

# Renewed rationale for sex- and gender-disaggregated research: A COVID-19 commentary review

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## Abstract

The COVID-19 pandemic provides a contemporaneous illustration of the need to consider sex and gender in research. Using surveillance, treatment and vaccine research examples, in this commentary review, we highlight opportunities for innovation in sex- and gender-sensitive and transformative health and medical research.

## Keywords

COVID-19, gender, gender differences, infectious diseases, sex, sex differences

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## Introduction

Sex- and gender-disaggregated analysis is critical to the interpretation, validation, reproducibility and generalizability of research findings.<sup>1</sup> Reports of the epidemiology of the SARS-CoV-2 pandemic and treatment effects in clinical trials for the resultant clinical disease, COVID-19, provide a contemporaneous illustration of how sex and gender impact health.<sup>2</sup> For example, global data indicate men to be more likely to acquire more severe forms of COVID-19 and die from it.<sup>2</sup> Incorporating sex-disaggregated analysis is important when women and men may be more (or less) likely to acquire severe forms of disease and where treatment effects depend on disease severity.<sup>3</sup>

In this commentary review, we report evidence gaps and opportunities for discovery through the collection, analysis and reporting of sex- and gender-sensitive COVID-19 surveillance, prevention and treatment data. We provide practical recommendations for collecting and reporting data, including the importance of moving beyond the gender binary, and discuss how different research stakeholders can improve research integrity through the mandatory incorporation of sex- and gender-disaggregated analyses.

As this study is a commentary review, informed consent was not sought nor relevant. The purpose of a commentary review is to provoke scholarly dialogue.<sup>4</sup> Research

methodology is not typically presented, and the selection and synthesis of included articles demonstrates author bias.<sup>4</sup> The authors have combined expertise in sex-disaggregated data analysis, women's health and critical care/sepsis research. Having closely followed evidence generated from the pandemic, we have selected examples to broadly demonstrate why the consideration of sex and gender in health and medical research is important.

## Surveillance data

Binary sex-disaggregated data show essentially equal numbers of confirmed COVID-19 cases in females (49%) and males (51%). Although women are more likely to be tested, men are more likely to acquire a severe COVID-19-related illness, and account for a higher proportion of

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hospitalisations (53%), intensive care unit admissions (64%) and deaths (57%).<sup>2,5</sup> Only half of all countries report COVID-19 cases and deaths by (male or female) sex, and only 28 (14%) and 19 (9.5%) countries report sex-specific hospitalization and intensive care unit (ICU) admission data, respectively.<sup>2</sup> By July 2021, several countries that had previously reported sex-disaggregated COVID-19 cases and deaths were no longer reporting these data to Global Health 50/50.<sup>2</sup> This is despite the World Health Organization (WHO) Strategy for integrating gender analysis and actions into the work of WHO, which encourages Member States to improve the collection, analysis and use of quantitative data on health, disaggregated by sex, age and other relevant social stratifications.<sup>6</sup>

Although sex disaggregation of data overlooks other intersecting social and demographic variables which influence health, including age, ethnicity and gender norms, these data are needed to understand the impacts of COVID-19 in the community and highlight areas for further investigation and targeted intervention.<sup>7</sup> Only through standard collection and reporting of sex-disaggregated surveillance data can future analysis of COVID-19 outcomes by sex, age, ethnicity and the interactions between these factors be possible.<sup>7,8</sup> This includes investigations to understand gender-related influences, such as how gender norms influence exposure and access to testing and treatment.<sup>7</sup>

### *Clinical trials*

The impoverished state of sex-sensitive or specific COVID-19 clinical research has been previously reported.<sup>9</sup> In a scoping review of 30 pharmacological prevention and treatment trials, one study included a post hoc sex-specific analysis. Sex-stratified randomization or assessment of treatment effects by sex is absent from preliminary reports of evidence that have led to practice changes globally.<sup>10</sup>

For example, in the RECOVERY trial of corticosteroids (dexamethasone), compared to usual care, in hospitalized COVID-19 patients,<sup>11</sup> the investigators observed an 18% reduction in 28-day risk of death for patients receiving dexamethasone and requiring oxygen therapy. The treatment was most effective in mechanically ventilated patients where the risk of death reduced by 36%.<sup>11</sup> The preliminary results of the trial were adopted into UK practice on the day of publication. Although females accounted for one-third of the study population, and were less likely than males to be mechanically ventilated, the authors did not report treatment effects by sex.<sup>11</sup> In a post hoc analysis of a similar trial of corticosteroids in mechanically ventilated patients with septic shock, females who received corticosteroid had a significant risk of shock recurrence, compared to males.<sup>3</sup> Although the evidence of a sex difference in response to corticosteroid for patients with severe infection is weak, whether corticosteroids reduce mortality in patients with septic shock has been studied by intensive

care researchers for over half a century. Of 22 published trials including 7297 patients,<sup>12</sup> there has been one post hoc analysis of treatment effects by sex.<sup>3</sup>

Addressing the pitfalls of underpowered and insufficiently informative studies<sup>13</sup> as research pivots to describe and address the long-term sequelae of SARS-CoV-2 infection is key. Long COVID, which occurs in more than one-third of survivors who report at least one symptom for 12 weeks or more, with women at an increased risk, compared to men (odds ratio (OR)=1.51; 95% confidence interval (CI)=1.46–1.55)<sup>14</sup> represents an important opportunity for discovery and innovation. As recruitment for Long COVID trials, like HEAL-COVID<sup>15</sup> – a platform trial based on the RECOVERY model, commences, trialists should take stock of the evidence of sex and gender differences in COVID-19 and incorporate sex-stratified randomization or, at the very least, incorporate an assessment of treatment effects by sex. This consideration may prove to be of great benefit not only to patients and society but also to science.

