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Conference report

Challenges and opportunities in RSV vaccine development: Meeting report from FDA/NIH workshop

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ABSTRACT

Respiratory syncytial virus (RSV) is the most common cause of serious acute lower respiratory illness in infants and young children and a significant cause of disease burden in the elderly and immunocompromised. There are no licensed RSV vaccines to address this significant public health need. While advances in vaccine technologies have led to a recent resurgence in RSV vaccine development, the immune correlates of protection against RSV and the immunology of vaccine-associated enhanced respiratory disease (ERD) remain poorly understood.

FDA's Center for Biologics Evaluation and Research (CBER) and NIH's National Institute of Allergy and Infectious Diseases (NIAID) organized and co-sponsored an RSV Vaccines Workshop in Bethesda, Maryland on June 1 and 2, 2015. The goal of the conference was to convene scientists, regulators, and industry stakeholders to discuss approaches to RSV vaccine development within the context of three target populations - infants and children, pregnant women, and individuals >60 years of age. The agenda included topics related to RSV vaccine development in general, as well as considerations specific to each target population, such as clinical and serological endpoints. The meeting focused on vaccine development for high income countries (HIC), because issues relevant to vaccine development for low and middle income countries (LMIC) have been discussed in other forums. This manuscript summarizes the discussion of clinical, scientific, and regulatory perspectives, research gaps, and lessons learned.

1. Introduction

RSV is an enveloped, negative-sense RNA virus. The envelope, which is a host cell derived lipid bilayer assembled during budding of the virus, contains 3 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 are the major neutralizing antigens and are the target for monoclonal antibodies and many investigational vaccines.

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, edema, and bronchoconstriction [2].

Globally, RSV is responsible for > 30 million episodes/year of acute lower respiratory infection (ALRI) among children < 5 years of age [3]. It is an important cause of childhood mortality, with an estimated 66,000–199,000 deaths per year worldwide [3]. Although the case fatality rate is dramatically lower in the U.S. compared with low and middle income countries (LMIC), the overall disease burden is substantial. It is one of the leading causes of hospitalization and health care visits in children < 5 years of age [4].

Most children are infected with RSV at least once in the first 2 years of life. In one US cohort study, the cumulative rate of infection was 68% in the first 12 months and 97% before 24 months of age [5]. Reinfection occurs frequently in early childhood [6], and

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recurs periodically throughout life. Severity of disease tends to diminish with subsequent reinfections until late in life; among older adults, the disease burden attributable to RSV is comparable to the burden attributable to influenza virus [7].

2. Previous and current vaccine development

In the 1960s, an RSV vaccine candidate was developed using wild-type virus isolated from a human volunteer. The "Bernett strain" was grown in vervet monkey kidney cell culture, formalin-inactivated, and precipitated with an aluminum adjuvant (herein referred to as FIRSV). In clinical trials, vaccination with FIRSV not only failed to prevent RSV infection, but caused an increased proportion of subjects with severe infections relative to the placebo group. In a study evaluating the vaccine in the youngest age cohort (infants enrolled between 2 and 7 months of age), among infants who contracted RSV, 16 of 20 (80%) vaccinated subjects compared with 1 of 21 (5%) control subjects required hospitalization at the time of infection [8]. Two vaccinated infants died as a result of severe RSV infection. This experience had a profound negative impact on subsequent RSV vaccine development.

Although the causal pathophysiologic and immune mechanisms that led to enhanced disease in the clinical studies of FIRSV have yet to be fully elucidated, the enormous effort to understand these mechanisms contributed greatly to the field of RSV vaccinology [9,10]. Recent years have seen significant new activity in RSV vaccine development. Some of the contributing factors include the success of the monoclonal antibody product (palivizumab), technological advances in the development of vaccine platforms and in protein characterization and production, characterization of FIRSV induced immune responses in animal models, and recognition of the potential for maternal immunization to prevent RSV ALRI in early infancy. Development of RSV vaccines is recognized as a global priority by national governments, the World Health Organization [WHO], the pharmaceutical industry, and nonprofit health organizations. As a result, approximately 60 RSV vaccine candidates are currently in development, ranging from early preclinical to pivotal Phase 3 trials. These vaccine candidates can be categorized broadly into three basic platforms:

Protein-based

- Whole, inactivated virus.
- Particle based (e.g., virus-like particles (VLP), virosomes).
- Subunit antigens (e.g., F, pre-F, and G proteins and peptides).

