Vaccines and Related Biological Products Advisory Committee Meeting

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FDA Briefing Document

Development of Vaccines for Prevention of Respiratory Syncytial Virus (RSV) Disease in RSV- Naïve Infants

1. Executive Summary

Respiratory syncytial virus (RSV) is the most common viral cause of serious acute lower respiratory illness in infants and young children, with most children infected at least once by the age of 2 years. Globally, RSV is responsible for over 30 million episodes per year of acute lower respiratory infection (ALRI) among children under 5 years of age. Infection is thought to occur at the apical surface of airway epithelial cells, triggering an exuberant local immune response leading to immune cell infiltrates, epithelial desquamation, and bronchiolar edema. Treatment is supportive and currently there is no licensed vaccine available. Although reinfection occurs throughout life, and is usually mild, RSV disease is also known to cause significant morbidity and mortality among older adults, who represent another target population for RSV vaccine development.

In the late 1960's evaluation of a formalin-inactivated RSV vaccine (FI-RSV) in RSV-naïve infants was associated with enhanced respiratory disease (ERD) following subsequent natural RSV infection. This devastating outcome directed focus on identifying the immunologic mechanisms that precipitated ERD as a prelude to further vaccine development. Some of the proposed immunologic mechanisms for ERD included induction of an exaggerated Th2 response leading to excessive pulmonary infiltration with inflammatory cells such as eosinophils and neutrophils, ineffective priming of RSV-specific cytotoxic T lymphocytes, and induction of low-affinity RSV antibodies associated with immune complex formation and complement deposition. Improved understanding of the immunology and pathogenesis of RSV infection combined with establishment of animal models has led to the development of novel candidate vaccines using protein-based, gene-based, vectored, and live-attenuated virus-based platforms. These vaccines prime the immune system in diverse ways and therefore vary in their potential risk for induction of ERD.

Another strategy to ameliorate severe RSV disease in young infants includes passive immunization, either through administration of monoclonal antibodies (i.e., Palivizumab) or via maternal immunization, an approach that could potentially confer protection by augmenting transplacental transfer of maternally-derived antibodies. Although these target populations and targeted interventions are important in the landscape of RSV vaccine development, these interventions are not likely to heighten risk of ERD and are, therefore, beyond the scope of material to be discussed.

The persisting unmet medical need for a vaccine that prevents RSV disease in infants < 6 months of age, combined with an improved understanding of the immunologic mechanisms (both host- and vaccine-intrinsic) that may confer risk for ERD, have encouraged a renewed effort in vaccine development, with products now poised to enter the target population of RSV-naïve infants. Therefore, the purpose of this VRBPAC meeting is to discuss the data needed to support clinical trials of candidate RSV vaccines in RSV-naïve infants, with a particular focus on mitigating the risk of ERD. We ask the committee to discuss the proposed approach to evaluation of promising candidate vaccines:

1. Using preclinical data that demonstrate a balanced cytokine response, animal studies that demonstrate absence of ERD, and human data in RSV-experienced individuals showing an acceptable safety profile with regard to reactogenicity to support the initiation of these new vaccines in otherwise healthy RSV-naïve infants via an age-de-escalation approach.
2. Contingent on acceptable supportive data outlined above, designing a phase 2 study that evaluates for an increased relative risk of severe RSV-disease between RSV-naïve vaccinees and placebo recipients through one RSV season postvaccination in the target population (i.e., > 28 days to < 6 months of age) to support initiating a larger phase 3 study in a comparable population.

2. Introduction

2.1 RSV Disease

RSV is an enveloped, negative-sense RNA virus. The envelope, a host cell-derived lipid bilayer assembled during budding of the virus, contains three transmembrane viral proteins – F (fusion), G (attachment), and the small hydrophobic (SH) protein. The F and G proteins mediate host cell attachment, fusion, and entry, they elicit virus-neutralizing antibodies and are the main targets for monoclonal antibodies and many investigational vaccines.

