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Editorial

Towards Precision Medicine: Inclusion of Sex and Gender Aspects in COVID-19 Clinical Studies—Acting Now before It Is Too Late—A Joint Call for Action

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The COVID-19 global pandemic is accelerating investigations for effective vaccines and repurposable validated therapeutics. Current data analyses strongly suggest that the disease mostly affects the elderly population and patients with pre-existing conditions [1,2]. Considerably less attention has been drawn towards the sex distribution of case fatalities, which is increasingly showing disparities in mortality rates that varies geospatially, and along socioeconomic factors [3,4]. Reported death estimates by sex vary greatly across contexts and population groups and may change over time. In addition, social factors, such as testing and reporting bias in females, or differences in exposure due to behavioral and risk differences, may play a role, e.g., due to comorbidities such as diabetes or differences in societal and gender norms. While the observed male dominance in COVID-19 prevalence and mortality across most countries and cultures may suggest a role for biological differences, the potential long-term impact of gender-related factors on mortality, especially in diverse socioeconomic contextS, cannot be underestimated [5,6].

The role of immunological differences between females and males in the responses to SARS-CoV-2 infection appears to be justified. There is ample evidence that antiviral immunity differs between the sexes [5]. These are caused by e.g., sex steroid hormone signaling (i.e., testosterone, estrogens, and progesterone), genetics (e.g., immune function genes that escape X inactivation), and sex-specific composition of the microbiome. Sex differences in immunosenescence and immune function not only impact immunity to viruses, but to vaccines and immunotherapies, as well [5–7]. In the context of SARS-CoV-2, these differences could impact susceptibility and initial response to the virus as well

as choice of acute and long-term therapy of the COVID-19 pathology. In current and future trials for COVID-19, sex as a biological variable should be factored in and understood, along with the wider gendered implications of the COVID-19 crises, with the broader concept of how biological factors intersect with gendered differences in exposure, transmission, and socio-economic means. Consequently, the pandemic may not just lead to differences in disease susceptibility and manifestation between men, women, and people with non-binary identities, but also exacerbate unequal access to treatment and long-term vulnerabilities.

Given their non-negligible impact on health, sex and gender dimensions, along with other socio-economic stratifiers, need to inform the design, conduct, analysis, and reporting of current and forthcoming trials. Moving beyond sex-disaggregated data collection and including variables such as disability, age, ethnicity, migration status, socioeconomic status, or geographic location, will contribute to ensure health benefits from clinical trials for all. To better understand and respond to the burden posed by COVID-19, both on health systems and different segments of human populations, gender dimensions must be recognized as an intersecting component of wider structural inequalities [8]. Moreover, the COVID-19 pandemic is exposing, most acutely, the wider social inequalities that are based on gendered social, cultural, and economic faultiness, whether it is leaving a majority of frontline workers (in many contexts mostly women) without PPE, the disproportionate burden of unpaid care on women, or gender-based violence perpetuated within the household, apart from the economic devastations experienced by the poor and women in the poorest quintiles.

Equity in clinical trials starts with the consideration of both sex and gender dimensions in studies on novel and repurposed drugs [9,10]. Biomedical AI-researchers can assist in this effort to reconceptualize the human subgroups included for analysis, emphasizing the rigorous justification of exclusion and avoiding assumptions that may have serious implications in terms of generalizability of outcomes [9,11,12]. Ignoring aspects of sex and gender in data collection and analysis in clinical trials has had detrimental consequences in the past. Eight out of ten drugs withdrawn from the US market in the late 1990s had significantly more side effects in women than men, including fatal torsade-de-pointe after excessive QT interval prolongation. The, yet to be accurately tested, proposed therapeutic regimen of hydroxychloroquine and azithromycin for COVID-19 includes two QT-prolonging agents. Next to potential sex differences in side effects, gender-related aspects have to be considered. For example, despite the disproportionately high mortality of Ebola viral disease (EVD) among pregnant women, the rVSV-ZEBOV vaccine clinical trials excluded pregnant women. This impacted access to critical life-saving interventions during the subsequent Tenth EVD epidemic in DRC, when—due to lack of evidence because of the beforementioned exclusions—pregnant and lactating women did not partake in ring vaccination campaigns, until the decision was reversed 10 months later. This not only led to unnecessary mortality of this vulnerable group, but severely impacted women's right to decide on research participation and community trust in the intervention, just as did the approval of Truvada solely for cisgender males and transgender women [13,14].

The inclusion of sex and gender aspects in drug development and clinical trials is essential, not just for a thorough understanding of efficacy and safety aspects of drugs, but also to ensure there is equity in the distribution of innovation and discovery benefits of COVID-19 therapeutics and vaccines [3]. A group of clinicians, scientists and gender specialists working on global health, sex and gender research and human rights are thus calling for action towards the inclusion of sex and gender, and other socially relevant variables, into the methodology of COVID-19-related trials. Such an approach should become a universal and manifest part of future clinical studies, to allow more personalized patient care and contribute to universal health coverage.

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Appendix A

Appendix A.1. The Sex and Gender in COVID-19 Clinical Trials Working Group

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Petra Verdonk	Amsterdam UMC-VUmc
Arne Ruckert	University of Ottawa
Luisa Enria	University of Bath
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Amber Peterman	University of North Carolina
Sean Hillier	York University

Appendix A.2. Gender and COVID-19 Working Group

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Julia Smith	Simon Fraser University
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Ilana Lowy	French National Centre for Scientific Research
Nazeen Damji	UN Women
Ann Keeling	Women in Global Health
Kate Hawkins	Pamoja Communications

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Manasee Mishra	IIHMR University, India
Sean Hillier	York University
Yara M. Asi	University of Central Florida
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Alan White	Leeds Beckett University
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