CRITICAL SEX AND GENDER CONSIDERATIONS FOR EQUITABLE RESEARCH, DEVELOPMENT AND DELIVERY OF COVID-19 VACCINES

BACKGROUND PAPER

Authors: Shirin Heidari and Tracey Goodman, WHO

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EXECUTIVE SUMMARY

There are notable variations between women and men in incidence, disease severity, morbidity and mortality due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Global aggregate data indicate a relatively even distribution of infections among women and men, with a higher prevalence of hospitalization and mortality among men, and studies point to a higher risk for long-term COVID-19 among women. However, there are variations across and within countries, across different age groups and in different underserved groups. These differences may change over time.

Sex-based differences in the immune response to pathogens (including to SARS-CoV-2) and vaccines are well documented. In general, women generate stronger humoral and cell-mediated immune responses to antigenic stimulation, vaccination and infections than men. Studies also indicate that adverse reactions to vaccines may be more prevalent among women compared to men. To what extent these findings contribute to observed greater vaccine hesitancy among women remains to be investigated. Inadequate attention to sex and gender differences in COVID-19 vaccine development and disregarding differences in immunogenicity, adverse reactions and efficacy can influence acceptability and uptake, and consequently coverage and effectiveness.

The effectiveness of a COVID-19 vaccine strategy in ending the pandemic will rely heavily on high coverage with vaccines to create community immunity (or herd immunity) and minimize community transmission. Failure to address gender-related vaccine hesitancy, confidence, acceptability and access will be detrimental to the success of any COVID-19 vaccine. Data on acceptability and uptake of vaccines among adults by sex and other indicators are limited; but these data must be collected and considered in the context of COVID-19 vaccination programmes.

COVID-19 is placing an unprecedented strain on the health workforce around the world, a majority of whom are women, with a disproportionate impact on their health and well-being. These effects will be compounded when COVID-19 vaccines become available and the workforce is called upon to deliver them rapidly on a massive scale. This also applies to other essential workforce occupations, such as teachers and workers in the service sector, who are predominantly women.

Ethical, regulatory and licensing pathways include important gatekeepers and are critical entry points for evaluating sex-based differences or gender implications in terms of safety, adverse events, efficacy and effectiveness in women, including pregnant and lactating women, and in men. Researchers, peer reviewers and editors of scientific journals are important actors who could ensure better incorporation of sex and gender dimensions in research and more complete reporting of data in publications.

Prioritization strategies for COVID-19 vaccination that seek to limit harm will be based on data that can identify specific populations at greater risk for infection, disease and death and that consider intersectional dimensions to ensure non-discriminatory and equitable access to vaccines. High-quality, accessible, trusted, timely, open and reliable data (including surveillance and uptake data) disaggregated by sex and other key dimensions are critical to generating valuable information for decision-making and monitoring performance in real time. The current COVID-19 pandemic highlights the importance of data disaggregation for targeting interventions,

allocating limited health resources and policy planning during and after the crisis. The better the available data, the more tailored and effective the vaccination response can be.

INTRODUCTION

The COVID-19 pandemic has once again revealed the importance of sex and gender in shaping the risk of infection, vulnerability to disease and experience of ill health *(1)*. There are important interplays between sex and gender and other variables, such as age, race and ethnicity, and other health conditions that create differential risks of COVID-19 exposure, acquisition, morbidity, and mortality and other outcomes *(2, 3)*. These dimensions need to be meaningfully considered when developing COVID-19 vaccines and immunization programmes. Not only do sex and gender influence vaccine safety, efficacy and effectiveness, but gender dimensions can also impact vaccine acceptance, access, uptake and, ultimately, the success of creating vaccine-induced community immunity and ending the pandemic *(4)*. Global, national and industry investment and policy decision processes are also not gender neutral. Gender dimensions are often overlooked, and women's leadership needs to be better represented in scientific and policy-making processes.

The purpose of this working paper is to present some examples with supporting evidence about key sex and gender considerations in COVID-19 vaccine research, development and delivery. The working paper is not meant to provide a systematic review or comprehensive overview of the literature on the topic, but rather to share evidence of areas where sex or gender have been shown to influence vaccine response, development, acceptance or access. We examined review articles and primary research articles identified through searches on PubMed, Google Scholar and the WHO website. Additional sources were identified through references of some of these articles and input from SAGE (Strategic Advisory Group of Experts on Immunization) members. The initial draft of the working paper was shared with the WHO SAGE COVID-19 vaccine working group to seek their scientific input. The subsequent version, incorporating the comments from the SAGE COVID-19 vaccine working group, was reviewed by WHO SAGE and their inputs were incorporated to produce the current version.

RISKS OF EXPOSURE, INFECTION AND DEATH

There are notable variations in transmission patterns and incidence of SARS-CoV-2 and mortality between women and men in different countries and within countries, including variations among racial and ethnic minorities and other underserved groups *(5–8)*. Infection rates among women and men also vary across age groups and can change over time *(8)*. Overall, recent global aggregate data indicate that incidence is evenly distributed between women and men. Data on hospitalization disaggregated by sex are available from a handful of countries but are often incomplete. These data show variations across age groups and countries, with some reporting a higher number of hospitalizations among men, indicating greater severity of disease among men. However, other factors related to hospital access and intensive care unit (ICU) admission policies cannot be excluded *(9)*. In most settings there seems to be a higher case fatality rate among men compared to women, with variation in the effect size between countries and different age groups (e.g. higher mortality in women compared to men in the 80+ age group) *(10)*. It is important to bear in mind that the incidence and case-fatality

rates largely depend on the extent of testing in countries and among the different population *(8)*. Unfortunately, data on testing are rarely available by sex, age and other indicators.

