Respiratory syncytial virus

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Introduction

The impact of respiratory syncytial virus (RSV) on global health is becoming increasingly appreciated. Advances in RSV diagnostic methods, with increasing availability of rapid sensitive and specific diagnostic tests, as well as enhanced understanding of the molecular structure and function of the virus, have accelerated our understanding of RSV biology and epidemiology over the past decade. Serious RSV disease in infants, elderly, and immunocompromised hosts is now well recognized, and development of potential RSV preventative measures are underway. Although no RSV vaccine is currently available to prevent RSV, the World Health Organization (WHO) estimates that an RSV vaccine will be in clinical use within the next 5–10 years [1]. Many strategies for the prevention of RSV in infants, children, and adults are under consideration. The potential of maternal immunization to prevent serious disease in infants will be discussed in this chapter.

Clinical burden of disease and epidemiology

Clinical burden of RSV in children

Respiratory syncytial virus is the primary cause of viral lower respiratory tract infection (LRTI) in infants worldwide. RSV is associated with high rates of hospitalization, particularly in infants less than 6 months of

age [2], with an estimated global burden of 33 million infections and 60,000 deaths annually in children under five [3]. In the United States (US) and many industrialized countries, RSV is the most common infection resulting in hospital admission among infants [2–4]. In temperate climates, RSV produces annual midwinter epidemics clinically characterized by bronchiolitis in infants. RSV outbreaks are less clearly delineated in tropical areas, where year-round infection may occur with or without epidemics [5]. An estimated 99% of deaths due to RSV in children occur in resource-limited settings, making the prevention of RSV-associated mortality in regions of the world with limited access to health care a high priority [3, 4, 6, 7].

Clinical manifestations of RSV infection in young children include nasal congestion, difficulty breathing potentially resulting in respiratory distress, bronchiolitis and pneumonia with or without fever, as well as apnea in young infants. While RSV associated illness is common in children less than 5 years of age, moderate to severe disease is seen primarily in infants. RSV disease in infants under 6 months of age accounts for about half of documented RSV cases in many studies. The vast majority of RSV-related hospitalizations occur in young children during the first two years of life. In one prospective cohort study in Arizona, US, almost 30% of infants with a medically attended illness in the first year of life was due to RSV, which was usually diagnosed as bronchiolitis or pneumonia [8] and similar rates have been observed in developing countries [9]. At least 2% of all US infants are hospitalized with RSV disease, with the peak occurrence in the second month of life. Hospitalization rates are higher in risk groups including premature infants and those with underlying cardiac or pulmonary diseases. Infants in aboriginal populations such as Native Americans or Alaska Natives may have hospitalization rates 3–5 times higher than that of the general US population [2, 10, 11]. To date, RSV treatment is mainly supportive and consists of respiratory support and fluid management. Support to treat apnea associated with RSV infection in preterm and very young infants may also be required. Despite the relatively minimal care typically administered to RSV-infected children in industrialized countries, RSV-related mortality is substantially higher in low and middle income countries [3, 4].

Clinical burden of RSV in pregnant women

RSV is a common cause of symptomatic respiratory illness in healthy adult populations between 18 and 60 years of age. Compared to influenza, RSV infection symptoms generally appear to last longer with less fever. In 2001 in a US study, 26% of adults with RSV had lower respiratory tract symptoms, defined as tracheobronchitis, bronchitis, or wheezing [12]. In a more recent study of pneumonia in hospitalized patients over the age of 18 years, RSV was responsible for between 0.2 and 5 cases of pneumonia

per 10,000 individuals, with increasing hospitalization rates associated with increasing age [13]. However, rates and severity of RSV infection or RSV pneumonia in pregnant women remains poorly characterized, reflecting a major gap in RSV epidemiology [14].

Most studies of RSV infection or disease during pregnancy are based on case reports or secondary analyses of influenza vaccine trials [15–17]. A recent prospective longitudinal community based study conducted in Houston, Texas, provides additional information regarding the epidemiology of RSV and other respiratory viruses in healthy pregnant women receiving prenatal care at a community obstetrical clinic [18]. This study evaluated both symptomatic and asymptomatic women in an obstetric population that reflected the contemporary make-up of pregnant women in the US, with a median age of 31 years and a broad representation of racial and ethnic backgrounds. The most significant finding in the Houston study was that over one-third of women with acute respiratory symptoms had disease consistent with LRTI, which the authors defined as difficulty breathing or shortness of breath, wheezing, or cyanosis. Morbidity was associated with multiple respiratory viruses including RSV, with considerable symptoms noted for all viruses. Common viruses detected in this study included rhinovirus (27%), coronavirus (17%), and RSV. The overall attack rate of RSV among ambulatory pregnant women in this population was 10% based on laboratory-confirmed RSV infection documented by polymerase chain reaction (PCR) testing of respiratory secretions, and up to 13% when serologic diagnosis was added [19].

