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Respiratory Syncytial Virus Vaccines:

Are We Making Progress?

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Globally, it is estimated that respiratory syncytial virus (RSV) causes 33 million new episodes of acute lower respiratory tract infection (LRTI) in children <5 years of age and ≈120,000 deaths annually. In infants, RSV represents the leading cause of hospitalization worldwide and the second commonest cause of mortality in low- and middle-income countries.[1,2] RSV also causes significant disease in immunocompromised hosts and the elderly and has been associated with the development of asthma.[3] The increasingly recognized burden of RSV disease has made the development of a vaccine(s) a global health priority. The World Health Organization recently released a roadmap to facilitate the development and implementation of vaccines and monoclonal antibodies (mAbs) and estimated that RSV vaccination will be available in the next 5–10 years.[4] This review summarizes the strategies and challenges associated with RSV vaccine development and the vaccine candidates undergoing clinical evaluation, with a focus on those geared toward the pediatric population.

THE STRUCTURE OF RSV

RSV has a negative sense nonsegmented RNA genome that encodes 11 proteins: 3 are nonstructural (NS1/NS2—that counteract interferon responses—and M2–2), and 8 are structural proteins. Of those 8 proteins, 5 are internal [N, P, M, M2–1, L]), and 3 are

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embedded in the virion membrane: the small hydrophobic (SH), fusion (F) and attachment (G) glycoproteins. RSV G and F carry antigenic determinants that elicit neutralizing antibodies. However, F is the preferred target for vaccine, mAb and antiviral development because it plays an essential role in host cell viral entry, is highly conserved within and among RSV A and B subtypes and because of its 6 antigenic sites that elicit the production of high-potency neutralizing antibodies (≥90% of neutralizing antibodies are directed against this protein).[5] Most of the G protein is covered in glycans, leaving the central conserved domain available for neutralizing antibody binding. Except for this domain, G is not well conserved and it is recognized by few neutralizing antibodies, which has reduced enthusiasm for it as a vaccine target.

Our understanding of the F protein in its 2 conformations, prefusion (pre-F) and postfusion (post-F), has revolutionized the field of RSV biology. Pre-F, the active form of F on the virion, is metastable and switches unpredictably to the stable post-F conformation that once it is folded cannot return to the pre-F form. Antibodies that bind to pre-F are more efficient at neutralizing RSV than those against post-F. As examples, antibodies against site ϕ, a pre-F-specific epitope, are 150 times more potent than palivizumab that binds to site-II, present in both F conformations, while antibodies against site I, exclusively present in post-F, show weak or no neutralization.[5] In addition, non-neutralizing antibodies to F, G and also SH, may inhibit infection by complement-mediated neutralization or antibody-dependent cell-mediated cytotoxicity. Furthermore, all viral antigens have the potential to induce protection by T-cell-mediated immunity.

CHALLENGES FOR RSV VACCINE DEVELOPMENT

Despite the burden associated with RSV, and after 60 years of active research, there is no licensed vaccine due in part of our incomplete understanding of the pathogenesis of the disease. In general, primary RSV infections are more severe; however, reinfections are common throughout life as immunity is neither complete nor long-lasting. The ideal vaccine should induce a more durable and improved immune response than natural infection.

Legacy of the Formalin-inactivated Vaccine

RSV vaccine development has been hindered after the safety concerns of the first RSV vaccine that was developed in the 1960s. The formalin-inactivated-whole virus alum-precipitated vaccine, which recent evidence indicating that it was directed against post-F, was associated in naive infants, but not older children, with enhanced RSV disease (ERD) and 2 deaths upon subsequent exposure to natural RSV. The mechanisms of ERD are not well understood, but it appears that an excess of non-neutralizing antibodies coupled with a skewed T-helper 2 (Th2) immune response, and complement deposition in the lungs contributed to its development. This is a critical aspect that is being considered for the development of inactivated vaccines, and strategies to assess safety risks according to the different vaccine platforms in the infant population are required.

Target Populations

There are different age groups that will benefit from RSV vaccines, and these might require different approaches: young RSV-naive infants (<4–6 months), children >6 months and the elderly. Vaccination of older children (2–5 years of age) may also limit transmission, as older siblings frequently introduce RSV into the household.