The higher case fatality rate among men is explained by both greater biological susceptibility and gender-related risk factors in social roles and health behaviours that contribute to the higher prevalence of pre-existing comorbidities among men, for example cardiovascular diseases, which increase the risk of COVID-19-related mortality. Some of these comorbidities are also influenced by gender-related factors. For example, cardiovascular diseases, obesity and diabetes are all also influenced by lifestyle choices/factors, such as smoking, drinking, and dietary habits and physical inactivity, some of which also shaped by internalization of oppression and psychosocial stress. There are also other gender-related behavioural factors influencing the risk of exposure. For example, studies show that women may be more likely to follow non-pharmaceutical prevention recommendations, such as handwashing, physical distancing and wearing masks, compared to men, who likely due to notions of masculinity may have poorer compliance with some of these recommendations *(11, 12)*.

Biological reasons for the observed sex-differences in disease outcome can likely be explained by the reliance of SARS-CoV-2 on X-linked ACE2 and TMPRSS2 proteins used by the virus for S-protein priming and entry. TMPRSS2 is a membrane-bound enzyme, the expression of which is associated with androgen signalling and testosterone levels. There are also sex differences in antiviral immunity, "caused by sex steroid hormone signalling (i.e., testosterone, estrogens, and progesterone), genetics (e.g., immune function genes that escape X inactivation), and sex-specific composition of the microbiome" *(13)*. Women seem to recover better from infection as they induce a stronger immune response to the virus. Estrogens have also been shown to help heal acute lung injury *(14)*. On the other hand, there are early indications that mid-adult women are at greater risk of post-COVID-19 conditions, with "a distinct female preponderance in the development of fatigue", the mechanism of which is not fully understood *(15, 16)*.

Transmission patterns are likely changing as the pandemic evolves. For example, early in the epidemic in Spain, nearly 70% of infections were among men. Now the trend has been slowly reversing, with slightly more than half of the infections occurring in women *(8, 17, 18)*. This is likely due to patterns of mobility, transmission and exposure. Women carry a greater share of the paid and unpaid burden of care, increasing their exposure risk. In the formal health sector, women constitute 70% of the health workforce, and the majority of frontline health-care workers. As a result, they are at a greater risk of frequent exposure to higher volumes of the virus. Risks may be amplified in the absence of adequate personal protective equipment (PPE). There have been concerns regarding the gendered impact of the shortage of PPE, and in particular potential risks with PPE that is inadequately designed to fit women's anatomy *(19, 20)*.

Gender differences can, furthermore, vary in population groups subject to structural disadvantages. Reports point to higher mortality rates among racial and ethnic minorities, explained by structural vulnerabilities *(21, 22)*. These groups are often overrepresented in lower-paid service and other sectors, work and live in crowded and sometimes multigenerational settings, and are at greater risk of exposure. They may also have limited access to accurate information on preventive measures and health services or access to reliable health services. However, data on minority groups as well as refugees and displaced people are rarely available, and the

available data are seldom disaggregated by sex. As such, gender differences within groups are rarely examined, although these likely do exist. A report from the United Kingdom and Wales shows great variation in the male-to-female ratio for mortality across ethnic minority groups, with mortality among men ranging between 1.3 and 3.5 times that in women in different ethnic groups. *(23)*

Key points: There are notable variations between women and men in the incidence, disease severity, morbidity (post-COVID-19 conditions) and mortality of SARS-CoV-2, with variations across and within countries, across different age groups, and in different minority and underserved groups. These variations may change over time.

IMMUNOGENICITY AND SAFETY PROFILE

Sex differences in the immune response to pathogens and in the context of autoimmune diseases are well documented *(24, 25)*. Sex differences in immunosenescence and immune function can also impact immune responses to vaccines and immunotherapies *(13)*. Females generally exhibit greater humoral and cell-mediated immune responses to antigenic stimulation, vaccination and infections than males. Both basal levels of immunoglobulin and antibody responses are consistently higher in females than in males. Females also exhibit higher cytotoxic T-cell activity along with upregulated expression of antiviral and pro-inflammatory genes, many of which have estrogen response elements in their promoters *(25, 26)*.

Males and females exhibit differences in immune responses to many viral vaccines, with females generally developing significantly higher levels of humoral immunity than males. For example, "after vaccination against influenza, yellow fever, rubella, measles, mumps, hepatitis A and B, herpes simplex 2, rabies, smallpox and dengue viruses, protective antibody responses are twice as high in adult females when compared with males" (27). Sex-based differences in vaccine-induced immune responses can be observed in children, adults in reproductive years, and persist in older age and after menopause. Yet, most vaccine studies do not analyse immune response outcome data by sex *(28)*.

Studies that look at sex differences in vaccine-induced immunity have mainly focused on influenza vaccines, showing notable differences in immune responses as well as adverse reactions to vaccination. Voigt et al. report higher levels of influenza A-specific memory B-cells in females relative to males after seasonal influenza vaccination, with transcriptional sex differences in vaccine responses observed in four gene clusters highly enriched for natural-killer cell, T-cell or B-cell genes *(28)*. They also found higher numbers of CD4+ T-cells in females relative to males, and that the ability of these cells to respond to vaccination appears to differ substantially between sexes. Klein and Morgan report higher haemagglutination inhibition antibody titres and greater neutralizing antibody (NAb) titres in females (in response to trivalent inactivation influenza vaccine [TIV]), and higher interleukin 6 and antibody responses in females (in response to monovalent 2009 H1N1 vaccine). The gender differences shrink with age due to reproductive senescence in females and a drop in circulating estradiol (which has been associated with vaccine-induced antibody responses) *(29)*. The hormonal milieu can have profound effects on the regulation of B-cell activity, antibody production and vaccine efficacy. For example, elevated concentrations of testosterone in males, in particular younger-aged males (18–45 years

old), are associated with reduced NAB responses against influenza vaccine viruses, while in females, greater concentrations of estradiol are associated with greater influenza vaccine-induced immunity *(29)*.