Data from influenza vaccine trials has been commonly used to determine the incidence of RSV and other respiratory viruses in order to estimate RSV epidemiology in pregnant women. This approach permits the evaluation of many pregnant women in prospective studies but has potential issues, with the main limitations being the use of influenza-like-illness (ILI) criteria requiring the presence of fever to guide which samples are obtained for the diagnosis of respiratory illness. Also, surveillance has often been ongoing only during influenza season. ILI criteria are typically based on the combination of fever and cough and/or sore throat, but the majority of cases of RSV in adults are afebrile [12]. Additionally, influenza and RSV seasons may not overlap, likely leading to underestimation of RSV burden if sampling is performed only during periods of influenza virus circulation [20]. Two large maternal influenza vaccine studies sponsored by the Bill & Melinda Gates Foundation evaluated the incidence of maternal respiratory disease due to RSV during pregnancy [21, 22]. In Nepal, where nasal swabs were collected prospectively from women with a fever and respiratory symptoms year round, RSV prevalence was 0.2%, with an incidence of 3.9/1000 person-years overall. In South Africa, RSV prevalence during the maternal influenza trial where specimens were

obtained based on the presence of any respiratory symptoms was much higher at 2%, or an incidence of 14.4–48.0 cases per 1000 person-years overall [23]. Importantly, no maternal RSV case in the South Africa trial had a fever documented. RSV was not associated with an increased risk of low birth weight or preterm birth in either the South African or Nepal studies, although numbers of RSV-infected women in both studies were small.

More recently, the Pregnancy Influenza Vaccine Effectiveness Network (PREVENT) of the US Centers for Disease Control and Prevention and sites in four countries evaluated the impact of RSV in hospitalization among pregnant women in high income countries – the US, Canada, Israel and Australia [24]. Among a total population of 1,604,2016 pregnant women hospitalized over various seasons from 2010 to 2016, 15,287 (15%) had at least one hospitalization associated with a diagnosis of acute respiratory or febrile illness, but only 6% of those admitted were tested for viruses, including RSV, highlighting the low level of awareness and testing for RSV by obstetric providers. Importantly, 2.5% (range 1.9–3.1%, 21 RSV-positive cases in total) of women tested were positive for RSV by PCR. Two-thirds of the tests and diagnoses of RSV occurred in the third trimester of pregnancy. A pre-existing health condition was documented in 38% of women, with asthma being the most common. Importantly, a diagnosis of pneumonia was more frequent among RSV-positive compared to RSV negative women (38% vs. 19%, $p = 0.046$), and nearly half of RSV-positive women required admission for ≥ 3 days. A significant association was documented between admission for RSV confirmed infection and subsequent preterm birth, which occurred in 29% of RSV-positive women compared to 15% RSV-negative women ($p = 0.034$). There were, however, no differences in the frequency of overall low birth weight and small-for-gestational age infants between RSV-positive and negative women. This study suggests that RSV is an important cause of LRTI in hospitalized pregnant women, particularly those with underlying medical conditions, however given the small proportion of pregnant women tested for RSV during a hospital admission with acute respiratory illness, further data is required to fully appreciate the burden in this population.

Protection against RSV

Maternally-derived antibody

RSV was first identified by Chanock in 1957 [25] and identified as a pathogen in young infants several years later [26]. Reasons for disease predilection in young children have been studied since that time,