Gene-based

- Nucleic acids (e.g., naked DNA or RNA).
- Replication- deficient vectors (e.g., adenovirus-based vectors).

Live-attenuated

- Recombinant/chimeric viruses (e.g., hPIV, SeV).
- Wild-type RSV, attenuated.

This conference was convened to assess the state of the science pertaining to RSV vaccine development and to address major questions faced by all stakeholders, such as how to mitigate the risk of enhanced respiratory disease (ERD), particularly through animal modeling, 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.

3. Assay development

Assays for vaccine evaluation need to match the vaccine approach being studied. Most RSV vaccines in development include the F and/or G glycoproteins and are intended to induce neutralizing antibody. Some vaccines are designed to induce antibody-dependent cell-mediated cytotoxicity (ADCC) via immunity to the SH protein. Others are intended to induce $CD8^+$ T cell responses alone or in combination with antibody-mediated immunity and include gene-based expression of F, N, M2-1, or other internal proteins. Some vaccine programs are focused on intranasal or oral delivery to directly induce mucosal immunity in addition to systemic immune responses, while others are delivered parenterally and depend on antibody transudation into mucosal secretions and/or T cell migration into the lung epithelium. Therefore, a variety of assay approaches will be needed to evaluate immunogenicity endpoints.

The majority of vaccine strategies involve induction of antibodies to the F glycoprotein. Solving the structure and identifying mutations that stabilize F in its functional prefusion trimer conformation provide new opportunities for measuring antibody binding for vaccines that include the F antigen. Since prefusion (pre-F) and postfusion (post-F) forms of F likely share exposed epitopes, simply measuring the magnitude of ELISA binding may not discriminate between these conformations. Pre-F and post-F constructs as reagents for either adsorption or competition assays are used to detect antibody that binds the unique surfaces of pre-F where the targets most sensitive to neutralization are present.

Epitope-specific responses can be measured in binding assays using monoclonal antibody competition (e.g., the palivizumab competing antibody (PCA) assay). This can be done in an ELISA format, using plasmon resonance (Biacore), biolayer inferometry (Octet), and other technologies. Importantly, because pre-F is likely the locus of most, if not all, of the immunodominant F-specific neutralizing epitopes, defining epitope-specific responses using pre-F antigen is likely to be useful. In addition to binding assays, competition using pre-F designed to knock out selected antigenic sites can be used to determine epitope-specific neutralizing activity [11].

RSV neutralizing activity in serum has been shown to correlate with protection against RSV ALRI in rodents [12] and human infants [13,14]. Neutralizing activity can be measured using live virus in a traditional plaque-reduction assay or a microneutralization format using plaque counting or colorimetric endpoints. These assays involve mixing virus and antibody dilutions and adding to cell monolayers (e.g., HEp-2) with or without the addition of exogenous complement. The activities being measured include attachment inhibition, fusion inhibition, cell-to-cell spread, and potentially Fc-mediated complement-dependent mechanisms because the assays require multiple rounds of virus replication. Other neutralization assays are based on reporter viruses using fluorescence or luminescence detected by flow cytometry or plate readers, but these assays only detect inhibition of F-mediated viral entry, either attachment or fusion inhibition. There is a major neutralizing epitope on the G glycoprotein in the central conserved region, so if G is an important antigenic component of an effective vaccine, binding assays using peptides or full-length G glycoprotein would be relevant. To measure G-specific neutralizing activity, assays using human airway epithelium or cells expressing CX3CR1 may be necessary because G is dispensable for RSV entry into immortalized cells lines due to the high content of heparin sulfate (which can mediate G-independent viral entry) on their surface.

In partnership with the National Institute for Biological Standards and Control (NIBSC), NIH and WHO, the international nonprofit group, PATH, is conducting a survey study across diverse neutralization assay formats (at least 10 different RSV neutralization assay methods are currently in use). The objectives of this effort include: (1) understand assay output variability, (2) assess feasibility for harmonization of results using a reference standard, and (3) evaluate sample types that could be appropriate for use as a standard. The goal is to establish reference reagents to allow

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