
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

JOGNN

EDITORIAL

# Sex-Based Vaccine Response in the Context of COVID-19

**Patricia Robin McCartney**
*Associate Editor*

We are in the midst of a global public health emergency with the spread of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19). A safe, effective, accessible, and acceptable vaccine is critically needed to prevent the spread of COVID-19. Reports indicate that the number of COVID-19 cases between men and women is similar, but men experience more severe outcomes, including hospitalization, admission to the intensive care unit, and death (Bischof et al., 2020; Global Health 5050, 2020; Klein et al., 2020; Scully et al., 2020). Although sex clearly plays a role in this disease, many states in the United States do not report or analyze differences in outcomes between men and women. In some cases, when differences in outcomes are reported by sex, findings are inconsistent (Klein et al., 2020). Data that are disaggregated for sex are necessary to compare outcomes, inform clinicians, and enable appropriate risk assessment and care, including the development and distribution of a vaccine. In this editorial, I offer a brief overview of what is known about sex-based responses to vaccines, development of a SARS-CoV-2 vaccine, and considerations for research and practice. While sex (biological characteristics of genetics, reproductive organs, and sex hormones) and gender (social and cultural characteristics) have been shown to influence vaccine uptake and related outcomes (Flanagan et al., 2017), I will limit my discussion to biological sex as a variable.

## Sex-Based Vaccine Response

The vaccine response includes the immune response and the likelihood of adverse events (AEs), and both are influenced by sex. Clinical research on many vaccines has shown differences between women and men: women exhibit a greater immune response that can facilitate vaccine efficacy, but they also experience more frequent and more severe AEs (Fink & Klein, 2015, 2018; Fischinger et al., 2019; Flanagan et al., 2017). Researchers have also shown that differences in response between women and men exist across the entire life span (Fink & Klein, 2018; Flanagan et al., 2017). However, few researchers who study vaccines in children separate data by sex. Of importance, the body of research on sex differences outside of the reproductive years indicates that genetics and hormones are involved in the vaccine response.

Women are known to have stronger immune responses to foreign antigens (a benefit with infections and vaccines) and to self-antigens (a susceptibility to autoimmune disease) than men (Klein & Flanagan, 2016). Although immune responses vary over the life span, women have more effective innate responses (pattern recognition receptors, cytokines) and adaptive (humoral and cell-mediated) responses (immunoglobulin, B cell, T cell) than men (Fink & Klein, 2018; Flanagan et al., 2017). Genetic factors responsible for the female immune response begin with the X chromosome, of which women have two. The X chromosome contains many genes, such as the angiotensin-converting enzyme 2, that regulate immune and cellular function (Scully et al., 2020). MicroRNAs facilitate immunity and are more numerous in women. Women also experience the beneficial effects of incomplete inactivation of some genes on the X chromosome (Fischinger et al., 2019; Flanagan et al., 2017; Scully et al., 2020). Sex steroid hormones, which vary over the life span, influence the female immune response by binding to hormone receptor sites on most immune cells, signaling immune pathways, and promoting gene expression (Scully et al., 2020). Estrogen downregulates the angiotensin-converting enzyme 2 receptor (a SARS-Cov-2 receptor; Klein et al., 2020). However, few researchers have examined the effect of hormones directly on vaccine response (Flanagan et al., 2017).

AEs related to vaccines, including systemic, local, and laboratory value findings, are graded as mild, moderate, severe, and potentially life threatening (characterized as serious or involving

emergency room or hospitalization; U.S. Food and Drug Administration, 2007). Data on vaccine AEs may be collected through active solicitation by the researcher in a trial or through passive surveillance in a self-report submission to a national vaccine event reporting system by the vaccine recipient. In the latter case, the potential for underreporting and reporting bias exist.

Injection site reactions are common vaccine AEs. In a systematic review of 1,074 studies on injection site reactions, Cook (2009) found that data were differentiated by sex in only 57 studies, and of those, researchers in 54 studies reported sex-related differences. Female children and adults reported greater pain than male children and adults. In this review, researchers in prospective trials designed to actively solicit AE data identified sex-related differences. Cook suggested that these differences may be related to immunity and subcutaneous and muscle tissue. In another systematic review on injection site hypersensitivity, Griffioen and Halsey (2014) found 11 studies in which researchers reported findings by sex. In eight of these studies, more women than men reported hypersensitivity, but the data were limited. Only two of the studies were prospective with active solicitation of AEs, seven were passive surveillance, one was self-report, and one was a medical record review. Most of the findings only included the frequencies of AEs without identification of sample sizes or analysis of rates of AEs.