### *Vaccine safety*

Vaccine studies have frequently demonstrated that females tend to develop stronger innate and adaptive immune responses to vaccines compared to males.<sup>16</sup> Subsequently, vaccine-related side effects and adverse events are more common in females, having been widely reported for influenza, yellow fever, measles, mumps, rubella, hepatitis A and B, herpes simplex 2, rabies, dengue and smallpox vaccines.<sup>17</sup> Very few trials of COVID-19 vaccines currently in use have reported the influence of sex on safety and efficacy outcomes.<sup>9</sup>

Between December 2020 and January 2021, 13.8 million vaccine doses were administered in the United States, with 61% administered to females. The Centres for Disease Control reported 79.1% of reported adverse events occurred in females.<sup>18</sup> Incorporating sex-specific analyses in COVID-19 vaccine trials would have enabled a comprehensive understanding of sex differences in immune response and the opportunity to develop, test and implement sex-specific strategies to mitigate the surplus of adverse side effects experienced by women. While the opportunity to understand and improve sex-specific vaccine impacts has been missed, gender-related factors associated with equitable vaccine access, including vaccine hesitancy, remain an important consideration.

### **Moving beyond binary sex and gender**

Epidemiological and clinical research surrounding the COVID-19 pandemic has primarily used binary terms for sex and gender (male/man/men and female/woman/women). There are a variety of ways sex and/or gender data are collected for clinical research, including population registries, healthcare records or survey self-report. However,

**Table 1.** Actionable steps to embed sex- and gender-responsive health and medical research into future pandemic preparedness.

Researchers	<ul style="list-style-type: none"> <li>• Ensure gender diversity in the research and publication teams. There is a positive association between women's authorship and the likelihood of a study incorporating sex and gender analysis.<sup>22</sup></li> <li>• Collect and analyse data by sex and/or gender using appropriate methods.<sup>23</sup></li> <li>• Design trials to enable appropriate consideration of sex and/or gender in analysis, for example, sex-stratified randomization and appropriate representation of women in trials.</li> </ul>
Peer-reviewed journals	<ul style="list-style-type: none"> <li>• Adopt, and implement, the SAGER guidelines.<sup>21</sup></li> <li>• Embed an electronic checklist on submission portals to promote a sex- and gender-responsive research culture into the publishing system.</li> <li>• Review the gender balance in authorship periodically and take action to rebalance where necessary.</li> </ul>
Research funders	<ul style="list-style-type: none"> <li>• Require grant applicants to explain how sex and/or gender analysis will be incorporated into their research.<sup>20</sup></li> <li>• Provide training for reviewers to build capacity in assessing sex- and/or gender-sensitive methods.</li> <li>• Hold grant recipients accountable for reporting sex- and/or gender-specific research outputs arising from funding.</li> </ul>

binary terms, particularly sex assigned at birth, are inaccurate for people who are transgender, non-binary or have variations of sex characteristics, also known as intersex. To enable a nuanced understanding of what is required for safe and effective care of all genders, a multistep approach is being increasingly recommended to accurately collect information about biological sex and gender identity.<sup>19</sup>

### What can research stakeholders do?

In the past two decades, improvements in understanding of sex and gender influences in health and disease has led to major granting agencies, including the Canadian Institutes of Health Research, the US National Institutes of Health and the EU Commission, requiring an explanation of how sex and gender analysis is relevant to, and incorporated into, grant proposals.<sup>20</sup> Several peer-reviewed journals have adopted the Sex and Gender Equity in Research (SAGER) guidelines,<sup>21</sup> although the degree to which their authors follow them is not always clear.<sup>9</sup>

To facilitate health equity for all genders, future pandemic preparedness and response planning should include sex- and gender-responsive research, including routine inclusion of sex- and/or gender-specific analyses in epidemiology studies, clinical trials and implementation research. To support this, evidence-informed actionable steps to researchers, peer-reviewed journals and research funders are provided in Table 1.

### Conclusion

The COVID-19 pandemic has demonstrated sex and gender differences in disease epidemiology, prevention, treatment and outcomes, advancing the evidence for the mandatory inclusion of sex- and gender-disaggregated analysis in health and medical research. This research is critical to the validation, interpretation, reproducibility and generalizability of research findings and a responsibility of all stakeholders in the global research community.

### Author contribution(s)

**Kelly Thompson:** Conceptualization; investigation; methodology; project administration; writing – original draft; writing – review and editing.

**Amy Vassallo:** Data curation; writing – original draft; writing – review and editing.

**Simon Finfer:** Writing – review and editing.

**Mark Woodward:** Supervision; writing – review and editing.

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