For COVID-19, a study by Takahashi et al. in patients with mild to moderate disease who had not received immunomodulatory medications reported that male patients had higher levels of innate inflammatory immune cytokines and chemokines when compared to females, whereas female COVID-19 patients induced more robust T-cell responses (activated and terminally differentiated T-cells) than males *(30)*. The study also reported higher anti-spike immunoglobulin G (anti-S IgG) levels in women who had stable disease, indicating that more robust anti-S IgG levels in women may be associated with their ability to control disease progression. They also observed that T-cell responses were significantly and negatively correlated with age in male but not female patients. They concluded that collectively, these data suggest that vaccines and therapies to elevate T-cell immune responses to SARS-CoV-2 might be more suitable for male patients, while female patients might benefit from therapies that dampen innate immune activation early on in the disease *(30)*.

Studies have also shown more local and systemic adverse reactions to influenza vaccines among women when compared to men, with both younger and older adult females showing larger (> 6 mm) injection-site reactions to TIV than males, and more women experiencing systemic adverse reactions such as fever, chills, nausea, headaches and body aches to TIV than men. Fatigue and headache have been reported as the most notable systemic reactions occurring more frequently in adult females than males. Similar trends have been observed in response to inactivated monovalent 2009 H1N1 vaccine *(29)*. An analysis of reported adverse effects following yellow fever vaccination to the Vaccine Adverse Event Reporting System (VAERS; 2000–2006) in the United States indicated that the majority of reported adverse events occurred in adult females (61%) *(4)*. It may also indicate a tendency for women to more frequently report their adverse reactions than men. The greater side effects in women may partially explain the higher degree of vaccine hesitancy observed among women than men *(29, 31)*.

Previous reports have shown higher rates of allergic reactions among women of childbearing age compared to men, but similar rates in other ages following influenza A(H1N1) vaccination *(32)*. Most recently, monitoring of the administration of the first dose of the Pfizer-BioNTech COVID-19 vaccine by VAERS reported 21 cases of anaphylaxis – a rare yet severe, life-threatening allergic reaction to vaccines – out of the administration of a reported 1,893,360 first doses. Notably, 19 (90%) of the cases were in females. More women (90%) also experienced non-anaphylaxis allergic reactions *(33)*. Reports following the administration of 4,041,396 first doses of the Moderna COVID-19 vaccine show similar findings, with 100% and 91% of anaphylaxis and non-anaphylaxis allergic reactions, respectively, reported in women) *(34)*. Authors suggest that the female predominance may be attributed to women receiving two-thirds of the vaccines (64% of the Pfizer vaccine doses and 61% of the Moderna vaccine doses), but other reasons cannot be ruled out. More recently, a rare yet severe type of blood clot has been observed predominantly in women under the age of 60 receiving the AstraZeneca vaccine (24 cases reported cases, 18 of which were fatal, out of 25 million people who received the vaccine in European Union and United Kingdom as of 22 March 2021 *(35)*) and the Janssen COVID-19 vaccine (six cases in women following administration of 6.8 million doses in the United States as of 12 April

2021 *(36)*). It's important to underline that these are very rare events. Nevertheless, their female predominance further points to the differential underlying mechanism that needs to be investigated.

The stronger immune response to influenza vaccines in females has prompted some researchers to study dose reduction strategies. Engler et al. showed that antibody responses among women given a half-dose of TIV were similar to or greater in magnitude when compared with responses among men given a full dose *(37)*. In the context of vaccine shortage, consideration of an alternative dosage or route for vaccine administration or frequency of administration could reduce adverse reactions in females and improve acceptability and uptake. But to date, such studies have not been reported *(29)*.

Historically, women have been under-represented in clinical trials, including vaccine trials, resulting in (white) males often being considered the point of reference, with optimal dosages determined for the male body as opposed to confirming whether the same dosage is also optimal for females (38–40). The lack of attention to equal representation and sex and gender dimensions may result in differences in frequency and severity of adverse reactions, which are often not well understood in females or not captured before approval and marketing. An illustration in point is the case in the United States, where out of 10 prescription drugs withdrawn from the market between 1997 and 2001, eight were withdrawn because they "posed greater health risks for women than for men" *(41)*. The lack of gender analysis results in gender bias in our understanding of the biological and immunological responses to vaccines (as well as drugs and other interventions), including differential experience and reporting of adverse reactions in women and the perceived implications of these reactions by women and men *(27)*.

The gender balance of vaccine trials has been improving, as indicated by clinical trials for recent COVID-19 vaccines. The various arms of the ChAdOx1 nCoV-19 (Oxford-AstraZeneca) vaccine trial included between 57% and 67.5% of women, likely because many health and social care workers were targeted *(42)*. Similarly, the BNT162b2 mRNA (messenger RNA) Covid-19 vaccine (Pfizer-BioNTech vaccine) had a gender balance, with 49.4% of all trial participants being women *(43)*.

