BILL & MELINDA GATES foundation

LIGHT TOUCH STRAIGHTFORWARD GRANT – INVESTMENT DOCUMENT

GRANT PROPOSAL

Investment Name	Risk benefit analysis of RSV maternal vaccine	**Investment Organization**	London School of Hygiene and Tropical Medicine
Investment Owner	[redacted]	**Investment Coordinator**	[redacted]
Investment ID	INV-069494	**Proposal Submitted Date**	18 January 2024

INVESTMENT DETAILS

Estimated Grant Start Date	1 February 2024	**Grant End Date**	30 March 2025
Organization Legal Name[1]	London School of Hygiene & Tropical Medicine	**Total Requested Amount (USD)**	$139,848.22
Organization Doing Business As/Trade Name[2]	London School of Hygiene & Tropical Medicine	**Total Direct Costs (USD)** Direct & Indirect Cost Guidance	$121,607.15
Tax Status (if known and applicable) Tax Status Definitions	Non-profit higher education institution	**Total Indirect Costs (USD)** Direct & Indirect Cost Guidance	$18,241.07
U.S. Employer Identification Number (EIN) (if applicable)	N/A	**Primary Contact Name**	[redacted]
Mailing Address		**Primary Contact Title**	[redacted]
Street Address 1	Keppel Street	**Primary Contact Email**	[redacted]
Street Address 2		**Primary Contact Phone**	[redacted]
City	London	**Authorized Signer Name**	[redacted]
State / Province		**Authorized Signer Title**	[redacted]
Zip / Postal Code	WC1E 7HT	**Authorized Signer Email**	[redacted]
Country	United Kingdom		

Charitable Purpose - completed by the foundation

- The following describes the charitable purpose of this project. It is written in a standard format by your foundation contact for publication on the foundation's public website should your project receive funding.

[1] Legal Name will be used in the agreement and should match the name on the bank account that receives the grant funds (assuming fully executed agreement).
[2] Trade Name or d/b/a ("doing business as") only required if different from Legal Name.

Project Description – completed by the grantee

❖ In this section, please describe the proposed work.

Background

Abrysvo, a Pfizer-developed bivalent pre-F subunit vaccine against respiratory syncytial virus (RSV), showed robust efficacy in phase III trials against lower respiratory tract infection among infants born to individuals vaccinated during pregnancy at 24-36 weeks gestation. However, vaccine recipients experienced a higher level of preterm births and preeclampsia compared to those who received placebo. Although the safety signal was statistically not significant, a phase 3 trial of a similar pre-F subunit vaccine by GSK was discontinued due an increase in pre-term infants to vaccinated mothers. This safety issue does not appear to occur in vaccinees from high income countries.

The vaccine obtained regulatory approval from the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) in early 2023. FDA stipulated a restricted gestational age window of 32-36 weeks. Pfizer is also pursuing licensure in other countries, including South Africa.

Recognising the significance of these findings, the WHO Strategic Group of Experts on Immunization (SAGE) will discuss RSV vaccination in March 2024. SAGE has expressed the need for a risk-benefit analysis of maternal RSV vaccination in several countries, including at least one currently eligible for support from Gavi, the Vaccine Alliance. National immunization technical advisory groups (NITAGs) in several countries (including South Africa) are also considering recommendations about maternal RSV vaccination.

Proposed approach

We will conduct risk-benefit and cost-effectiveness analyses of maternal RSV vaccination. Because the units of risk (potential disbenefit) and benefit are different, we will use a dashboard approach showing possible positive and negative health consequences of RSV in quantitative terms. Some of the outcomes may include: recurrent respiratory illness, bronchopulmonary dysplasia, prematurity, RSV-associated LRTI, RSV hospitalization and RSV HDU/ICU admission. However, we will also include generic measures (all-cause hospital admission, DALYs and deaths) that will allow comparison between the two. The outcomes to include with the dashboard will be decided in discussion with the Advisory Group, but with special weight given to input from the WHO SAGE Secretariat for phase 1 of the work, and to members from South Africa and Kenya for phase 2 of the work.

The work will take place in three phases, to meet the timelines of different decision makers:

Phase 1: Work to inform WHO SAGE

We will prepare a report for WHO SAGE on the risk-benefit of maternal RSV vaccination in South Africa and Kenya. This will build on our previous cost-effectiveness model of RSV vaccination in South Arica and Kenya, updated to include the latest phase III trial results (Koltai et al.). The previous model used recent health and economic burden of disease data collected by South African and Kenyan teams as part of a BMGF-funded project. However, the model will be expanded to cover many of the outcomes listed above (not all may be feasible within the time scale).

The potential pre-term birth risk due to vaccination will be informed by the phase III trial data from South Africa, where the strongest safety signal was seen. We will explore scenarios with an age restriction on vaccination (e.g. after 32 weeks gestation, as imposed by US FDA) and those without.

Phase 2: Work to inform South African and Kenyan NITAG

South Africa's National Advisory Group on Immunization (NAGI) has convened an RSV subgroup and is likely to consider a recommendation about maternal RSV vaccination in 2024. To advise the subgroup and main committee, we will work with the South African team to conduct a more extensive cost-effectiveness and risk-benefit analysis. Depending on the needs of NAGI and time availability, the extensions may include (i) prevention of all cause LRTI, (ii) consideration of programmes using RSV monoclonal antibodies instead of vaccination, (iii) determining the threshold price for each intervention to be cost-effective.

