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Hidden in Plain Sight: Sex and gender in global pandemics

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Abstract

Purpose of the review: The global pandemic caused by the severe acute respiratory virus coronavirus 2 (SARS-CoV-2) has a male bias in mortality likely driven by both gender and sex-based differences between males and females. This is consistent with sex and gender based features of HIV infection and overlap between the two diseases will highlight potential mechanistic pathways of disease and guide research questions and policy interventions. In this review, the emerging findings from SARS-CoV-2 infection will be placed in the context of sex and gender research in the more mature HIV epidemic.

Recent findings: This review will focus on the new field of literature on prevention, immunopathogenesis and treatment of SARS-CoV-2 referencing relevant papers in HIV for context from a broader time period, consistent with the evolving understanding of sex and gender in HIV infection. Sex-specific features of epidemiology and immunopathogenesis reported in COVID-19 disease will be discussed and potential sex and gender specific factors of relevance to prevention and treatment will be emphasized.

Summary: Multilayered impacts of sex and gender on HIV infection have illuminated pathways of disease and identified important goals for public health interventions. SARS-CoV-2 has strong evidence for a male bias in disease severity and exploring that difference will yield important insights.

Keywords

sex; gender; COVID-19; SARS-CoV-2; immunopathogenesis

Introduction

The COVID-19 pandemic has brought many clinical and scientific questions into sharp relief, among them is the role of sex and gender-based factors in determining risk and pathogenesis of disease[1]. Understanding the impact of both sex (defined by anatomy, chromosomes and hormones) and gender (defined by sociobehavioral norms) has multilayered impacts for disease[2]. There are clear parallels to the HIV epidemic[3,4] and the community of HIV clinicians, basic science researchers, and community advocates are positioned to direct the research efforts on SARS-CoV-2 infection to maximal impact, drawing from the insights and unsolved questions from the HIV pandemic. This review

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addresses the relevance and scientific impact of sex and gender in the COVID-19 pandemic framed by the experience with HIV and suggesting implications for measures targeting prevention and treatment of SARS-CoV-2.

Sex and gender-based differences in infectious diseases and SARS-CoV-2

The impact of sex and gender on infectious disease pathogenesis is broad, spanning multiple pathogens with different modes of transmission[5]. It encompasses both biological (or sex-based) differences in immune responses[6] and differences grounded in gendered social norms. The latter includes sociobehavioral norms that vary across cultures and geography including time spent outside of the home, professional and family caregiving responsibility, exposure to animal reservoirs of disease, patterns of healthcare utilization, and knowledge about medicine and the science of transmission and prevention of infections[7]. Gender and sex-based risks also have variation across the lifespan. Biological differences in sex steroid hormone exposure and immune adaptation during pregnancy[8,9] occur in the context of access to healthcare services for family planning or antenatal care that may engage women more efficiently, as has been suggested in HIV[10]. Similarly, differences emerge in the elderly; lifespan is generally longer in females[11], and when diseases have disproportionate impact on the elderly analyses need to control for age and population structure in order to assess the impact of sex/gender on disease outcomes.

Early reports during the emergence of the SARS-CoV-2 epidemic noted a male bias in mortality from COVID-19[12,13]. This was consistent with prior reports of a male bias in disease severity for the earlier Severe Acute Respiratory Sydrome (SARS) epidemic (caused by SARS-CoV)[14,15]. WHO data for the approximately 8,000 cases in the 2003 report indicated that slightly more than 50% were in females, but with higher mortality rates in males. Data from Hong Kong and China demonstrated mortality of 22% and 13% for males and females respectively[11]. The overrepresentation of women among healthcare workers in the affected countries may account for the higher rate of diagnosis, but the determinants of differences in mortality are unknown. Middle East respiratory syndrome (MERS), caused by MERS-CoV, also demonstrated a male bias[16] with gender-based differences in contact with dromedaries possibly accounting for some differences in exposure risk. It is notable that in the case of SARS-CoV, a murine model of infection recapitulated an increased risk of death among male animals[17], suggesting that sex-based biological differences may impact pathogenesis. Taken together, the prior experience with epidemic coronavirus strains supports sex and/or gender effects on the risk of acquisition and on disease severity.