and the impact of maternal antibody on the subsequent development of RSV disease in young children has been under investigation for years. Originally, concern for potential augmentation of RSV disease in the presence of maternally-derived antibody in young infants was considered a possibility, but subsequent studies utilizing different study designs and laboratory analysis of RSV-specific antibodies dispelled that theory, and actually demonstrated that infants with RSV disease have a 2–4-lower concentration of RSV-specific antibodies compared to infants with no disease [27–32]. In a landmark study conducted by Glezen et al. in Houston, Texas, RSV-specific serum neutralizing antibodies were shown to be efficiently transferred from the mother to the newborn and high levels of neutralizing antibodies acquired transplacentally by the neonate protected the infant against LRTI during the first few months of life [27]. A later study from Denmark calculated a 26% reduction in hospitalization during the first 6 months of life for every two-fold increase in cord blood neutralizing antibody [33]. Efficient transplacental transfer of maternal RSV antibody has been demonstrated in multiple studies in industrialized countries as well as in Africa and Asia [34–37]. In healthy full-term maternal/cord blood pairs, maternal: cord RSV-specific antibody ratios in these studies demonstrated more antibody in infants than in the mothers, with transplacental transfer ratios in both vaccinated and non-vaccinated women to be approximately 1.02–1.03 [27–32]. The decline of virus-specific immunity provided by maternal RSV antibodies closely mirrors the half-life of immunoglobulin G1 (IgG1) (approximately 30–40 days), the principal IgG subclass antibody to RSV that is transplacentally transferred in preterm and term neonates. Currently, both human and animal data from mice, cotton rats, lambs, calves, and non-human primates support serum neutralizing antibody as a good correlate of immunity against RSV disease of the lower respiratory tract but not necessarily of the upper respiratory tract. Standardization of RSV neutralization assays and work toward developing an international standard are underway [38].

The structure of RSV and immunity

RSV is a member of the genus pneumovirus, one of two Paramixoviruses in this group, with human metapneumovirus, and has two antigenically distinct subgroups, RSV-A and RSV-B. RSV has a negative sense non-segmented RNA genome that encodes 11 proteins (Table 1). Two glycoproteins in the virion membrane, the fusion (F) and attachment or binding (G) proteins, carry the antigenic determinants that elicit neutralizing antibodies against RSV (Table 1). While immunity against RSV relies primarily on the development of neutralizing antibodies to

TABLE 1   The structure of respiratory syncytial virus and antigenic sites [39].

RSV structure and protein function	

Non Structural Proteins
  NS1 and NS2
  M2-2
	Counteract interferon responses

Internal Structural Proteins N, P, M, M2-1, L	

Surface Structural Proteins
  Fusion (F)
  Attachment (G)
  Small hydrophobic (SH)
	F – determines viral entry to host cells
	G – determines binding to host cells
	F and G proteins have the antigenic determinants that elicit neutralizing antibodies to RSV

Main antigenic sites of RSV F-protein listed by order of ability to elicit neutralizing antibodies	
Site Φ Site V	Sites Φ and V are pre-F specific epitopes, present at the apex of the pre-F protein and therefore highly neutralizing sensitive. Antibodies to these sites have the highest neutralizing potency
Site III Site IV Site II	Sites III, IV and II are present in both pre-F and post-F conformation. Palivizumab binds to site II.
Site I	Site I is mostly present in post-F conformation

these surface proteins, non-neutralizing antibodies to the F, G and Small Hydrophobic (SH) surface proteins can inhibit infection by complement mediated neutralization or antibody dependent cell mediated toxicity, and all viral antigens can induce protection by T cell mediated immunity. Given that the F-protein plays a critical role in viral entry to the host cell, and that it is highly conserved within RSV-A and RSV-B subtypes, it is the preferred target of RSV vaccines and monoclonal antibodies. The F-protein contains 6 antigenic sites that elicit the production of more than 90% of the high potency neutralizing antibodies against RSV. The F-protein presents two structural conformations, a pre-fusion (pre-F) and a post-fusion (post-F) form, in the course of infecting host cells. Antibodies directed to antigenic sites present in the pre-F conformation are more efficient at neutralizing RSV than those directed to antigenic sites present in the more stable post-F confirmation. Although it contains a central conserved domain available for neutralizing antibody binding, the G-protein is not a primary target for vaccine development because it is mostly covered in glycans, and it is not as well conserved within RSV types as the F-protein [39, 40].