RSV is a common infection of childhood, with most children affected by 2 years of life. Annually, in the United States, approximately 800,000 infants (20% of the annual birth cohort), seek medical attention for signs and symptoms of RSV infection. While the majority of these infections present as mild upper respiratory illnesses, RSV is also the most common cause of viral lower respiratory tract infection (LRTI) in children in the first year of life, with more severe disease in infants 2-4 months of age. In the US, of those children with severe RSV LRTI, 2-4% are hospitalized due to

bronchiolitis or pneumonia. Globally, RSV is responsible for over 30 million episodes per year of acute lower respiratory infection (ALRI) among children under 5 years of age [1]. Worldwide, RSV disease is an important cause of childhood mortality, with an estimated 66,000 to 199,000 deaths per year [1]. Although the fatality rate in the US of approximately 100 deaths per year is dramatically lower compared with low and middle income countries (LMIC), the overall disease burden is nevertheless substantial, representing the most common reason why previously healthy infants and young children are hospitalized, approximately 2-3% of the US birth cohort [3].

Infection is thought to occur at the apical surface of airway epithelial cells. The infection itself causes some cytopathology, but does not appear to be the primary cause of disease [1]. Instead, an exuberant local immune response influenced by the viral antigen load leads to immune cell infiltrates, epithelial desquamation, and bronchiolar edema[2]. The resulting narrowing of the infant airway further increases the airway resistance. The combination of obstruction and increased airway resistance characterizes acute bronchiolitis in infants [3]. Treatment is largely supportive and based on the severity of disease. Ribavirin is the only U.S. licensed drug approved for the treatment of RSV infection in infants however, it is not recommended for routine use and is used in frequently in part because of concern about potential toxicity to health care providers and conflicting results of efficacy studies. [4,5].

2.2 RSV Prevention

Strategies for prevention of RSV disease in the infant include both passive and active immunization. Active immunization of infants, the topic of this briefing document, will be discussed in detail in the remaining sections. Passive immunization (including perinatal administration of RSV-neutralizing recombinant monoclonal antibodies or maternal immunization intended to enhance transplacental transfer of RSV-specific antibodies) is another approach to RSV prevention. One product conferring passive immunity is currently available and approved; Palivizumab, a monoclonal antibody targeting the RSV-F protein. Palivizumab, which is administered by IM injection once monthly throughout the RSV season, is indicated “for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in children at high-risk of RSV disease.” Based on their ongoing assessment of peer-reviewed publications in areas including RSV disease epidemiology and clinical manifestations, effectiveness of palivizumab in certain pediatric subpopulations, and economic analyses, the American Academy of Pediatrics currently

recommends palivizumab prophylaxis only in preterm infants born before 29 weeks gestation and infants with certain chronic illnesses like congenital heart disease or chronic lung disease [6].

3. Enhanced Respiratory Disease

3.1 Clinical Experience

Vaccine development for RSV is uniquely challenging because in the late 1960's a formalin-inactivated RSV vaccine (FI-RSV) was associated with enhanced respiratory disease (ERD) following subsequent natural RSV infection [7-10]. For example, in one study, the investigators reported that among the 31 FI-RSV vaccine recipients 23 went on to develop RSV infection, 18 (80%) of whom were hospitalized for severe lower respiratory tract infection (LRTI), leading to death in 2 cases. In subjects who received the formalin-inactivated parainfluenza control vaccine, 21 of the 40 subjects developed RSV infection but only 1 (5%) subject was hospitalized for severe LRTI, consistent with background epidemiological rates, and no deaths were observed [9]. Importantly, vaccine-associated ERD after natural RSV infection appeared limited to those infants who were RSV-naïve prior to immunization [11]. RSV-naïve infants given FI-RSV vaccine IM demonstrated neutralizing and complement fixing (CF) antibodies against RSV post immunization at levels comparable to those seen in control subjects after natural infection [7,9]. Interestingly, while the levels of CF antibodies post FI-RSV vaccination are comparable to those after first natural infection, subsequently, in those who developed ERD, CF-antibodies further increased to a level much higher than the CF antibodies observed after natural infection in the unvaccinated controls.

3.2 Immunologic Mechanisms

The immunologic mechanisms responsible for FI-RSV vaccine-associated ERD in RSV-naïve infants have been studied in the decades following the initial observations of ERD in RSV-naïve infants. Histopathologic examination of tissue from the two affected infants who died has been complemented by the development of animal models as outlined below.

