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VIEWPOINTS

Identifying Gaps in Respiratory Syncytial Virus Disease Epidemiology in the United States Prior to the Introduction of Vaccines

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Respiratory syncytial virus (RSV) causes lower respiratory tract illness frequently. No effective antivirals or vaccines for RSV are approved for use in the United States; however, there are at least 50 vaccines and monoclonal antibody products in development, with those targeting older adults and pregnant women (to protect young infants) in phase 2 and 3 clinical trials. Unanswered questions regarding RSV epidemiology need to be identified and addressed prior to RSV vaccine introduction to guide the measurement of impact and future recommendations. The Centers for Disease Control and Prevention (CDC) convened a technical consultation to gather input from external subject matter experts on their individual perspectives regarding evidence gaps in current RSV epidemiology in the United States, potential studies and surveillance platforms needed to fill these gaps, and prioritizing efforts. Participants articulated their individual views, and CDC staff synthesized individuals' input into this report.

Keywords. respiratory syncytial virus; vaccine; monoclonal antibody; epidemiology; vaccine impact.

Respiratory Syncytial Virus (RSV) is a common cause of lower respiratory tract illness and hospitalization in infants and young children [1–3], and may also cause significant morbidity and mortality in older adults and persons with compromised immune, cardiac, and pulmonary systems [4, 5]. Currently, no broadly effective RSV-specific antivirals for active infection or preventive vaccines are available. RSV immune prophylaxis with targeted monoclonal antibodies (mAbs) is available for a limited population of high-risk infants and young children [6]. More than 50 vaccine and mAb products are in development; several are in clinical trials [7, 8]. The increasing number of RSV products in development emphasizes the need for up-to-date information to measure the impact of vaccines, antivirals, and mAb on disease burden, once approved. In the United States, updated epidemiologic information, such as pediatric and adult RSV burden, and surveillance data prior to the introduction of vaccines and RSV therapeutics are needed on hospitalizations, severe illness, and mortality. Further characterization of the outpatient burden is also needed, including medically attended acute respiratory illness (MAARI) and disease in high-risk groups, such as immunocompromised individuals and those with chronic obstructive pulmonary disease and congestive heart failure. Last, improved ways to characterize temporal and geographic patterns of RSV circulation at the local, regional, and national levels are important to help target interventions.

The Centers for Disease Control and Prevention (CDC) convened a 2-day technical consultation with individual US external subject matter experts from academia, epidemiology, government, and public health in Atlanta, Georgia, on 16–17 May 2016. The objectives of the meeting were to solicit individual consultants' input on gaps in the RSV evidence base related

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to the epidemiology of RSV in US populations, how these gaps could be addressed, and relevant activities to be completed prior to RSV vaccine introduction. Individuals' input was solicited topically by vaccine target populations and broader themes, including the integration of laboratory investigations with epidemiologic and surveillance initiatives. Brief presentations were given by the external subject matter experts followed by moderated discussion to obtain the full range of individual perspectives. CDC staff then synthesized individuals' input into this report, which summarizes the technical consultation while highlighting CDC's assessment of important epidemiologic gaps to be addressed prior to the introduction of vaccines, mAbs, and antiviral agents (Table 1).

SURVEILLANCE FOR BURDEN ESTIMATES

Robust RSV surveillance systems are needed to document the RSV disease burden in all age groups, including MAARI and hospitalizations. Much data on RSV disease burden in infancy has been stratified in 3- to 6-month intervals; finer stratification will be needed to anticipate the effect of passive prophylaxis (via maternal immunization or extended half-life mAb) on reducing RSV burden in infancy. To reduce costs of such a surveillance system, bronchiolitis might be used as a surrogate measure of RSV disease in young children, similar to what has been done previously for the inpatient setting [9, 10], and could be analyzed using national ambulatory or hospital databases (eg, Healthcare Cost and Utilization Project's Kids' Inpatient Database) or data from specific health plan systems. Among older children and adults, RSV-associated illness is not clinically different from that due to other respiratory viruses, such that RSV testing will likely be necessary to define disease burden. The age strata included in such analyses should include the oldest age groups (eg, 80 years and older). Studies have documented disease incidence and rates of MAARI and hospitalizations in one aggregate age group in adults (eg, 65 years and older) [11, 12], but using finer age strata to document how burden changes as adults age will be important, yet challenging [13]. In addition, RSV disease severity measures in several age groups across years are needed.

