Society for Women's Health Research

June 22, 2020

Chairman Lamar Alexander
United States Senate
455 Dirksen Senate Office Building
Washington, DC 20510-4206

Dear Chairman Alexander:

The Society for Women's Health Research (SWHR) is pleased to provide comments in response to your recent white paper, "Preparing for the Next Pandemic." SWHR is a 30-year-old national nonprofit dedicated to promoting research on biological sex differences in disease and improving women's health through science, policy, and education. Because of SWHR's advocacy efforts, women are now routinely included in most major medical research studies, and scientists funded by the National Institutes of Health (NIH) are required to consider sex as a biological variable in their research.

The current COVID-19 pandemic provides a stark example of why sex and gender must be critical considerations in pandemic response and preparedness. COVID-19 appears to be infecting similar numbers of women and men, but the majority of people dying from the virus are men.

Early data from China analyzed more than 40,000 COVID-19 cases and showed that men accounted for nearly two-thirds of deaths.[1] Additionally, data show that in most countries, men have been upwards of 50% more likely to die following a COVID-19 diagnosis.[2] There are a variety of hypotheses as to why we are seeing these notable disparities, but research is still in the early stages and the answers are not yet clear.[3]

As you note in your white paper, COVID-19 is not the only disease outbreak that has occurred in our recent history. Ebola, Zika, severe acute respiratory syndrome coronavirus (SARS-CoV), and the H1N1 virus have all affected the United States. Further, all of these diseases have shown clear evidence of sex and/or gender disparities:

[1] Novel Coronavirus Pneumonia Emergency Response Epidemiology Team (2020). The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) — China, 2020. *China CDC Weekly.* Accessed at: http://weekly.chinacdc.cn/en/article/id/e53946e2-c6c4-41e9-9a9b-fea8db1a8f51
[2] Global Health 5050 (2020). COVID-19 sex-disaggregated data tracker. Accessed at: https://globalhealth5050.org/covid19/
[3] Ortman, E (2020). Sex and gender: Critical considerations in COVID-19 research and response. Accessed at: https://swhr.org/sex-and-gender-critical-considerations-in-covid-19-research-and-response/

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- During the 2014-2016 West African Ebola outbreak, women were more likely to be infected by the virus, likely because they are more frequently engaged in caregiving work or employed as front-line healthcare workers.[4]

- During the 2016 Zika virus outbreak, women were more likely to be infected than men, even when accounting for higher rates of testing among pregnant women. This suggests women may be at higher risk for sexual transmission of the virus.[5] The Zika virus was also of particular concern for pregnant women, given the likelihood of maternal-fetal transmission leading to adverse neonatal outcomes.[6]

- Data from both SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) show sex-dependent differences in disease prevalence and outcome. Men had higher incidence rates and higher case fatality rates for both diseases.[7]

- Finally, research on the 2009 H1N1 virus indicated that young women made up a significant majority of critically ill patients. Rates of hospitalization were also higher in women. Pregnant women represented a disproportionately high percentage of severe H1N1 cases as compared to the general population.[8]

These disparities are not surprising, given what we know about infectious disease. Cultural and behavioral differences between genders play a prominent role in disease exposure. Women and men also differ in immune responses to infection.[9] Infectious disease research has historically overlooked sex as a biological variable,[10] meaning there is much we still do not understand about how sex affects immune response and disease outcomes.

Per the World Health Organization's 2007 publication, "Addressing sex and gender in epidemic-prone infectious diseases," taking sex and gender into account can help us to better understand disease epidemiology, course, and outcomes. We can also improve detection and treatment, as well as public health efforts aimed at preventing or controlling disease outbreaks.[11] For these reasons, SWHR is hopeful future preparedness legislation will address the crucial roles played by sex and gender in disease transmission, diagnosis, and outcome.

Here, we provide comments on three of the topics you identified as priority areas in preparing for future pandemics: Tests, Treatments, and Vaccines; Disease Surveillance; and Public Health Capabilities.

