Supplementary appendix

Natalie I. Mazur, Jonne Terstappen, Ranju Baral, Azucena Bardají, Philippe Beutels, Ursula J. Buchholz, Cheryl Cohen, James E. Crowe Jr, Clare L. Cutland, Linda Eckert, Daniel Feikin, Tiffany Fitzpatrick, Youyi Fong, Barney Graham, Terho Heikkinen, Deborah Higgins, Siddhivinayak Hirve, Keith Klugman, Leyla Kragten-Tabatabaie, Philippe Lemey, Romina Libster, Yvette Löwensteyn, Asuncion Mejias, Flor M. Munoz, Patrick K. Munywoki, Lawrence Mwananyanda, Harish Nair, Marta C. Nunes, Octavio Ramilo, Peter Richmond, Tracy J. Ruckwardt, Charles Sande, Padmini Srikantiah, Naveen Thacker, Kody A. Waldstein, Dan Weinberger, Joanne Wildenbeest, Dexter Wiseman, Heather J Zar, Maria Zambon, Louis Bont. Respiratory Syncytial Virus Prevention within Reach: The Vaccine and Monoclonal Antibody Landscape

Table of contents

Impact of COVID-19

The foundations of a SARS-CoV-2 mRNA vaccine were laid in the RSV vaccine development landscape. SARS-CoV-2 vaccines benefited from knowledge generated of the RSV surface protein pre-F conformation as vaccine antigen. Not only has RSV influenced SARS-CoV-2 vaccine development, but the COVID-19 pandemic has influenced RSV vaccine development across three domains: (1) decreased RSV circulation with implications on trial execution and interpretation; (2) development of COVID vaccine candidates by manufacturers, which could potentially compete with RSV vaccine development resources with implications for the timeline of availability of RSV vaccines globally; and (3) accelerated vaccine development through proof-of-principle of mRNA vaccination and cheaper development of mAbs.

First, the COVID-19 pandemic and related non pharmaceutical interventions (NPIs) were associated with lack of or delayed RSV circulation globally during the 2020/2021 season.[1,2] The long-term impact of COVID-19 on the circulation of RSV is the subject of ongoing studies. The impact of decreased or absent RSV circulation has posed a challenge to RSV vaccine clinical trials powered on expected RSV attack rates. There may be a transient upward age shift: with the median age at RSV admission shifting towards children older than 1 year in empirical and modelling studies[3,4] due to lack of early life exposure. The shift could pose challenges to the interpretation of maternal vaccine or mAb trials as the duration of protection may not be sufficient: maternal vaccines likely do not afford protection to children infected after 6 months of age. However, other studies do not confirm this age shift[5,6].

Second, development of similar SARS-CoV-2 vaccine candidates could potentially compete for resources with RSV vaccines. Ten RSV vaccine developers harnessed the same vaccine platform technology from their RSV pipeline for COVID vaccine development. All RSV vaccine developers are performing COVID research. In this way, vaccine developers may have shifted priority away from RSV vaccines and potentially also shifted resources such as laboratory personnel and clinical trial facilities or alternatively increased the workload of clinical and scientific teams who needed to carry out COVID-19 vaccine trials.

Finally, the pandemic has accelerated RSV vaccine development. Although mRNA technology was already in use for RSV at an early stage, SARS-CoV-2 mRNA vaccines have proved the principle that mRNA technology can be used to produce safe and effective vaccines with high manufacturing efficiency which has accelerated RSV mRNA vaccine development. Furthermore, a single shot vaccine combining COVID-19, influenza and RSV is in development. Additionally, SARS-CoV-2 vaccine development has facilitated more affordable mAb development and resulted in the establishment of expedited regulatory revision which could benefit the development of RSV vaccines.

Proteins relevant to vaccine development

The RSV fusion, F, surface protein is the primary vaccine target as it has the most neutralizing epitopes, is required for host cell fusion, and is highly conserved[7] . Discovery of the prefusion F conformation and methods for its stabilization allowed further human studies showing that the level of pre-F antibodies correlates with serum neutralizing capacity[8]. Structure-based vaccine design has resulted in a clear shift in immunogenicity of vaccine candidates with vaccination, in some cases resulting in a >10-fold increase in neutralizing capacity compared to previous 2-fold increases. Moreover, stabilization of pre-F allowed more precise targeting of mAb epitopes. Antibodies targeting F can be classified from highest to lowest neutralizing potency: those binding epitopes unique to pre-F (site Ø and V), those binding sites on pre-F>post-F (Site III), those specific for sites present on both pre-F and post-F (site II), those binding sites on post-F>pre-F (site IV), and those binding epitopes unique to post-F (site I).
Other surface proteins in use as vaccine antigen include glycoprotein, G, (attachment protein which has both membrane-bound and secreted forms) and small hydrophobic, SH, (the transmembrane protein likely playing a role as a viroporin). The nucleocapsid protein, N, (together with the phosphoprotein P, the polymerase protein L and the M2-1 transcription processivity factor) facilitates formation of the ribonucleocapsid complex to protect the single-stranded RNA genome and guide replication. The M2-2 protein is an RNA synthesis regulatory protein[9] whose deletion results in decreased replication and increased transcription and protein synthesis[10]. The non-structural genes 1 and 2 (NS1 and NS2) antagonize interferon and innate immune responses[11]. The expression of M2-2, NS1 or NS2 has been manipulated by reverse genetics to develop live-attenuated vaccine candidates that are attenuated while retaining strong immunogenicity.

Supplementary Table 1 - Data Collection Template

Type of Vaccine
Vaccine/mAb candidate from RSV PATH Snapshot
RSVVW'21 related program items / names
Manufacturing process
Adjuvant
Animal models
Pre-F immunity
Immunity (general)
Expected herd immunity
Antigen(s)
Mechanism of action
Route of administration
Target populations
Summary clinical study results
Efficacy
Endpoints
PMID results
Timing Phase I Trial
Trial size Phase I
Timing Phase II Trial
Trial size Phase II
Timing Phase III Trial
Trial size Phase III
Controlled Human Challenge Model
Current development status
Expected Date of Unblinding of Phase III Trial
Expected Date of Market Access Authorization
Trial names
Previous successes of vaccine platform
Description current trial(s) in trial registry, trial registry numbers
Summary on corporate website
Information regarding LMIC target population
Expected price
Important Links

Legend
RSV: respiratory syncytial virus
mAb: monoclonal antibody
RSVVW'21: Respiratory Syncytial Virus Vaccines for the World Conference 2021
PMID: PubMed Identifier
LMIC: Lower middle-income country

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