TECHBRIEF

HORIZON SCANNING REPORT

RESPIRATORY SYNCYTIAL VIRUS (RSV) VACCINE

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"DOKUMEN TERHAD"

MaHTAS
Medical Development Division
Ministry of Health, Malaysia

TechBrief

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SUMMARY

Respiratory Syncytial Virus (RSV) candidate vaccines contain a recombinant subunit pre-fusion RSV antigen (RSVPreF3) which is believed to trigger the required immune response. These candidate vaccines have been tested in older adults and maternal immunisation and have shown positive results.[1] The RSV candidate vaccines for maternal immunisation and older adults were well-tolerated and highly immunogenic in Phase I/II clinical studies. GlaxoSmithKline (GSK) has kicked off a phase III GRACE study of its RSV candidate vaccine for maternal immunisation to evaluate the safety of the candidate vaccine for pregnant mothers and infants, and its efficacy in infants born to vaccinated mothers. The end of the study is estimated in early 2024, with interim results expected by the second half of 2022.[2] The candidate vaccines have received FDA fast-track designation.[1] However, for this vaccine to be beneficial for many, the cost must be within the affordability of the country.

Keywords: Respiratory Syncytial Virus Vaccine, RSV vaccine, subunit vaccine, respiratory infection

INTRODUCTION

Respiratory Syncytial Virus belongs to the genus Orthopneumovirus within the family Pneumoviridae and order Mononegavirales. Members of this genus include human RSV, bovine RSV and murine pneumonia virus. There are two major antigenic subtypes of human RSV (A and B) determined largely by antigenic drift and duplications in RSV-G sequences, but accompanied by genome-wide sequence divergence, including within RSV-F.[3]

Human RSV is a globally prevalent cause of lower respiratory tract infection in all age groups. In young infants, RSV is an acute respiratory viral infection that can result in severe disease and death. Respiratory Syncytial Virus is also a nosocomial threat both to young infants and among immunocompromised and vulnerable individuals.[3] It is being increasingly recognised as an important cause of morbidity and mortality globally. Shi et al. have estimated that globally RSV-associated lower respiratory tract infection (LRTI) accounted for between 94,600 and 149,400 deaths annually. In addition, 33 million RSV-associated LRTI resulted in 3.2 million hospital admissions.[4]