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[4] Davies, SE, Bennett, B (2016). A gendered human rights analysis of Ebola and Zika: Locating gender in global health emergencies. *Int Aff.*, *92:* 1041-1060.
[5] McNeil Jr., DG (2016). Sex may spread Zika virus more often than researchers suspected. *New York Times.* Accessed at: https://www.nytimes.com/2016/07/05/health/zika-virus-sex-spread.html
[6] Meany-Delman, D, Rasmussen, SA, Staples JE, Oduyebo, T, Ellington, RE, Petersen, EE, Fischer, M, Jamieson, DJ (2016). Zika virus and pregnancy: What obstetric health care providers need to know. *Obstet Gynecol., 127*(4): 642-8. doi: 10.1097/AOG.0000000000001378.
[7] Channappanavar, R, Fett, C, Mack, M, Ten Eyck, PP, Meyerholz, DK, Perlman, S (2017). Sex-based differences in susceptibility to SARS-CoV infection. *J Immunol., 198*(10): 4046-53. doi: 10.4049/jimmunol.1601896.
[8] Klein, SL, Passaretti, C, Anker, M, Olukoya, P, Pekosz, A (2010). The impact of sex, gender and pregnancy on 2009 H1N1 disease. *Bio Sex Differ., 1*(5). doi: 10.1186/2042-6410-1-5.
[9] Van Lunzen, J, Altfeld, M (2014). Sex differences in infectious diseases – Common but neglected. *Jour Infect Diseases, 209*(suppl_3), S79-S80. doi: 10.10893/infdis/jiu159.
[10] Ingersoll, MA (2017). Sex differences shape the response to infectious diseases. *PLoS Pathog., 13*(12), e1006688. doi: 10.1371/journal.ppat.1006688.
[11] World Health Organization (2007). Addressing sex and gender in epidemic-prone infectious diseases. Accessed at: https://www.who.int/csr/resources/publications/SexGenderInfectDis.pdf

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Priority Area: Tests, Treatments, and Vaccines

SWHR recommends requiring vaccine researchers to incorporate sex as a biological variable into research study design. Researchers should be required to analyze results for sex differences, given known variances in immune response between women and men.

Research suggests that biological sex differences have a significant impact on vaccine acceptance, response, and outcomes. Clinical data indicate women and men show differences in immune responses, adverse events, and disease protection following vaccination. More specifically, women tend to develop higher antibody response as compared to men and also report more adverse events following vaccination.[12]

Unfortunately, most preclinical animal studies and randomized controlled trials for vaccines fail to incorporate sex or gender in either experimental study design or analysis of outcomes. Scientists receiving government funding should be required to utilize designs with balanced numbers of male and female subjects in order to ensure sufficient analytical power for sex-disaggregate analyses to return statistically significant outcomes. Researchers must also incorporate subjects across the lifespan and ensure appropriate racial and ethnic representation.

Per Flanagan et al.'s 2017 paper on the subject, there should exist an a priori hypothesis within all vaccine trials that sexes will differ in regard to vaccine response. Researchers should be encouraged to consider optimal doses and scheduling of vaccines across the lifespan, as this too may differ based on sex. Finally, any educational materials developed for patient use when a vaccine comes to market should be sex specific and provide additional information that addresses the needs of pregnant women and lactating women.

SWHR recommends putting in place measures that ensure appropriate inclusion of pregnant and lactating women within clinical trials related to treatment and vaccine development.

Each year in the United States, 6 million women are pregnant,[13] nearly 4 million women give birth,[14] and more than 3 million women breastfeed.[15] Despite these profound statistics, there is a paucity of human data on safety and efficacy of therapeutics in pregnant and lactating women. Exclusion of pregnant and lactating women in research has led to significant, unacceptable gaps in women's health.

The Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC), established in the 21st Century Cures Act, released a report in 2018 recommending the inclusion of pregnant and lactating women in clinical research. This recommendation is especially important for infectious disease-related trials.

