13 December 2024

To:

Dr. Alemnew Dagnew
Head of Clinical Development
Bill & Melinda Gates Medical Research Institute

Dr. Alexander Schmidt
Head of Vaccine Development
Bill & Melinda Gates Medical Research Institute

Cc:

Dr. Patrice Matchaba, Chief Executive Officer, Bill & Melinda Gates Medical Research Institute
Dr. Nina Russell, Director, TB & HIV Research and Development, Bill & Melinda Gates Foundation
Dr. Alexander Pym, Director of Infectious Disease, Wellcome Trust
Dr. Soumya Swaminathan, Co-Chair, M72 International Advisory Group
Prof. Helen Rees, Co-Chair, M72 International Advisory Group

Open letter: Capitalizing on the opportunity to collect timely data on the use of M72/AS01$_E$ in breastfeeding populations

Dear Drs. Dagnew and Schmidt,

We are the tuberculosis (TB) advocates who authored the Washington, D.C. Community Consensus on the Earlier Inclusion of Pregnant Women and Persons in TB Research. We write to applaud the initiation and rapidly progressing enrollment of the phase III trial of M72/AS01$_E$, but also to express our grave concern that the current study excludes breastfeeding women.[1] Breastfeeding women and persons, as well as those in close contact with them, represent a substantive portion of people at risk for TB, and there is no medical or ethical reason to exclude them from this research. Doing so would effectively exclude this population from rollout of the vaccine if the trial is successful, as we hope it will be. We urge you, as the trial sponsors, to pioneer the inclusion of breastfeeding populations in TB vaccine research by initiating a sub- or side-study to evaluate the vaccine's safety in breastfeeding women and persons.

Our urgent call for closing this vital gap is supported by the following reasons:

First, there are no anticipated risks of M72/AS01$_E$ vaccination particular to breastfeeding. As we wrote in our consensus statement, "there is little justification for excluding breastfeeding women and persons from TB vaccine studies."[2] Indeed, there is significant precedent for the safety of vaccination during lactation; it is not known to affect the safety of women or their infants, other than in the case of live attenuated vaccines for smallpox and yellow fever, which carry a small theoretical risk of transmission to the infant.[3] And even for these two live attenuated vaccines, the

[1] A Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter, Clinical Trial to Assess the Prophylactic Efficacy, Safety, and Immunogenicity of the Investigational M72/AS01E-4 Mycobacterium Tuberculosis (Mtb) Vaccine When Administered Intramuscularly on a 0,1-month Schedule to Adolescents and Adults. In: Wellcome T, Bill, Melinda Gates F, editors.; 2023.
[2] Washington, D.C. Community Consensus on the Earlier Inclusion of Pregnant Women and Persons in TB Research 2023. https://www.treatmentactiongroup.org/wp-content/uploads/2024/02/pregnancy_consensus_statement_full_final.pdf.
[3] Centers for Disease Control and Prevention. Advisory Committee on Immunization Practices (ACIP) General Best Practice Guidelines for Immunization — Special Situations. 2023.

World Health Organization still recommends their use in breastfeeding women when the risk of disease is high (such as in endemic areas or during outbreaks).[4]

M72/AS01$_E$ is a recombinant fusion protein vaccine, not a live attenuated vaccine, and therefore, to our knowledge, carries no risk of transmission to the infant through breastmilk (and may even confer protective antibodies to the infant, as observed with COVID-19 vaccines[5]). Similarly, the saponin-based adjuvant system AS01$_E$ also carries little theoretical risk of harm during lactation and an adjuvant with shared components has been widely used in breastfeeding populations via the Novavax COVID-19 vaccine with no known safety concerns.[6,7]

Second, excluding breastfeeding women and persons is inequitable. By definition, rates of TB incidence in the general population are high in the settings selected for the trial, and for eventual rollout if successful. As many people as possible in these populations require vaccination for their protection as well as prevention of onward transmission. In the absence of special risk of adverse effects of the vaccine, breastfeeding individuals deserve the same right to consent to informed participation in trials and the same chance of benefitting as the rest of the general population—especially given that TB predominately affects people in their fertile years[8], and women in high TB burden countries spend a significant portion of their life being either pregnant or postpartum. Furthermore, as the postpartum period poses challenges for optimal adherence[9], and the short-course TB preventive therapy options are not currently recommended in breastfeeding women[10], vaccines may be the preferable prevention option, making it even more inequitable if only their male and non-postpartum counterparts are able to access vaccines.

Third, postpartum is a high-risk period for TB disease. We argue that in addition to being included as members of the general population as they do not present additional risks, breastfeeding women and persons merit inclusion in M72/AS01$_E$ and other TB vaccine studies as they face significantly increased risk of developing TB disease. Postpartum women face an incident risk ratio of 1.62-2.3 compared to women outside of the pregnancy/breastfeeding period, and even higher than the risk during pregnancy.[11,12,13] Exposed infants are at especially high risk of developing life-threatening