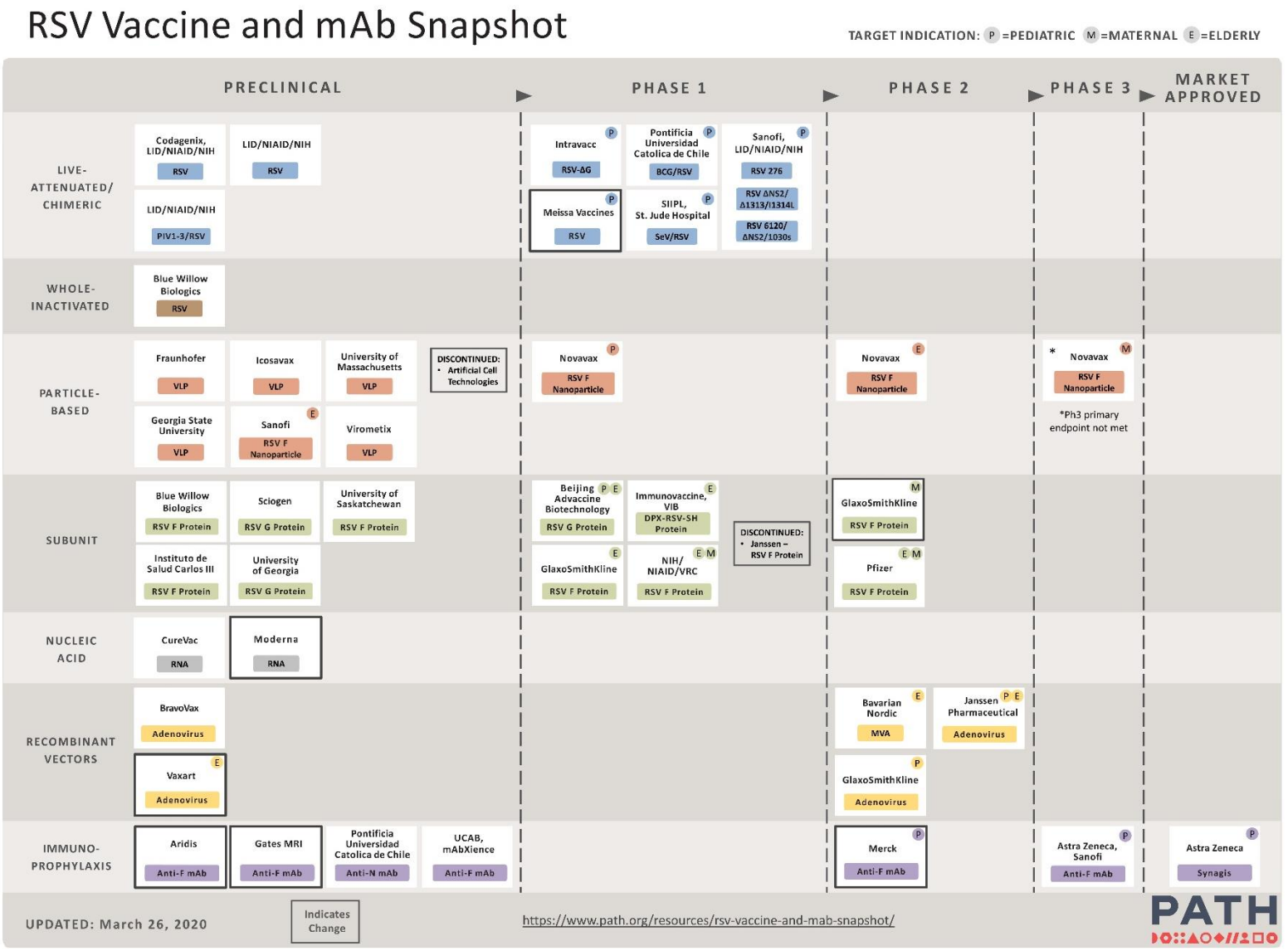
Most studies, including those in Asia, showed that the most common causes of respiratory viral infections are RSV and rhinoviruses. Respiratory Syncytial Virus was the most frequently detected respiratory virus, particularly in infants less than one-year-old. This suggests that maternal antibodies were ineffective in preventing RSV infections. Older

children may be less prone to RSV infection due to the maturity of their immune system or natural immunity obtained through repeated infections of RSV.[5]

In Malaysia, it was reported that 26.4% of samples for respiratory virus detection from children ≤5 years were positive for the common respiratory viruses. The viruses detected were RSV (1913, 70.6%), parainfluenza viruses 1 - 3 (357, 13.2%), influenza A and B viruses (297, 11.0%), and adenovirus (141, 5.2%).[5] A cross-sectional study in Sarawak revealed more than 30% of samples collected from children under one year of age were positive for RSV.[6]

Respiratory Syncytial Virus vaccine development began in the 1960s with an unsuccessful formalin-inactivated RSV (FI-RSV) vaccine that induced a severe and in two cases lethal lung inflammatory response during the first natural RSV infection after vaccination of RSV-naive infants. This response to natural RSV infection has been referred to as vaccine-associated enhanced respiratory disease (ERD). The concerns over the FI-RSV vaccine hindered the development of alternative RSV vaccines for many years. In recent years, the development of the RSV vaccine restarted with an increasing understanding of the biology of RSV and technological advances. These have resulted in the entry of multiple vaccine candidates into clinical development and some of them may receive regulatory approval soon.[1] These vaccine candidates were developed to prevent RSV infection among infants and older adults.

