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The changing landscape of respiratory syncytial virus

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ABSTRACT

Recognition of the acute and chronic burden of respiratory syncytial virus (RSV) lower respiratory tract infections (LRTI) sparked a wave of initiatives to develop preventive and therapeutic products against the pathogen in recent years. RSV is a leading cause of hospitalization in infants in industrialized and developing countries, has been causally linked to recurrent wheezing during childhood, associated with pediatric asthma, and is an important cause of mortality in the first months of life in the developing world. Significant changes in the epidemiology, clinical manifestations, and severe consequences of LRTI may emerge in the next decade with the advent of novel preventive strategies against RSV. This manuscript outlines some of these changes and discusses potential scenarios based on the current literature and experiences with other pathogens.

Respiratory syncytial virus (RSV) is the main cause of hospitalization in infants in industrialized and developing countries [1,2]. Millions of children are hospitalized and an estimated 66,000–199,000 die every year worldwide due to RSV disease [2]. In addition, the virus has been causally linked to recurrent wheezing and associated with pediatric asthma [3–5]. The only licensed intervention to prevent severe RSV disease is the administration of a neutralizing anti-RSV humanized monoclonal antibody (palivizumab®) in specific high-risk populations, including infants born prematurely and those with congenital heart disease [6]. But cost and the need for recurrent administration hamper its use in all infants. No specific treatment is available for RSV infections to date. Severe cases require supportive therapy, mainly oxygen supplementation and, less frequently, ventilatory support.

Recognition of the acute and chronic burden of RSV lower respiratory tract infections (LRTI) sparked a wave of initiatives to develop preventive and therapeutic products against the pathogen in recent years. A promising strategy under evaluation to prevent severe RSV disease is immunization of pregnant women against the virus. Maternal immunization aims to elicit high levels of protective antibody in pregnant women, fostering transplacentally acquired antibody-mediated protection in infants during the first months of life [7–9]. Other promising approaches to RSV prevention in infants are under study, including but not limited to passive prophylaxis with long-lived monoclonal antibodies against a neutralizing epitope in the RSV fusion (F) protein and immunization with recombinant live attenuated RSV vaccines [6,10–12]. In fact, the potential benefits of passive immunization with a long-lived monoclonal antibody are supported by prior experience with palivizumab in infants from high-risk groups [6].

The surge of old and novel approaches to prevent RSV suggests that we may witness a significant change in the landscape of respiratory infections in the near future, if the main cause of infant hospitalization worldwide is tamed. While the burden of RSV disease may decrease, predicting the magnitude of change is premature. Yet, numerous important lessons will emerge from this international effort. First, RSV is responsible for a significant proportion of infant hospitalizations worldwide [1,2]. Second, decreasing its impact may affect other acute and chronic consequences of RSV infection, from secondary bacterial infections and mortality to recurrent wheezing and asthma [2–5]. Finally, RSV prevention may inform about other factors influencing maternal-infant health such as human milk protection and/or the acute and long-term effects of respiratory illness during pregnancy [13–16].

This manuscript is an attempt to address questions that may emerge during or after RSV prevention, using current knowledge from the RSV literature and extrapolating from previous experiences with other pathogens.

How likely are new vaccine strategies to elicit enhanced RSV disease (ERD)? In 1966, a formalin-inactivated vaccine against RSV (FIRSV) was administered to infants and young children in the United States [17–20]. During the winter of 1967, immunized children infected with RSV developed an enhanced form of RSV disease (ERD)

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characterized by severe wheezing and bronchopneumonia [17–20]; two vaccinated infants died as toddlers when contracting RSV [17]. The mechanism of illness of ERD has not been completely elucidated, but three immune correlates are generally accepted to identify candidate RSV vaccines that may prime for enhancement: the presence of low avidity, non-protective antibodies [21,22] and the absence of RSV-specific cytotoxic T lymphocytes after immunization [23–25], coupled with a Th2 polarization of the immune response in the respiratory tract after RSV infection [17,26–28]. The presence of alveolitis in cotton rats also correlated with autopsy findings in children with ERD during 1967 [29]. All these manifestations are routinely elicited in murine models by a variety of RSV vaccine antigens that are not processed in the cytoplasm.

Fortunately, concerns for ERD are minimal in several leading approaches to RSV prophylaxis. For instance, immunization of pregnant women to protect infants through transplacental transfer of antibody will boost responses in women of childbearing age seropositive for the virus. No seropositive individual ever developed ERD [17]. In fact, polyclonal antibody avidity against RSV in these women is improved throughout life by repetitive infections [22], preventing priming for low affinity responses during immunization (precisely the same mechanism that protected seropositive infants and children from FIRSV in 1967). Moreover, ERD manifestations associated with an aberrant antibody response, after deposition of immune complexes and complement activation, are mediated by the pathogenic effect of primed $CD4^+$ T lymphocytes [30–32]. And primed T cells will not be elicited in infants after maternal immunization. Similarly, new strategies to confer long-standing passive protection at birth using monoclonal antibodies would also rely strictly on antibody. And previous experiences with palivizumab and motavizumab have a long track record of safety in vulnerable infants [6]. Finally, infant intranasal immunization with live attenuated RSV vaccines (LAV) mimic natural infection, and after extensive testing in early phase trials never associated with ERD in seronegative subjects [33].