However, while the gender balance of studies has improved, in publishing the results the trials do not always disaggregate outcome data by sex, and sex- or gender-based differences are often inadequately examined *(44)*. The results of the Oxford-AstraZeneca vaccine published in the *Lancet* provide data on the proportion of women in the different study arms but do not provide other outcome data (symptomatic or asymptomatic COVID-19) or data on adverse events disaggregated by sex *(42)*. The Pfizer-BioNTech vaccine results published in the *New England Journal of Medicine* do provide efficacy data by sex, reporting similar efficacy rates, but do not present data on discontinuation after the first and second dose or adverse reaction data by sex *(43)*.

Applying a gender lens to COVID-19 vaccine research requires the incorporation of sex and gender dimensions in trial design (including preclinical and animal studies) and study protocols, but also requires considering gender aspects in how the trials are organized and conducted. To successfully enrol and retain sufficient numbers of women in vaccine trials, a gender lens must be applied to every aspect of the trial's design, including how information and invitation for recruitment are formulated and distributed, how trials are designed to

facilitate participation (in terms of timing, location, considering issues related to childcare and financial implications in terms of income loss or indirect costs related to participation) as well as providing accurate information about the potential experience of adverse effects to ensure women and men are adequately informed, facilitating equitable participation.

More importantly, there is continuing concern about the failure to take into account the needs and interests of pregnant and lactating women in the research and development of vaccines *(45)*. Historically, pregnant women have been excluded from clinical trials due to ethical concerns of potential harm to the fetus. This has resulted in pregnant women even often being left out of trials for vaccines whose primary target was pregnant women, such as Zika *(45)*. In recent years, there has been a growing concern about the exclusion of pregnant women in clinical trials, including vaccine trials, as an ethical dilemma as this exclusion denies pregnant women "opportunities to receive vaccines that would have protected them and their offspring from the ravages of these diseases" *(45, 46)*. Efforts are being made to address these concerns. The United States Department of Health and Human Services has established the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) to "identify and make recommendations to address gaps in knowledge and research about safe and effective therapies [including vaccines] for use during pregnancy and lactating women, and to explore ethical issues of including pregnant women and lactating women in clinical research" *(47)*. Another effort is the guidance by the Pregnancy Research Ethics for Vaccines, Epidemics and New Technologies (PREVENT) Working Group, which provides 22 recommendations on how to consider pregnant women in trials of vaccines for emerging and re-emerging epidemic threats *(45, 48)*.

Despite these recommendations, all current clinical trials with COVID-19 vaccine candidates exclude pregnant women, and development and reproductive toxicology animal data are often lagging. The *WHO SAGE roadmap for prioritizing use of COVID-19 vaccines in the context of limited supply* recognizes the greater risk of serious disease faced by pregnant women and highlights how lack of data about the safety and efficacy of COVID-19 vaccines during pregnancy renders the prioritization of pregnant women problematic *(49)*. There are, however, ongoing conversations on how to ensure vaccines are not withheld from pregnant women and efforts to collect data on women trial participants who become pregnant during studies, as well as pressure to design specific studies with pregnant women, some of which are expected to begin in Q1/Q2 2021. Initial developmental and perinatal/postnatal reproductive toxicity study of Moderna's mRNA-1273 vaccine in rats has not indicated "any adverse effects on female reproduction, fetal/embryonal development, or postnatal developmental except for skeletal variations which are common and typically resolve postnatally without intervention" *(50).* Recent WHO Interim recommendations for use of the Pfizer-BioNTech, Moderna and AstraZeneca COVID-19 vaccines state that "[i]n the interim, pregnant women should receive AZD1222 only if the benefit of vaccination to the pregnant woman outweighs the potential vaccine risks, such as if they are health workers at high risk of exposure or have comorbidities that place them in a high-risk group for severe COVID-19", shifting the burden of decision-making in the absence of any supporting evidence to women and their clinicians (see WHO *Interim recommendations for use of the Pfizer-BioNTech COVID-19 vaccine, BNT162b2, under Emergency Use Listing: interim guidance, 8 January 2021*; *Interim recommendations for use of the Moderna mRNA-1273 vaccine against COVID-19: interim guidance, 25 January 2021*; and *Interim recommendations for use of the AZD1222*

[ChAdOx1-S (recombinant)] vaccine against COVID19 developed by Oxford University and AstraZeneca: interim guidance, 10 February 2021) *(51–53)*.

While limited, there is growing evidence about the risks and implications of COVID-19 infection during pregnancy on the health of women, fetuses and infants. As noted in the *WHO SAGE roadmap for prioritizing uses of COVID-19 vaccines in the context of limited supply, "*evidence is emerging that pregnant women are at elevated risk of serious disease, further increased if they have pre-existing comorbidities, and maybe at elevated risk of adverse pregnancy and birth outcomes as well" *(49, 54–58)*. A systematic review and meta-analysis of mainly small case series reported that a high proportion of women with confirmed COVID-19 infection had preterm birth (< 37 weeks [22%]) and caesarean delivery (48%). Estimated rates of admission to the ICU among pregnant women (7%) were higher than those of non-pregnant women (4%), and around 1.9% of infants born to these women tested positive for SARS-CoV-2 *(58–60)*. Similarly, a recent study in the United States found that pregnant women aged 35–44 years with COVID-19 were nearly four times as likely to require invasive ventilation and twice as likely to die than were non-pregnant women of the same age, with notable differences among racial minorities *(60)*.

