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RSV—Still More Questions Than Answers

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RECENT ADVANCES

Respiratory syncytial virus (RSV) infection is the leading cause of hospitalization for acute respiratory infection among infants[1] and an important etiology of lower respiratory infection in young children and the elderly.[2] By the end of the second year of life, most children have experienced at least 1 episode of RSV infection, and repeat infections with RSV are common. Approximately 1–3% of all healthy term infants are admitted to hospital for lower respiratory tract infection (LRTI) due to primary RSV infection,[1] and this admission rate can increase to and above 10% in high risk populations. Risk factors for severe RSV disease include bronchopulmonary dysplasia, birth at less than 36 weeks gestation, clinically significant congenital heart disease, Down syndrome, neuromuscular disease and severe immunosuppression. Long-term respiratory morbidity associated with RSV LRTI includes recurrent wheeze and an increased risk of developing asthma. There is no vaccine or antiviral treatment against RSV available. Passive immunization with palivizumab, a humanized antibody against the RSV fusion glycoprotein, is used for prevention of RSV-related hospitalization in prematurely born infants and children with congenital heart disease. Supportive care consists of oxygen and fluid supplementation. Further airway support is provided preferentially by noninvasive ventilatory assistance.

The interest in RSV research has increased dramatically in the past decade. In 2013, there were more annual publications (343 PubMed publications) than ever before (240 publications in 2007). Four major *breakthroughs* have boosted RSV research during the last decade. First, RSV has been reported to be a major cause of death in the world during infancy.[3] Annual RSV-related deaths have been estimated at 253,000, accounting for up to 6.7% of the mortality in children aged <1.[4] Of these deaths, 99% occur in developing countries. Second, a recent randomized clinical trial using passive RSV immunization showed that RSV infection is associated with recurrent wheeze, at least in the first year of life in otherwise healthy prematurely born infants, providing strong evidence that RSV infection is causally related to long-term airway disease.[5] Third, a new highly antigenic RSV antigen was discovered.[6] The metastable prefusion state of RSV F glycoprotein has an antigenic site "zero", which is lacking at the postfusion RSV F glycoprotein. Highly potent neutralizing antibodies are developed against antigenic site zero of the prefusion F glycoprotein. A stable form of RSV F in its prefusion conformation is now used to develop RSV vaccines as well as next generation neutralizing antibodies for therapeutic usage. Fourth, there is a major activity in the development of RSV therapeutics, including next generation antibodies, vaccines, fusion inhibitors and other antivirals. Many of these therapeutics have entered clinical development.

GAPS IN KNOWLEDGE/UNMET NEEDS

Major advances in translational research on *RSV pathogenesis* have been achieved. Nevertheless, there are important gaps in our understanding of the pathogenesis of this highly frequent disease, preventing progression of treatment and vaccine development. The host and the virus clearly play an important role in determining disease severity. Host genetic factors suggest innate immune responses are critically important determining disease severity. The host immune response is characterized by a profound neutrophilic airway inflammation in infants with severe RSV bronchiolitis. In addition, postmortem studies revealed paucity of mononuclear cells in the airway of those patients. Further evidence for a major role of innate immunity in the pathogenesis of RSV bronchiolitis are host genetic studies

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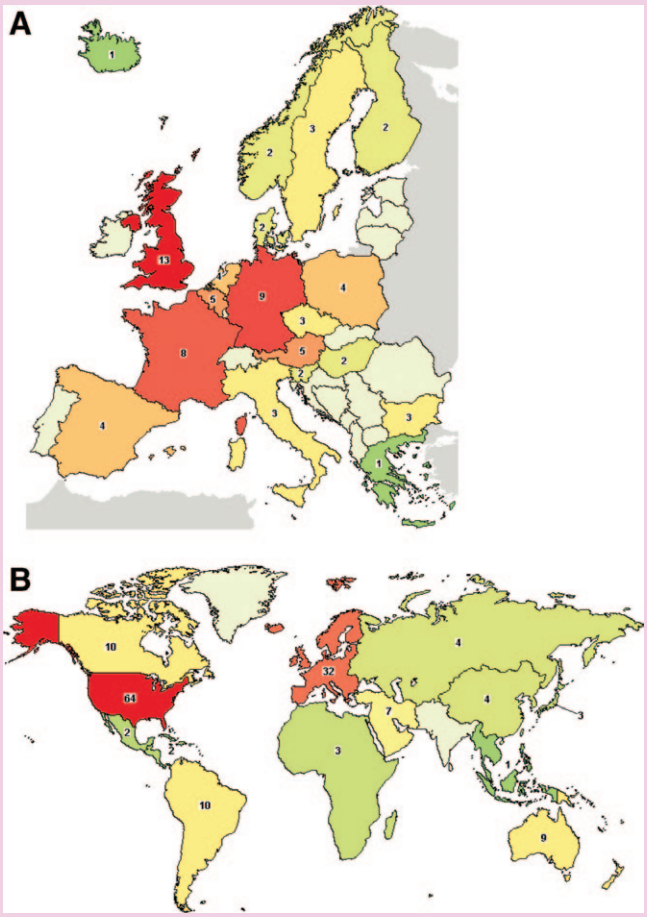

FIGURE 1. Map of RSV-registered trials worldwide (A) and in Europe (B) as of July 2014, based on data from Clinical Trials Gov database (www.clinicaltrials.gov).

predominantly showing an association with innate immunity pathways. Local mucus production is a key characteristic of bronchiolitis patients resulting in airway obstruction. One of the open questions is to what extent direct virus-mediated cytotoxicity versus immune-mediated destruction of lung tissue contributes to disease severity. The answer to this question will be instrumental predicting the potential success of treatment strategies including antivirals, immune modulation or their combination.

