To our knowledge, this trial provides the first clinical evidence that FXIIa inhibition has a good safety profile in patients and supports the hypothesis that FXIIa inhibition can be an effective prophylactic strategy for HAE-C1-INH. The full study also included patients with HAE-nC1-INH with FXII or plasminogen mutations, the findings of which will be reported elsewhere. Besides the effect garadacimab might have on the bradykinin-mediated angioedema field, FXII and FXIIa inhibition might have wider applications—for example, as an antithrombotic agent in contact-mediated thrombosis triggered by medical devices (eg, vascular catheters, or extracorporeal membrane oxygenation)—but this use would first need to be confirmed in clinical trials for these indications.

A clear limitation of this phase 2 study is the paucity of diversity in the patient population. The population was predominantly White and older patients (age >65 years) were not eligible for participation. Therefore, increased diversity of patients in future studies is needed. Another limitation is that the treatment groups were not balanced in terms of age and sex, as well as, most importantly, baseline attack rate. Hence, the randomisation process was not very effective, which is not surprising given the small sample size.

Pending a phase 3 study investigating garadacimab in a larger group of patients with hereditary angioedema, the results here are promising.

FXIIa inhibition with garadacimab is a promising prophylactic strategy for patients with hereditary angioedema and is once again broadening the pharmacological resources for patients with severe, debilitating, and sometimes therapy-resistant angioedema. Garadacimab might bring us a step closer to reaching the ultimate treatment goal for patients with hereditary angioedema: an angioedema attack-free life, without restrictions or severe side-effects.

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1 Banerji A. The burden of illness in patients with hereditary angioedema. *Ann Allergy Asthma Immunol* 2013; **111:** 329–36.
2 Bork K, Hardt J, Witzke G. Fatal laryngeal attacks and mortality in hereditary angioedema due to C1-INH deficiency. *J Allergy Clin Immunol* 2012; **130:** 692–97.
3 Fijen LM, Bork K, Cohn DM. Current and prospective targets of pharmacologic treatment of hereditary angioedema types 1 and 2. *Clin Rev Allergy Immunol* 2021; **61:** 66–76.
4 Reshef A, Kidon M, Leibovich I. The story of angioedema: from quincke to bradykinin. *Clin Rev Allergy Immunol* 2016; **51:** 121–39.
5 Busse PJ, Christiansen SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 guidelines for the management of hereditary angioedema. *J Allergy Clin Immunol Pract* 2021; **9:** 132–50.
6 Cohn DM, Viney NJ, Fijen LM, et al. Antisense inhibition of prekallikrein to control hereditary angioedema. *N Engl J Med* 2020; **383:** 1242–47.
7 Banerji A, Davis KH, Brown TM, et al. Patient-reported burden of hereditary angioedema: findings from a patient survey in the United States. *Annal Allergy Asthma Immunol* 2020; **124:** 600–07.
8 Dewald G, Bork K. Missense mutations in the coagulation factor XII (Hageman factor) gene in hereditary angioedema with normal C1 inhibitor. *Biochem Biophys Res Commun* 2006; **343:** 1286–89.
9 Craig T, Magerl M, Levy DS, et al. Prophylactic use of an anti-activated factor XII monoclonal antibody, garadacimab, for patients with C1-esterase inhibitor-deficient, hereditary angioedema: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet* 2022; published online Feb 24. https://doi.org/10.1016/S0140-6736(21)02225-X.
10 Renné T. The procoagulant and proinflammatory plasma contact system. *Semin Immunopathol* 2012; **34:** 31–41.

Prioritise research on vaccines for pregnant and breastfeeding women

Pregnant women, their fetuses, and infants are at increased risk of severe disease and death from many vaccine-preventable diseases, including COVID-19.[1,2] However, they are typically excluded from pre-implementation vaccine research aimed at generating robust data in support of evidence-informed decision making. This was initially the case with COVID-19 vaccines. In 2019, the PREVENT Working Group published 22 recommendations on how to include pregnant and breastfeeding women in vaccine research and implementation for emerging infections.[3] In February, 2021, the COVAX Maternal Immunization Working Group (MI-COVAX) developed guidance on responsible inclusion in the context of COVID-19 vaccination.[4] Nonetheless, responsible inclusion of pregnant and breastfeeding women in pre-implementation clinical trials has yet to become standard research practice.