In December 2020, the American College of Obstetricians and Gynecologists published a general statement regarding pregnant individuals and COVID-19 on its website: "Available data suggest that symptomatic pregnant patients with COVID-19 are at increased risk of more severe illness compared with nonpregnant peers *(55, 56, 60–62)*. Although the absolute risk for severe COVID-19 is low, these data indicate an increased risk of ICU admission, need for mechanical ventilation and ventilatory support (ECMO), and death reported in pregnant women with symptomatic COVID-19 infection, when compared with symptomatic non-pregnant women *(60)*. Pregnant patients with comorbidities such as obesity and diabetes may be at an even higher risk of severe illness consistent with the general population with similar comorbidities *(55, 60, 62, 63)*…Similar to the general population, Black and Hispanic individuals who are pregnant appear to have disproportionately higher rates of COVID-19 infection and death *(55, 60, 64)*. Further, risk of ICU admission was higher for pregnant Asian and native Hawaiian/Pacific Islander individuals *(60)*. These disparities are due to a range of social and structural factors including disparities in socioeconomic status, access to care, rates of chronic conditions, [and] occupational exposure.*"* (65)

The immune responses to vaccination in pregnant women cannot be assumed from those of non-pregnant women. The assessment of the safety of vaccination in pregnancy is also unique, and as such, pregnant women should be included in appropriately designed vaccine trials *(59)*. The document published by the PREVENT Working Group in 2019 provides comprehensive ethical guidance for preparedness, research and response for pregnant women and vaccines against emerging epidemic threats *(45, 48, 59)*. The *WHO SAGE roadmap for prioritizing uses of COVID-19 vaccines in the context of limited supply* further highlights that '[i]t is imperative that data specific to pregnancy be generated now from, for example, pregnancy-specific safety and bridging studies and from participants who inadvertently become pregnant during Phase III trials. Vaccine developers and funders should prioritize an assessment of vaccine safety and immunogenicity among pregnant women in their clinical development and of safety and effectiveness in post-marketing surveillance plans" *(49)*. The WHO SAGE suggested it should be extended to include lactating women *(59, 66)*.

Key points: There are sex-based differences in immune responses to pathogens (including to SARS-CoV-2) and vaccines. In general, women generate stronger humoral and cell-mediated immune responses to antigenic stimulation, vaccination and infections than men. Studies also indicate that adverse reactions to vaccines may be more prevalent among women when compared to men. To what extent this may contribute to the observed greater vaccine hesitancy among women remains to be investigated. Inadequate attention to sex and gender differences in COVID-19 vaccine development and ignoring differences in adverse reactions and efficacy can influence acceptability, uptake, and consequently coverage and effectiveness.

REGULATORY, SAFETY AND MONITORING

Ethical, regulatory and licensing pathways must pay attention to sex and gender implications on vaccine safety, efficacy and effectiveness. Research ethics committees responsible for review and approval of study protocols need to review whether sex and gender dimensions are adequately integrated and considered in the study design. Editors of scientific journals also play an important role and can require that all data be published and made available disaggregated by sex, even as supplementary material *(67)*. Evaluation of the COVID-19 vaccine candidates for approval or prequalification needs to include evaluation of evidence of safety and efficacy, including alternative dosing strategies for women, including pregnant and lactating women, and men. The expert group that is involved in the product evaluation process should include individuals with expertise in sex-based differences in immune response and infectious diseases to support a thorough assessment of the implications of any observed differences on safety and efficacy, including the frequency and severity of adverse effects, but also on gender-related factors that can impact effectiveness.

In particular, given the anticipated COVID-19 vaccine supply shortages, the safety, adverse events and efficacy profile of different dosages for women and men should be provided disaggregated and analysed by sex by vaccine producers and regulatory agencies. Evidence of an equal safety and efficacy profile of a potential lower dosage for women (as could be expected based on preliminary immunogenicity data and some indications from studies with influenza vaccines) need to be generated through well-designed research and could influence the availability, cost and affordability of COVID-19 vaccines. Although the implications for delivery implementation and acceptance of such "sex-specific" vaccine doses is unknown, experiences from differential dosing of medications may provide some insights.

Key points: Ethical, regulatory and licensing pathways are important gatekeepers and critical entry points for evaluating sex-based differences or gender implications in terms of safety, adverse events, and efficacy and effectiveness in women, including pregnant and lactating women, and men.

VACCINE DELIVERY AND PRIORITIZATION STRATEGIES

The goal of the Access to COVID-19 Tools (ACT) Accelerator and COVAX facility is to deliver 2 billion doses by the end of 2021 and ensure fair and equitable access for all participating countries. In the context of supply constraints, there is a need for prioritization strategies to target specific populations at greater risk for infection, disease, morbidity and death. In September 2020, the WHO SAGE developed a values framework to guide equitable allocation of COVID-19 vaccines and prioritization of groups in countries in light of supply constraints.

Drawing from key principles such as equal respect, and global and national equity and reciprocity, it calls upon countries to "ensure that vaccine access is equitable based on gender, race, socio-economic status, ability to pay, location and other factors that often contribute to inequities within population" *(68)*. It further encourages the application of the "Values Framework to emerging evidence on specific vaccines, and the evolving epidemiology and economic impact of the pandemic" *(68)*. The *WHO SAGE roadmap for prioritizing uses of COVID-19 vaccines in the context of limited supply* (Version 1.1, 13 November 2020) *(49)* further provides guidance on the prioritization of groups, recommending giving priority to health-care workers (a majority of whom are women), older adults (where men have been shown to be at higher risk of severe disease and death with the exception of the > 80 age group, where the reverse is the case due to longer life expectancy of women), others with high-risk conditions and high-risk settings. The roadmap includes a section on gender and adheres to an equal respect principle that underlines the importance of ensuring that "immunization delivery systems place equal focus on reaching both men and women in every priority group."(49) Monitoring and implementation of this principle need to be an integral part of any vaccine delivery strategy.

WHO SAGE is expected to offer policy recommendations for vaccination of prioritized groups, based on vaccine product performance and safety evidence, in light of evolving evidence on transmission, disease and death. While SAGE is tasked to provide continuous guidance based on emerging evidence, their recommendations will be constrained by what data are collected, produced and made available. Hence, failing to collect, analyse and report data by sex and age (concurrently) on a range of indicators that inform these decisions will hamper effective gender-responsive guidance from SAGE. SAGE can also play an important role by requesting that disaggregated data be provided.

For example, so long as data about safety in pregnancy continue to lag behind evidence about safety for non-pregnant adults, pregnant women may be unfairly excluded from COVID-19 vaccination programmes, contradicting the goal of offering equitable and fair access. Although the absence of pregnancy-specific evidence should not necessarily result in a public health policy denying pregnant women access to an epidemic vaccine (as recommended in the PREVENT guidance *(48)*), the failure to collect timely pregnancy-specific data increases the likelihood that pregnant women, even those in high-risk settings or high-risk occupations or those with pre-existing high-risk conditions, will be excluded as potential targets for COVID-19 vaccination.

The disproportionate burden of paid and unpaid care on women and their frequent contact with children and the elderly either as caregivers or in predominantly female workplaces, such as nurseries and schools, nursing homes and homes for elderly care) put them at greater risk of contact with others who may have a symptomatic or asymptomatic infection, yet many may not be categorized as high risk. The notion of reciprocity is also important to bear in mind, not only in relation to health workers but also the overall greater contribution of women to sustaining the well-being, education and immunization of children during the pandemic.

Policy recommendations and guidance are also intended to be informed by mathematical models. However, the reliability and precision of mathematical models are highly dependent on the accuracy and completeness of the data that underpin them. Studies already show how prediction models can reproduce and reinforce biases, "producing biased prediction models due to unrepresentative datasets and other limitations during

model development" *(69)*. As such, it is advisable that any priority and equity models take into account these dimensions.

SAGE is tasked to provide guidance on equitable access, including as more safety data are made available. Timing of the access to vaccines will also be informed by a risk assessment of vulnerability and COVID-19 threat, both of which are influenced by gender dimensions. These require collection and analysis of data, including post-marketing surveillance and pharmacovigilance data, by sex and age, including among different ethnic groups and across different occupations. WHO SAGE has a critical role in communicating the importance of disaggregated data and encouraging better collection and reporting of data by sex and age, allowing meaningful gender analysis. As countries will be responsible for the final decision on national policy, allocation and vaccination strategy, investment in country capacity to improve data collection and monitoring will be essential to ensure that reliable gender-sensitive data underpin policy decisions.

Strategies for vaccine delivery across the life course and via different modalities (e.g. campaign, routine) must be designed with gender dynamics and other equity concerns in mind. The many gender-related barriers that can affect regular immunization services will also come into play for COVID-19 vaccines, that is, quality of services, provider attitudes, education and health literacy, decision-making, autonomy and agency, access and control over resources (e.g., time and money) and mobility, gender-based violence (known to have increased during the pandemic) and other harmful practices (e.g., son preference).

Guidance and resource materials to facilitate country decision-making and deployment planning for COVID-19 vaccination should emphasize the importance of ensuring women and minority groups are included in the decision-making processes and implementation for better outcomes.

Key points: Prioritization strategies for the COVID-19 vaccine will be based on data that can identify specific populations that are at greater risk for infection, disease and death. Quality sex and gender-relevant data must be collected to facilitate equitable vaccine access.

ACCEPTABILITY AND UPTAKE

Vaccine hesitancy can be an important threat to global public health by contributing to suboptimal vaccine coverage. Vaccine hesitancy is likely due to a number of factors; however, it is often linked to concerns or misperceptions about vaccine safety or confidence in vaccine effectiveness, which are strongly correlated with not getting vaccinated *(70, 71)*. Lower formal educational levels are associated with vaccine scepticism. The gender gap in education in many settings may further limit access to accurate vaccine information and result in less vaccine confidence for women. Furthermore, vaccine uptake is associated with *disease risk appraisals*, that is, better uptake is associated with the perception that infectious diseases are 'likely, serious, and regrettable' and with *vaccine confidence*, that is, "believing that vaccines are important, save lives, and have few side effects" *(72)*.

Experience or perception of safety, adverse reactions, the risk of serious disease and confidence in the vaccine can all influence vaccine uptake and can vary between women and men across different settings. Failure to

consider the differential adverse effect profiles of COVID-19 vaccines among women and men could influence vaccine confidence, and acceptability, and together with other gender-related factors, such as access barriers, impact vaccination coverage. Limited data show that there may also be social-behavioural differences between men and women in doubts about vaccine efficacy and fear of adverse effects. Some studies have shown lower acceptability of vaccines among women compared to men. For example, studies of seasonal influenza vaccines found lower acceptance and higher vaccine hesitancy among women than men, resulting in differences between males and females in vaccine uptake *(29)*. A systematic review by Bish et al. on factors associated with uptake of vaccination against pandemic influenza among both the general population and health professionals concluded that men were more likely to intend to be vaccinated and to be vaccinated than women *(73)*. The study found that in some countries, women were more likely to express fears about the efficacy and safety of the pandemic influenza vaccine, which may explain their lower uptake *(73)*.

In contrast, a recent global survey in 19 countries on the potential acceptance of a COVID-19 vaccine found men in this study were less likely than women to accept vaccines in general or their employer's recommendation to get vaccinated; however, this association was not strong *(74)*. Another United States survey further revealed that male respondents who state that they're "completely masculine" reported more resistance to COVID-19 vaccines , with 21% stating they are "very unlikely" to get a COVID-19 vaccine compared with 17% of other men *(75)*. On the other hand, a more recent survey among nearly 1800 health-care workers in the United States showed a different picture, with half as many men than women reported to be vaccine resistant (13% vs 27%), with vaccine resistance defined as unwillingness to be vaccinated *(71)*. While studies on gender differences in COVID-19 vaccine hesitancy and resistance are limited and offer contradicting results, these studies point to the fact that gender differences exist and may vary across settings, occupations and different groups, and underlying causes need to be examined.

Gender and equity dimensions will also prove important when developing communication and advocacy materials and messaging (i.e. videos, posters, talking points, etc.); regarding who is portrayed, whom they reach and how they are perceived, in particular by those most underserved. How information and campaigns on vaccine safety are communicated, including consideration of graphic communications, the languages used, the way information is distributed and disseminated (and choice and use of social media and the messaging), the role (and gender) of health professionals in communicating accurate and accessible vaccine information, including correct information about the differential severity and frequency of adverse events, alleviating vaccine safety concerns and other factors that influence the acceptability of vaccines must be developed and designed with gender dynamics and dimensions in mind *(76)*.

There are other gender-related barriers to vaccination, beyond those related to acceptability. In studies with influenza vaccine, in some settings, more males than females received an influenza vaccination. Intersectional gender considerations related to affordability and accessibility must be considered in different countries, as they will influence demand, access and uptake. Reports indicate a higher economic impact on women and people of racial and ethnic minorities, due to structural and gender-related factors, which may impact demand and uptake of vaccines.

Key points: The effectiveness of a COVID-19 vaccine strategy to end the pandemic will heavily rely on high coverage with vaccines that can create community immunity and minimize transmission. Failure to address gender-related vaccine hesitancy, confidence, acceptability and access will be detrimental to success. These factors vary between groups and are influenced by gender, among other factors. Gender may also create barriers to reliable and acceptable vaccine information and vaccination services. Data on acceptability and uptake of vaccines among adults by sex and other indicators are limited but must be collected and considered in the context of optimising COVID-19 vaccination programmes.

THE HEALTH WORKFORCE

The health workforce will be critical for the successful delivery and roll-out of the COVID-19 vaccine, and their health and safety are paramount during vaccination both of themselves and others *(77)*. Given that women constitute the majority of these health workers, issues related to equal pay, a respectful and enabling working environment with zero-tolerance policies for sexual harassment and gender-based discrimination, equitable access to relevant training on infection prevention and control measures, PPE, essential products for hygiene and sanitation, and psychosocial support must be ensured. These factors are vital to maintain health and social workers' well-being and resilience during the pandemic and when COVID-19 vaccines become available.

During this pandemic, women, in particular, are being confronted with the challenges of balancing an increased workload, the anxiety of spreading the virus to loved ones and managing their care responsibilities at home. Some health facilities are providing free childcare for health workers to reduce that burden. This is especially relevant in areas where schools have closed due to COVID-19 and children have been home for long periods.

Previous outbreaks have shown the importance of integrating a gender analysis into public health emergency preparedness and response since women play a predominant role as informal carers and health workers *(78)*. The pressing demands on health workers with family responsibilities, most of whom are women, highlight the compelling need for flexible working time arrangements that are predictable and gender responsive, and that allow and encourage men and women to better balance their work and family responsibilities, as well as efforts to encourage more balanced and gender-sensitive care arrangements.

The scale and rapid roll-out of COVID-19 vaccines will create an additional workload on already stretched, and in many places weak, health services. In most settings, the majority of the health workforce are women. In addition, as stated in a recent report, there are "3.5 million semi-formal and informal health workers", with 70% of these women who will be critical in vaccine delivery; yet they are often less recognized, underpaid or poorly protected *(79)*. Working hours and shift assignments must aim to prevent burnout, in particular among female semi-formal and informal health workers, who may experience higher risk of mental health concerns. Resources for mental health and psychosocial support, sick leave, insurance and equal pay as well as access to COVID-19 vaccines should be equitably available to health-care workers. A recent survey among health-care workers in the United States reports that male health-care workers responding to the survey were nearly twice as likely to have been vaccinated than female health-care workers, indicating potential inequities in access to COVID-19 vaccines among the health workforce in that setting *(71)*.

To bolster the availability of the health workforce with surge capacity to deal with COVID-19 outbreaks, several countries have sought assistance from professional volunteers, other sectors such as the military, retired doctors and nurses, medical and nursing students and even migrant workers. In the United States where unemployment is high, the idea of training residents to become community health workers to help respond to the pandemic is becoming attractive *(80)*. While these are practical measures to secure needed human resources, they require careful implementation to ensure that these workers are afforded the same protection as other workers. For these reasons, decision-making processes at national, subnational and international levels must ensure "that women health workers, including women nurses, [are] meaningfully involved in the distribution of resources, equipment, policies and practices that have an impact on their health and well-being" *(19)*.

Key points: COVID-19 is placing an unprecedented strain on the health workforce around the world, a majority of whom are women, with a disproportionate impact on their health and well-being. This situation will be compounded when COVID-19 vaccines become available and the workforce is called upon to deliver them rapidly at a massive scale.

DATA AND MONITORING

Immunization programmes should always be driven by data, but the current global gender data gap means that health actors often lack sufficient knowledge of the gender dynamics to appropriately target immunization. For COVID-19 vaccines, identifying and prioritizing target populations and implementation strategies will require solid and complete disaggregated data that can meaningfully identify who is at greatest risk of infection, severe disease or death and strive to ensure equitable access to those at greatest risk.