Initial review of the autopsy material from the two subjects who died from RSV disease after receipt of the experimental FI-RSV vaccine demonstrated peribronchiolar monocytic infiltration with prominence of eosinophils [9]. Subsequently, a cotton rat model was developed by Prince et al. in which animals challenged with wild-type RSV after receipt of the FI-RSV vaccine demonstrated histopathological evidence of ERD in lung tissues when compared with animals infected with RSV

initially and with unvaccinated controls [12]. Histopathologic examination of ERD-affected lung tissue in cotton rats demonstrated peribronchiolitis and alveolitis with neutrophilic and some lymphocytic infiltrates [12,13]. In addition to their cotton rat studies, the authors conducted their own review of the pathology slides still stored at the treating hospital from the two patients who died from ERD [13]. They concluded that, in contrast to the original report by Kim et al., the predominating pulmonary lesions seen in humans mirrored those seen in cotton rats [13], with the presence of neutrophils, macrophages and lymphocytes more notable than that of eosinophils.

Further exploration of ERD in mice suggested that eosinophils, although not directly causal, might be a marker of an exaggerated Th2 response to FI-RSV vaccination [14]. Studies in mice exploring T helper responses via cytokine profiling have demonstrated an abundance of Th2 cytokines such as interleukin (IL)-4 [15,16] and IL-5 [16] following FI-RSV vaccination compared with intranasal inoculation with live-attenuated RSV [15] and that blocking IL-4 activity with anti-IL4 antibody abrogates the differential effects to FI-RSV vaccination[17]. Similarly, exuberant expression of the Th2-associated cytokine, IL-13, along with pulmonary eosinophilic infiltrates (that are not observed in IL-13 deficient mice) has been reported [18]. It is notable that in this study the vaccine was not FI-RSV but rather a recombinant vaccinia virus expressing the RSV G protein (vvG), suggesting that vaccine associated ERD may not be limited to FI-RSV vaccine. Furthermore, while immunizing mice with vvG induced a Th2-biased immune response, immunization with the same construct containing the RSV F glycoprotein (vvF) did not [19].

Immune complement deposition in the lungs in conjunction with Th2 polarization may be another contributing factor. Th2 skewing, eosinophilic infiltrates, and immune complex deposition were observed in a mouse model mirroring the histopathological presentation seen with atypical measles, which represents another syndrome observed in the setting of natural infection (with measles) following immunization with a formalin inactivated measles vaccine[20].

Th2 polarization [21] may also depend on priming for an over-exuberant RSV-specific CD8+ CTL response [19,22]. Mice challenged with RSV after priming with vvF glycoprotein mounted a strong RSV-specific, MHC class I-restricted cytolytic response, whereas those primed with vvG did not [16]. However, priming with vvF in wild-type mice results in a cytolytic response and mononuclear cell infiltrate after RSV challenge, whereas CTL-deficient mice develop pulmonary eosinophilia [19] and a Th2 cytokine profile [23]. Effective generation of RSV-specific CTLs may require internalization and processing of viral proteins leading to class I MHC-driven antigen presentation. Use of inactivated

vaccines, such as FI-RSV, and protein subunit antigens do not allow for antigen processing and presentation via MHC Class I. However, it could be expected that live-attenuated vaccines and viral vectored RSV products could circumvent the hazards of inactivated vaccines since they would presumably undergo cytoplasmic processing, leading to MHC Class I presentation and an immune response more closely resembling natural infection.

With regard to the impact of other T-cell subsets, murine studies also suggest that a decrease in the numbers of pulmonary regulatory T cells (Tregs) can contribute to inflammatory responses seen in mice given FI-RSV prior to RSV-challenge. These findings were complemented by an evaluation of RSV-infected infants under 1 year of age in which the amount of IL-33 protein present in nasal washes (a cytokine important in maintaining Treg homeostasis in mucosal tissues) was decreased and associated with a concomitant decrease in the numbers of Tregs seen in infants with severe RSV LRTI. Interestingly, and somewhat surprisingly, Th17 related cytokines IL-1β, IL-17A, and IL-23 were increased but associated with a reduction in clinical symptoms of respiratory distress[24].