## Development of a SARS-CoV-2 Vaccine

The World Health Organization (2020) listed 23 candidate SARS-CoV-2 vaccines currently in clinical trials worldwide. The focus of vaccine action is predominately the spike glycoprotein receptor on the surface of the virus that facilitates its entry into cells. The primary endpoints for vaccine efficacy are seroconversion and prevention of clinical disease. The National Institutes of Health has spearheaded a public-private collaboration, Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV), to conduct harmonized, parallel, and transparent vaccine safety and efficacy trials with several vaccine candidates (Corey et al., 2020; National Institutes of Health, 2020). Data sharing is key to the ACTIV collaboration; data elements will be coordinated, and immunological endpoints (seroconversion) and clinical endpoints (clinical disease) will be aggregated to increase the power of the trials (Ogburn et al., 2020). Plans for data disaggregation by sex in the ACTIV collaboration have not been reported.

At a recent federal hearing, members of the House of Representatives and representatives from five pharmaceutical companies that are developing vaccines discussed progress to date (U.S. House of Representatives, Committee on Energy and Commerce, 2020). Pharmaceutical representatives projected that a vaccine would be approved by the end of 2020 or early 2021. Discussions involved the potential need to tailor vaccines by age; sex differences were not discussed. A key concern among all participants was hesitancy regarding vaccine uptake.

Early reports of vaccine trials have just been published. In a preliminary report of the use of the candidate vaccine mRNA-1273 (a nucleic acid-based vaccine) among 45 healthy adults (22 men, 23 women) who received two injections of three dosage levels, researchers reported promising immunogenicity and safety outcomes (Jackson et al., 2020). At day 57 of the trial, participants had positive antibody immune responses that increased from the first to the second dose. Local and systemic AEs were solicited from the participants; injection-site reactions were mild, and no life-threatening AEs were reported. The study data on immunogenicity and AEs were not disaggregated for sex, nor was disaggregation by sex identified as a trial outcome. Participants will be followed for 12 months after the second vaccination, and Phases 2 and 3 of the mRNA-1273 trial are ongoing (Jackson et al., 2020).

Two other studies of an adenovirus-vector vaccine candidate also had positive immunologic and safety findings. In an open label, single blind trial of ChAdOxx1 with 1,077 adults (541 men, 536 women), Folegatti et al. (2020) reported an acceptable T cell immune response in all participants. Local and systemic AEs were solicited from the participants; reactions were mild or moderate, and no serious adverse reactions were reported. The data on immunogenicity and AEs were not disaggregated for sex, and participants will be followed for one year. In a trial of the adenovirus-vector vaccine candidate Ad5, Bar-Zeev and Moss (2020) analyzed for sex differences and found that more women experienced fever as an AE.

## Considerations for Research and Practice

Guidelines from the U.S. Food and Drug Administration previously indicated that clinical drug trials should exclude women of childbearing age. However, current guidelines require the inclusion of women, the analysis of safety and effectiveness data by sex, and sufficient women participants for data analysis by sex (U.S. Food and Drug Administration, 2019). The Office of Research on Women's Health (n.d.) indicated that federally funded research protocols should enroll women as participants; include sex as a biological variable; and disaggregate and analyze data by sex and gender in study design, reporting, analysis, and dissemination.

Evidence on sex-based differences in vaccine response is necessary because one vaccine dose or schedule may not be suitable for men and women. Will women exhibit a more robust immune response to a SARS-CoV-2 vaccine? Will women require a booster vaccine? Will women experience more AEs? Will we need vaccines tailored to individuals? Data need to be separated by sex in epidemiological reporting and research findings. The nongovernmental organization Global Health 5050 (2020) has launched an online COVID-19 tracker to share sex-disaggregated data on confirmed cases of infection, hospitalizations, intensive care unit admissions, and deaths. Data are collected from official government sources, updated every 2 weeks, and are available for download. Data are limited, however, to countries in which sex-disaggregated data are available. The designs of studies on vaccines should include sex as a biological variable, and researchers should recruit enough female participants for meaningful analysis. Data should be disaggregated in the analyses of outcome measures. Reporting data related to sex differences will support more thoughtful interpretation and enable comparison among studies. Individual studies that are underpowered could be suitable for future meta-analyses with greater power.

Clinicians should be aware of sex differences in vaccine developments and stay informed about the evidence reported in scientific studies published in peer-reviewed journals. We need to identify vaccine studies that are inclusive and expect sex to be a biological variable evident in the disaggregation of data and analyses. Hesitancy about vaccine uptake is a recognized threat to global health, and clinicians should promote vaccine acceptance (Ratzan et al., 2019). We must know and understand the science to help women trust the science. Practice strategies should include the provision of accurate and transparent information about any differences in the effectiveness, safety, or side effects of the COVID-19 vaccine related to sex. Clinicians should address vaccine misinformation and listen to women's questions and concerns. We must start to prepare ourselves to meet this challenge now.