Monoclonal antibody prophylaxis to protect young infants against RSV

Early studies targeting antibody prophylaxis to prevent RSV infection in high-risk infants utilized high-titer human immunoglobulin products obtained from screened volunteers administered to infants intravenously [41]. In one study, where high-risk children were administered monthly doses of intravenous immunoglobulin containing high levels of RSV neutralizing antibody (RSV-IVIG) had reduced rates of hospitalization from RSV infection. This human immunoglobulin product, Respigam (MedImmune, Gaithersburg, MD), was licensed in 1996. Subsequently, a humanized monoclonal antibody specific for the F-protein of RSV, Palivizumab (Synagis; MedImmune and AstraZeneca, Cambridge, UK), was evaluated and approved in 1998 by the US Food and Drug Administration (FDA) for use by intramuscular injection in high-risk children. The studies definitively demonstrated that RSV-specific antibody alone may prevent or reduce RSV disease in infants [42]. Currently, Palivizumab is the only FDA- and European Medicines Agency-approved therapy utilized for the prophylaxis of RSV in infants and young children who are at increased risk of hospitalization. Palivizumab was originally approved for preterm infants <35 weeks gestational age, infants with chronic lung disease of prematurity, and those with hemodynamically significant congenital heart disease. This preventive approach, requiring the intramuscular administration of 15 mg/kg of Palivizumab at 4-week intervals during the RSV season, has been shown to be safe and effective in preventing serious RSV illness and hospitalization in high-risk young children [43]. Further refinements of recommendations for Palivizumab prophylaxis have changed over the past decades due in part to considerations of cost effectiveness [44, 45]. Impacts of a more restrictive policy on Palivizumab use in the US which limits its use among preterm infants to those less than 29 weeks of gestation at birth have been described, with increasing cases of RSV hospitalizations and morbidity in young infants 29–34 weeks gestation reported in some studies [46, 47]. Surveillance systems in place and other studies, including birth cohorts, will further inform policy on the use of Palivizumab for the prevention of severe RSV in high-risk infants in the US. Specific recommendations for pediatric populations that should receive Palivizumab therapy currently varies by country.

RSV F-protein and novel monoclonal antibodies

Major advances in the understanding of the structure and function of the highly conserved RSV F-protein, the target of most antibodies and current vaccine candidates, have been made this century. For

example, it is known that activation of the RSV F-protein from the pre-fusion state to the post-fusion state requires a structural change [48]. This conformational change exposes various antigenic sites, which each elicit the production of neutralizing antibodies that vary in potency depending on the site. The RSV F-protein has been crystallized and its pre-fusion form stabilized [40, 49]. A substantial proportion of the neutralizing antibody response to RSV has been shown to be directed against the pre-fusion conformation of the F protein. Pre-F antibody has been postulated to serve as a more accurate correlate of protection allowing for the identification of novel antigenic sites that may serve as potential antigens for monoclonal antibody or vaccine development [40, 48, 50].

Next generation RSV F-protein monoclonal antibodies that target antigenic sites on the pre-fusion protein that have enhanced neutralizing activity are under active study. Motavizumab (MedImmune), a derivative of Palivizumab with higher affinity and a longer half-life, was effective in reducing RSV hospitalization in high-risk full-term infants in the US, but was not licensed due to safety concerns (allergic reactions) [51]. Another monoclonal antibody product, Suptavumab (Regeneron Pharmaceuticals, Tarrytown, NY) failed to meet the primary outcome of preventing medically attended RSV infection in preterm infants born at >29 weeks of gestation in a 2017 Phase III infant clinical trial (http://investor.regeneron.com/releaseDetail.cfm?releaseid1037184). A novel investigational monoclonal antibody, MEDI8897 (MedImmune and AztraZeneca LLC), is a recombinant human immunoglobulin G1 monoclonal antibody that targets the pre-fusion conformation of the RSV F-protein [52]. This monoclonal antibody binds a highly conserved epitope on RSV F and neutralizes a diverse group of RSV A and B strains with over 50-fold higher activity than Palivizumab. MEDI8897 has an extended half-life compared to Palivizumab due to mutations in the Fc-domain (YTE). This antibody has been studied for safety, tolerability and pharmacokinetics in adults and healthy preterm infants [53, 54] and is currently undergoing clinical efficacy studies in preterm young infants who do not qualify for Palivizumab in the US (Clinical Trials. Gov ID: NCT02325791 and NCT02290340). The US FDA granted Breakthrough Therapy Designation of this product in February 2019, indicating this product has received an expedited development and regulatory review (website accessed May 14, 2019: www.astrazeneca.com/media-centre/press-releases/2019/us-fda-grants-breakthrough-therapy-designation-for-potential-next-generation-rsv-medicine-medi8897.htmlww).