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[12] Flanagan, KL, Fink, AL, Plebanski, M, Klein, SL (2017). Sex and gender differences in the outcomes of vaccination over the life course. *Annu Rev Cell Dev Biol., 33*, 577-99.
[13] Curtin, SC, Abma, JC, Ventura, SJ, Henshaw, SK (2013). Pregnancy rates for US women continue to drop. *National Center for Health Statistics Data Brief, 138.* Accessed at: https://www.cdc.gov/nchs/data/databriefs/db136.pdf
[14] Martin, JA, HaMilton, BE, Osterman, MJK, Driscoll, AK (2019). Births: Final data for 2018. *National Vital Statistics Reports, 68*(13). Accessed at: https://www.cdc.gov/nchs/data/nvsr/nvsr68/nvsr68_13-508.pdf
[15] Centers for Disease Control (2018). Breastfeeding report card, United States, 2018. Accessed at: https://www.cdc.gov/breastfeeding/pdf/2018breastfeedingreportcard.pdf

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Research across a variety of infectious diseases — including the Zika virus, the H1N1 flu virus, and the SARS, MERS, and COVID-19 coronaviruses — suggests pregnancy places women at particular risk for disease-related complications. Accordingly, pregnant women and lactating women must be included within clinical trials related to disease treatment and/or vaccines. Within current COVID-19 treatment research, pregnant women and breastfeeding women are actively being excluded from federally-funded studies, including the Adaptive COVID-19 Treatment Trial. One recent paper suggests that across more than 300 trials investigating possible COVID-19 treatments, there is near universal exclusion of pregnant women.[16]

SWHR recommends consulting with the PRGLAC Task Force to determine best practices for incentivizing and/or requiring inclusion of pregnant women and lactating women within pandemic-related trials. In safeguarding population health during future pandemics, women who are pregnant and/or breastfeeding must likewise be protected. Vaccines and treatments should be readily available to this population without concern for adverse outcomes for either mother and/or child. The best way to achieve this goal is to ensure inclusion of pregnant women and lactating women in research.

SWHR recommends careful consideration regarding access to new vaccines: Frontline health care workers and communities experiencing significant disease burden or who are at heightened risk of disease complications should be provided efficient and affordable vaccine access.

SWHR is largely in agreement with current Centers for Disease Control and Prevention (CDC) protocol regarding prioritization of vaccines when they come to market. Given high risk for complications, we support initial vaccination efforts that prioritize pregnant women, as well as frontline health care providers, who make up about 75% of health care workers in most U.S. cities.[17]

In addition, SWHR encourages Congress to consider the needs of at-risk communities hit hardest by pandemics. Among health care workers deemed essential during the pandemic, almost 7 million citizens are currently employed in low-wage medical support jobs, such as orderlies, phlebotomists, home health aides, and health care service workers. Over 80% of these individuals are women, and the large majority are people of color.[18]

Even outside of the health care space, low-income communities of color are hardest hit by the current COVID-19 pandemic. Data show that Blacks and Latinos are dying at twice the rate of the general population in New York City. In Los Angeles, low-income individuals are three times as likely to die as compared to individuals in wealthier neighborhoods.[19]

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[16] Whitehead, CL, Walker, SP (2020). Consider pregnancy in COVID-19 therapeutic drug and vaccine trials. *The Lancet, 395*(10237), E92. doi: 10.1016/S0140-6736(20)31029-1
[17] Associated Press (2020). Pandemic's front-line work falls on women, minorities. *CBS News.* Accessed at: https://www.cbsnews.com/news/fontline-work-women-minorities-pandemic/
[18] Kinder, M (2020). Meet the COVID-190 frontline heroes. *Brookings Institute.* Accessed at: https://www.brookings.edu/interactives/meet-the-covid-19-frontline-heroes/
[19] Jauhar, S. (2020). When a COVID-19 vaccine becomes available, who should get it first? *STAT News.* Accessed at: https://www.statnews.com/2020/05/23/when-a-covid-19-vaccine-becomes-available-who-should-get-it-first/

A vaccination strategy, especially if vaccines are in short supply, must seek to address the needs of communities and workers more likely to contract the disease and those who are most likely to face significant consequences of the disease. SWHR encourages Congress to direct the CDC in developing a vaccination strategy that prioritizes these groups.

