International Journal of Medical and Health Research
ISSN: 2454-9142
Received: 01-10-2020; Accepted: 16-10-2020; Published: 03-11-2020
www.medicalsciencejournal.com
Volume 6; Issue 11; 2020; Page No. 09-11

Biological sex could impact vaccine efficacy for covid-19

Sushmita Das
Associate Professor, Department of Microbiology, All-India institute of Medical Sciences (AIIMS), Patna, Bihar, India

Abstract
The virus SARS-CoV-2 causes COVID-19, the pandemic that has posed overwhelming effects on the global health and is causing millions of death worldwide. The virus spreads easily, and the majority of the world's population is still vulnerable to it. Research is happening at breakneck speed for vaccine development as it would provide some protection by priming our immune systems to fight the virus. About 240 vaccines are in early development, and 40 more in clinical trials with nine already in the final stage of testing on thousands of people. Globally, most countries have reported sex-disaggregated COVID-19 data for cases, deaths or both**.** Notably, the data from several COVID-19 affected countries have pointed towards male-biasness of the disease, severity being two-times lower in females. In this article, we have discussed why there could a possibility for biological sex to impact vaccine efficacy for COVID-19.

Keywords: covid-19, vaccine, immune system, sex-bias, estrogen

Introduction
The virus SARS-CoV-2 causes COVID-19, the pandemic that has posed overwhelming effects on the global health and is causing millions of death worldwide [1]. Worldwide clinical and research data are unveiling several unknown facts related to disease pathogenesis, disease outcomes/fate, patient management methodologies, efficient vaccine strategies, risk/susceptibility factors, protection measures etc. The diversity of human population biology has posed significant challenges in understanding the disease dynamics of COVID-19. Proper understanding of the disease dynamics is very important for successful patient management and cure. Involvement of the immune system has been documented as the primary culprit forthe disease severity in COVID-19 patients [2]. Notably, the severity of 'cytokine storm' in COVID-19 patients has resulted in derestricted pro-inflammation leading to damage in multiple organs, especially lungs. Multiorgan engagement at later stages of the infection has led to permanent damage and/or death. Much information on the immune-modulatory aspects of the virus on human beings is still lacking.

The viewpoint
Globally, most countries have reported sex-disaggregated COVID-19 data for cases, deaths or both [3]. On this context, it is very noteworthy to mention that data from several COVID-19 affected countries have pointed towards male-biasness of the disease, severity being two-times lower in females [4]. Especially, it was noted that mortality was higher in males than females [5, 6].The influenza virus has also been called "the man flu", as men suffer more than females (7).Similar male predominance was also observed in SARS-CoV and Middle East respiratory syndrome (MERS). Male-biasness for COVID-19 disease could also emerge from increased smoking and drinking habits that leads to vulnerability of the lungs, higher risk towards co-morbid conditions of cardiovascular diseases and diabetes, higher health-care seeking behaviour etc. in males. Previous reports from animal studies of SARS-CoV indicated that the difference in male Vs Female mortality was due to the effect of sex hormones [8]. It is already known that the immune system is modulated by sex hormones, sex steroids, genetic characteristics and epigenetic makeup of the individual [9-12]. The immune system of plays vital role in progression of COVID-19 pathology, thus there is good scope for sex hormones to promote gender-biasness in the disease. Importantly, it was observed that COVID-19 patients above 70 years of age show almost equal mortality among both sexes, advancing age having no significant effect on mortality among males and females [13].

The sex hormones, *viz*. testosterone, oestrogen, progesterone, follicle stimulating hormone (FSH), LH etc. have direct and/or indirect effects on immune cells functions. Males and females have variability in cellular signalling mechanisms, transcriptional immune signatures, cellular regulatory networks, epigenetic modifications. SARS-CoV-2 enters the human pneumocytes through angiotensin-converting enzyme type 2 (ACE2) receptors [14]. Interestingly, ACE2 receptor is X-linked and the ACE2 variants have differential expression in both sexes [15, 16]. Oestrogen has a prominent role in modulating the immune system in a dose-dependent manner and also affects the expression of ACE2 [17]. Even smoking leads to higher ACE2 expression [18].Though detailed research is required, we can speculate that oestrogen can play a vital role in protecting females from COVID-19 disease and mortality.