Nearly 30 years ago, law and ethics professor Rebecca Dresser advocated for ending research practices that normalised male bodies as quintessential research participants.[5] The resulting systematic exclusion of women from medical research, Dresser

argued, meant that research done with primarily white male participants was less informative for women and people of colour. In subsequent decades, calls for the inclusion of women in research extended to pregnant and breastfeeding women on the grounds of equitable access to pharmaceuticals for maternal, fetal, and infant health.[6] In the 2010s, international and US policy advisers removed the designation of pregnant women as "vulnerable" in oversight guidance, with the goal to improve their opportunities to consent to research participation and advance knowledge about pharmaceutical use in pregnancy.[3] Regulators developed guidance on how pregnant women could be included in clinical trials.[7,8] Yet, assumptions about vulnerability and related exclusion of pregnant and breastfeeding women in clinical trials persist.[9]

Throughout COVID-19 vaccine development, researchers, clinicians, and regulators called for the inclusion of pregnant and breastfeeding women in vaccine trials.[4,9–11] However, trials involving breastfeeding women were not initiated, while trials involving pregnant women began after emergency use authorisation of the vaccines was granted and were not completed due to low recruitment.[1]

Despite the absence of clinical trial data, some countries, including Brazil, Canada, Israel, and the USA recommended that pregnant and breastfeeding women may receive COVID-19 vaccination early in the roll-out on the basis of previously developed standards and enhanced post-implementation vaccine safety monitoring.[3,4] Post-implementation surveillance and research generated reassuring observational evidence of vaccine safety,[12] vaccine effectiveness among pregnant and breastfeeding women, and placental and breastmilk antibody transfer to offspring.[13] However, the UK, India, and many African and Latin American countries initially advised against COVID-19 vaccination for most pregnant women[4] or restricted early access to vaccines.[14] Eventually, many countries updated policies to recommend COVID-19 vaccination during pregnancy and breastfeeding[14] on the basis of post-implementation data generated by countries with robust surveillance systems and mounting evidence of severe COVID-19 outcomes in pregnancy.[2,12,13,15] Yet, some health-care providers and women hesitate to accept these recommendations. Responsible inclusion of pregnant women from the outset would have improved acceptance and benefited women in all countries, including low-income and middle-income countries, where there were delays in vaccine procurement and production.

Wide-ranging changes are needed to ensure responsible inclusion of pregnant and breastfeeding women in research (panel). To inform responsible inclusion and decisions about prioritisation for early vaccine access, data about disease risks in pregnant and breastfeeding

***Panel:* Barriers and countermeasures to ensure responsible inclusion of pregnant and breastfeeding women in vaccine research**

Barriers to responsible inclusion

- Erroneous assumptions about vulnerability
- Gaps in evidence about disease burden
- Normalised practices of systematic exclusion
- Disincentives (eg, increased cost, liability concerns, and potential for trial delays)[16]
- Pragmatic challenges (eg, potential trial delays, public trust, and recruitment)

Examples of countermeasures

- Revise and enforce research guidelines and regulations to promote responsible inclusion
- Develop training materials for students, staff, faculty, grant applicants, reviewers, safety committee members, and research ethics committee members
- Collect data about disease risks in pregnant and breastfeeding women, fetuses, and infants
- Prioritise development and reproductive toxicology (DART) studies when pertinent[3]
- Require inclusion of pregnant and breastfeeding women in pre-implementation vaccine trials when appropriate
- Continue trials in non-pregnant populations concurrently with DART studies and trials in pregnancy and breastfeeding
- Require active surveillance[4] and develop programmes that can quickly scale up to monitor vaccine safety and effectiveness for pregnant and breastfeeding women[1]
- Fund research into outcomes for pregnant and breastfeeding women and their offspring
- Require regulatory and ethics approval requirements for responsible inclusion
- Provide no fault national and global compensation programmes
- Include post-vaccination adverse pregnancy and neonatal events in national and global no-fault vaccine compensation programmes[3]
- Invest in public education about potential benefits of research participation
- Normalise practices from successful non-pandemic vaccine development among pregnant and breastfeeding women[3]

women, fetuses, and infants must be collected at the onset of disease outbreaks. Adaptable, robust surveillance systems should be developed in obstetric and perinatal care that can be scaled up during disease outbreaks to collect data on disease burden, and monitor vaccine safety and effectiveness in these high-risk populations.

Responsible inclusion has yet to be required in vaccine development. Clinical development plans for new vaccines must incorporate responsible inclusion of pregnant and breastfeeding women, with maximum diversity across age, ethnicity, and other social stratifiers in all aspects of research, from epidemiological and surveillance studies to interventional trials. Research funders, research ethics committees, and regulators must require and enforce responsible inclusion for funding, ethics approval, trial authorisation, design, and conduct unless exclusion is justified. Academic and research institutions should develop or improve training materials about responsible inclusion for researchers, ethics committees, and data safety monitoring boards on the basis of the PREVENT and MI-COVAX guidelines.[3,4]