In the case of SARS-CoV-2, the male bias in mortality persisted as the virus evolved into a global pandemic with higher case fatality ratios across multiple countries reporting sex-disaggregated data[1]. Analysis of medical record data from ~40% of all patients in England including 10,926 COVID-19 deaths, reports a hazard ratio for death of 1.59 for male sex[18]. Country level data from France demonstrates higher rates of hospitalization, severe illness and death in males[19], and in the U.S. male sex was linked to higher risk of hospitalization[20] and severe disease [21]. Excess burden of comorbidities among males may account for some of this increase in risk, but even with propensity matching, male sex carries additional risk of severe outcomes[22]. The emergence of a consistent male bias

across cultures suggests that sex-based biology does contribute to differential outcomes. Taken together, these data demonstrate that, consistent with other infectious diseases, SARS-CoV-2 is impacted by sex and gender-specific factors; the remaining question is how this observation can be used to drive discovery and arrest the spread of infection. These striking findings have both parallels and differences from the HIV pandemic.

The role of sex and gender in driving mortality in HIV has to be considered within the epidemiologic context. In regions where the epidemic is concentrated in specific segments of the population, differences in risk of acquisition make it is difficult to compare outcomes across sex and gender. In contrast, in regions with generalized epidemics where HIV care is not specifically targeted to every individual, social and structural barriers to care may be unbalanced by sex or gender. Highlighting this point, while there is an excess of new infections among young women in Sub-Saharan Africa, males still account for more deaths[23]. This has been postulated to derive from both gendered testing strategies[24,25] and from gender and sex based differences in linkage to care, treatment and risk of complications[10]. Parsing the contributions of sex-based biological differences in immune responses as well as gender-based sociobehavioral factors is a work in progress for HIV. Through the lens of the HIV epidemic, sex and gender-specific themes emerge in the domains of prevention, treatment and immunopathogenesis and may inform research approaches to COVID-19.

Prevention

Prevention of infection is a foundation of the response to both HIV and to SARS-CoV-2. Nonpharmacologic interventions including condoms for sex to protect against HIV and other sexually transmitted infections and social distancing, masking and handwashing to reduce SARS-CoV-2 are universally recommended. But implementation must be thoughtful. In the case of HIV, care to avoid imprecise and potentially stigmatizing language is a key feature of effective communication about harm reduction strategies[26]. The locus of control for prevention strategies is another key factor, and when key interventions rely on asking others to either wear a condom or wear a mask many people will be unable to enforce protective behaviors. Likewise, implementation of social distancing strategies for COVID-19 should have some nuance, defining the spectrum of risk activities[27] and considering the profound effect of socio-economic conditions on the ability of individuals to observe social distancing[28]. Gender-based factors are also a key factor in determining risk of acquisition. Globally, females are the majority of healthcare workers[29], in the US, they are >70% of this workforce[30] with the attendant increased risk of exposure to SARS-CoV-2. However, behavioral gender characteristics also modify this risk, as females may be more accepting of mitigation strategies such as masking[31]. Autonomy and the economic impact of the pandemic have gendered differences globally and policy level interventions should specifically address risk mitigation in ways that are reaching those most in need[32].