RSV vaccines

The development of vaccines for the prevention of RSV has been ongoing since its initial isolation in infants with severe LRTI in the 1960s. The first vaccine evaluated in a clinical trial in infants was a formalin-inactivated vaccine, which resulted in inadequate neutralizing antibody responses and augmentation of disease after subsequent wild-type infection in vaccine recipients [50]. This experience led to the careful consideration of the potential strategies for RSV prevention and the development of various RSV vaccine candidates which are currently undergoing evaluation, that include live attenuated and chimeric vaccines, subunit vaccines, particle based vaccines, including virus-like particle and nanoparticles, nucleic acid and recombinant vector vaccines. While no vaccine is yet licensed for the prevention of RSV, there are more than 20 vaccines candidates in various phases of preclinical and clinical development, targeting specific populations at risk, including infants and young children, the elderly, and pregnant women who would receive vaccines to protect their newborns against severe RSV disease (Table 2 and https://www.path.org/resources/rsv-vaccine-and-mab-snapshot/). Vaccines specifically tailored for each of these populations are necessary to establish an effective multi-prong approach to reduce the burden of RSV, particularly in young children. For example, live attenuated RSV vaccines may be administered directly into the nasal mucosa in young children to induce a robust local and systemic immune response, given that responses to vaccination under 6 months of age may be limited by interference from maternal antibody and overall lower immunogenicity, requiring repeated doses of vaccines before lasting protection can be achieved [55]. A particular challenge is that infants with low RSV antibody concentrations are at greater risk to acquire infection earlier in life, and natural RSV infection does not confer long lasting immunity, therefore reinfections in childhood and through life are common. Furthermore, the highest morbidity and mortality from RSV in both healthy term infants and those with underlying conditions that increase the risk for complications, such as prematurity and cardiopulmonary disease, occur in the first 3–6 months of life, too early for active immunization to be effective. Consequently, passive antibody administration has been the major strategy for RSV prevention in high-risk infants until now. However, passive immunization is limited by the need to restrict this costly intervention to the groups with highest risk, leaving the majority of infants, those born at term, susceptible to RSV infection and its complications.

III. Future vaccines for use in pregnancy

TABLE 2 RSV vaccines in development, by vaccine type, phase of development and target population. Number of vaccine products in development is shown in parenthesis.

RSV vaccine type	Preclinical	Clinical phase I	Clinical phase II	Clinical phase III
Live attenuated/Chimeric	RSV (3) RSV/PIV-1-3 (1)	RSV-ΔG (1) Pediatric RSV ΔNS2/Δ1313/I11314L (1) Pediatric RSV 6120/ΔNS2/1030s (1) Pediatric RSV Δ46/NS2/N/ΔM2-2-*Hind*III (1) Pediatric SeV/RSV (1) Pediatric BCG/RSV (1) Pediatric	–	–
Whole virus inactivated	RSV (1)	–	–	–
Particle based	VLP (7) Peptide microparticle (1)	RSF F Nanoparticle (1) Pediatric	RSV F Nanoparticle (1) Elderly	RSV F Nanoparticle (1) **Maternal**[a]
Subunit	RSV F-protein (2) RSV G-protein (2)	RSV F-protein (2) **Maternal**[b] (3) Elderly RSV G-protein (1) Pediatric and Elderly DPX-RSV-SM Protein (1) Elderly	RSV F-Protein (1) **Maternal**[c] and Elderly	–

Nucleic acid	RNA (1) DNA (1)	–	–	–
Recombinant vector	Adenovirus (1)	Adenovirus (1) Elderly	Adenovirus (2) Pediatric (1) Elderly MVA (1) Elderly	–

[a] *RSV F nanoparticle (Novavax, Rockville, MD) Post-F "prefusogenic", adjuvanted with ALPO$_4$ or Matrix M.*
[b] *DS-Cav 1 (NIH) Pre-F subunit, Alum adjuvanted vaccine and GSK RSV F (GlaxoSmithKline, Brentford, UK) Pre-F with and without adjuvant.*
[c] *RSV F (Pfizer, New York, NY), Pre-F with and without adjuvant.*
Bold highlights represent maternal vaccines.
Source: Adapted from PATH https://www.path.org/resources/rsv-vaccine-and-mab-snapshot/.

Maternal immunization for the prevention of RSV in infants

Maternal vaccination appears to be the most direct and optimal strategy to prevent early RSV disease in most neonates and young infants. This strategy is supported by the following observations:

- Maternal RSV infection prior to delivery correlates with decreased incidence of RSV bronchiolitis in infants.
- Higher concentrations of RSV-specific maternally-derived antibody at birth are associated with lower incidence and later onset of RSV disease in neonates during the first months of life.
- Passive anti-F IgG (e.g. Palivizumab) administration reduces the incidence of severe RSV disease.
- Pregnant women are primed for RSV from previous infections and vaccination will boost their antibodies, achieving higher concentrations at a time when active antibody transfer mechanisms in the placenta favor the passage of antibodies to the fetus.
- Transplacental transfer of RSV-specific IgG from mothers to neonates is highly efficient.
- In addition to transplacental antibody transfer, there is also a potential for protection of lactating infants from RSV-specific breastmilk antibodies (natural and vaccine induced).
- There is a precedent of success of maternal immunization as a strategy for the prevention of maternal and infant tetanus, pertussis, and influenza.