Regulatory agencies require minimum data to support vaccine trials in pregnancy, which may include developmental and reproductive toxicity studies in animals and demonstration of safety and immunogenicity with potential for efficacy in phase 1 and 2 trials of non-pregnant populations.[4] Collection of these data must be prioritised early in the development pathway[3] so that phase 1 and 2 trials in pregnant and breastfeeding women can be initiated after phase 1 and 2 studies in non-pregnant populations or concurrently with phase 3 trials in the general population.[17] During vaccine roll-out, regulators must require inclusion of pregnant and breastfeeding women and infants in phase 4 studies and pregnancy registries to carefully monitor vaccine effectiveness and safety, with attention to differences among groups of women on the basis of age, ethnicity, and diverse intersectional identities.[4] Public health should strengthen and expand passive and active surveillance systems to capture adverse pregnancy and neonatal outcomes after vaccination with scalability to respond to new epidemic threats.[1]

Support is needed to remove real and perceived barriers to responsible inclusion (eg, increased cost, liability, safety concerns).[16] Such supports include mechanisms to prioritise regulatory review of trials involving pregnant women and the establishment of national and global no-fault compensation programmes that include adverse pregnancy and neonatal outcomes.[3] Funding is needed for the additional costs of evaluating vaccine safety and efficacy during and after pregnancy in women, their fetuses, and infants.[1] Prelicensure trials of respiratory syncytial virus and group B streptococcus vaccines designed specifically for pregnant women are examples of successful participant recruitment and trial progression, while maintaining public confidence.[3] With time and public education about the potential benefits of research participation, responsible inclusion should become a prerequisite for vaccine research.

All groups of women deserve equitable access to life-saving vaccines and therapeutics when these become available to the general population and priority access when appropriate (eg, during pregnancy). The actions we propose here need to be adopted to change the status quo and provide policy makers and women with timely, robust evidence to inform their decisions about vaccination.

KAT has received grants from GlaxoSmithKline to her institution for work related to vaccines that could be given to pregnant women. FMM is a member of the Data and Safety Monitoring Boards for vaccines manufactured by Pfizer (respiratory syncytial virus [RSV]), Moderna (RSV, human metapneumovirus, parainfluenza, SARS-CoV-2, influenza), Virometix (RSV), and Meissa (RSV vaccines). FMM is an investigator in research supported by Pfizer (SARS-CoV-2 vaccines), Gilead (remdesivir), the US National Institutes of Health (safety of vaccines in pregnancy, Zika virus), and the US Centers for Disease Control and Prevention (respiratory virus epidemiology) for work directly or indirectly related to vaccines that could be given to pregnant women. TM has received funding from an IWK Health Centre postdoctoral fellowship grant and is funded by the Public Health Agency of Canada and Canadian Institutes of Health Research through a Canadian Immunization Research Network postdoctoral grant. FB declares no competing interests.

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1 COVAX Maternal Immunization Working Group. Advances in maternal immunization science and implementation in times of COVID-19—how has the COVID-19 pandemic impacted the future of maternal immunization? 2021. https://media.tghn.org/medialibrary/2022/01/COVAX_MIWG_Webinar_Report_NOV2021_Final.pdf (accessed Feb 23, 2022).

2 Kasehagen L, Byers P, Taylor K, et al. COVID-19–associated deaths after SARS-CoV-2 infection during pregnancy—Mississippi, March 1, 2020–October 6, 2021. *Morb Mortal Wkly Rep* 2021; **70:** 1646–48.

3 Krubiner CB, Faden RR, Karron RA, et al. Pregnant women and vaccines against emerging epidemic threats: ethics guidance for preparedness, research, and response. *Vaccine* 2021; **39:** 85–120.

4 COVAX Maternal Immunization Working Group. Considerations for the evaluation of COVID-19 vaccines in pregnant and lactating women. 2021. https://epi.tghn.org/covax-overview/clinical-science/maternal-immunization/reports-mi/ (accessed Feb 23, 2022).

5 Dresser R. Wanted single, white male for medical research. *Hastings Cent Rep* 1992; **22:** 24–29.

6 Lyerly AD, Little MO, Faden R. The second wave: toward responsible inclusion of pregnant women in research. *Int J Fem Approaches Bioeth* 2008; **1:** 5–22.

7 US Department of Health and Human Services, US Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Pregnant women: scientific and ethical considerations for inclusion in clinical trials. April, 2018, p 1–11, clinical/medical, report no revision 1. https://www.fda.gov/media/112195/download (accessed Feb 23, 2022).

8 Government of Canada. Guidance document: considerations for inclusion of women in clinical trials and analysis of sex differences. May 2013. https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/clinical-trials/considerations-inclusion-women-clinical-trials-analysis-data-sex-differences.html#a23 (accessed Feb 23, 2022).