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[4] World Health Organization. Vaccines and vaccination against yellow fever. WHO position paper -- June 2013. *Weekly Epidemiological Record*; **88**(27): 269 - 83.
[5] Shook LL, Edlow AG. Safety and Efficacy of Coronavirus Disease 2019 (COVID-19) mRNA Vaccines During Lactation. *Obstetrics & Gynecology* 2023; **141**(3).
[6] Stertman L, Palm AE, Zarnegar B, et al. The Matrix-M™ adjuvant: A critical component of vaccines for the 21(st) century. *Hum Vaccin Immunother* 2023; **19**(1): 2189885.
[7] World Health Organization. The Novavax vaccine against COVID-19: What you need to know;. 2022. https://www.who.int/news-room/feature-stories/detail/the-novavax-vaccine-against-covid-19-what-you-need-to-know.
[8] World Health Organization. Global tuberculosis report. 2024. https://www.who.int/publications/i/item/9789240101531.
[9] Nachega JB, Uthman OA, Anderson J, et al. Adherence to antiretroviral therapy during and after pregnancy in low-income, middle-income, and high-income countries: a systematic review and meta-analysis. *AIDS* 2012; **26**(16): 2039-52.
[10] World Health Organization. WHO consolidated guidelines on tuberculosis: Module 1: Prevention – Tuberculosis preventive treatment, second edition. 2024. https://www.who.int/publications/i/item/9789240096196.
[11] Morton AJ, Mitchell AR, Melville RE, et al. Mycobacterium tuberculosis infection in pregnancy: a systematic review. *medRxiv* 2024: 2024.08.10.24311783.
[12] Jonsson J, Kuhlmann-Berenzon S, Berggren I, Bruchfeld J. Increased risk of active tuberculosis during pregnancy and postpartum: a register-based cohort study in Sweden. *Eur Respir J* 2020; **55**(3).
[13] Zenner D, Kruijshaar ME, Andrews N, Abubakar I. Risk of tuberculosis in pregnancy: a national, primary care-based cohort and self-controlled case series study. *Am J Respir Crit Care Med* 2012; **185**(7): 779-84.

disseminated disease even despite BCG vaccination at birth.[14] The psychological toll of a TB diagnosis during the postpartum period cannot be overstated. Mothers with TB face incredible stigma, discrimination from the community, families and healthcare workers, and the threat of separation from their infants—all of which could likely contribute to poorer outcomes and reduced health seeking behavior.[15]

Fourth, the postpartum period offers opportunities for engagement with the healthcare system. The lack of infrastructure and resources for adult vaccination in low- and middle-incomes countries will pose a challenge to TB vaccine rollout.[16] Successful implementation will depend on leveraging existing programs and finding ways to meet people where there are already seeking care. During the postpartum period, while they are breastfeeding, women regularly interface with the health care system, attending postnatal checkups and visits for maternal and infant immunizations. Linking vaccination to one (or more) of these time points is a known strategy for increasing vaccine uptake, such as in the case of postpartum measles, mumps and rubella (MMR) vaccination to protect future pregnancies against congenital rubella syndrome.[17]

Fifth, an absence of data for breastfeeding populations leads to conflicting guidelines and misinformation, which threaten to limit vaccine uptake. We have seen too often in TB and other fields, that the exclusion of key populations from research, however well-intentioned, results in inequitable access to novel prevention and treatment options, as World Health Organization and national guidance are based on available data.[10,18] For this reason, a paradigm shift is underway to prioritize inclusion of breastfeeding (and pregnant) populations in research.[19] Indeed, the recent update to the Declaration of Helsinki noted that even with vulnerable groups (which we actually do not consider breastfeeding persons to be), "their exclusion from medical research can potentially perpetuate or exacerbate their disparities.[20] Therefore, the harms of exclusion must be considered and weighed against the harms of inclusion."

In the case of breastfeeding people at risk for TB, the harms of exclusion undoubtedly outweigh the harms of inclusion. In principle, we believe that in the absence of a scientifically justified rationale for their exclusion, breastfeeding individuals (and pregnant individuals, for that matter) should be included in primary phase III efficacy trials. While it is unfortunately too late for that for M72/AS01$_E$, the next best option is timely initiation of a rigorous sub- or side-study in breastfeeding individuals

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[14] Perez-Velez CM, Marais BJ. Tuberculosis in children. *N Engl J Med* 2012; **367**(4): 348-61.
[15] Loveday M, Hlangu S, Furin J. Healthcare Provider Discrimination toward Pregnant Women with Rifampin-Resistant Tuberculosis. *Emerg Infect Dis* 2019; **25**(3): 609-10.
[16] Gerste AK, Majidulla A, Baidya A, et al. Lessons from a decade of adult vaccine rollout in low- and middle-income countries: a scoping review. *Expert Review of Vaccines* 2024; **23**(1): 688-704.
[17] Alzeidan RA, Wahabi HA, Fayed AA, Esmaeil SA, Amer YS. Postpartum rubella vaccination for sero-negative women. *Cochrane Database of Systematic Reviews* 2013; (9).
[18] World Health Organization. WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update. 2022. https://www.who.int/publications/i/item/9789240063129.
[19] National Academies of Sciences E, Medicine. Advancing Clinical Research with Pregnant and Lactating Populations: Overcoming Real and Perceived Liability Risks. Washington, DC: The National Academies Press; 2024.
[20] Association WM. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Participants. *JAMA* 2024.

that will enable specific regulatory and policy guidance for this population, ideally at the time of initial licensure of M72/AS01$_{E.}$

We call on Gates MRI, the Gates Foundation, and Wellcome Trust to rapidly develop, initiate, fund, and conduct a study evaluating the safety of M72/AS01$_{E}$ in breastfeeding individuals. We strongly urge you to not miss out on this opportunity to align with global ethical, scientific, and normative calls and generate timely data for an important population.

Please kindly reply to our letter by 22 January 2025 by contacting Edna Tembo at ednatembo66@gmail.com, and please let us know if you would like to discuss further.

Sincerely,

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