Yet, the logarithmic increase in RSV vaccine candidates in preclinical and clinical development potentially targeted to naïve infants confronts the field with new challenges. In addition to traditional approaches to immunization, a surge of novel platforms stresses the need for *bona fide* biomarkers and animal models to minimize the risk for ERD in this population. Replication-defective gene-based single-cycle vectors [34,35]; virus-like particles (VLPs) with protective antigens [36–38]; subunit vaccines adjuvanted with various *TLR agonists* [39]; new formulations with the pre-fusion conformation of RSV F [40–44] and others, challenge our current ERD models and may alter our current enhanced disease criteria. For example, vaccine replication may be unnecessary to prevent priming for ERD in PAMP-adjuvanted vaccines, or stabilized pre-fusion RSV F protein may elicit protective antibodies of high affinity.

Assessing safety in animal models will be critical for new formulations, because ERD never occurred in children who were seropositive for RSV before immunization with FIRSV [17–20]. Therefore, evaluation of vaccine candidates in seropositive individuals will likely not offer any clues about risk for ERD, as it is precisely naiveté what allowed the immune system to mount an aberrant response.

Consequently, animal models will play a fundamental role in predicting ERD before novel RSV vaccines reach seronegative infants. In this context, evaluation of new candidates in more than one model is ideal, as even subtle differences in the vaccine-dosing schedule, contaminants in vaccine preparations, and challenges with ERD reproducibility in large animal models can affect interpretation of results [45,46]. Therefore, evaluation of novel candidates in well-established murine models, like BALB/c mice and cotton rats, followed by testing in a large animal model may be necessary.

Therefore, while new platforms targeted for infant immunization should benefit from testing in animal models of ERD during preclinical evaluation, maternal immunization, anti-RSV monoclonal antibodies and live attenuated vaccines present a theoretical and practical record that mitigates concerns about ERD priming.

Can specific preventive strategies against RSV protect every infant? Experience with protective drugs against RSV is limited. A licensed prophylactic intervention widely available today is the intramuscular administration during the respiratory season of the monoclonal antibody palivizumab to premature babies and those with cyanotic congenital heart disease [6,47]. The efficacy of palivizumab was initially evaluated in a placebo-controlled, randomized trial (RCT) using as primary end point reduction in hospitalization attributable to RSV LRTI [47,48]. Prophylaxis resulted in a 55% overall decrease in the rate of RSV-related hospitalizations in premature babies [47]. Palivizumab protected against LRTI, but did not prevent viral replication in the upper respiratory tract [49]. With this in mind and experience from other mucosal vaccines, a primary goal for maternal immunization and passive transfer of antibody in term infants is to achieve protective titers of antibody to prevent severe LRTI. Protecting the upper airways seems challenging.

The reason why a number of severe RSV LRTI cases still occurred despite palivizumab or RSV-IG administration during the RCT remains unclear [47,48]. Failure rates were higher in infants with bronchopulmonary dysplasia, suggesting a component of lower airways reactivity during RSV upper respiratory tract infections [47]. Another explanation may be that palivizumab failures reflected infections in the last week of the monthly dosing cycle, when serum antibody fell below protective levels. Yet, 89.5% of palivizumab failures in North American trials were in infants heterozygous for a single nucleotide polymorphism in Asp299Gly of Toll-Like receptor 4 (from now, $TLR4^{+/-}$ infants) [50]. The rate of $TLR4^{+/-}$ individuals in the North American population is 10.5% [51]. Therefore, it seems logical to wonder what is peculiar about $TLR4^{+/-}$ infants during RSV infection, who seem to develop severe LRTI despite passive protection in the lungs (but not in the upper respiratory tract) with anti-RSV antibody.

Two observational studies in $TLR4^{+/-}$ urban infants born at term in Tel Aviv and Buenos Aires (and receiving no prophylaxis) found them to have significantly higher odds for severe RSV disease than wild type RSV-infected controls [52,53]. A notable 80% of middle class $TLR4^{+/-}$ infants in Tel Aviv and >85% in Buenos Aires required hospitalization when visiting pediatric clinics or the emergency room with respiratory symptoms [52,53]. In fact, a distinguishing characteristic of $TLR4^{+/-}$ urban infants was their propensity to mount a pathogenic T helper type 2 (Th2) response during RSV infection leading to severe lung disease [53]. Therefore, it is plausible to speculate that $TLR4^{+/-}$ infants (who constitute ~10% of all infants in industrialized western societies [51]) may respond "atopically" to RSV upper respiratory tract infections and – as observed in premature babies with palivizumab [47] – wheeze severely despite having protective antibody titers in the lungs.

Notably, a gene by environment interaction mediates the effects of TLR4 on RSV disease [53]. $TLR4^{+/-}$ infants from poor neighborhoods in developing countries, typically exposed to high levels of environmental bacterial endotoxin (LPS), do not experience Th2 bias and have milder RSV disease than urban $TLR4^{+/-}$ babies living in low LPS environments in industrialized nations [53]. In fact, the polymorphism protects these infants in impoverished areas of low-income countries from severe RSV LRTI [53].

Therefore, efficacy and subsequent effectiveness of preventive strategies against RSV may depend in part on environmental exposures, particularly those related to poverty and farming, and $TLR4^{+/-}$ frequency in different regions of the world. Other genes

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