Another potential mechanistic component of ERD is FI-RSV induction of low-affinity antibodies. Cotton rats vaccinated with FI-RSV (or purified F protein) developed histopathologic evidence of ERD and demonstrated RSV antibodies with low neutralizing activity compared with those elicited following inoculation with live RSV , despite similar antibody levels by ELISA[25]. Passive transfer of antibodies, generated in response to FI-RSV or purified protein vaccine (a protein F and G chimera in this case), to RSV naïve animals did not protect animals against RSV challenge, nor did they induce ERD; suggesting that although these antibodies may play a role in pathogenesis, the antibodies themselves are not causal independently [26]. This phenomenon of low-affinity antibodies is likely due to ineffective TLR stimulation by the FI-RSV vaccine resulting in lack of effective affinity maturation [27]. It is also thought that the FI-RSV vaccine and affinity purified F subunit vaccines used to immunize these animals likely contained RSV-F in the post-fusion conformation and lacked the critical pre-fusion epitopes needed to elicit a high affinity neutralizing response[28]. Thus, vaccines engineered which induce a sufficiently robust and neutralizing antibody response might overcome the contribution of low-affinity, poorly-neutralizing antibodies to development of ERD.

Taken together, the data suggest several biologically plausible causal mechanisms acting in concert [11]: an exaggerated Th2 response along with insufficient regulatory T cell activity or presence; lack of cytoplasmic antigenic processing that typically occurs with viral infection, leading to poor priming of cytotoxic T lymphocytes (CTLs); and failure to produce high-affinity, neutralizing antibodies including a diminished response to the pre-fusion form of the RSV-F protein.

4. Potential RSV Vaccine Platforms

Recently, there has been significant new activity in RSV vaccine development. One contributing factor has been the success of the monoclonal antibody product Palivizumab, which provides a proof of concept demonstration that neutralizing anti-RSV F antibodies can indeed protect against RSV disease. Technological advances in the development of vaccine platforms and in protein characterization and production, characterization of FI-RSV-induced immune responses in animal models, and recognition of the potential for maternal immunization to prevent RSV LRTI in early infancy have also stimulated progress in the field. As a result, approximately 60 RSV vaccine candidates are currently at various stages of development, ranging from early preclinical studies to pivotal Phase 3 trials. These vaccine candidates can be categorized broadly into three basic platforms. The risk of vaccine-associated ERD may vary according to the specific platform and is likely influenced by characteristics of the product itself (e.g., the presence of cellular antigens in the vaccine preparation, the presence of adjuvants, and the dose and route of administration) as well as host circumstances (e.g., the age at time of immunization, since younger infants are likely more predisposed to exhibit a Th2-driven response to antigen exposure, and the interval between vaccination and natural infection, since waning immunity may contribute to ERD). The in vitro, preclinical and human studies performed which have illuminated the mechanisms underlying ERD may also be employed to evaluate the immunologic profiles induced by promising vaccine candidates.

4.1 Protein-based Vaccines

Protein-based approaches, including subunit antigens (e.g., pre and post-fusion F, and G proteins or peptides) whereby antigen is processed through MHC class II pathways would be theoretically more likely to induce a T-cell response pattern similar to FI-RSV. It is not yet clear whether inducing highly functional antibody would be sufficient to overcome the effects of a Th2-biased T-cell response associated with some subunit protein vaccines.

4.2 Gene-based and Vectored Vaccines

Gene delivery approaches include nucleic acid vaccines (e.g. naked DNA or RNA) and replication-deficient vectors such as human and chimpanzee adenovirus vectorss or MVA-vectored vaccines containing one or more RSV antigen inserts. Such vaccines likely behave biologically more like live-virus vaccines in which antigens would be produced intracellularly, leading to induction of cytotoxic CD8+ T cells and a more Th1-biased cytokine response.

4.3 Live-Attenuated Viruses

Clinical data evaluating several hundred infants given intranasal, live-attenuated RSV vaccines have demonstrated that risk of ERD is minimal with this vaccine approach [29], likely because live-attenuated RSV inoculation closely resembles natural infection. The concept is also supported mechanistically: by the absence of ERD in RSV-experienced children who participated in the FI-RSV studies; by clinical data that consistently show decreases in severity of RSV infection among non-naïve populations with each subsequent exposure; and by the basic science of antibody-affinity maturation. This platform provides encouraging proof-of-concept data that ERD is not universal to all RSV-vaccines.

5. Recent Workshops

The public health imperative and the improved understanding of the mechanisms underlying ERD have encouraged RSV vaccine development efforts in recent years, leading experts to convene at numerous workshops and conferences to address the topic. Two of the recent meetings described below highlight some of the conclusions that have collectively emerged from these endeavors.