Infants <4–6 Months

This age group has an immature/developing immune system characterized by low expression of interferon, abundance of regulatory T cells with tolerogenic reactivity and a limited B-cell repertoire because of inefficient generation of somatic hypermutations. All these factors are associated with a poor response to foreign antigens and the generation of high-affinity matured antibodies. In addition, the presence of maternal antibodies may interfere with vaccine immunogenicity. Young infants represent the main target population because the peak of severe RSV disease occurs in the first 2–3 months of life. This age group would likely benefit from maternal vaccination or neutralizing mAbs administered at birth.

The main goal of maternal vaccination is to boost neutralizing RSV titers and thereby transplacental antibody transfer. However, the optimal timing for vaccination (2nd or 3rd trimester) and the durability of protection in the infant need to be defined. This coupled with the high prevalence of hypergammaglobulinemia in low- and middle-income countries, associated with HIV or malaria, which impairs transplacental antibody transfer, suggest the need for high maternal antibody titers to compete for transfer. Nevertheless, RSV antibody transfer through breast-feeding (IgG > IgA) may complement the maternal vaccination strategy.[6] Vaccinating pregnant women could be questioned if it exclusively benefits the infant and not the mother. The limited data available in pregnant women are mostly derived from influenza surveillance studies with rates of RSV infection varying from 0.2% to 13%, which likely underestimates the real incidence of RSV during pregnancy. The concerns regarding adverse fetal outcomes are relatively low, because this would not be the first time the mother's immune system encounters RSV antigens and the safety profile of other vaccines used in pregnancy, such as tetanus, diptheria and acellular pertussis (Tdap) or influenza, is excellent. A number of RSV maternal vaccines are currently in clinical development (Table 1).

Older Infants and Children

Based on the experience of the formalin-inactivated-RSV vaccine, within this age group those who are naive at the time of vaccination might be at risk of ERD with protein vaccines. This target population would likely benefit most from live-attenuated or vectored vaccines.

The Elderly

On the other side of the spectrum, the immunosenescence of adults >65 years of age and the presence of additional comorbidities may compromise vaccine responses and the ability to assess efficacy. This population might benefit most from adjuvanted vaccines.

Clinical Endpoints

The ideal vaccine should be able to prevent severe disease and limit transmission, but the lack of a standard definition of severe disease or precise markers to assess severity in infants has been a barrier for vaccine development. Clinical endpoints that define a successful vaccine might be different depending on the target population. Hospitalization and other endpoints that capture the inpatient/outpatient burden of the disease, such as a reduction in medically significant visits for RSV infection, should be considered.[7] Developing composite endpoints that include a combination of viral (and possibly bacterial) factors, clinical parameters, and fast turn-around point of care biomarkers could help with patient classification and to standardize definitions.[8] Also, long-term follow-up is recommended, as studies suggest that interventions reducing the acute burden of RSV disease may also impact the development of recurrent wheezing/asthma.[9]

Immune Correlates of Protection

Serum neutralizing antibodies (IgG against pre-F > post-F and G) represent the main surrogate of protection, as shown by the effectiveness of immunoprophylaxis with anti-F mAb (palivizumab) in high risk infants. However, a standardized protective threshold has not been defined yet. Newer systems biology approaches are helping to define the optimal correlates of protection, which are complex and depend on multiple factors, rather than a single cutoff value in antibody assays, and will need to be adjusted to each target population. Other cocorrelates of protection may include, F-specific epitope antibodies, mucosal IgA, interferon responses, antibody-dependent cell-mediated cytotoxicity and cell-mediated immunity. In addition, a balanced Th1/Th2 immune response, indicated by a high IgG2a/IgG1 ratio, is desirable.

Other Factors

The lack of an ideal animal model has also slowed down RSV vaccine development. Human challenge models mostly reproduce upper but not LRTI, limiting the generalizability of the results or the ability to assess the impact of vaccines on disease severity. There are also gaps in RSV epidemiology with lack of accurate information defining the temporal and geographic patterns of RSV circulation in inpatients/outpatients, across different age groups or RSV-associated mortality. Implementing robust multiplex polymerase chain reaction-based surveillance platforms could help to assess the impact of interventions on the burden of RSV disease, to identify possible escape mutants, or the contribution of other respiratory viruses causing RSV-like illnesses.