Figure 1: Respiratory Syncytial Virus Vaccine and Monoclonal Antibody Snapshot



THE TECHNOLOGY

Respiratory Syncytial Virus candidate vaccines contain a recombinant subunit pre-fusion RSV antigen (RSVPreF3) believed capable to trigger the required immune response. The dosages of the RSV vaccine are 30, 60 and 120µg. The candidate vaccine for older adults includes the AS01 adjuvant system to boost the immune response as this population tends to show a weaker immune response to vaccination than younger adults.[1] AS01 is a liposome-based vaccine adjuvant system containing two immunostimulants i.e. 3-O-desacyl-4'-monophosphoryl lipid A (MPL) and the saponin QS-21. The effects of AS01 are rapid and transient, being localised to the injected muscle and draining lymph nodes. AS01 is efficient at promoting CD4+ T cell-mediated immune responses and is an appropriate candidate adjuvant for inclusion in vaccines targeting viruses or intracellular pathogens. AS01 adjuvant shows good prospects to use in new vaccines targeted to populations with challenging immune statuses and against diseases caused by complex pathogens.[7]

This vaccine has been tested in older adults and maternal immunisation. The latest study follows positive Phase I/II safety, reactogenicity and immunogenicity results of the candidate vaccine. The Phase III clinical programme has two studies i.e. AReSVi 004 and AReSVi 006. AReSVi 004 is a randomised, open-label study, which will enrol up to 1650 adult participants. It will assess the safety, reactogenicity, immunogenicity and long-term persistence of immune response up to three years on administering the RSV candidate vaccine in participants aged ≥60 years. The study is estimated to end in early 2024, with interim results expected by the second half of 2022. AReSVi 006 study, which will analyse the efficacy of the candidate vaccine in protecting older adults against LRTI linked to RSV, will be initiated soon.[8] In total, it is expected that more than 10,000 participants will be enrolled in the Phase III programme for the RSV candidate vaccine for older adults, as it is standard for late-stage clinical trials where correlate of protection has not been established yet.

The candidate vaccines have received FDA fast-track designation.[1]

PATIENT GROUP AND INDICATION

This vaccine is used to trigger the required immune response and prevent RSV infection among infants and older adults.[1]

CURRENT PRACTICE

There is currently no vaccine available to prevent RSV infection in infants. In 1998 the US Food and Drug Administration (FDA) approved immunoprophylaxis with palivizumab to prevent RSV infection for those at high risk of RSV disease.

Palivizumab is a monoclonal antibody that must be injected once each month during the RSV season typically from November to March. Palivizumab has been found to be effective in reducing hospitalisations and preventing serious lower respiratory tract infections in high-risk infants.[9]

The burden of RSV in young infants in tropical countries, including Malaysia, emphasises the likely global benefits of developing a safe and effective vaccine for RSV.

SAFETY & EFFICACY

Electronic searches were performed in Medline, EBM Reviews, EMBASE via OVID and PubMed, by using various combinations of the keywords respiratory syncytial virus, RSV vaccine, subunit vaccine and respiratory infection. In addition, Google was used to search for additional web-based materials and information. Two randomised controlled trials were included in this review.

A) Efficacy

A Phase I/II study investigates the safety, reactogenicity and immune response of GSK's RSV candidate vaccine in older adults aged 60 to 80 (NCT03814590). This candidate vaccine contains GSK's proprietary AS01 adjuvant. The safety, reactogenicity and immune responses (humoral and cellular-mediated) were first assessed in 48 healthy adults aged 18 - 40 years who were vaccinated with either 30, 60 or 120 µg dose level of RSVPreF3 non-adjuvanted vaccine or placebo. Following favourable safety outcomes, 1005 adults aged 60 - 80 years were randomised in a 2-step staggered manner to receive one of the nine RSV vaccine formulations containing either 30, 60 or 120 µg dose level of RSVPreF3, non-adjuvanted or adjuvanted with AS01E or AS01B, or placebo.[1]

Interim data showed that within one-month post-immunisation, the adjuvanted candidate vaccine has been well tolerated with no safety concerns identified. It also showed that the candidate vaccine prompted a robust humoral and cellular immunity compared with baseline:[1]

- High levels of RSVPreF3 IgG antibodies (geometric mean antibody concentrations were 8.4 - 13.5 for the 18 - 40 years old vaccinees, and 7.2 - 12.8-fold-higher in the 60 - 80 years old vaccinees)
- RSV-A neutralising antibodies (geometric mean antibody titers were 7.5 - 13.7 in the 18 - 40 years old vaccinees, and 5.6 - 9.9-fold-higher in 60 - 80 years old vaccinees) were induced in all vaccinated groups
- After vaccination, a robust RSVPreF3 CD4+ T-cells response in older adults had been boosted to reach a similar range than the one observed in younger adults, with significantly higher immune response in the groups who received the adjuvanted formulation.