Pharmacologic prevention interventions including pre-exposure prophylaxis (PrEP) have been one of the outstanding successes of HIV clinical science. But the pathway to the current state of the science has been marked by sex and gender effects. After initial demonstrations of efficacy among populations of men who have sex with men, studies in

women failed to show efficacy. From a biological standpoint, differences in the vaginal microenvironment have implications for local but likely not systemic therapy[33,34]. But the larger impact was traced to low adherence, highlighting the need to engage people in the interventions to reduce risk.[35] For SARS-CoV-2 infection, no effective prophylactic strategies have emerged. A randomized, placebo-controlled trial of hydroxychloroquine as postexposure prophylaxis in exposed individuals failing to show any benefit in prevention[36]. Likewise, a similarly randomized, placebo-controlled pre-exposure prophylaxis with hydroxychloroquine trial in ~1400 healthcare workers failed to show protection against COVID-19[37]. Importantly, informed by the lessons of adherence in HIV PrEP, the latter study confirmed that there was no difference in hydroxychloroquine levels in those who developed disease versus those who did not[37]. Of note, testing of HIV PrEP agents has not always included both males and females[38], a mistake that should be avoided in COVID-19, as differences in efficacy or tolerability cannot be found in populations that are not studied. The experience of HIV does support the development of a similar approach, but a more effective antiviral agent with high tolerability and low rates of adverse effects will be needed.

Finally, the gold standard of prevention, an effective vaccine, also highlights critical sex and gender-based variables. Females mount higher responses to vaccines in general[39] with females showing higher titer responses to influenza vaccination across age and dose groups[40] but also a higher incidence of adverse effects[41]. Among HIV vaccine trials, RV144, the only trial with any signal for protection had an estimated vaccine efficacy of 25.8% among males and 38.6% among females, with wide confidence intervals and no statistically significant difference by sex[42]. Efforts to understand participation of females in the RV144 HIV vaccine trial noted higher reported participation impact events among females, and identified pregnancy as the most frequent reason for discontinuation of participation[43]. In a pandemic, addressing incident and prevalent pregnancy events in vaccine trials is an important question for both policy and science.

For a COVID-19 vaccine strategy to be effective, there needs to be public trust in the safety and importance of vaccination. A recent survey by the Pew Research Center of >10,000 U.S. adults noted a decline between May and September of 2020 in the percentage of adults who reported that they would probably or definitely get a COVID-19 vaccine if one became available[44]. A lower percentage of women at both timepoints indicated that they would likely get the vaccine, although it is not clear whether this reflects differences in education, age, or other demographic features that also impact vaccine acceptance rates in the survey[44]. An online survey of 672 U.S. adults about COVID-19 vaccine acceptance identified variation by geographic location and demographics; women appeared less likely to endorse vaccine uptake in this survey (OR 0.72, $p=0.07$)[45]. In data from a European survey of more than 7,000 adults, men were more likely to report they would accept a vaccine (78% versus 70% $p<0.001$) with fear of side effects as the most common reason for hesitation[46]. Representative enrollment of vaccine trials is needed to support public trust in a vaccine. As novel vaccine platforms are explored, understanding the role of sex and gender in threshold for protection and for adverse events will be a critical part of effective deployment.

Sex-based differences in immunopathogenesis

As introduced above, there is a male bias in mortality from SARS-CoV-2 infection that appears to be independent of exposure risk and not fully explained by the burden of comorbid conditions. In HIV, there is not a clear excess in mortality related to sex, although there are sex-based variations in disease progression. Females are more likely achieve the rare outcome of spontaneous control of HIV infection[47,48]. However, in the more common situation of progressive disease, women have lower viral loads but are not protected from immunopathogenesis, progressing to immunodeficiency at the same rate as men with higher viral loads. This sex specific relationship between viral load and CD4 T cell depletion had clinical implications with early clinical guidelines capturing the majority of males progressing to advanced disease, but missing the majority of females[49]. This clinical finding was then linked to sex differences in the immune response; plasmacytoid dendritic cell responses to the same amount of HIV RNA stimulation are higher in women leading to more production of interferon alpha, and linked to higher T cell activation[50]. These findings support a model of enhanced sensitivity of viral detection systems in females, consistent with the higher activity of TLR7 reported in some autoimmune diseases and potentially linked to bi-allelic expression of this X-chromosome encoded gene[51,52]. HIV provides a model of sex-specific interaction between host immunity and a virus, highlighting the potential for sex-specific features to drive pathogenesis.