VACCINE STRATEGIES

The most effective approach to protect young infants and children from severe RSV infection may be a combined strategy using passive and active immunization: either maternal vaccination with stabilized pre-F or virus-like particles containing the F protein or mAb against pre-F at birth; followed by pediatric active immunization with a live vaccine, either attenuated RSV or the pre-F protein expressed from a virus vector. There are 39 vaccines candidates under development (http://www.path.org); of those 19 are undergoing clinical trials (Table 1).[10]

Protein Vaccines

Particle Based—The recombinant adjuvanted RSV post-F nanoparticle vaccine is the most advanced vaccine in clinical development. Results from a phase-3 clinical trial that enrolled 4636 pregnant women on the third trimester demonstrated a decrease in RSV hospitalizations in the offspring; however, the study did not meet the primary endpoint defined as prevention of medically significant RSV LRTI. The potential approval of this vaccine is being evaluated. It also aims to target elderly individuals and children >6 months to 5 years of age.

Subunit Vaccines—These vaccines consist of purified, adjuvanted proteins and use stabilized pre-F as the main antigen with promising results. They are mainly directed at pregnant women or the elderly because of the risk of ERD in RSV-naive infants. Other subunit vaccines in clinical or preclinical stages are using SH or G as main vaccine antigens.

Live Vaccines

Vector Based—There are 5 vector-based vaccines in clinical development. The first 4 use adenovirus as a vector, while the other uses a modified vaccinia Ankara virus. Two of them are intended for use in pediatric seronegative patients. All of these vaccines express RSV F (pre-F > post-F depending on the vaccine) and 2 of them also express other viral antigens (N, M2 or G proteins).

Live-attenuated vaccines—(LAVs) represent an attractive alternative for older infants and young children. LAVs are administered intranasally and are able to elicit broad innate, humoral and cellular responses and replicate in the respiratory tract despite the presence of maternal antibodies. Importantly, these vaccines have not been associated with ERD and are considered safer in infants. The use of reverse genetics has made possible to incorporate different mutations in the viral genome, making LAV sufficiently immunogenic and, except for rhinorrhea, not associated with adverse events. There are 6 intranasal LAVs undergoing phase-1 clinical trials; 4 are using attenuated RSV, one Sendai virus as a backbone expressing RSV F and the last one is a chimeric vaccine using bacille Calmette-Guerin (BCG). The BCG/RSV vaccine is the only LAV intended to be administered systemically (subdermal) and in newborns.

MONOCLONAL ANTIBODIES

mAbs are also being evaluated for the prevention of RSV LRTI in young infants. Of those, suptavumab (REGN-2222), that targeted the pre-F-specific site V, has been discontinued from the market after it failed to prevent serious RSV LRTI in premature infants (primary endpoint). During the study, RSV type B was the predominant circulating strain and developed escape mutations that conferred resistance to this mAb. MK-1654 is an extended half-life mAb currently undergoing phase-I clinical trials and it is directed against antigenic site-IV (present the pre-F and post-F forms). Nirsevimab (MEDI8897) is a highly potent human neutralizing IgG_{1K} targeting the pre-F-specific antigenic site ϕ. It also has an extended half-life because of modifications in the FC region using YTE technology. MEDI8897 is entering phase-3 clinical trials with the intent to provide passive immunization

for prevention of severe RSV LRTI to all infants (preterm and full term), using a fixed, once per season intramuscular dose.

SUMMARY

Over the past decade, there have been significant advances in our knowledge of RSV molecular and structural biology and in the understanding of the human immune response to RSV. Despite the barriers, there are several opportunities for RSV vaccine development to protect the most vulnerable populations. The increasing interest of academic, industry and international bodies, such as the World Health Organization or Bill & Melinda Gates Foundation, is helping to move the field forward, promoting the implementation of surveillance platforms and standardization of clinical definitions, assays and surrogate markers of protection.

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TABLE 1.

