COVID-19 vaccine trials must include helminth-infected cohorts

To the Editor — The COVID-19 vaccination roll out is ongoing in Africa, albeit at a much slower pace than in Western countries owing to constraints to vaccine supplies. However, the promise of COVID-19 vaccination in Africa and other lower- and middle-income countries (LMICs) must be tempered with caution as 2 billion people in LMICs — around one-quarter of the global population — harbor helminth parasites[1] that can impair human immune responses to several other vaccines[2]. This immunosuppression occurs through the involvement of interleukin (IL)-10 and type 1 regulatory T cells[3]. Despite this potential confounding risk factor, clinical trials of COVID-19 vaccines have not included a cohort infected with helminths, and as such the effects of helminths on COVID-19 vaccine immunogenicity and safety remain unknown.

Several million COVID-19 vaccine doses have been administered in Africa, but it is not known whether helminth parasites have affected immunogenicity of these vaccines in the small proportion of the population that have been fully vaccinated so far. If helminth-infected individuals are confirmed to have lower antibody titers or a shorter-duration antibody response than the rest of the population, then this population should be prioritized for COVID-19 vaccine booster doses, just as older people and other vulnerable populations have been prioritized.

Helminth parasites induce type 2 immune responses characterized by an increase in immunoglobulin E (IgE) antibody titers, eosinophilia, mastocytosis and basophilia[4]. This immune state is the perfect scenario for the occurrence of type 1 hypersensitivity reactions such as urticaria, angioedema and anaphylaxis[5]. Anaphylaxis after a first dose of a COVID-19 vaccine has been reported and attributed to non-IgE-mediated mast cell activation by vaccine excipients[6]. It is reasonable to anticipate that people with helminth infections and type 2 immune responses might have a higher risk for both non-IgE-mediated and IgE-mediated anaphylaxis on receiving the first vaccine dose and second (or booster) dose, respectively. People with helminth infections might have an increased risk of IgE-mediated anaphylaxis after the second or third vaccine dose because they respond to the first dose by producing IgE antibodies to excipients. These IgE antibodies sensitize mast cells and basophils by binding to the high-affinity IgE receptor FcεR1 (ref. [5]). On receiving subsequent boosters, immune complexes containing excipients cross-link mast-cell-bound or basophil-bound IgE, causing degranulation and release of histamine and other pathogenic mediators that can trigger anaphylaxis[5,6].

Although a previous study in support of the hygiene hypothesis has reported that helminths can protect against allergy[7], this idea is hardly reassuring for recipients of COVID-19 vaccines in Africa. 'Breakthrough' severe allergic reactions do occur among Africans residing on the continent. Helminths (such as *Ascaris lumbricoides*) are also associated with allergic reactions in Africa[8]. Furthermore, *Ascaris* spp. hookworms and some other helminths obligatorily pass through the lungs of human hosts during their life cycle and induce type 2 immune responses in these organs[9]. This response probably escalates the risk of pulmonary anaphylaxis in vaccine recipients. The specter of severe allergic adverse reactions therefore hangs over the rollout of COVID-19 vaccination in LMICs.

Finally, owing to current vaccine supply constraints in LMICs, the use of fractional doses of COVID-19 vaccines to cover a greater number of people is under consideration[10]. This concept has been validated for other vaccines. But fractional doses that boost antibody responses in people with and without helminth infections might be different.

Given these concerns, we here provide a call to action for the scientific research community and funders to support clinical trials of full, fractional and booster COVID-19 vaccine doses in people with helminth infections as a priority population that represents one-quarter of humanity. These trials should confirm whether this population has lower titers of SARS-CoV-2-neutralizing antibodies and non-neutralizing antibody functional activities that promote cellular phagocytosis and complement deposition crucial for viral clearance. Other factors that are important to identify include whether members of this population have increased IgE titers coupled with a higher risk of severe allergic reactions, the fractional vaccine dose that works in these populations, and whether this population needs booster doses after being fully vaccinated. In the meantime, healthcare workers and COVID-19 vaccination programs in LMICs must remain vigilant for type I hypersensitivity reactions and maintain continuous training and preparedness for emergency intervention with life-saving measures. ❐

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Competing interests

T.G.E. and T.J.O. declare that they may conduct clinical research involving helminth-infected cohorts that might, in the future, drive revenue to Med Biotech Laboratories. M.K. declares no competing interests.