The innate immune response has crucial roles in COVID-19 via sensing of the virus and early anti-viral responses. TLR-7, that senses the viral RNA and induces immediate response, is also X-linked with bi-allelic expression in females [19, 20]. Thus, innate response can also present with gender-bias. For greater expression of TLR-7, there is increased production of type-I IFN (especially IFN-α) from plasmacytoid dendritic cells in females compared to males [21-23]. Notably, earlier experiments have shown that pre-exposure to pegylated IFN-α results in increased lung protection from SARS-CoV in animals **[24].** Interferons have also been shown to be important for COVID-19 pathology

[25]. On the other hand, anti-inflammatory effects of oestrogen against coronaviruses, in animal model, are well documented [8]. Low level of testosterone in aging men results in higher pro-inflammation (especially IL-6) and lead to increased lung damage risk [26], whereas testosterone deficiency is related to autoimmune disease.

The scientific fraternity has fully focussed on the rapid innovation of therapeutic and prophylactic strategies to counter the spread of the disease. Gender bias has been well documented in inflammation and is mainly attributable to the factor that most immune regulatory genes are encoded by the X-chromosome, making females to be more immunologically potent [27-29]. Collectively, sex differences have significant differential effects on cytokine and chemokine production, gene expression of immune modulators, recruitment of immune cells (especially neutrophils), T and B cell activity, epigenetic accessibility, development of regulatory T cells etc. Therefore, it is quite natural that gender-bias will be recorded in inflammatory responses towards a COVID-19 and also have effects on the vaccination results. It is also known that females mount significant amount of antibody response to viral infections and vaccinations [30]. Notably, men with high testosterone levels and associated gene signatures demonstrated immunosuppressive effect to influenza vaccination [31].

Male-bias in COVID-19 patients has been reported from India [32]. A recent single-centre study from India has reported young age bias among 144 hospitalized patients with confirmed COVID-19. Notably, it was observed that 93.1% (n=134) were males among the total of 144 patients. Another recent study reported inconsistent SARS-CoV-2 IgG antibody generation in both sexes, with relatively higher levels in female patients [33]. Reportedly, biological sex has been an important deciding factor for the outcome of viral infection establishment, prophylaxis and treatment [30]. The percent reduction in disease incidence in a vaccinated population is called vaccine efficacy. The biological sex of an individual can impact acceptance, response and outcomes of a vaccine that can vary vis-à-vis with age [34]. Females have generally reported to develop higher levels of antibody responses and adverse effects following vaccination. Results of preclinical and clinical studies of vaccines could have impact of sex and gender variables. The influence of biological sex has been well studied for inactivated influenza virus vaccines that is administered annually [31]. Importantly, it has been suggested to include sex as an important variable for COVID-19 clinical trials and research [35]. The rapid increase in mortality rate has accelerated global efforts for vaccine development and implementation. With the rapid advent of vaccine development approaches in India, I strongly support that all investigators and policy makers should design the objectives of vaccines trials with special focus on male-female differences on immune responses that could directly or indirectly impact on such interventions.