Priority Area: Disease Surveillance

SWHR recommends creating and implementing a national testing strategy requiring mandatory, standardized data collection and reporting of demographic information, including sex/gender and race/ethnicity.

A national testing strategy should require all states to collect comprehensive demographic data from patients who test positive for the disease as well as those who test negative. States should be required to track sex differences as they relate to deaths, disease symptoms, risk factors, and virus exposure. We must also seek to understand how certain demographic factors, such as race and gender, intersect in potentially harmful or helpful ways. States should also be directed to include information about pregnancy status, as it affects response to a virus.

While the Department of Health and Human Services recently issued guidance requiring states to report more comprehensive demographic information,[20] prior to this guidance states were not required to report certain demographic data including race, ethnicity, age, and sex. Thus, some states, such as New York, were consistently including sex in daily disease reporting, while others like Louisiana were not including this information as recently as the end of April.[21]

The lack of an immediate and unified nationwide process for reporting COVID-19 information on sex and gender, as well as race and ethnicity, put the U.S. at a distinct disadvantage in trying to understand the virus and respond adequately, especially in the first crucial months of the pandemic. Consistent reporting of sex and gender differences must be a priority in state and federal data collection for future pandemic response efforts. Understanding the sex disparities will help the U.S. develop better vaccines, disease treatments, and public health policies.

Priority Area: Public Health Capabilities

SWHR recommends expanding access to telehealth services on a permanent basis, in order to allow Medicare beneficiaries to access virtual health care services during pandemic and non-pandemic times.

Women are frequently in charge of health care decision-making for themselves and for family members, and they are often unduly burdened by in-person health care appointments. Telehealth services have previously been suggested as one method of addressing unmet women's health needs in rural populations, as well as for women facing transportation and childcare barriers.[22]

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[20] United States Department of Health and Human Services (2020). HHS announces new laboratory data reporting guidance for COVID-19 testing. Accessed at: https://www.hhs.gov/about/news/2020/06/04/hhs-announces-new-laboratory-data-reporting-guidance-for-covid-19-testing.html

[21] Ortman, E (2020). Sex and gender: Critical considerations in COVID-19 research and response. Accessed at: https://swhr.org/sex-and-gender-critical-considerations-in-covid-19-research-and-response/

[22] Weigel, G, Frederiksen, B, Ranji, U, Salganicoff, A (2019). Telemedicine in sexual and reproductive health. *Kaiser Family Foundation.* Accessed at: https://www.kff.org/womens-health-policy/issue-brief/telemedicine-in-sexual-and-reproductive-health

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Given the potential benefit to women, SWHR supports the recent expansion of Medicare coverage for telehealth care. The expanded coverage allows patients to use their own homes as an originating site for telehealth appointments and permits a larger variety of health care providers to bill Medicare for telehealth services. Following these expansions, the number of Medicare beneficiaries using telehealth increased more than 11,718% — from 11,000 beneficiaries using telehealth services in the week ending March 7 to almost 1.3 million beneficiaries using these services for the week ending April 18.[23]

Making the Medicare expansions permanent would benefit many who struggle to access health care, especially when going to a doctor's office in person may be inadvisable. Additionally, it will allow our national health care system and infrastructure time to adapt to large-scale telehealth provisions, ensuring that we are adequately prepared for future disease outbreaks.

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Thank you for your leadership in advancing legislative strategies designed to help the United States prepare for future pandemics. We look forward to continued engagement with your office on this and other topics. If you have any questions, please do not hesitate to contact our Director of Science Policy, Melissa Laitner, PhD, MPH, at melissa@swhr.org.

Sincerely,

Kathryn G. Schubert, MPP
President and Chief Executive Officer
Society for Women's Health Research

[23] Pifer, R (2020). Medicare members using telehealth grew 120 times in early weeks of COVID-19 as regulations eased. Healthcare Dive. Accessed at: https://www.healthcaredive.com/news/medicare-seniors-telehealth-covid-coronavirus-cms-trump/578685/