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EDITORIAL

COVID-19 and SARS-CoV-2: A Virus of Sexism?

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Coronavirus disease 2019 or COVID-19 is an infectious disease caused by a novel coronavirus now identified as severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2. The SARS-CoV-2 virus is a new human coronavirus which was first reported from Wuhan, China at the end of December 2019, and since then it has spread to more than 150 countries in just four months. The genomic structure of SARS-CoV-2 is similar to other betacoronaviruses, possessing 14 open reading frames (ORFs), encoding for 27 proteins: the ORF1 and ORF2 at the 5'-terminal region of the genome encoding the 15 non-structural proteins, which is important for virus replication (Malik *et al.*, 2020; Wu *et al.*, 2020). A research by University of Oxford found three central variants distinguished by amino acid changes, which was classified as type A, B, and C (Forster *et al.*, 2020). The most common variant type detected in Malaysia and east Asian regions is type B, implying a 'founder event' in Wuhan.

To date, the SARS-CoV-2 has infected more than 4.9 million people worldwide with more than 320,000 deaths. The world's most cumulative number of confirmed cases is reported in the United States of America (where more than 1.5 million cases were reported with more than 85,000 deaths, or with a fatality rate of 5.20%. Other countries like Italy (with more than 210,000 confirmed cases and almost 29,000 deaths reported with fatality rate of 13.71%), China (more than 84,000 confirmed cases and almost 4,700 deaths reported with fatality rate of 5.50%) and Singapore (more than 25,000 confirmed cases and not more than 20 deaths reported with fatality rate of less than 1%). In Malaysia, more than 6,000 confirmed cases have been reported to date with more than 100 deaths (fatality rate of 1.67%)

Advanced age and concurrent co-morbidities are the biggest risk factors for the fatalities. Based on currently available information and clinical reports, older adults (60 years and above), babies, children, pregnant women and those who have serious underlying medical conditions especially with the presence of chronic diseases, particularly heart disease, diabetes and cancer, are at higher risk of developing severe illness from SARS-CoV-2 infection.

Are men at higher risk to COVID-19 infection compared to women?

The Global Health 5050 statistics fact has shown that, in Italy, 71% of all COVID-19 death cases were men and countries like China, Spain and Germany recorded 65% male fatalities. The higher ratio for men were also seen in other countries such as England, Wales, Thailand, Philippines and even a greater proportion in Wuhan, China (75%) and Malaysia (79%) (http://globalhealth5050.org/covid19/). Overall, men are 50% to 80% more likely to die of the coronavirus following diagnosis than women (Graves, 2020; Maragakis, 2020). The differences in mortality may partly be attributed to social behaviours which make men more susceptible such as the use of tobacco and alcohol which are more prevalent in men. Additionally, most men, being the head of households are more likely to go out of their homes and risk themselves being exposed to the infection.

Is there a scientific basis to this gender differences?

Could there be a scientific explanation to what seems to be an immunological advantage for women? Can genetics provide an explanation to this advantage? Men and women differ in their sex

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chromosomes. Women have two copies of the X chromosomes while men have only one. A woman with any defective gene on one X chromosome will most often be unaffected as long as she has a normal copy of the gene on the other X chromosome (Ørstavik, 2017) and that copy of the X chromosome escaped partial or full inactivation. A double expression of genes on the X chromosome that have escaped and skewed the inactivation may have conferred women with a more responsive immune system as it makes women more susceptible to autoimmune diseases such as Primary Sjögren's syndrome, Systemic Lupus Erythematosus (SLE), primary biliary cirrhosis and multiple sclerosis (Ngo *et al.*, 2014; Ørstavik, 2017; Voskuhl, 2011).

About 10-15% of the genes on X chromosome escaped inactivation, leading to double expression of the genes (Ørstavik, 2017; Syrett and Anguera, 2019). One example of this has been found in a mouse model of Systemic Lupus Erythematosus (SLE). The female mice had overexpression of the immune-related X-linked gene toll-like receptor 8 (*TLR8*) due to incomplete inactivation (McDonald *et al.*, 2015; Smith-Bouvier *et al.*, 2008). Additionally, the higher prevalence of autoimmune disease in women may be indicative that the dose of certain X-linked genes is critical. Since 10–15% of the genes on the X chromosome are not inactivated, a double expression of genes on the X chromosome may also arise in women with a normal number of X chromosomes.

Many of the X-linked genes are involved in the innate and adaptive immune system, such as *CD40L, CXCR, OGT, FOXP3, TLR7, TLR8, IL2RG, BTK, and IL9R*, and women produce more immunoglobulins than men (Brooks, 2010; Libert *et al.*, 2010). Majority of X-linked genes which escape the inactivation are located on the short arm of the X chromosome (Disteche, 1999) including *HDHD1, STS, ZFX, EIF2S3, CXorf38, DDX3X* (Zhang *et al.*, 2013), *TLR7* (Souyris *et al.*, 2018), *OGT (*Olivier-Van Stichelen and Hanover, 2014*)* and *TLR8* (McDonald *et al.,* 2015). Two versions of a specific gene on the X chromosome, *TLR7*, in women gives them positive effects on the resistance to viral or bacterial infections and advantage in recognizing single-stranded RNA viruses like the novel coronavirus (Souyris *et al.*, 2018). Biallelic B lymphocytes from women displayed greater *TLR7* transcriptional expression than the monoallelic cells, correlated with higher *TLR7* protein expression in female than in male leukocyte populations (Souyris *et al.*, 2019).

Another gene that can be found on the X chromosome is the *ACE2* gene. The spike protein of COVID-19 is used to enter cells in the body by unlocking the *ACE2* protein on the surface of the cell (Conti and Younes, 2020). In men, only one version of this *ACE2* gene can be perfectly unlocked by the spike protein of the COVID-19 strain. Women, though, have two different *ACE2* genes on their two X chromosomes, (Moalem, 2020; Vince, 2019; Vince, 2020).

Another gene, the *SRY* gene which is found on the Y chromosome in men contains repetitive sequences ("junk DNA"). The "toxic Y" could lose its regulation during ageing which might hasten ageing in men and render them more susceptible to the virus. The high level of testosterone hormone unleashed by *SRY* action and low levels of oestrogen, are to men's disadvantage and are implicated in many diseases, particularly heart disease, and may also affect lifespan.

While the focus and resources are gathered to find a cure for COVID-19 it is also important to determine if SARS-CoV-2 is indeed a virus of sexism. It has been seen that as a virus, SARS-CoV-2 knows no border, does not differentiate social class, status or ethnic group. It is timely now to determine if genetics play a role in determining the infectivity of SARS-CoV-2 and its gender preferences.

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