Conflict of interest

None

References

1. Covid19.who.int (Accessed 11 August 2020)
2. García LF. Immune Response, Inflammation, and the Clinical Spectrum of COVID-19. Front. Immunol. 2020; 11:1441. doi: 10.3389/fimmu.2020.01441.
3. Sex, gender and COVID-19. URL: https://globalhealth 5050.org/covid19/ [accessed Aug 11, 2020].
4. Peckham H. Sex- bias in COVID-19: a meta-analysis and review of sex differences in disease and immunity. Preprint at Research Square, 2020. https://doi.org/ 10.21203/rs.3.rs-23651/v2.
5. Chen N, Zhou M, Dong X, Qu J. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020; 395:507-513.
6. Guan WJ, Ni Z, Hu Y, Liang W, Ou C. Clinical characteristics of coronavirus disease 2019 in China. N. Engl. J. Med. 2020; 382:1708-1720.
7. Sue K. The science behind "man flu". BMJ. 2017; 359:5560.
8. Channappanavar R, Fett C, Mack M, Ten Eyck PP, Meyerholz DK, Perlman S, *et al*. Sex-based differences in susceptibility to severe acute respiratory syndrome coronavirus infection. J Immunol. 2017; 198(10):4046-4053.
9. Giefing-Kröll C, Berger P, Lepperdinger G, Grubeck-Loebenstein B. How sex and age affect immune responses, susceptibility to infections, and response to vaccination. Aging Cell. 2015; 14(3):309-321.
10. Ghosh S, Klein RS. Sex drives dimorphic immune responses to viral infections. J. Immunol. 2017; 198:1782-90.
11. Piasecka B, Duffy D, Urrutia A, Quach H, Patin E. Distinctive roles of age, sex, and genetics in shaping transcriptional variation of human immune responses to microbial challenges. Proc. Natl Acad. Sci. USA 115, E488–E497, 2018.
12. Vom Steeg LG, Klein SL. SeXX matters in infectious disease pathogenesis. PLoS Pathog. 2016; 12:e1005374.
13. Scully EP, Haverfield J, Ursin RL, Tannenbaum C., Klein SL. Considering how biological sex impacts immune responses and COVID-19 outcomes. Nature reviews immunology, 2020. https://doi.org/10.1038/ s41577-020-0348-8
14. Hoffmann M. SARS- CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020; 181:271-280.
15. Liu J. Sex differences in renal angiotensin converting enzyme 2 (ACE2) activity are 17betaoestradiol-dependent and sex chromosome independent. Biol. Sex. Differ. 2010; 1:6.
16. Gibson WT, Evans DM, An J, Jones SJ. ACE 2 coding variants: a potential x- linked risk factor for COVID-19 disease. Preprint at bioRxiv, 2020. URL: https://doi.org/ 10.1101/2020.04.05.026633.
17. Straub RH. The complex role of estrogens in inflammation. Endocr. Rev. 2007; 28:521-574.
18. Leung JM, Sin DD. Smoking, ACE-2, and COVID-19: Ongoing Controversies. EurRespir J, 2020. in press (https://doi.org/10.1183/13993003.0 1759-2020).
19. Iwasaki A. A virological view of innate immune recognition. Annu. Rev. Microbiol. 2012; 66:177-196.
20. Souyris M, Mejia JE, Chaumeil J, Guery JC. Female predisposition to TLR7- driven auto immunity: gene dosage and the escape from X chromosome inactivation. Semin. Immunopathol. 2019; 41:153-64.
21. Berghofer B. TLR7 ligands induce higher IFN- alpha production in females. J. Immunol. 2006; 177:2088-

2096.
22. Meier A. Sex differences in the Toll- like receptor-mediated response of plasmacytoid dendritic cells to HIV-1. Nat. Med. 2009; 15:955-959.
23. Laffont S. X- Chromosome complement and estrogen receptor signaling independently contribute to the enhanced TLR7- mediated IFN- alpha production of plasmacytoid dendritic cells from women. J. Immunol. 2014; 193:5444-5452.
24. Haagmans BL. Pegylated interferon- alpha protects type 1 pneumocytes against SARS coronavirus infection in macaques. Nat. Med. 2004; 10:290-293.
25. Sallard E, Lescure FX, Yazdanpanah Y, Mentre F, Peiffer-Smadja N. Type 1 interferons as a potential treatment against COVID-19. Antivir. Res. 2020; 178:104791.
26. Li H, Manwani B, Leng SX. Frailty, inflammation, and immunity. Aging Dis. 2011; 2(6):466-473.
27. VomSteeg LG, Klein SL. Sex steroids mediate bidirectional interactions between hosts and microbes. Horm. Behav. 2017; 88:45-51.
28. Markle JG, Fish EN. SeXX matters in immunity. Trends Immunol. 2014; 35:97-104.
29. Klein SL, Flanagan KL. Sex differences in immune responses. Nat. Rev. Immunol. 2016; 16:626-638.
30. Klein SL. Sex influences immune responses to viruses, and efficacy of prophylaxis and treatments for viral diseases. Bioessays. 2012; 34:1050-1059.
31. Furman D. Systems analysis of sex differences reveals an immunosuppressive role for testosterone in the response to influenza vaccination. Proc. Natl Acad. Sci. USA. 2014; 111:869-874.
32. Mohan A, Tiwari P, Bhatnagar S, Patel A, Maurya A. Clinico-demographic profile & hospital outcomes of COVID-19 patients admitted at a tertiary care centre in north India. Indian J Med Res, 2020. DOI: 10.4103/ijmr.IJMR_1788_20
33. Zeng F, Dai C, Cai P, Wang J, Xu L, Li J, *et al*. A comparison study of SARS-CoV-2 IgG antibody between male and female COVID-19 patients: a possible reason underlying different outcome between Gender. medRxiv preprint, 2020. https://doi.org/10.1101/2020.03.26.20040 709.
34. Flanagan KL, Fink AL, Plebanski M, Klein SL. Sex and Gender Differences in the Outcomes of Vaccination over the Life Course. Ann Rev Cell Dev Biol. 2017; 33(1):577-599.
35. Bischof E, Wolfe J, Klein SL. Clinical trials for COVID-19 should include sex as a variable. J Clin Invest, 2020. https://doi.org/10.1172/JCI139306.