SARS-CoV-2 infection has multiple potential intersections with known points of sex-based variation. Of the cellular proteins required for entry, ACE2 is X-encoded and expression can be altered by estrogens and TMPRSS2 is androgen regulated in prostate cancer cells.[1] The same TLR7 viral sensing pathway implicated in HIV can recognize SARS-CoV-2, and sex-differential immune gene expression may further shape immune responses[53]. Early studies have supported these hypotheses: one report identified four young, male patients with severe COVID-19 disease who were found to have a putative loss-of-function mutation in *TLR7* associated with blunted interferon responses[54]. This may point to a protective role for interferon activation at some point in disease course. The frequency of this variant, sex-differential penetrance of effects and association with outcomes will be important to determine. Another intriguing finding is the identification of interferon-neutralizing auto-antibodies in a minority of patients with severe COVID-19 infection[55]. These auto-antibodies were not found in mild disease and were rare in uninfected controls and were markedly enriched in males (94% of individuals with antibodies), including when compared to the cohort of individuals with severe disease[55]. Separate studies identified loss-of-function variants in type I interferon pathway proteins enriched among the individuals with severe COVID-19[56], further underlining the importance of this pathway in disease progression. These findings suggest that interferon pathway activity is linked to disease progression, which may be one factor in the sex-differential outcomes seen in COVID-19.

A sex-stratified immunophenotyping analysis of SARS-CoV-2 infection identified differential patterns of immune activation, with higher levels of IL-8 and IL-18 (a signature of inflammasome activation) and higher induction of non-classical monocytes in males versus females, with females demonstrating more robust induction of T cell activation[57]. These studies also identified unique relationships to other factors linked to disease severity,

with females showing a link between salivary viral load and outcomes not seen in males, and males showing a link to body mass index not seen in females[57]. In this study, antibody titers to the spike protein did not show sex variation, but in a of study multiple isotypes and binding targets, male sex, older age and hospitalization were also associated with antibody titers[58]. Another cohort study found levels of IL-6 were lower among females although other cytokines, including IL-8 were not significantly different[59]. More work is needed to determine whether there are sex-specific thresholds for these markers that associate with severe disease, or whether the observed differences represent more efficient viral control and lower disease severity among females.

Therapeutics

The SARS-CoV-2 pandemic has brought a therapeutic focus to immunomodulation as ongoing efforts to develop antivirals move in parallel. The precise role of immunomodulation in infectious diseases has been difficult to parse, but has recently been of significant interest in the field of HIV cure efforts. Use of monoclonal antibodies alone and in combination[60], immune checkpoint blockade[61] and TLR agonist therapy[62] have all been deployed in clinical trials towards the goal of HIV cure. To date, there has been limited enrollment of females in these trials[63,64], with little ability to assess whether these interventions will have sex differential effects despite strong scientific rationale to believe that they may. In this setting, the SARS-CoV-2 pandemic, afflicting millions of people worldwide, may advance the understanding of sex-differential responses to immunomodulation more rapidly. Of note, in the RECOVERY trial, which reported the beneficial effect of dexamethasone, subgroup analysis of females did not show the benefit of treatment observed in the male and overall analysis[65]. To meet the goal of understanding the impact of sex to guide both risk stratification and therapeutic choice, there must be thoughtful consideration of sex in analyses of outcomes after treatment with immunomodulators including inhibition of the IL-6 axis, exogenous administration of interferons, and use of plasma or monoclonal antibodies.

Conclusion

The impact of sex and gender on the HIV epidemic has led to surprising scientific insights on disease pathogenesis. It remains a clear example of how variation introduced by sex and gender can be a rich source of discovery that can now be applied to the COVID-19 pandemic.

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