5.1 FDA/NIH Workshop

In June 2015, the FDA and NIH cosponsored a meeting aimed at identifying solutions to key clinical, scientific, and regulatory challenges, such as how to mitigate the risk of enhanced respiratory disease (ERD), the appropriate endpoints for phase 3 trials to support licensure of RSV vaccines, and critical gaps in knowledge that require additional support to be addressed in the near-term [30]. The scope of the conference discussed assay development, preclinical testing of RSV vaccine candidates, considerations regarding clinical endpoints in RSV vaccine trials to assess prevention of disease in infants, development of RSV vaccines for use in pregnancy, RSV vaccine development in older adults, and challenges, research gaps, and resources. Relevant to the challenges of

immunizing RSV-naïve infants the pathogenesis of ERD was discussed. For vaccine candidates intended for active immunization of seronegative infants, participants discussed the importance of evaluating the mechanisms that may contribute to ERD, such as Th2-biased immune responses and induction of RSV antibody repertoires with low binding affinity and weak neutralizing activity. It was noted that data from vaccine studies in seropositive children will not be conclusive with regard to the risk of ERD in RSV-naïve infants. Experts generally concurred that the testing of live-attenuated vaccine strains may proceed in RSV-naïve infants so long as the virus replication and reactogenicity profiles are acceptable. It was acknowledged that, although feasible, initial clinical studies of other classes of candidate vaccines in RSV-naïve infants will need to be approached judiciously.

5.2 WHO Consultation on RSV Vaccine Development

In March 2015, the World Health Organization convened a meeting to develop consensus and guidance on clinical development pathways and licensure routes for anticipated vaccine candidates currently in development [31]. The meeting's primary objective was to provide guidance on clinical endpoints and development pathways for vaccine trials with a focus on considerations of low- and middle-income countries (LMIC). [These issues were also considered for high-income countries during the June 2015 meeting sponsored by FDA and NIH (Section 5.1)].

Topics included case definitions for RSV disease, clinical efficacy endpoints, and the clinical development pathway for active and passive immunization trials in maternal and pediatric populations, and development of reference reagents for vaccine trials. An overview of RSV disease was provided, including epidemiology, the history and immunology of ERD, including discussion of relevant animal models. A discussion of the current candidate vaccines included specific presentations by industry representatives describing their views on target populations, clinical endpoints, trial designs, and safety measures for products in late-stage development. Regulators from the US, UK, South Africa, and Ghana offered their perspectives on licensure pathways for RSV vaccines; it was emphasized that endpoints should be relevant to target populations.

The following discussion points from the meeting are highlighted due to their pertinence to the design of studies in RSV- naïve infants:

- Duration of follow up for clinical studies in infants should continue through two RSV seasons to provide evidence of efficacy, cross-protection against multiple viral strains, and durability of response.
- In general, there should be an initial requirement for studies of safety and immunogenicity in healthy adults followed by safety data from RSV-experienced subjects before progressing to the target population of RSV-naïve infants.
- Safety and immunogenicity should be assessed with co-administration with representative routine vaccines.

6. Data Supporting Studies in RSV-Naïve Infants

Preclinical testing or studies in adults may help to evaluate reactogenicity and in the case of live-attenuated products, the degree of attenuation. Adult studies are limited by the fact that all adults have typically experienced multiple RSV infections. Antibody responses in this population thus reflect an anamnestic response and may not predict the ability of the vaccine to elicit protective immunity in RSV-naïve infants. Nevertheless, immunogenicity data and RSV-challenge studies in humans may indicate the potential for effectiveness to support continued development of promising candidates. Similarly, safety data in adults and repeat dose toxicology studies could be employed to evaluate vaccine-associated reactogenicity.