It is important to establish burden of RSV and risk factors for severe illness in pregnant women, including incidence of RSV infection and disease, range of clinical presentations, disease severity during different trimesters of gestation, and the proportion of mothers who are unable to transfer protective concentrations of neutralizing antibody to the newborn. Studies should include investigation of optimal timing for vaccination, quantity and composition of antibody transfer, and duration of protection in infants. Establishment of RSV surveillance platforms for pregnant women would require significant resources, so leveraging ongoing intervention studies might be most cost-efficient.

Surveillance should also include high-risk populations, including preterm infants, children, and adults with underlying heart and lung disease, neurologic diseases, and the immunocompromised [14–16]. Assessment of disease severity among high-risk infants and children should include chronologic age in an effort to determine when risk for a specific RSV outcome equals that of non-high-risk infants and children. Characterization of RSV infections and disease among these high-risk groups will be critical to develop specific vaccine guidance. These studies will allow assessment of risk of RSV infection and spectrum of disease, with documentation of specific outcomes. Data from these populations will inform cost-effectiveness analyses.

Additionally, among all age groups, special populations are at higher risk for more severe RSV disease [17], including human immunodeficiency virus (HIV)–infected individuals [17–19], Alaska Natives [20–25], and Native Americans/American Indians [23, 25, 26]. For the HIV-infected population, well-established research networks could serve as platforms for collection of RSV epidemiological data as well as data on immunologic responses to vaccine.

Similarly, conducting epidemiologic studies among children and adults living in high-risk settings will provide important baseline data for future studies to assess the impact of RSV vaccine. These settings include assisted living and skilled nursing facilities as well as other congregate living arrangements. Studies will need to collect epidemiologic data for residents and healthcare personnel.

Surveillance platforms should be designed to acquire outcome data on proposed target populations. First, there is a need to test for other respiratory pathogens in surveillance studies and platforms. Data on only 1 or 2 respiratory pathogens will not inform the relative contributions of each respiratory pathogen to the disease outcome being studied. Respiratory viruses, other than RSV, important for inclusion in surveillance platforms include influenza, human metapneumovirus, parainfluenza viruses 1–4, adenoviruses, rhinoviruses, enteroviruses, and coronaviruses. Determination of the presence of some viral agents in control subjects, such as adenoviruses and rhinoviruses, should also be assessed, as these can be common in asymptomatic individuals [27]. With future RSV vaccine introduction, documenting how such vaccines impact the relative contribution of each pathogen to the burden of acute respiratory illness will be important. Second, if feasible, surveillance platforms and research studies should not use the traditional influenza-like illness and severe acute respiratory infection definitions, which include fever, but rather, a respiratory symptom–based definition. RSV-infected patients are often afebrile and will be missed if fever is required, particularly among infants and adults [28, 29]. Last, with the introduction of *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes, it will be important to assess the effect that these codes have on RSV case ascertainment. Studies should be conducted to identify which *ICD* codes are best at identifying persons with RSV-associated illness.

DOCUMENTING MORTALITY

Severe outcomes such as mortality are of great interest to clinicians, public health professionals, and policy makers. Although some estimates of RSV-associated mortality in the United States exist [30–32], improved information on pediatric deaths associated with RSV infection in both community and medical settings is highly desirable prior to implementation of RSV vaccines for both pregnant women and infants. Monitoring pediatric deaths associated with acute RSV infection and not due to an underlying medical condition will enable documentation of the potential impact of maternal and pediatric immunization programs, inform vaccine policy and cost effectiveness, and if favorable, support vaccine acceptability. Collecting pediatric RSV death information might be accomplished through local, state, and/or federal public health authorities, similar to reporting of pediatric deaths associated with influenza. State and local health departments can also collect information on pediatric deaths to improve systematic assessment of community-associated mortality. In addition to monitoring pediatric deaths, characterizing the contribution of RSV to adult mortality will be important to capture, particularly among adults with underlying conditions.

