

## Gender differences in Covid-19: the importance of sex-disaggregated data

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The Covid-19 pandemic is affecting the entire world population, although its impact varies based on several factors. Sex and gender seem to play a very important role in this regard.

A person's sex – meaning their underlying biological make-up – determines both the immunological and hormonal profiles that may be important in responding to an infection. These differences in the biological response of males and females might be of relevance in determining the clinical outcome in patients with Covid-19. However, it is unlikely that biological differences alone could fully explain the aforementioned variances; in addition, gender – a term that refers to the roles, behaviors, activities and attributes that any given society considers appropriate for men and women – is almost certainly also playing a critical role. For instance, some gender-dependent aspects play an important role in determining a higher risk of infection or more severe forms of the disease: i) the risk of exposure to environmental conditions and products that may be unhealthy (eg., workplace hazards, smoking tobacco or drinking alcohol); ii) the patterns and timeliness in using the health service, the pathways of care within the health system, including who can access the services (eg., testing, diagnosis, treatment); iii) the level and quality of care that a person receives from/within the health system; iv) whether healthcare professionals and social care workers at various levels are more likely to be one gender or another (eg., in Italy, as well as in several other Countries, nursing staff and social care personnel are more likely to be female).<sup>1,2</sup> Understanding the role that sex and gender are playing in the Covid-19 outbreak is essential in order to build an effective, equitable response to the pandemic. Updated and disaggregated data are needed to provide a clear answer to this important question.

### Lack of sex-disaggregated data

Before examining any sex differences in the Covid-19 pandemic in more detail, it is worth noting that only

an incomplete picture can be presented, since not all Countries have collected and reported sex-disaggregated data. Global Health 50/50 – an international organization promoting gender equality in healthcare – started compiling publicly available the sex-disaggregated data on Covid-19 reported by national governments.<sup>3</sup> Among the 179 Countries considered: 77 reported sex-disaggregated data on both cases and deaths at the same time point, 53 reported data on either cases or deaths, 49 did not provide any sex-disaggregated data. Among the total, just 8 reported sex-disaggregated data on testing or confirmed cases among healthcare workers. Just 11 Countries reported data on ICU admissions and 18 on hospitalizations (October 12, 2020 update). Reaffirming its strong commitment to studying gender differences, Italy released disaggregated data from the start of the pandemic.

### Deaths: more men are dying than women

Global Health 50/50's analysis clearly shows that men are dying from Covid-19 at a higher rate than women across most of the Countries providing comprehensive data. According to the data published in the Italian integrated surveillance bulletin (October 6, 2020 update),<sup>4</sup> the case fatality rate for men is 13.2%, vs 9.0% for women. The proportion of death in confirmed cases (male/female ratio) in Italy is 1.34. Comparable ratios are being recorded in other European Countries (including Greece, the Netherlands, Germany, Denmark and France) and elsewhere in the world (eg., USA and Indonesia). In some Countries, such as Tunisia and Thailand, the male/female ratio is even higher (2.49 and 2.51, respectively). Among the Countries providing sex-disaggregated data, only 9 reported a higher Covid-19 fatality rate for women; Vietnam and Maldives have the lowest ratios (0.58 and 0.6, respectively). Of note, as part of the surveillance activity of the Italian National Institute of Health, a sex-stratified analysis was performed, with the aim of looking for differences in the

presentation and clinical course among women and men who died from Covid-19 in Italy. Covid-19-related mortality in men was characterized by specific clinical manifestations and transitions of care, as compared with women: older age, dementia, and autoimmune disease were the specific characteristics of women dying from Covid-19, whereas ischemic heart disease, chronic obstructive pulmonary disease, and chronic kidney disease were significantly more commonly observed in men. In addition, men were more often symptomatic with fever, experienced acute kidney injury more commonly, and were more often treated with experimental therapies, such as antivirals and tocilizumab, than women.<sup>5</sup>

### The diagnosis of SARS-CoV-2 infection in men and women

Sex and gender differences in diagnosed cases are less clear. The available data are insufficient to draw any conclusion on the infection rates by sex. It is important to note that data on confirmed cases in men and women will be affected by who has access to testing in each Country. Data on testing by sex is available from only 8 Countries, meaning that it is difficult to assess whether figures on confirmed cases are being misrepresented due to certain people having greater access to testing than others. Overall, in Italy a higher number of cases were found in women (52%), even if in the initial phase of the epidemic the number of cases diagnosed in men was higher. Special consideration should be given to reported cases of infection among healthcare workers. In Italy, 70% of infected healthcare workers are women, and other Countries, such as Germany, Republic of Ireland, Spain and Romania have reported similar or even higher data (73%, 74.2%, 76.34% and 81.04%, respectively). An explanation could be that women account for the majority of workers in this category, but further studies are needed to draw definitive conclusions. The Italian National Institute for the promotion of the health of migrant populations and for the fight against the diseases of poverty (INMP) recently published a Covid-19 national survey conducted in the structures part of the reception system for migrants. Among the results obtained, it is interesting to note that, within the migrant population, 90.8% of the infected are male.<sup>6</sup> This high proportion of cases among men has also been detected in some populations or Countries (eg., Qatar: 91% of positive cases are males). The reasons of these high levels of infection among men are still unknown. However, they could be likely related to gender norms around the use of pub-

lic space and working habits, which are often male-dominated, and low levels of women's participation in the paid labour market. Additional social and structural inequalities are also likely to be playing a role in driving Covid-19 outcomes; there is also a need for more data that take into account other inequalities, such as ethnicity, geography, disability, socioeconomic status, etc.

### Why are sex-disaggregated data important?

A proper understanding of sex and gender differences in terms of incidence and fatality is a first step to investigate the biological and/or social mechanisms underlying such differences, with a view to identifying specific preventive strategies and therapeutic targets for men, women and people with non-binary gender identities. Intervention policies that take into account the needs of female frontline workers (eg., healthcare workers) could help prevent the higher infection rates currently observed among women in this group. Sex-disaggregated testing data can provide a window into gender inequalities in accessing health services. In addition, since men and women tend to respond differently to potential vaccines and treatments, access to sex-disaggregated data would be essential for the conduction of more appropriate clinical studies. An interesting example of how these data can guide clinical research is provided by the new phase II clinical trial to promote recovery from Covid-19 with endocrine therapy. The hypothesis of Catherine H. Marshall and colleagues is that hormones may partially contribute to the gender disparity seen in Covid-19 patients, with high levels of testosterone being harmful and high levels of estrogen being helpful. The trial is aimed to determine if bicalutamide (a nonsteroidal antiandrogen) benefits patients with a clinical improvement by day 7.<sup>7</sup>

Supporting gender analysis and sex-disaggregated data is an integral part of a strong Covid-19 response; understanding sex and gender in relation to global health should not be seen as an optional add-on, but as a core component of ensuring effective and equitable global health systems, while recognizing the role that both biology and social factors play in the risk of infection and disease, in the clinical presentation and in the severity of the outcomes, both at individual and population level.

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