6.1 Preclinical Testing

In general, animal models provide important preliminary evidence of effectiveness as well as safety to support introduction of an experimental product into humans. The immune response to inoculation with an RSV vaccine is likely intrinsically different in RSV-naïve infants than other age groups due to their immunological immaturity. This may lead to unique characteristics of host-virus interactions during primary RSV infection in this population. Animal models have been developed that may reproduce some of the pathogenic features consistent with ERD and may therefore be used to assess the potential risk for ERD imparted after immunization. While no single animal model demonstrates all features of FI-RSV associated ERD in infants, it is generally agreed that certain features might be predictive, including a Th2-biased response to immunization and high-titer antibody with low neutralizing activity. Lung eosinophilia, while not causally related to ERD, is a marker of a Th2 type cytokine response and deserves careful consideration if present in vaccinated animals post-challenge. RSV-specific CD8+ T cells mediate virus clearance, but if present

in excessively large numbers may also contribute to increased pulmonary pathology [32]. Thus, use of animal models may help predict whether a candidate vaccine induces immunologic features that coincide with ERD.

6.1.1 Mouse Model

Murine models have the advantage of relatively low cost and well-characterized, homogeneous, strain-specific genetics. Mice are relatively resistant to infection with human RSV, requiring high-dose inoculations to manifest relatively mild disease. However, in addition to providing a preliminary evaluation of immunogenicity, certain strains, such as the BALB/c mouse, are relatively more susceptible and have been used to explore mechanisms of ERD, such as CD4+ Th2/Th1 cytokine balance post-vaccination, evaluation for pulmonary eosinophilia after RSV challenge and production (or lack) of RSV-specific CD8+ CTLs.

6.1.2 Cotton Rat Model

Cotton rats are more permissive to RSV infection than mice, manifesting a disease that more closely resembles human infection, with diffuse infection of the nasal mucosa and replication limited to the bronchiolar rather than the alveolar mucosa, which is seen in the mouse lung. Like humans, they are also susceptible to reinfection [33]. Evidence for alveolitis, interstitial pneumonitis, perivascular and peribronchiolar infiltration with neutrophils and/or eosinophils may be considered markers of ERD [12,34]. An important consideration in evaluation of this model is optimizing the vaccine dose to achieve adequate viral replication in the setting of vaccine -induced neutralizing antibodies: high doses of vaccine might elicit enough neutralizing antibody to prevent substantial viral replication thereby abrogating signs of ERD after RSV challenge while very low doses may elicit meager immune responses, and may be insufficient to induce characteristic pathology.

6.1.3 Bovine Model

The bovine model, though logistically more challenging and expensive to work with, most closely resembles human RSV disease, epidemiologically, clinically, and antigenically. The viruses are host-specific and infection produces a spectrum of disease ranging from subclinical to severe bronchiolitis and pneumonia, with the peak incidence of severe disease in animals less than 6 months of age. Bovine RSV infection in calves reproduces many of the clinical signs associated with human RSV in infants, including fever, rhinorrhea, coughing, and tachypnea [35]. Vaccination with FI-RSV in calves demonstrates a similar clinical and histopathological presentation to what was

observed in the original human trials, including detection of poorly neutralizing antibodies [36]. Homology between the human and bovine RSV F ectodomain results in cross-neutralizing antibodies. Furthermore, bovine and human CD8+ CTLs recognize similar conserved viral proteins. Thus, the bovine model may provide an opportunity to assess for both safety and effectiveness. One concern is that in calves, due to large lungs and patchy pathology, sampling error could interfere with an accurate evaluation for ERD.

6.2 Human studies

6.2.1 Adults

Outside of maternal immunization programs for prevention of RSV disease in the newborn, healthy adults likely do not represent a target population for an RSV vaccine since the disease manifestations are generally mild and usually limited to the upper respiratory tract. However, vaccine studies in adults may be useful for proof-of-concept purposes (e.g., vaccinees are exposed to subsequent RSV challenge with the goal of selecting the most promising candidates for further development), and to generate preliminary safety and immunogenicity data supporting age de-escalation into potential target pediatric populations.

Over 300 healthy adults have participated in human RSV challenge studies [37], which have been designed with the goals of exploring the basic immunology and pathogenesis of RSV infection [38-41] (and reinfection [42]). Well-characterized strains [43] have been used to evaluate the potential effectiveness of antiviral therapies as well [44-46], but this approach is yet to be utilized in vaccine trials. Because adults are immunologically mature and generally have experienced repeated RSV infection, extrapolation of observations in adults to infant populations should be made with caution. Nevertheless, these studies might have utility in identifying both mechanisms and correlates of protection against RSV [47].