Landscape of RSV Vaccines Undergoing Clinical Trials

Vaccine Type	Viral Target	Adjuvanted	Target Population	Route of Administration	Clinical Development	Advantages	Disadvantages
Protein vaccines							
Particle based							
RSV F nanoparticle; (Novavax, Rockville, MD)	Post-F (prefusogenic)	AlPO4 or matrix M	Pediatrics[*]; elders[†]; maternal[‡]	Systemic	Phase-1[*]; phase-2[†]; phase-3[‡]	Safe Immunogenic	Post-F based Risk of ERD Ab durability
Subunit							
DS-Cav1; (NIH)	Pre-F	Alum	Maternal, elders	Systemic	Phase-1	Induce high-affinity neutralizing Ab	Factors affecting transplacental transfer
GSK RSV F[§]; (GlaxoSmith-Kline, Brentford, UK)	sPre-F	±Al(OH)3	Maternal, elders	Systemic	Phase-1		Instability of pre-F[§] Ab durability
DPX-RSV; (Immunovaccine, Nova Scotia, Canada and VIB)	SHe	Al(OH)3, lipid in oil	Elders	Systemic	Phase-1	Facilitate crosspriming	No protection for premature infants
RSV-F (Janssen, Beerse, Belgium)	Pre-F	ND	Elders	Systemic	Phase-1		
RSV-F (Pfizer, New York, NY)	Pre-F	ND	Maternal, elders	Systemic	Phase-2		
RSV-G (Beijing Advaccine Biotech, Beijing, China)	G	ND	Pediatrics, elders	Systemic	Phase-1		
Live vaccines							
Vector based							
AdV26 RSV; (Janssen)	Pre-F	No	Pediatrics, elders	Systemic	Phase-2	Not attenuated Low risk of ERD	Potential for developing antivector immunity
ChAdV155-RSV; (GlaxoSmith-Kline)	Pre-F, N, M2–1	No	Pediatrics	Systemic	Phase-2	No interference with maternal Abs	
VXA-RSV (AdV5); (Vaxart, San Francisco, CA)	Post-F	dsRNA	Elders	Mucosal and systemic	Phase-1		
MVA-BN RSV; (Bavarian Nordic, Kvistgaard, Denmark)	Post-F, GA/GB, N, M2	No	Elders	Systemic	Phase-2		
Live attenuated/chimeric							
rBCG/N-hRSV; (Universidad de Chile)	N	No	Newborn	Systemic	Phase-1	Predominant Th1 immune responses	
RSV/ΔG (Intravacc, Bilthoven, Netherlands)	Lacks G	No	Pediatric	Mucosal	Phase-1	Low risk of ERD	Balance of attenuation/ immunogenicity

Vaccine Type	Viral Target	Adjuvanted	Target Population	Route of Administration	Clinical Development	Advantages	Disadvantages
RSV ΔNS2 Δ1313/1314L; RSV D46/NS2/N/ΔM2–2; RSV 6120/ΔNS2/1030$_S$ (Sanofi-Pasteur, Lyon, France and NIH)	RSV Pre/Post-F	No	Pediatric	Mucosal and systemic	Phase-1	Intranasal delivery Replication in presence of maternal Ab	Reverse to wild type Stability for mass production
SeV/RSV; (St Jude Hospital)	F	No	Pediatric	Mucosal	Phase-1	Broad stimulation of immune responses	

For VXA and MVA, it appears that expression of post-F > pre-F. ERD indicates: enhance RSV disease.

*Phase-1 in Pediatrics.

†Phase-2 in Elders.

‡Phase-3 in Maternal.

§Withdrawn.

Adv indicates adenovirus; Al(OH)3, aluminum hydroxide; AlPO4, aluminum phosphate; BN, Bavarian Nordic; ChAdV155, chimpanzee adenovirus 155; DPX, small cell epitope peptide vaccine; dsRNA, double stranded RNA; GSK, GlaxoSmith-Kline; MVA, modified vaccinia Ankara virus; ND, not disclosed; NIH, National Instutes of Health; rBCG/N-hRSV, recombinant bacillus of Calmette-Guérin/N-human RSV; s, soluble; Th, T-helper; VXA, Vaxart.