

## Viewing the COVID-19 Vaccination Through a Sex and Gender Lens

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**Abstract:** The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) responsible for the COVID-19 pandemic has revealed extensive differences in the way men and women respond to infection. Historically, sex has not been viewed as a critical biological variable in clinical trials. The National Academy of Sciences defines *sex* as based upon one's genes and *gender* as a person's self-representation as male or female based upon social interactions. In response to the sex and gender differences exacerbated by the pandemic, I aim to focus this commentary on why biomedical researchers need to analyze the differences between men and women in the treatment of the COVID-19 disease and incorporate a sex and gender analysis in vaccine development.

### 1. Introduction

In medical research, there has been a long history of not analyzing data by sex and gender. In 2011, a groundbreaking research study conducted showed a sex and gender bias in biomedical research. Females were left out of clinical trials due to the notion that their hormonal cycles might confound the results of the experiment and skew study designs.<sup>1</sup> Though this idea has consistently been proven inaccurate, the concept gave rise to the assumption that results from male-centric research designs may also apply to females. In order to increase female representation in research studies, the National Institutes of Health initiated a policy requiring medical scientists to consider “sex as a biological variable” to receive grant funding.<sup>2</sup> Despite these efforts, there has been no explicit consideration of gender biases in randomized clinical trials related to COVID-19. Moreover, the National Institute of Allergy and Infectious Diseases considered sex only “as part of subgroup analysis” for Phase 1 of a potential coronavirus vaccine. If this trend continues in the COVID-19 pandemic, critical differences between men versus female response to the vaccine may be overlooked.

### 2. Methods

The world is currently racing to develop a vaccine to combat COVID-19, but sex and gender differences must be at the forefront of the research and development process. The initial reports from Wuhan have revealed that men accounted for nearly two-thirds of deaths.<sup>3</sup> These disproportionate findings propelled countries to disaggregate their data by sex. As reports disaggregated by sex emerged from Italy, Spain, and France, similar results have surfaced. Through the Global Health 50/50 initiative providing sex-disaggregated data from these countries, it has been found that men have consistently been twice as likely to die from COVID-19 as women.<sup>4</sup> Despite the United States having the most COVID-19 cases in the world and also

following this trend, the country continues to neglect applying a sex and gender analysis on reports of COVID-19 cases, hospitalizations, and deaths.

With males comprising 53.6% of deaths in the U.S., the COVID-19 mortality rate is disproportionately higher among the male population globally, indicating profound sex-specific differences, like immunity, in how men and women respond to COVID-19.<sup>5</sup> The same overactive immune response that makes females more susceptible to autoimmune conditions, such as rheumatoid arthritis and multiple sclerosis, could also help women battle infections like COVID-19. Women have been shown to have stronger innate and adaptive immunity, where their immune memory allows a more rapid, effective immune response against pathogens post-vaccination and upon reinfection.<sup>6</sup> This is critical to understand when developing a vaccine that trains the body to recognize the COVID-19 antigen to prevent infection. If women innately have stronger immune responses, then clinical trials may need to consider vaccine administration for women in smaller or less frequent doses. If a lower quantity is needed to achieve equally effective and safe vaccination in women, then vaccines could be better conserved for use in a larger number of individuals.

In current drug testing, there has been no clear consideration of male-female differences, such as in immunity, in efficacy or adverse effects. In July 2020, there had been over 1,000 registered drug trials on COVID-19, but none initiated an objective to compare the results between men and women.<sup>7</sup> While these trials may include both men and women, researchers do not analyze the outcomes of the data through a sex and gender lens. As a result, a sex-blind approach to the analyses of the data may lead to adverse and detrimental reactions. As of June 2020, there have only been two identified COVID-19 studies that have disaggregated and analyzed immunological outcome data by sex.<sup>8</sup> Moreover, in a still to be peer-reviewed study, scientists discovered that only 416 of the 2,484 COVID-19 clinical trials mention sex and gender as part of the recruitment criteria on the ClinicalTrials.gov database.<sup>9</sup> If this lack of sex and gender analysis further permeates into vaccine clinical trials, then an effective vaccine will not be created. For these reasons, clinicians and epidemiologists during vaccine development need to report data pertaining to COVID-19 disaggregated by sex.

### **3. Discussion**

As immunity and other sex-specific differences may alter female and male responsiveness to treatments and vaccines against COVID-19, it is vital that the sexes are equally represented in all phases of clinical trials and research data is analyzed by gender. Reporting sex-specific data will ensure that COVID-19 vaccination has comparable efficacy and safety profiles in both men and women. In order to improve the safety and quality of life during this pandemic, all investigators developing approaches for a vaccine must adopt a policy of incorporating a sex and gender lens in development. It is when researchers design studies that are inclusive of male versus female differences that an effective vaccine will be developed.

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