## REFERENCES

Bar-Zeev, N., & Moss, W. (2020). Encouraging results from phase 1/2 COVID-19 vaccine trials. *The Lancet, 396*(10249), 448–449. https://doi.org/10.1016/S0140-6736(20)31611-1

Bischof, E., Wolfe, J., & Klein, S. L. (2020). Clinical trials for COVID-19 should include sex as a variable. *Journal of Clinical Investigation, 130*(7), 3350–3352. https://doi.org/10.1172/JCI139306

Cook, I. F. (2009). Sex differences in injection site reactions with human vaccines. *Human Vaccines, 5*(7), 441–449. https://doi.org/10.4161/hv.8476

Corey, L., Mascola, J. R., Fauci, A. S., & Collins, F. S. (2020). A strategic approach to COVID-19 vaccine R&D. *Science, 368*(6494), 948–950. https://doi.org/10.1126/science.abc5312

Fink, A. L., & Klein, S. L. (2015). Sex and gender impact immune responses to vaccines among the elderly. *Physiology, 30*(6), 408–416. https://doi.org/10.1152/physiol.00035.2015

Fink, A. L., & Klein, S. L. (2018). The evolution of greater humoral immunity in females than males: Implications for vaccine efficacy. *Current Opinion in Physiology, 6*, 16–20. https://doi.org/10.1016/j.cophys.2018.03.010

Fischinger, S., Boudreau, C. M., Butler, A. L., Streeck, H., & Alter, G. (2019). Sex differences in vaccine-induced humoral immunity. *Seminars in Immunopathology, 41*(2), 239–249. https://doi.org/10.1007/s00281-018-0726-5

Flanagan, K. L., Fink, A. L., Plebanski, M., & Klein, S. L. (2017). Sex and gender differences in the outcomes of vaccination over the life course. *Annual Review of Cell & Developmental Biology, 33*, 577–599. https://doi.org/10.1146/annurev-cellbio-100616-060718

Folegatti, P. M., Ewer, K. J., Aley, P. K., Angus, B., Becker, S., Belij-Rammerstorfer, S., … Oxford COVID Vaccine Trial Group. (2020). Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: A preliminary report of a phase 1/2, single-blind, randomised controlled trial. *The Lancet, 396*(10249), 467–478. https://doi.org/10.1016/S0140-6736(20)31604-4

Global Health 5050. (2020). *COVID-19 sex-disaggregated data tracker.* https://globalhealth5050.org/covid19/sex-disaggregated-data-tracker/

Griffioen, M., & Halsey, N. (2014). Gender differences in immediate hypersensitivity reactions to vaccines: A review of the literature. *Public Health Nursing, 31*(3), 206–214. https://doi.org/10.1111/phn.12073

Jackson, L. A., Anderson, E. J., Rouphael, N. G., Roberts, P. C., Makhene, M., Coler, R. N., … mRNA-1273 Study Group. (2020). An mRNA vaccine against SARS-CoV-2—Preliminary report.

*New England Journal of Medicine*. Advance online publication. https://doi.org/10.1056/NEJMoa2022483

Klein, S. L., Dhakal, S., Ursin, R. L., Deshpande, S., Sandberg, K., & Mauvais-Jarvis, F. (2020). Biological sex impacts COVID-19 outcomes. *PLOS Pathogens, 16*(6), Article e1008570. https://doi.org/10.1371/journal.ppat.1008570

Klein, S. L., & Flanagan, K. L. (2016). Sex differences in immune responses. Nature Reviews. *Immunology, 16*, 626–638. https://doi.org/10.1038/nri.2016.90

National Institutes of Health. (2020). *Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)*. https://www.nih.gov/research-training/medical-research-initiatives/activ

Office of Research on Women's Health. (n.d.). *NIH policy on sex as a biological variable*. https://orwh.od.nih.gov/sex-gender/nih-policy-sex-biological-variable

Ogburn, E. L., Bierer, B. E., Brookmeyer, R., Choirat, C., Dean, N. E., De Gruttola, V., … Scharfstein, D. O. (2020). Aggregating data from COVID-19 trials. *Science, 368*(6496), 1198–1199. https://doi.org/10.1126/science.abc8993

Ratzan, S. C., Bloom, B. R., El-Mohandes, A., Fielding, J., Gostin, L. O., Hodge, J. G., … Rabin, K. (2019). The Salzburg statement on vaccination acceptance. *Journal of Obstetric, Gynecologic, & Neonatal Nursing, 48*(6), 591–592. https://doi.org/10.1016/j.jogn.2019.10.001

Scully, E. P., Haverfield, J., Ursin, R. L., Tannenbaum, C., & Klein, S. L. (2020). Considering how biological sex impacts immune responses and COVID-19 outcomes. *Nature Reviews: Immunology, 20*(7), 442–447. https://doi.org/10.1038/s41577-020-0348-8

U.S. Food and Drug Administration. (2007). *Guidance for industry toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials*. https://www.fda.gov/media/73679/download

U.S. Food and Drug Administration. (2019). *Regulations, guidance, and reports related to women's health*. https://www.fda.gov/science-research/womens-health-research/regulations-guidance-and-reports-related-womens-health

U.S. House of Representatives, Committee on Energy and Commerce. (2020, July 21). *Pathway to a vaccine: Efforts to develop a safe, effective, and accessible COVID-19 vaccine*. [Hearing]. https://www.youtube.com/watch?v=tnWwJPe7p2A

World Health Organization. (2020). *Draft landscape of COVID-19 candidate vaccines*. https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines