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EDITORIAL

COVID-19 vaccine trials and sex-disaggregated data

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1. COVID-19 vaccine trials and sex-disaggregated data

In the pandemic era, global immunization programs against COVID-19 are being implemented. Serious adverse events after COVID-19 vaccination are rare but may occur that include anaphylaxis, thrombosis with thrombocytopenia syndrome (TTS), myocarditis, and pericarditis [1]. Non-serious adverse reactions following COVID-19 vaccination include headache, dizziness, injection site pain, lethargy, nausea, fever, musculoskeletal pain, chest discomfort, feeling of body temperature change, and numbness.

It is the right time to remind the regulatory authorities and researchers about the significance of biological sex as a variable in trial data analysis and reporting [2] because vaccine efficacy and safety may be sex-dependent as well as COVID-19 does not strike the sexes equally [3]. Data collected from ClinicalTrials.gov, for the period 1 January 2020 to 26 January 2021, regarding inclusion of sex and/or gender in COVID-19 studies, revealed 4,420 registered SARS-CoV-2/COVID-19 studies. Among them, 21.2% (935 studies) address sex/gender solely in the context of recruitment, 5.4% (237 studies) plan sex-matched or representative samples or emphasized sex/gender reporting, and only 4% (178 studies) explicitly report a plan to include sex/gender as an analytical variable. Until 15 December 2020, just 8 (17.8%) out of the 45 COVID-19-related clinical trials were published in scientific journals that reported sex-disaggregated results or subgroup analyses [4]. Consistently, a smaller study including 30 COVID-19 trials published in January 2021 revealed that none of the studies investigated effect modification by sex [5]. Another observational study published in April 2021 revealed that only 14 out of 121 analyzed whether sex affected the results [6].

Additionally, growing evidences suggest that sex is certainly 'just' one factor of multiple factors affecting vaccine efficacy, while other factors include age, immune history, obesity (body mass index (BMI)), and pregnancy [7]. When weighting the different factors against each other, immune history, in particular, pre-vaccination status, is certainly the (trivially) most important factor of vaccine response and further protection against infectious diseases. Furthermore, disparities, e.g., between the sexes, but also between other host factors, are context dependent. For example, sex was a significant determinant of seroconversion to H1N1 influenza vaccine. However, the male-bias as H1N1 vaccine response was not observed in seroconversion against the H3N2 virus. Immunosenescence, which refers to the age-associated decline in immune responses, has been shown to impact immunity, and has been recognized as a significant factor, with different dosage regimes between older and younger adults (and the special treatment in the case of young children due to their unique immune response). Another factor is BMI. Under specific conditions, BMI seems to be a larger factor for seroconversion outcome than sex. In addition, antibody responses decline with greater BMI in females but not in males [8]. Pregnancy, associated with physiological and immunological changes, contributes to immunological shifts in pregnant compared to nonpregnant females. Pregnant females are at higher risk of virus infection compared to nonpregnant females. In order to develop safe, immunogenic, and highly efficacious vaccines, pregnancy-associated changes and their impact on vaccine-induced immunity should be considered in experimental studies [7].

Why it is necessary to know about biological sex related, as well as sex-disaggregated survey? Biological sex has an impact on vaccine-induced humoral immunity [9] and clinically important health outcomes, such as sex-specific differences in pharmacology, immune response, and vaccine outcomes including efficacy and side effects [10].

With COVID-19, approximately 15 men die for every 10 women, and for every 18 COVID-19 intensive care unit (ICU) admissions among men, there are 10 COVID-19 ICU admissions for women. According to data from the Centers for

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Table 1. The most promising vaccines, the clinical phases, platforms, and their developers [19].