IMPACT OF RESPIRATORY SYNCYTIAL VIRUS INFECTION

Investigation of long-term outcomes of RSV infections will be important to document, particularly the long-term effects of RSV infection on recurrent wheezing and asthma. While the relationship between early-life RSV infections and recurrent wheezing and/or asthma has been studied [33, 34], there is a need for long-term (ie, 5–10 years) studies that account for other factors that might confound the association. Reduction of RSV disease through vaccination would allow reexamination of a causal vs a temporal relationship between early RSV infection and asthma. For efficiency, study designs could be nested within the context of a clinical intervention trial, though the population participating in a trial might be different and not reflective of the general population. A potential outcome measurement might be obtained through the use of pulmonary function testing; guidance from pulmonologists would be useful in designing future studies. In addition, studies of pregnant women will help determine the impact of maternal RSV disease on pregnancy and on neonatal outcomes, including fetal loss, preterm labor, and prematurity. This could be done through surveillance or cohort studies of mother–infant pairs followed through pregnancy, birth, and postpartum. Last, in older adults with RSV infection and/or RSV-associated hospitalizations, assessment of frailty and impact on activities of daily living can be used to document the impact of the disease. This has been studied for other infections, such as influenza.

PREPARING FOR VACCINE INTRODUCTION

As RSV vaccines progress through clinical development, 3 major gaps were identified that, if filled, could inform vaccine development and introduction. More studies of correlates of protection among different populations and vaccine types are needed to determine which immune correlates can be used to assess the likely protection afforded by a vaccine. Although neutralizing antibody assays have been used in some candidate vaccine studies, additional immune assays may be helpful to more fully characterize vaccine response. An absolute threshold of protection has not been demonstrated for neutralizing antibody assays due to the different methods used, and a reference standard has not yet been established for neutralizing assays [35]. Specifically, additional studies regarding correlates of immunity among both young children and older populations should be conducted to investigate whether different markers correlate with protective immunity in these 2 populations. Studies may also include assessment of the durability of respiratory mucosal antibodies and their role in protection, correlation of neutralization and viral protein– or epitope-specific antibodies with protection from disease, and the role of cellular immunity in RSV disease outcome.

Second, recording the prevalence of baseline adverse events prior to vaccine introduction should be carefully conducted to ascertain what can be attributed to an RSV vaccine and what is not vaccine-related. Adverse events, including apneic events, sudden infant death syndrome, and recurrent wheezing, will need to be monitored before and after vaccine implementation to assess safety. A better understanding of the epidemiology of these events prior to vaccine introduction would be important to differentiate background from vaccine-associated adverse events.

Last, cost-effectiveness analyses will need to be performed to determine the costs and benefits of vaccine introduction in the target populations. Burden of disease data and indirect and out-of-pocket costs associated with RSV-associated MAARI, hospitalizations, and deaths will be pivotal for performing these analyses. Although challenging to assess, an understanding of collateral damage caused by RSV infection, such as bacterial complications, exacerbations of comorbid diseases, and functional loss, will be important to understanding the true cost associated with infection.

INTEGRATING RESPIRATORY SYNCYTIAL VIRUS LABORATORY DETECTION WITH EPIDEMIOLOGY

In recognition of the rapidly changing landscape of respiratory pathogen diagnostics, such as multiplex molecular platforms, determining how to best integrate laboratory detection with epidemiology before vaccine introduction will be essential. Real-time polymerase chain reaction use provides several benefits of understanding RSV disease including enhancing the

Table 1. Summary of Respiratory Syncytial Virus Epidemiologic Gaps

Epidemiologic Gap	Summary
Surveillance for burden estimates	• Needed for all age groups, with finer age strata for extremes of age • Include MAARI and hospitalizations • Include high-risk populations, including preterm infants, children, and adults with underlying heart and lung disease, neurologic diseases, immunocompromised, Alaska Natives, American Indians, pregnant women, and residents of congregate settings (eg, long-term-care facilities) • Ensure design of surveillance platforms: -Can test for multiple respiratory pathogens -Avoid influenza-like illness and severe acute respiratory infection definitions
RSV-associated mortality	• Collect hospital and community-associated RSV deaths in all age groups
Short- and long-term outcomes of RSV infection	• Investigate effects of RSV on recurrent wheezing and asthma, particularly long-term effects • Conduct studies in pregnant women to determine impact of maternal RSV disease on pregnancy and neonatal outcomes • Assess impact on frailty in older adults
Correlates of protection	• Assess durability of respiratory mucosal antibodies and role in protection • Study correlation of neutralization and viral protein– or epitope-specific antibodies with disease protection • Investigate role of cellular immunity in RSV disease outcome
Cost-effectiveness	• Costs and benefits of vaccine introduction in target populations, which will need up-to-date burden estimates, indirect and out-of-pocket costs associated with RSV-associated MAARI, hospitalizations, and deaths
Assessing RSV diagnostic practices	• Needed to document potential underestimation of disease burden due to testing behaviors
Surveillance once vaccine is introduced	• Adverse events • Genomic sequencing of breakthrough infections to document changes in the virus

Abbreviation: RSV, respiratory syncytial virus.

sensitivity of detection of RSV over classical detection methods such as culture, ability to determine viral load to assess association with clinical outcome and vaccine efficacy, and permitting co-detection of other respiratory pathogens to assess contribution to clinical outcomes.