6.2.2 RSV-Experienced children and infants

It is generally agreed that although other aspects of vaccine safety may be evaluable, the risk of ERD in RSV-experienced children and toddlers is minimal, due to priming by prior natural infection and to the ontogeny of the fetal/neonatal immune system. Longitudinal data show substantial changes in immune responses over time, particularly during the first 6 months of life. Some data suggest that the immune system in early infancy (e.g., less than 6 to 12 months) is prone to an

imprinting phenomenon, wherein exposure to antigens can predispose to a Th2-predominant response even when re-exposure occurs months later, when the immune system has matured. Thus, while these in RSV-experienced infants may not help to predict risk of ERD for RSV-naïve infants, clinical testing in RSV-experienced children can provide important information about vaccine reactogenicity.

In the initial studies of RSV vaccines in RSV-experienced infants, one issue to address is the possibility that due to persistence of maternal antibody in the infant, some RSV-naïve infants would meet a seropositivity cutoff (i.e., the accepted practical strategy for identifying those who have had prior RSV infection) and be placed at unanticipated risk for ERD due to misclassification as RSV-experienced. However, it is expected that by 6 months of age and thereafter, a positive RSV titer most likely reflects prior natural infection and after 12 months of age it would be nearly indisputable, given the kinetics of maternal antibody in infants [48,49].

6.2.3 Initial studies in seronegative infants

Given the history of vaccine-associated ERD in infants, the development of a vaccine for prevention of RSV disease in RSV-naïve infants must be undertaken with an abundance of caution. In addition to developing preclinical data to support safety in the seronegative population, risk mitigation could include appropriate features in trial design. For example, the selected sample size should expose the fewest infants (recognizing that the whole study cohort might already be immunized by the time potential cases of ERD are observed) while generating sufficient safety data to support a larger phase 3 trial. Similarly, it could be important to explore how vaccine-associated ERD will be identified, as it likely will not be clinically discernable from severe infection, which also occurs intermittently in unvaccinated infants. To address the potential similarity in clinical presentation, enhanced disease could be evaluated by estimating a relative risk of severe RSV disease between vaccine recipients versus controls, (assuming a background rate of hospitalization for severe disease in the range of 3-5%). It will also be important to evaluate duration of protection, since it may be necessary to follow infants through more than one RSV season (or until natural infection with RSV has occurred) to evaluate the impact of waning immunity on the risk of ERD. Ultimately, it is anticipated that answers to these questions will be product specific, and will also depend on the supporting preclinical data, the mechanism of activity of the specific candidate vaccine, and the magnitude of the antibody response seen.

7. Summary

RSV is the leading cause of hospitalization for respiratory disease for infants both in the US and globally. Development of a vaccine remains an important approach to addressing this important public-health need. The observation of FI-RSV vaccine-associated ERD upon subsequent natural RSV infection in the 1960's dampened enthusiasm for introducing new vaccine candidates into RSV-naïve infants. Instead, efforts were redirected towards understanding the immunobiology of this phenomenon and included careful review of the histopathology from the original FI-RSV vaccine-associated ERD cases, development of animal models, and conduct of RSV challenge studies in adults. The work revealed important etiologic factors underlying ERD including (Th2 polarization, vaccine-induced low-affinity antibodies, and a failure to respond to vaccination with RSV-specific CTLs). The same in vitro and preclinical models that were established can now be employed to assess candidate vaccines for immunologic patterns thought to be associated with ERD. A resurgence of product development targeting RSV-naïve infants has ensued driven by the disease burden in this age group, and numerous vaccine candidates with different mechanistic activities are now in development. Given the history of ERD and the anticipated differences for risk of ERD intrinsic to different vaccine platforms, discussion about how to optimize safety when initiating these important studies is imperative.

8. Committee Discussion

CBER will provide final questions for the committee to discuss at the meeting. However in general, the committee will be asked to discuss the value of various types of preclinical (e.g., a balanced cytokine response along with absence of histopathologic evidence of enhanced disease in an animal model) and clinical (e.g., studies in RSV-experienced infants) evidence in supporting initiation of vaccine studies in RSV naïve infants. The committee will also be asked to discuss clinical trial approaches to initiating clinical studies in RSV-naïve infants, including the value of staged designs in which a pilot group is followed through an RSV season prior to enrollment of additional study subjects.

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