between developing and industrialised countries. In 2015, the number of episodes of severe RSV LTRI in developing countries was 6.1 million vs 212,000 in industrialized countries. Hospital admissions showed a similar difference, 2.6 million vs 344,000 hospitalizations, respectively (2). In children <6 months of age, rates exhibit logarithmic differences between developed and developing nations: 36.1 vs 3.2 per 1,000 children per year. Rates in 0 to 59 months old also differ from 10.2 to 3 per 1,000 children per year (2). Most episodes of severe RSV LTRI occur during the first 6 months of life, when infants experience the highest hospitalization rates (20.1 per 1,000 infants per year) (12). Rates are increased among preterm infants to 63.8 per 1,000 per year (12). In developing countries, the hospital case fatality rate (hCFR) is 2.2 for infants <6 months of age, and 2.4 in those between 6 and 11 months.

Socioeconomic factors affect the risk of experiencing respiratory failure due to RSV LTRI. Increased risk is observed in infants living in homes with no sewage or exposed to indoor smoke (13). In addition, medical practice in impoverished areas of the world also affects the odds for survival. RSV mortality in a low-income region of Argentina strongly associated with the development of clinically-significant pneumothorax during hospitalization (13). Rate of pneumothorax in these intensive care units was several-fold higher than those reported in association with RSV LRTI in industrialized countries (14). In this same low-income region, precarious household conditions including homes made of tin or wood with a dirt floor (OR 2.30), no running water (OR 6.14) and crowding (OR 3.54) increased the risk for at-home death. Additional socioeconomic risk factors for mortality included being born to a young mother (<19 years old) and incomplete vaccination for age (6). In these situations, parents often experience deficient interactions with the healthcare system before their children die. It is not infrequent to encounter fatal cases with a history of incomplete prenatal healthcare. Evidently, beyond the offending agent itself, the home environment of babies and parental communication with the health care system are important determinants of the children's chances of survival (6).

Recurrent Wheeze and Asthma

Severe RSV LRTI in early life is associated with an increased risk of recurrent wheeze and asthma (8-11). A longitudinal study that followed children <1 year hospitalized with RSV-LTRI up to 18 years of age showed an increased prevalence of asthma/recurrent wheeze (39% vs 9%), clinical allergy (43% vs 17%) and sensitization to perennial allergens (41% vs 14%) in the RSV cohort compared with controls (9). Furthermore, a second cohort study reported that 31% of children with early childhood asthma had clinically significant bronchiolitis during infancy, with a prevalence of asthma among hospitalized children due to bronchiolitis of 22% (10). In fact, birth before the winter virus peak has been shown to associate with a greater risk of developing asthma in later life (15). Infants born 4 months before the virus peak had 29% more risk of developing asthma compared to infant birth 12 months before the peak (16).

Interventional studies are most informative in defining the role of RSV in long-term wheezing. A double-blind, placebo-controlled trial with palivi-

zumab (a monoclonal antibody targeted against the RSV neutralizing fusion protein) in healthy preterm infants in The Netherlands, resulted in a 61% reduction of wheezing days and 10% reduction in recurrent wheeze, 11% in infants that received the mAb vs 21% in those that received placebo (8). Interestingly, a similar study with a high-affinity mAb against RSV (motavizumab) in healthy Native Americans born at term in Arizona had no effect on rates of medically attended wheezing in 1- to 3-year-old children despite preventing severe acute RSV LRTI.

Many of these studies reported follow-ups at the age of 6 years. In the Dutch study, palivizumab significantly reduced parent-reported asthma on the basis of different rates in infrequent wheezing (one to three episodes per year) when compared with placebo recipients, but physician-diagnosed asthma and lung function did not differ between groups (16, 17). In a second study in Japan, palivizumab prophylaxis failed to suppress atopic asthma but reduced recurrent wheezing. Evidently, ongoing vaccine and monoclonal antibodies phase 3 studies are a superb opportunity to address these questions and define the precise role of RSV in asthma inception. Yet asthma is a set of heterogeneous conditions with different molecular mechanisms of illness but common symptoms. Therefore, it is likely that preventing severe RSV LRTI will modulate one or a few of these "asthmas" but fail to alter others.

RSV and All-Cause Pneumonia

Today, there is enough evidence to support conducting a detailed evaluation of the role of RSV vaccines and monoclonal antibodies in modulating the burden of all-cause severe LRTI and pneumonia months after immunization and after the RSV season. Recent observations suggest that interventions may have a greater-than-expected impact on long term mortality given the aforementioned effects, and -through these unclear mechanisms- contribute to modulate the burden of lung disease overall, with potential long-term consequences in lung function.

Coinfections

Multiplex polymerase chain reactions (PCR) often detect other viruses combined with RSV showing that coinfection with more than one respiratory virus is frequent in children (18). Yet, the clinical implications of more than one infectious virus in infants with LRTI remain unclear. Several studies suggest that respiratory virus co-infections may increase severity of RSV disease (19-21), reporting infants with longer hospital stays and a greater need for supplemental oxygen; however, other studies do not confirm these results (22, 23). The frequency of co-infection with other viruses in RSV LRTI varies considerably in different studies, ranging from 11% to 56% (19, 22). This may be affected by the population composition in different studies, seasonal variation of respiratory viruses, and the breadth of pathogens explored in each report.

Disease Prevention

Palivizumab, a humanized monoclonal antibody targeting the fusion protein, the main neutralizing antigen in RSV, is the only licensed intervention to prevent severe RSV LRTI. Palivizumab prevents 55% hospitalizations in high risk preterm infants, and decreases the total days of hospitalization, oxygen supplementation, and intensive care (24). The antibody is used in high-risk preterm populations in high and middle-income countries (25, 26). Unfortunately, due to its high cost, its requirement for four to five injections per child per season, and the challenge of defining the exact timing and duration of the RSV season in subtropical and tropical regions, its adequate use in the developing world is infrequent. Another important strategy for RSV disease prevention is breastfeeding, and its effectiveness has been extensively documented.