Assessing diagnostic practices and procedures will be important to document the degree and type of testing that occurs and the magnitude of possible underestimation of disease burden due to testing behaviors. For example, adults may be less often tested for RSV, and they may be tested using methods particularly insensitive for them such as rapid antigen assays. The availability of future RSV antivirals will likely have an impact on testing practices and might lead to perceived increases in RSV disease incidence. It will be important to disentangle the impact of these treatments from the possible impact on RSV testing practices, so as to get a more accurate assessment of RSV epidemiology. Lastly, genotyping of RSV strains prior to and after antiviral and vaccine introduction will help assess for potential antiviral resistance and to monitor for any adaptive genetic mutations following vaccine introduction, respectively. Genome sequencing of breakthrough infections, such as infections that occur after receiving vaccine or mAbs, should also be conducted to document any changes in the virus that might result in enhanced or altered fitness.

DISCUSSION

As RSV vaccines progress in clinical development, priorities for RSV epidemiologic investigations in the United States should be developed with the overarching goal of filling critical knowledge gaps and planning for future vaccine impact studies. Because there are no therapeutic agents or vaccines available currently, relying on physician testing practices to capture RSV cases prior to vaccine introduction will likely be an underestimation of the true burden; therefore, using prospective active surveillance with sensitive diagnostic testing, ideally across diverse ages, populations, and pathogens, would be the optimal method. These platforms would allow further refinement of current disease burden estimates and provide the ability to compare rates of disease outcomes over time, before and after vaccine introduction. Additionally, these surveillance platforms may be useful in determining the relative contributions of other pathogens such as human metapneumovirus, influenza, and other viruses that cause RSV-like illness. Partnerships among academia, local and state health departments, and federal agencies will be instrumental in establishing such platforms.

Developing new surveillance platforms or enhancing existing platforms will allow for an opportunity to implement new assays, both for molecular sequencing information and immunologic assays. Monitoring RSV sequences within platforms in different geographic areas at different times and age groups and within high-risk populations will be important for baseline data. In addition, continued monitoring of RSV sequences among children who have had breakthrough infections after palivizumab prophylaxis as well as children and adults with vaccine failure will need to be documented over time. New immunologic assays may be implemented within surveillance platforms and cohort studies. Advancing the understanding of correlates of immunity while gathering other epidemiologic information will serve as an opportunity to maximize the usefulness of these types of platforms. Furthermore, additional knowledge regarding correlates of protection will be helpful for designing studies to address the potential impact of herd immunity. Coupling the latest molecular tools and immunologic assays with epidemiologic platforms and studies will be crucial for preparation of vaccine implementation recommendations.

Epidemiologic platforms will also need to be expanded to include data collection for short- and long-term outcomes after RSV infection. Evaluation of recurrent wheezing and the

development of asthma following RSV infection requires a multiyear longitudinal study design, and therefore, these types of studies are resource intensive. In addition, a better understanding of the impact of RSV infection among older adults, particularly those adults who may need either home nursing care or long-term facility-related care and those adults who may live with young children, will be important before vaccines become available. Because these types of studies require additional resources, innovative and collaborative approaches will be crucial, as economists and the public health community will need the results of such studies for development of future vaccine recommendations.

Additionally, assessing RSV-associated mortality is a priority. Policy makers want to know the number of deaths caused by RSV and the number of deaths that could have been prevented with an antiviral or a vaccine. However, there are no existing methods of national surveillance for RSV mortality, although a few local jurisdictions and states have made RSV a reportable condition and can collect RSV-associated death data.

These gaps in RSV epidemiology will inform future planning for a pre-RSV vaccine research agenda in the United States. Coordination of efforts among academia, public health, and local, state, and federal partners will be instrumental in ensuring minimal duplication of efforts and harmonizing a comprehensive research agenda for domestic RSV prior to vaccine introduction.

Notes

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