The goals of a maternal immunization program for the prevention of RSV in infants include the prevention of infant death and hospitalization, the prevention and/or reduction of severe RSV LRTI, and the delay in the onset of the first episode of RSV infection. This delay in onset is important given that infants may be more capable to resist and overcome the initial RSV illness when it occurs later in the first or even second year of life. Indirect benefits from breastmilk antibodies prolonging the duration of protection of transplacentally derived antibodies, and reduction of household transmission of infection through maternal and infant protection have been documented [56]. Protection of mothers during pregnancy against obstetric and illness complications associated with RSV infection in the third trimester of gestation may be additional potential benefits.

An ideal RSV vaccine for maternal immunization is one that is not a live virus vaccine, can be administered as a single dose during pregnancy, preferably in the second or early third trimester of gestation to allow for sufficient time for transplacental antibody transfer, is safe for mother and infant, and is able to induce protective antibodies that are efficiently transferred to the infant via the placenta to achieve high concentration of neutralizing antibodies to protect the infant long enough in the first months

of life. The natural decay of passively acquired maternal antibodies allows for the highest protection in the infant to be in the first 2–3 months of life, declining afterwards. Therefore, maternal immunization will likely need to be followed by active infant immunization starting as early as the second month after birth, to reduce the impact of RSV in the first year of life. This strategy, maternal followed by infant immunization, would be most effective for infants born at term, for whom passive antibody administration might not be an option. Infants of vaccinated mothers who receive active immunization would less likely acquire RSV infection in the first 3 months of life, the period of greatest vulnerability, or experience acquired infections that are modified or rendered less severe by the presence of maternally derived and vaccine induced antibodies. Maternal immunization is not likely to be an effective method to prevent early disease among premature infants who would not benefit from a sufficient duration of gestation to achieve optimal transplacental transfer and high antibody concentrations at birth. Therefore, administration of passive RSV antibodies (e.g. Palivizumab) followed by active infant immunization would be the most adequate strategy for prevention of RSV in preterm infants. The duration of protection of maternally-derived antibodies in all infants is limited by the concentration of antibodies present at birth, and the relatively short antibody half-life, which results in a rapid natural antibody decay in the first 6 months of life. Therefore, both passive and active immunization will have an important role in the prevention of RSV in infants, even if routine maternal immunization or administration of monoclonal antibodies after birth become available. One remaining challenge in the development of RSV vaccines is the lack of a known serologic correlate of protection to evaluate vaccine efficacy and effectiveness. Until a correlate of protection is identified, large clinical trials are required to assess the efficacy of candidate RSV vaccines for maternal or infant immunization. Another important area of research in the field of RSV addresses the need to better understand the mechanisms of protection beyond antibodies, such as innate and cellular immunity. Definitive progress in the design and development of RSV vaccines was driven by a better understanding of the conformation depending immunogenicity of the F-protein and the need to target neutralization sensitive epitopes on the functional forms of F-protein [40, 57]. All RSV vaccines for maternal immunization developed to date have been based on the F-protein of RSV. There are currently four vaccines in development for maternal immunization, two in phase I clinical trials, and one each in phase II and III clinical trials (Table 2).

A non-adjuvanted purified F-protein (PFP-2) vaccine for RSV was the first vaccine evaluated in pregnancy nearly 20 years ago, in the early 2000s [36]. This was a small proof of concept, randomized, placebo-controlled study in 35 healthy women who were vaccinated at 30–34 weeks of gestation, and in whom the RSV PFP-2 vaccine was well tolerated, though

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it did not significantly increase neutralizing antibody titers to RSV, and was not further developed. Nevertheless, maternal immunization with this experimental vaccine was safe in mothers and infants, no obstetric adverse events were associated with vaccination, efficient transplacental passage of vaccine induced antibodies was demonstrated, the half-life of these antibodies was estimated to be between 30 and 40 days, and anti-F IgA and IgG were present in breastmilk of vaccine recipients at higher concentrations than placebo recipients in the first 6 months after delivery. Importantly, after close follow up of these infants for natural infection in two consecutive viral seasons, no enhanced RSV disease was observed.

