RSV—Still More Questions Than Answers

Louis Bont, MD, PhD,* Eugenio Baraldi, MD, FCCP † Brigitte Fauroux, MD, PhD,‡ Anne Greenough, MD, FRCPCH,§ Terho Heikkinen, MD, PhD,¶ Paolo Manzoni, MD, PhD,¶¶ Federico Martinón-Torres, MD, PhD,** Harish Nair, MD, PhD,†††† and Nikolaos G. Papadopoulos, MD, PhD†††††, on behalf of ReSViNET

RECENT ADVANCES
Respiratory syncytial virus (RSV) infection is the leading cause of hospitalization for acute respiratory infection among infants¹ 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 available against RSV. Passive immunization with palivizumab, a humanized antibody against the RSV fusion glycoprotein, is used for prevention of RSV-related hospitalization in premature 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...
infants with RSV LRTI may have abnor-
tomy system. In addition, in a longitudinal
infants with higher resistance of the respira-
tional premorbid lung function, in particular
their combination.
including antivirals, immune modulation or
the potential success of treatment strategies
this question will be instrumental predicting
contributes to disease severity. The answer to
immune-mediated destruction of lung tissue
direct virus-mediated cytotoxicity versus
One of the open questions is to what extent
airway obstruction. Local mucus produ-
duction is a key characteristic of bronchioli-
tis 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 severe RSV bronchiolitis. In
addition, postmortem studies revealed pau-
city 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
predominantly showing an association with
innate immunity pathways. Local mucus pro-
duction is a key characteristic of bronchioli-
tis patients resulting in airway obstruction.

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).

profound neutrophilic airway inflammation
infants with severe RSV bronchiolitis. In
addition, postmortem studies revealed pau-
city 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
predominantly showing an association with
innate immunity pathways. Local mucus pro-
duction is a key characteristic of bronchioli-
tis 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 abnor-
mal premorbid lung function, in particular
infants with higher resistance of the respira-
tory system. 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 air-
way 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. 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, includ-
gene function. Viral loads are related to
disease severity, at least to some extent, but
high loads may be found in infants and chil-
dren 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.

Much of RSV epidemiology is known.
Nevertheless, for the RSV development of
RSV therapeutics and vaccines some criti-
cal questions have not yet been addressed.
There is a lack of reliable, good quality mor-
tality 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, paren-
tal work absenteeism) are needed for cost-
effectiveness evaluations in different coun-
tries. Current global mortality data are based
on excess mortality estimates during RSV
seasons, but little data exist on virologically
confirmed cases. In addition, another chal-
lenge is to account for post-RSV secondary
mortality, for example, by bacterial pneumo-
nia. Morbidity and mortality data in middle
and low income countries (where the disease
burden is disproportionally 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 treat-
ment for patients with RSV infection, and
care is mainly supportive. Ribavirin, mono-
clonal antibodies, macrolide antibiotics,
leukotriene receptor antagonists, glucocorti-
costeroids and bronchodilators have not been
proven effective. There is some literature to
suggest that nebulization with hypertonic
saline is associated with some clinical ben-
fit, but no large trials have been published.
A number of antivirals have entered clinical
trials, including fusion inhibitors and nucleo-
side analogs. Designing trials for RSV anti-
virals is quite challenging. The highest likeli-
hood of a beneficial effect from antivirals is
expected when administered at an early phase
of infection. However, only a small propor-
tion of untreated children with early RSV
infection will develop severe disease requir-
ing hospital admission. Consequently, trials
with antivirals in infants with early phase
disease require large study populations, mak-
ning 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 notori-
ously difficult, but perhaps essential to treat
children with RSV bronchiolitis at the time
they present at the hospital. Vaccine devel-
opment is promising. Various novel vaccine
strategies have been developed, including
use of recombinant RSV F-based nanopar-
ticles, live-attenuated mucosal vaccines and
adenovirus vector-based vaccines. 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 to 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 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.

REFERENCES