A Phase I/II randomised observer-blind placebo-controlled study was conducted to evaluate the safety, reactogenicity and immunogenicity of different dose levels of GlaxoSmithKline (GSK) Biologicals' recombinant protein-based RSVPreF3 compared to placebo when administered to healthy non-pregnant women aged 18 - 45 years.[1]

In this Phase I/II study (NCT03674177), 502 healthy non-pregnant women were randomised in a 1:1:1:1 ratio to receive one of three dose levels (30, 60, 120 micrograms [µg]) of the recombinant protein-based RSVPreF3 or placebo, administered as a single intramuscular injection (IM). They have been screened on Day 1 and continued four study

visits at Day 8, 31, 61 and 91 to evaluate the primary and secondary objectives of safety/reactogenicity and immunogenicity profiles of the three-dose levels. Subjects were also contacted on Day 181. The safety, reactogenicity and immunogenicity was monitored for 6 months.[1]

The data showed that the candidate vaccine elicited a rapid and persistent immune response in all RSVPreF3 groups. The immune response peaked at Day 8 with a 14-fold increase in neutralising RSV-A and RSV-B titers from baseline. The neutralising titers declined over time but a >6-fold increase was still maintained at Day 91. Anti-RSVPreF3 IgG antibodies were boosted substantially in all groups with geometric mean concentrations of anti-RSVPreF3 IgG antibody (≥12-fold at Day 8 and ≥6-fold until Day 91 vs baseline). The 60 and 120 µg dose levels of RSVPreF3 were more immunogenic than the 30 µg formulation.[1]

B) Safety

The data of one-month post-immunisation showed that all vaccine dose levels were well tolerated, with no safety concerns identified. The most frequently reported solicited adverse events were minor and included pain at the injection site and headache.[1]

Safety and immunogenicity data from the first study in pregnant women will be presented at the end of 2021. The available data currently provides the confidence to facilitate late-stage clinical work.

COST

There was no retrievable data on the cost of RSV vaccine. However, it was estimated to be the same as a single course of palivizumab ranging from USD1,500 to USD4,300 per month, costing as much as USD6,000 to USD20,000 per child for four to five doses in one RSV season.[9]

ORGANISATIONAL ISSUES

There was no organisational issue identified. RSV vaccine could be integrated into existing immunisation programmes for the child or pregnant women to protect the vulnerable infants when more clinical data are available. However, affordability could be an issue.

SOCIETAL/ETHICAL ISSUES

There was no societal or ethical issue identified. Nevertheless, the acceptability of vaccination in pregnant women will be an issue.

POTENTIAL IMPACT

Respiratory Syncytial Virus candidate vaccines for maternal immunisation and older adults were well-tolerated and highly immunogenic in Phase I/II clinical studies. However, the phase III GRACE study is important to evaluate the safety of the candidate vaccine for pregnant mothers and infants, and its efficacy in infants born to vaccinated mothers.

For this vaccine to be beneficial for many, the cost must be within the affordability of the country.

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Prepared by:
Pn. Siti Aisah Fadzilah
Senior Principal Assistant Director
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

Reviewed by:
Dr. Syaqirah Akmal
Public Health Physician
Senior Principal Assistant Director
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

Dr. Izzuna Mudla Binti Mohamed Ghazali
Public Health Physician
Deputy Director
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

External Reviewer:
Dato' Dr. Wong Peng Shyan
Infectious Disease Physician
Hospital Pulau Pinang

Dr. Norshireen Nazli binti Abdul Razak
Consultant Paediatrician
Hospital Tunku Azizah

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Horizon Scanning Unit,
MaHTAS,
Medical Development Division,
Ministry of Health, Malaysia,
Email: htamalaysia@moh.gov.my
Web: http://www.moh.gov.my

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MALAYSIAN HEALTH TECHNOLOGY ASSESSMENT SECTION


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