Respiratory research suggests that infants with RSV LRTI may have abnormal premorbid lung function, in particular infants with higher resistance of the respiratory system.[7] In addition, in a longitudinal study of prematurely born infants, despite no significant differences in lung function at 36 weeks post-menstrual age, those who had viral LRTIs compared with those who had not had LRTIs had significant worse airway resistance at 1 year corrected. Fourteen of the 32 infants in the viral group had RSV LRTIs. Those data suggest RSV LRTIs, at least in prematurely born infants may further impair lung function.[8] There is additional evidence that children with a history of RSV bronchiolitis have decreased lung function up to adulthood, sometimes accompanied by asthma symptoms. In addition to host factors, RSV is one of the most virulent viruses. The virus has long been characterized, including gene function. Viral loads are related to disease severity, at least to some extent, but high loads may be found in infants and children with upper respiratory symptoms only and conversely prematurely born infants may suffer severe disease with low viral loads. The impact of viral genotype is yet largely unknown and understudied.[9]

Much of RSV *epidemiology* is known. Nevertheless, for the clinical development of RSV therapeutics and vaccines some critical questions have not yet been addressed. There is a lack of reliable, good quality mortality data in different regions of the world. Mortality is known to be very low in high income countries, but more precise estimates of RSV-associated morbidity (eg, outpatient visits, complications, hospitalizations, parental work absenteeism) are needed for cost-effectiveness evaluations in different countries. Current global mortality data are based on excess mortality estimates during RSV seasons, but little data exist on virologically confirmed cases. In addition, another challenge is to account for post-RSV secondary mortality, for example, by bacterial pneumonia. Morbidity and mortality data in middle and low income countries (where the disease burden is disproportionately high) are needed to determine the potential impact of RSV vaccines. Information on the proportion of children dying from RSV infection younger than 6 months will be a crucial determinant for the potential impact of a future maternal versus a paediatric RSV vaccine.

Presently, there is no specific *treatment* for patients with RSV infection, and care is mainly supportive. Ribavirin, monoclonal antibodies, macrolide antibiotics, leukotriene receptor antagonists, glucocorticosteroids and bronchodilators have not been proven effective. There is some literature to suggest that nebulization with hypertonic saline is associated with some clinical benefit, but no large trials have been published. A number of antivirals have entered clinical trials, including fusion inhibitors and nucleoside analogs. Designing trials for RSV antivirals is quite challenging. The highest likelihood of a beneficial effect from antivirals is expected when administered at an early phase of infection. However, only a small proportion of untreated children with early RSV infection will develop severe disease requiring hospital admission. Consequently, trials with antivirals in infants with early phase disease require large study populations, making these trials costly. There is little progress in the development of therapeutics targeting the immune system, in particular therapeutics targeting airway neutrophils. Dampening the neutrophil response in the airway is notoriously difficult, but perhaps essential to treat children with RSV bronchiolitis at the time they present at the hospital. Vaccine development is promising. Various novel vaccine strategies have been developed, including use of recombinant RSV F-based nanoparticles, live-attenuated mucosal vaccines and adenovirus vector-based vaccines.[10] At least 6 maternal and pediatric vaccines are currently undergoing clinical trials.

THE NEED FOR RSV RESEARCH NETWORKS

Key research questions can seldom be answered without multidisciplinary and networking approaches. For influenza such approaches have been developed (GABRIEL, isirv, MISMS and CEIRS). The BRaVe initiative by World Health Association is an action plan to decrease the unmet global burden of respiratory viruses in general. TB-net is a network to promote clinically oriented research in the field of tuberculosis in Europe

by sharing and developing ideas and research protocols. Despite the major burden of disease, there is no international, integrated, multidisciplinary and translational research approach focused on RSV infections. National RSV networks, such as the Italian Neonatology Study Group on RSV Infections and the Dutch RSV Neonatal Network do not have the multidisciplinary potential do address most major scientific challenges. At the same time, research interest in RSV keeps growing, with an increasing number of studies underway and more to appear with the development of new preventive and therapeutic molecules. Most trials are currently being performed in the United States and Europe, with twice as much studies in the United States as in Europe (Fig. 1). In this setting, ReSViNET is a new fully independent research network with the mission to decrease the global burden of RSV infection by integrating expertise. It addresses the burden of RSV by establishing a European translational research framework and by delivering a comprehensive training and education program. ReSViNET is stimulating and performing research aiming to understand and tackle the burden of RSV infection, to advocate for better care for patients with RSV infection, to provide education related to RSV infection and to provide effective partnerships with relevant stakeholders. Although founded by European researchers, the network open up to researchers outside of Europe, such as investigators from developing countries through RSV GEN led by University of Edinburgh. Combining expertise will eventually enable streamlining research efforts to decrease the global burden of RSV infection.

CONCLUDING REMARKS

RSV bronchiolitis is a major cause of mortality and morbidity in children around the world. Although its pathogenesis is poorly understood, excellent opportunities to prevent and treat RSV infections are emerging, in particular through the discovery of the highly immunogenic prefusion F glycoprotein. Multidisciplinary networks are needed to increase our understanding of the pathogenesis, epidemiology and management of the disease.

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