Vaccine	Development Phase	Platform	Developer
AZD1222	Phase IV	Virus vector (ChAdOx1)	University of Oxford/AstraZeneca, UK
Inactivated SARS-CoV-2 vaccine (Vero cell)	Phase IV	Inactivated virus	Sinopharm + China National Biotec Group Co + Wuhan Institute of Biological Products
CoronaVac	Phase IV	Inactivated virus	Sinovac Research and Development Co., Ltd.
BBIBP-CorV	Phase IV	Inactivated virus	Beijing Institute of Biological Products/Sinopharm, China
Ad5-nCoV	Phase IV	Virus vector (Ad5)	CanSino Biological, Inc./Beijing Institute of Biotechnology, China
Ad26.COV2.S	Phase IV	Virus-vectored (Ad26)	Janssen Pharmaceuticals, USA
mRNA-1273	Phase IV	LNP-mRNA	Moderna/NIAID, USA
BNT162b2	Phase IV	LNP-mRNA	BioNTech SE and Pfizer, Inc., USA
Sputnik V	Phase III	Virus vector (Ad26 and Ad5)	Gamaleya Research Institute, Russia
NVX-CoV2373	Phase III	Protein subunit (CHO)	Novavax, USA
Recombinant SARS-CoV-2 vaccine	Phase III	Protein subunit (CHO)	Anhui Zhifei Longcom Biopharmaceutical + Institute of Microbiology, Chinese Academy of Sciences
WIBP-CorV	Phase III	Inactivated virus	Wuhan Institute of Biological Products/Sinopharm, China
CVnCoV Vaccine	Phase III	RNA-based vaccine	CureVac AG
SARS-CoV-2 vaccine (Vero cells)	Phase III	Inactivated virus	Institute of Medical Biology + Chinese Academy of Medical Sciences
BBV152	Phase III	Inactivated virus	Bharat Biotech BBV152 vaccine
Coronavirus like particle	Phase III	Virus-like particle	Medicago Vaccine
QazCovid	Phase III	Inactivated virus	Research Institute for Biological Safety Problems, Rep of Kazakhstan
INO-4800	Phase III	DNA-based vaccine	Inovio Pharmaceuticals + International Vaccine Institute + Advaccine (Suzhou) Biopharmaceutical Co., Ltd.
nCov vaccine	Phase III	DNA-based vaccine	Zydus Cadila
sinophar	Phase III	Inactivated virus	Bharat Biotech International Limited
VAT00002	Phase III	Protein subunit	Sanofi Pasteur + GSK
Inactivated SARS-CoV-2 vaccine (Vero cell)	Phase III	Inactivated virus	Shenzhen Kangtai Biological Products Co., Ltd.
SCB-2019 + AS03	Phase III	Protein subunit	Clover Biopharmaceuticals Inc./GSK/Dynavax
COVAX-19	Phase III	Protein subunit	Vaxine Pty Ltd./CinnaGen Co.
MVC-COV1901	Phase III	Protein subunit	Medigen Vaccine Biologics + Dynavax + National Institute of Allergy and Infectious Diseases (NIAID)
FINLAY-FR-2 anti-SARS-CoV-2 Vaccine	Phase III	Protein subunit	Instituto Finlay de Vacunas
EpiVacCorona	Phase III	Protein subunit	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology 'Vector'
Recombinant SARS-CoV-2 vaccine (Sf9 Cell)	Phase III	Protein subunit	West China Hospital + Sichuan University
DelNS1-2019-nCoV-RBD-OPT1	Phase III	Viral vector (Replicating)	University of Hong Kong, Xiamen University and Beijing Wantai Biological Pharmacy
ARCoV	Phase III	RNA-based vaccine	Academy of Military Science (AMS), Walvax Biotechnology and Suzhou Abogen Biosciences
COVI-VAC	Phase III	Live attenuated virus	Codagenix/Serum Institute of India
CIGB-66	Phase III	Protein subunit	Center for Genetic Engineering and Biotechnology (CIGB)
VLA2001	Phase III	Inactivated Virus	Valneva, National Institute for Health Research, United Kingdom
BECOV2	Phase III	Protein subunit	Biological E. Limited
Nanocovax	Phase III	Protein subunit	Nanogen Pharmaceutical Biotechnology
ERUCOV-VAC, inactivated virus	Phase III	Inactivated Virus	Erciyes University, Turkey

Disease Control and Prevention, there is a gender gap in vaccination coverage, with women several percentage (almost 6%) points higher than men [11]. ChAdOx1 nCoV-19 (AstraZeneca's vaccines) and Ad26.COV2.S or JNJ-78436735 (Johnson & Johnson's vaccines) cause rare clotting disorders in women [12–15], whereas BNT162b2 (Pfizer-BioNTech's vaccines) and mRNA-1273 (Moderna's vaccines) are more likely to cause anaphylaxis in females, and mRNA-1273 caused large local rashes in more females and than males, but myocarditis was more common in males [16–18]. But investigators have not yet reported or discussed how data could be impacted by biological sex. In the future, a report on how sex-disaggregated data and sexual factors affect trial results will help regulatory and public decision-making as well as the development of mass vaccination programs. Clinical trials of Phase III and IV are depicted in Table 1.

Multiple clinical trials of the vaccine have shown that there is a difference between men and women that exist across the entire life span: women have a strong immune response to the vaccine that can assist vaccine efficacy, but they often experience more recurrent and more severe side effects [20–23]. Additionally, vaccine studies reveal that cisgender females have a greater ability to produce higher antibody response, and relatedly, greater efficacy as well as side effects, recommending the requirement for sex-differentiated dosing schedule [10,24].

Studies on influenza vaccines have shown that women's immunological response to half-dose vaccines is the same as men's to full-dose vaccines [25]. In SARS-CoV-2 infections, sex-based differences in adaptive and innate immunity are likely contributors to increased risk of intensive care unit admission and overall death in men as well as increased reporting of long COVID-19 symptoms in women [26]. Hence, the impact of

sex factors on immune responses may be present in COVID-19 vaccine-induced immunity and adverse outcomes.

We now have the opportunity to course-correct the integration of biological sex as a core variable in research reporting, design, and analysis because sex factors (sex-disaggregated analysis and reporting) are being ignored globally during the era of COVID-19 vaccine innovative research and regulation [27] as well as in COVID-19 trial data reporting (8 from lancet). A review of approximately 2,500 COVID-19-related studies revealed that less than 5% of researcher/investigators had intended for sex-disaggregated data analysis in their research [28]. Recently, a systematic review and meta-analysis revealed that the correlation between sex and COVID-19 vaccine efficacy and safety should be considered in enhancing vaccine decision-making programs [29]. Vaccine trial reports those included sex-disaggregated primary outcomes data should be applauded [30,31]. Hence, the correlation between sexual orientation (physiological characteristics of the genitals and sex hormones) and the effectiveness of the COVID-19 vaccine must be considered in enhancing vaccine decision-making plans, and mentioning sex-disaggregated adverse reactions and secondary consequences would be beneficial in future reports.

However, sex-disaggregated-based analysis and reporting benchmark would be collectively set not only for future candidate of COVID-19 vaccines but also for all pharmaceuticals, biologicals, and other therapeutic interventions present in the research pipelines.

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