A purified recombinant pre-F protein vaccine prepared in Chinese Hamster Ovary Cells (GlaxoSmithKline [GSK] Investigational Vaccines) [58], has been evaluated in approximately 600 non-pregnant women to assess the reactogenicity and immunogenicity of various dosages of adjuvanted and non-adjuvanted formulations. All formulations of this vaccine boosted pre-existing antibodies in these 19–45 year old women, with comparable immunogenicity, and the safety profile was similar to that of tetanus, diphtheria, and pertussis (Tdap) vaccine, which is administered routinely during pregnancy in the US and various countries [58]. This vaccine construct is planned to be evaluated in pregnant women in a global phase I/II study expected to begin in 2019–20.

Lastly, an aluminum-adjuvanted RSV F-protein nanoparticle vaccine (Novavax, Inc., Gaithersburg, Maryland, US) was evaluated in women of childbearing age [59] and in a phase II study in pregnant women prior to being the first vaccine evaluated in a phase III clinical trial, seeking an indication for administration in pregnancy. The phase II study demonstrated that the vaccine was safe and well tolerated, and induced significantly higher concentrations of both anti F-IgG, but also neutralizing antibodies and Palivizumab competing antibodies [60]. This study also found that maternal antibody responses peaked at 14 days after vaccination, and that an interval of $\geq$30 days from maternal vaccination to delivery maximized transplacental antibody transfer for all measured antibodies [60]. This study allowed the progression to a global phase III efficacy clinical trial to evaluate this maternal vaccine for the protection of RSV in infants. This clinical trial in healthy pregnant women was conducted in 11 countries worldwide from 2015 to 2019. The primary objective of the study was to determine the efficacy of maternal immunization against medically significant RSV LRTI in infants through various time points including the first 90 days of life, and up to 180 days, when mothers were vaccinated with a single dose of vaccine at 28–36 weeks of gestation. The clinical definition of medically significant RSV LRTI included the presence of at least two clinical symptoms of illness, laboratory confirmation of RSV infection by PCR, and objective assessment of tachypnea and hypoxemia (O_2 saturation < 95%). Secondary endpoints

included the reduction of RSV LRTI hospitalization and RSV LRTI with severe hypoxemia (O$_2$ saturation <92%). Preliminary data shared to date by the manufacturer indicates that among 4636 women who were randomized 2:1 to receive vaccine or placebo, the vaccine was well tolerated and was not associated with any vaccine-related maternal, infant or obstetric adverse event. This study failed to meet its primary objective of efficacy against medically significant RSV LRTI in infants, which was estimated to be 39.4% (97.5% CI, −1 to 63.7) at 0–90 days of life, and the secondary outcome of RSV LRTI with severe hypoxemia was also not met. However, maternal vaccination was effective in protecting infants against RSV-associated LRTI hospitalization in the first 90 days and up to 180 days after birth (Table 3) (http://ir.novavax.com/news-releases/news-release-details/novavax-announces-topline-results-phase-3-preparetm-trial#). While vaccine licensure based on this study is unlikely in the US given the observed geographic variability in vaccine efficacy and overall lower numbers of cases than expected, the results are encouraging. When pre-specified analyses were conducted to evaluate these results utilizing expanded data (which increased the number of evaluable subjects), the vaccine efficacy achieved in the first 90 days of life varied between 40% and nearly 60% for these primary and secondary outcomes (Table 3), which is considered a result worthy of continuing the development and evaluation of this vaccine. This study was pivotal in generating data to better understand the potential for maternal RSV immunization to prevent the most severe outcomes of RSV in infants, and to answer specific programmatic questions, such as the impact of the timing of immunization during pregnancy and the interval between vaccination and

TABLE 3 Preliminary efficacy of the maternal RSV F-protein nanoparticle vaccine (Novavax) against severe RSV infection in infants.

Endpoints	Per-protocol analysis	Pre-specified expanded data analysis which includes data from hospitalization records
Primary		
Medically significant RSV LRTI	39% (97.5%CI, −1% to 64%)	41% (95%CI, 16% to 58%)
Secondary		
RSV LRTI Hospitalization	44% (95%CI, 20% to 62%)	42% (95%CI, 17% to 59%)
RSV LRTI with severe hypoxemia	48% (95%CI, −8% to 75%)	60% (95%CI, 32% to 76%)

Source: Novavax press release, available at http://ir.novavax.com/news-releases/news-release-details/novavax-announces-topline-results-phase-3-preparetm-trial#.

delivery to optimize the impact of maternal immunization in protecting the infant. The observation that geographic, seasonal, and potentially, population based differences in vaccine efficacy can occur will help inform the design of future clinical trials. While these and other results from this study continue to be evaluated, the experience of this trial has provided further impetus for the ongoing development and evaluation of RSV vaccines for maternal immunization, with an important contribution to defining the clinical endpoints to which clinical trials should be powered to.