The Kenya National Immunisation Technical Advisory Group (KENITAG) is also interested in this work, although with less definitive timelines, so we will conduct a similar analysis for Kenya in collaboration with the Kenyan team.

Phase 3: Work to inform Gavi

We will extend the cost-effectiveness and risk-benefit analysis to other Gavi eligible and Gavi transitioning countries, extending the previous work conducted to inform Gavi decision-making (Li et al).

Timeline and deliverables

- Mid February: Preliminary risk-benefit analysis for SAGE working group on RSV.
- Mid March: Risk-benefit analysis for main SAGE.
- End June: Detailed risk-benefit analysis for South Africa.
- End August: Detailed risk-benefit analysis for Kenya (if required).
- End December: Risk-benefit analysis for all Gavi countries.

Personnel and organisation

- The main initial analysis for WHO SAGE will be conducted by [redacted], a joint LSHTM/Nagasaki University PhD [redacted]
- The work will be supervised by [redacted] (LSHTM).
- We will also benefit from close collaboration with the following people, with the frequency of their involvement depending on their capacity. For those with the capacity for this commitment, we propose to set up an advisory group that will meet regularly to input into the development of the analysis.
    - Co-supervisors [redacted] (LSHTM), [redacted] (Nagasaki University and National University of Singapore)
    - South Africa: [redacted] (NICD), [redacted] (University of the Witwatersrand), [redacted] (University of Cape Town)
    - Kenya: [redacted] (KEMRI-WT), [redacted] (CDC Kenya), [redacted] (KEMRI-WT)
    - [redacted] (Imperial; formerly LSHTM) [redacted] (University of Antwerp) [redacted].
    - WHO: [redacted]
    - BMGF: [redacted]
- We will also liaise with key stakeholders (BMGF, WHO, country NITAGs and Gavi) to ensure that our work is closely aligned with their needs.

References

Kampmann B et al. Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants. N Engl J Med. 2023 Apr 20;388(16):1451-1464. doi: 10.1056/NEJMoa2216480.

Koltai M et al. Estimating the cost-effectiveness of maternal vaccination and monoclonal antibodies for respiratory syncytial virus in Kenya and South Africa. BMC Med. 2023 Mar 31;21(1):120. doi: 10.1186/s12916-023-02806-w.

Li X et al. Health and economic burden of respiratory syncytial virus (RSV) disease and the cost-effectiveness of potential interventions against RSV among children under 5 years in 72 Gavi-eligible countries. BMC Med. 2020 Apr 6;18(1):82. doi: 10.1186/s12916-020-01537-6. PMID: 32248817; PMCID: PMC7132892.

Budget – completed by the grantee

❖ In this section, please describe the direct and indirect costs, and total requested grant amount.

❖ The work will be done by a PhD student [redacted] for the first two months, and then transition to a research fellow (to be appointed; 100% fte from 1 May 2024 – 30 Mar 2025). We are not charging for [redacted] time, but have budgeted $7,000 [redacted] to complete the work and then transition it to the research fellow (costed at $87,266.00 for 11 months). Other staff costs (running from 1 Feb 2024 – 30 Mar 2025) include: [redacted] (5% fte, $10,722.63), [redacted] (5% fte from 1 July 2024, $3,762.37), [redacted] (10% fte from 1 Jan 25, $3,459.95), [redacted] (5% fte, $4,846.19). We have also included recruitment ($350.01) & visa fees ($2,800) for the research fellow plus a laptop ($1,400). Indirect costs at 15% total $18,241.07.

Geography Served – completed by the grantee

❖ List all countries, sub-regions, and/or states where this work will have impact. For additional information, see the Geography and Location of Work – Frequently Asked Questions.

Location of Work	Amount

Global	$

Location(s) of Work – completed by the grantee

- List all countries, sub-regions, and/or states where this work would be performed. For additional information, see the Geography and Location of Work – Frequently Asked Questions.

Location of Work	Amount
United Kingdom	$

FINAL NARRATIVE

For completed grants only. At the end of your grant, complete this final narrative section and submit to your foundation contact by the date indicated in your grant agreement or latest amendment. If you have any questions or need support, please reach out to your foundation contact. Please find contact information under Investment Details.

Grant Start Date	Grant End Date	Final Report Due Date	Remaining / Unexpended Grant Funds, Interest, and Currency Gains (if applicable)
[DD Month YYYY]	[DD Month YYYY]	[DD Month YYYY]	$

Grantee Confirmation

By submitting this report, I declare that I am authorized to certify, on behalf of the grantee identified under Investment Details, that I have examined the responses provided and related attachments, and that to the best of my knowledge, they are true, correct, and complete.

I also confirm that the grantee identified under Investment Details has complied with all of the terms and conditions of the grant agreement.

Your Name	Report Submitted Date
	[DD Month YYYY]

Final Results

- Provide information about what you achieved during the grant and your progress towards achieving the project's desired outcomes and outputs.