9 Farrell R, Michie M, Pope R. Pregnant women in trials of Covid-19: a critical time to consider ethical frameworks of inclusion in clinical trials. *Ethics Hum Res* 2020; **42:** 17–23.

10 Kweder S, Thor S, Vasisht K, Yao L, Everett D. Global regulators envision paradigm shift toward inclusion of pregnant and breastfeeding women in clinical research for medicines and vaccines. US Food and Drug Administration. July 19, 2021. https://www.fda.gov/news-events/fda-voices/global-regulators-envision-paradigm-shift-toward-inclusion-pregnant-and-breastfeeding-women-clinical (accessed Feb 22, 2022).

11 International Coalition of Medicines and Regulatory Authorities. ICMRA pregnancy and lactation workshop. Feb 9, 2021. https://www.icmra.info/drupal/en/covid-19/9february2021 (accessed Feb 22, 2022).

12 Shimabukuro TT, Kim SY, Myers TR, et al. Preliminary findings of mRNA Covid-19 vaccine safety in pregnant persons. *N Engl J Med* 2021; **384:** 2273–82.

13 Gray KJ, Bordt EA, Atyeo C, et al. COVID-19 vaccine response in pregnant and lactating women: a cohort study. *Am J Obstet Gynecol* 2021; **225:** 303.e1–17.

14 Berman Institute of Bioethics and Center for Immunization Research, Johns Hopkins University. COVID-19 Maternal Immunization Tracker (COMIT). 2021. http://www.comitglobal.org/ (accessed Feb 22, 2022).

15 DeSisto CL, Wallace B, Simeone RM, et al. Risk for stillbirth among women with and without COVID-19 at delivery hospitalization—United States, March 2020–September 2021. *Morb Mortal Wkly Rep* 2021; **70:** 1640–45.

16 Price N, Sachs R, Sherkow JS, Larrimore Ouellette L. How does pregnancy factor into COVID-19 innovation? Dec 6, 2021. https://writtendescription.blogspot.com/2021/12/how-does-pregnancy-factor-into-covid-19.html?m=1 (accessed Feb 22, 2022).

17 Baylis F, Halperin S. Research involving pregnant women: trials and tribulations. *Clin Investig* 2012; **2:** 139–46.

The bleak future of Afghan women's health under the Taliban

Gender-based violence (GBV) is threaded through the lives of many Afghan women. Estimates from the United Nations Population Fund suggest that 87% of women in Afghanistan experience at least one form of GBV during their lifetime and 62% are subjected to multiple forms of violence, such as physical, sexual, and psychological harms.[1] The impacts of associated psychological trauma affect many women in Afghanistan and the regression of the rights of women and girls under the country's Taliban government aggravates this reality. As the situation in Afghanistan becomes increasingly precarious after some 6 months of the new Taliban regime, there are grave fears for the future of Afghan women's health.

The misogyny that underlies violence against women and girls in Afghanistan is entrenched in the fundamentalist Taliban regime and is emerging in the current context through the violent ways women claiming their fundamental rights are being treated.[2,3] In the immediate aftermath of the Taliban's takeover, the fragile gains made by women in the past two decades were undone.[4] Most non-governmental and civil society organisations working in different women-related fields have closed, either due to insufficient funding or safety concerns. The former Ministry of Women's Affairs (MoWA) is now the Ministry for the Propagation of Virtue and the Prevention of Vice[5] and imposes severe restrictions on women's basic rights and freedoms, including a ban on women travelling more than 45 miles without a male guardian,[6] which reduces women's access to health care in many areas. Women are not allowed to be examined by male health professionals even with a male guardian—a restriction that shrinks spaces to disclose health needs and GBV even further. These restrictions will ultimately cost women their lives.

Restricting women's right to health, combined with the deteriorating humanitarian crisis and economic collapse in the country, creates a breeding ground for violence against women and girls in a country that was already one of the worst places to be a woman before the Taliban takeover.[7] Health and women's rights were curtailed during previous governments. Under the influence of religious figures, the Afghan legislature and judiciary view is of GBV as a moral crime committed by a woman.[8] Afghan women who were threatened with or experienced violence were not protected or offered psychosocial health services.[9] Despite these serious challenges, non-governmental organisations (NGOs) and the MoWA had implemented referral pathways in several districts of Afghanistan to assist vulnerable women. One of the boldest initiatives taken by NGOs, some of them locally run by Afghan women, was setting up secret safe homes to protect women escaping violence. Women without access to such support remained exposed to GBV and desperate for help. Afghanistan has some of the highest rates of self-immolation of women globally, which may be regarded as a form of protest against GBV for some women.[10]

Protection networks for women have been dismantled.[11] Today, there is no escape for women

Ali Khara/Reuters Pictures

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