Other experimental vaccines in advanced development for potential administration during pregnancy include an aluminum hydroxide adjuvanted RSV stabilized pre-fusion F subunit vaccine, which began enrollment in a phase IIB placebo controlled randomized clinical trial in pregnant women in the US in August 2019 (Pfizer. NCT04032093 – https://clinicaltrials.gov/ct2/show/NCT04032093), and an unadjuvanted pre-F subunit vaccine that will begin phase II evaluation in pregnant women in 2020 after having completed dose ranging immunogenicity and safety evaluation in non-pregnant healthy women (GSK Biologicals, GSK3888550A, NCT03674177, https://clinicaltrials.gov/ct2/show/NCT03674177) (Table 2).

In parallel, the research field is active in establishing standardized methods for the assessment of RSV infection and immunity, the clinical assessment of severity of disease, and the determination of correlates of protection against RSV. Preferred product characteristics for RSV vaccines have been developed by the WHO [61] and a clear road map for the research and development of technology associated with RSV vaccines is in place [62]. Various vaccine candidates remain in preclinical and clinical phases of development, while work to identify the key necessary elements for the implementation of maternal RSV vaccines worldwide continues with the support of multiple stakeholders [63–66]. Implementation of RSV vaccines for maternal immunization should be guided by accurate estimates of RSV disease burden in infants to determine their potential impact. Establishing robust surveillance systems to assess vaccine safety and efficacy outcomes after implementation is key, as is the support from key policy makers, national and local maternal and child health systems and other funding and administrative organizations (Fig. 1). A successful maternal immunization delivery platform would include integrated antenatal and neonatal care services and immunization programs, informed by existing vaccination (e.g. tetanus and influenza) and routine antenatal care interventions (e.g. HIV diagnosis and prevention), which would likely need strengthening, financial and policy support. Lastly, effective communication plans and advocacy planning are important elements to ensure vaccine uptake by educating providers, pregnant women, parents, and the public about the impact of
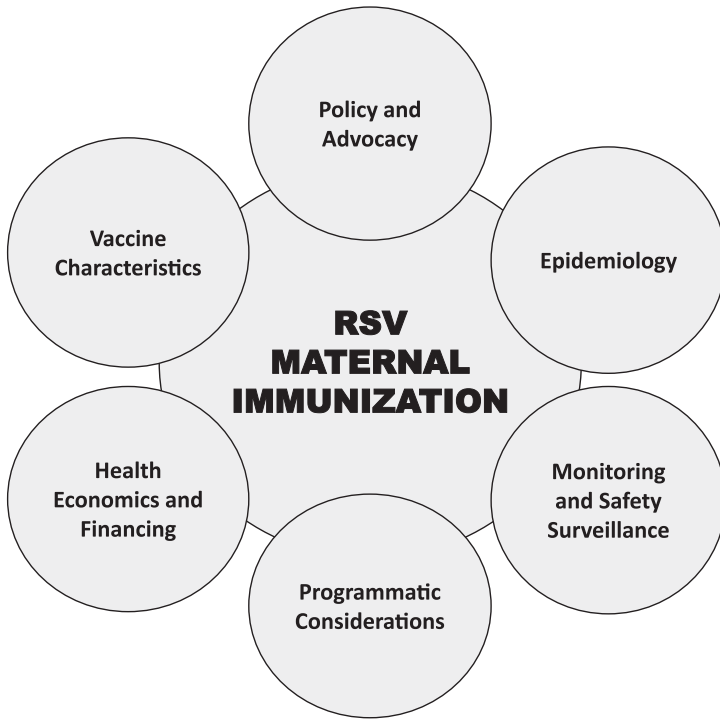
FIG. 1   Key elements for the implementation of RSV maternal immunization. Source: Adapted from PATH, 2018. Advancing RSV maternal immunization: A gap analysis report. PATH, Seattle, WA.

RSV and the role of maternal immunization in the prevention of infant disease and its associated mortality.

Conclusion

The global burden of morbidity and mortality associated with RSV disease in infants is substantial, particularly in low and low-middle income countries. Maternal immunization is a feasible strategy that has the potential to significantly reduce the impact of RSV disease in young infants worldwide. Vaccines for maternal immunization are in active preclinical and clinical development, with encouraging results. Ongoing research and implementation planning activities support the concept of RSV prevention through maternal immunization and the possibility to achieve tangible progress in the control of RSV disease in young infants in the near future.

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