Motavizumab, a second generation humanized monoclonal antibody with higher affinity for RSV than palivizumab, was studied in children in Navajo and Apache reservations (27). This population routinely experiences high rates of severe RSV disease. Motavizumab showed an 87% relative reduction in the proportion of hospitalizations but

elicited skin reactions that precluded its use (28). Newer mAbs have been undergoing evaluation in recent years. Suptavumab (REGN2222), a mAb of extended half-life against site V in RSV F, did not meet its primary efficacy endpoint in preterm infants (NCT02325791). Despite protecting against disease caused by RSV subgroup A, an unexpected mutation in site V of RSV F in circulating RSV B viruses affected its overall efficacy. Medimmune, the manufacturer of palivizumab, is now undertaking phase 3 studies with MEDI8897, which presents amino acid substitutions in the Fc region (YTE technology) that enhance binding to the MHC class I-neonatal Fc receptor and extend its half-life to 85 to 117 days. The mAb targets antigenic site Φ in the pre-fusion conformation of RSV F. Another mAb of extended half-life advancing into late phases of clinical evaluation is MK-1654 from Merck (NCT03524118) targeting RSV F site IV.

RSV vaccine development has been a sustained goal since the 1960s, when a formalin-inactivated RSV (FIRSV) vaccine was used to immunize children and elicited a non-protective and disease-enhancing response (29, 30). After RSV exposure, two immunized infants died and 80% of those infected with RSV were hospitalized. FIRSV associated with non-neutralizing, low-avidity anti-F IgG responses and a Th2 bias of the cytokine and cellular response (31, 32). Natural immunity, instead, presents innate responses with polymorphonuclear and mononuclear cells and type I and III interferon (33-35).

Antibodies, as demonstrated with palivizumab and a polyclonal immune globulin enriched for RSV antibodies (Respigam), are able to prevent severe RSV LRTI. RSV infection elicits polyclonal, high avidity, neutralizing antibody responses against RSV F (36), which is highly conserved between RSV subgroups A and B (37). The RSV attachment (G) protein also elicits polyclonal neutralizing responses but presents increased variability between subgroups. T cell responses are also important for protection against RSV, as $CD8^+$ T lymphocytes clear the virus from infected cells and $CD4^+$ T lymphocytes contribute to orchestrate T-dependent antibody responses (38).

Several studies demonstrated an association between severe illness in young infants with low concentrations of cord-blood RSV antibody (39, 42). Chu et al. showed that infants with higher cord blood antibody titres are at lower risk of infection during the first 72 weeks of life (43). And a second study showed the risk of hospitalization in the first 6 months to be inversely correlated with concentrations of cord-blood neutralizing antibody (44). Therefore, immunization during pregnancy aims to protect the infant in these first few months of life through transplacental transfer of antibodies (45). Maternal immunization strategies to protect newborns and infants proved effective against influenza, pertussis and tetanus (45, 46).

Transplacental transfer of immunoglobulin concentrates in the third trimester of pregnancy. Prematurity is, therefore, associated with reduced transfer of antibodies, particularly in infants born before 28 weeks' gestation. Hence, premature infants may not benefit from a maternal immunization strategy. In a study performed by Yildiz et al., antibody transplacental transfer rates were lower in small for gestational age and large for gestational age infants in comparison to those appropriate for gestational age, but these observations have not been replicated (47, 48).

Recently, a RSV F protein nanoparticle vaccine was tested in pregnant women in a randomised, double-blind, placebo-controlled trial and demonstrated good safety and immunogenicity. Transplacental antibody transfer ranged between 90%–120%, with higher transfer efficiency noted among women immunized ≥30 days before delivery as contrasted with those immunized for <30 days (49, 50). The vaccine failed to meet its primary endpoint to reduce the rate of medically significant RSV LTRI in infants through 90 days of life, despite an overall efficacy of 39.4%. However, it was effective in protecting against RSV hospitalizations and severe disease worldwide (40% and 44% respectively) (51). Novel pre-fusion constructs from Pfizer and GSK designed for maternal immunization entered late phase trials in 2019.

Live attenuated RSV vaccines do not prime infants for enhanced RSV disease. In addition, these

vaccines are administered intranasally, needle-free and can generate an immune response even in the presence of passively acquired maternal antibodies (52). A variety of live-attenuated RSV vaccines are under development by a joint effort of Sanofi and NIH. An important challenge will be to attain an adequate balance between attenuation and immunogenicity (53, 54). Vectored based-vaccines using adenoviruses are also in clinical trials, as well a recombinant BCG expressing RSV N protein. Adenoviruses are highly immunogenic and induce both innate and adaptive immune responses, and are being investigated as vectors targeting viral, bacterial and protozoan pathogens. The chimeric candidate rBCG-N-hRSV vaccine presents the advantage that BCG induces Th1 immunity, turning the immune response away from the undesirable Th2 priming. This vaccine is expected to mainly elicit cellular immunity against RSV, which is yet to demonstrate sufficient protection against RSV.

Conclusions

The burden of RSV LRTI in infants and young children worldwide is significant. Mortality due to the virus is a serious problem in developing countries. Disparities in disease outcome between developed and developing countries might associate with differences in access to health care, health care resources, living conditions, and the high cost of preventive measures like palivizumab for high risk populations. Yet, the situation may improve in coming years. Numerous prophylactic interventions are steadily advancing in late phase trials and may provide effective solutions against the pathogen in the next decade.

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