Yet, these dimensions are often not sufficiently captured nor analysed to guide decisions. To illustrate this point, a rapid review of WHO's Global Advisory Committee for Vaccine Safety (GACVS) website shows that gender-related issues for safety monitoring have never been discussed.

The Global Polio Eradication Initiative has noted a distorted M : F sex ratio (e.g. 60% boys against 40% girls) in acute flaccid paralysis (AFP) reporting in countries with high numbers of AFP cases. Gender-sensitive indicators will be needed to monitor progress towards equitable access to COVID-19 vaccines and to capture the frequency and severity of adverse effects in different groups. Risk–benefit assessments, preparedness assessment, global benchmarking, surveillance and pharmacovigilance must consider the impact of these critical dimensions. Any modelling by SAGE to provide guidance on priority groups or optimal vaccination strategies must consider epidemiology and efficacy not only in different age groups but also between women and men across age groups.

Gender (and diversity) can influence broad research structures and processes, impact what gets researched, what is funded, how funding is distributed and how trials are designed. International COVID-19 vaccine governance structures, as well as regional and national committees related to vaccination, need to ensure they are gender balanced.

A review of the international COVID-19 vaccine governance structures points to a relative gender balance in the majority of the groups: WHO SAGE COVID-19 vaccine working group (10 female : 7 male); GACVS (7 female : 8 male); Gavi Board (oversight for COVAX) (13 female : 14 male); CEPI Board (5 female : 7 male); COVAX Coordinating Meeting (7 female : 5 male); Research Development and Manufacturing Investment Committee (RDMIC voting members) (1 female : 8 male); Technical Review Group (5 female : 7 male); Enabling Sciences SWAT (Support Work to Advance Teams) (8 female : 3 male); Manufacturing SWAT (4 female : 8 male); Clinical Development & Operations SWAT (6 female : 10 male); Regulatory Advisory Group (8 female : 6 male); Independent Product Group (5 female : 5 male); Market-Sensitive Decisions Committee (7 female : 7 male); Audit & Finance Committee (4 female : 7 male).

Key points: High-quality, accessible, trusted, timely, open and reliable disaggregated data, including sex, is critical to generating necessary information for decision-making and monitoring performance. The current COVID-19 pandemic highlights the importance of data disaggregation for targeting interventions, allocating limited health resources and policy planning during and after the crisis. The better the data available, the smarter the vaccination response can be.

RECOMMENDATIONS

Recommendation 1: Addressing gender data gap

Epidemiological data on infection, comorbidities, the severity of disease, hospitalization, morbidity and mortality need to be disaggregated by sex and age concurrently, as well as other indicators to understand the patterns of exposure and transmission and to inform the development of priority groups and vaccination strategies. Data must be regularly analysed to capture evolving patterns of transmission and risk.

Recommendation 2: Designing gender-sensitive vaccine research and development

Clinical and other studies on COVID-19 vaccines must analyse potential sex- and gender-based differences in vaccine safety and efficacy (including in early trials determining dosing and safety) and the impact of gender dimensions on the effectiveness of vaccines in men and women. Investment in qualitative studies (including ethnographic research) can provide valuable insights into contextual gender dimensions and help address hesitancy and misinformation, particularly among women and underserved populations. Research ethics committees responsible for review and approval of study protocols need to review whether sex and gender dimensions are adequately integrated and considered in the study design. Pharmaceutical companies and investigators must make all data publicly available by sex. National regulatory agencies and WHO prequalification mechanisms should require complete data by sex, and sex- and gender-based analysis, so that review ensures that vaccines are equally safe and efficacious in both women and men. This would allow these committees to review the evidence and consider whether different optimal dosing strategies for women vs men would be justified. Regulatory mechanisms responsible for review, approval and safety monitoring need to adequately evaluate sex and gender aspects in their review.

Recommendation 3: Prioritizing vaccine research and development in pregnant and lactating women

Safety, efficacy and effectiveness of vaccines in pregnant and lactating women must be examined in studies designed for these groups. Reproductive toxicology animal studies must be initiated at an early stage. A protocol attached to all Phase 3 clinical trials can identify women who become pregnant during the trial and ensure mandatory follow-up of mother and infant. Furthermore, safety, efficacy and effectiveness of vaccines in pregnant and lactating women must be examined in studies designed for these groups.

Recommendation 4: Considering intersectional gender dimensions in deployment and delivery of vaccines

Intersectional gendered aspects must be considered in any risk and benefit assessments, and when developing COVID-19 vaccination policies and strategies. Technical guidelines or guidance documents developed by WHO, ministries of health or other international, regional or national bodies must adequately incorporate gender considerations. Discussions on prioritization must be mindful of the incompleteness and biases in data (including with respect to sex/gender, age, race/ethnicity and other important aspects), and prioritization strategies should consider not only those who are at greater biological risk of severe disease or death but also the gendered socioeconomic and cultural factors that make people more exposed to risks and at higher risk of infection, disease or death. Delivery strategies for COVID-19 vaccines must be mindful of the gender-related barriers to immunization and tailor programmes based on gender-sensitive evidence to ensure equitable and fair access to vaccines and leave no one behind. Countries need to carry out baseline gender assessment to

identify those at greatest risk as well as identify gender and other equity-related barriers to vaccination to tailor strategies for equitable administration of vaccines. Gender implications must be considered in decision-making regarding the workforce needed for rapid delivery of vaccines at a massive scale.

Recommendation 5: Capturing intersectional gender aspects in post-marketing surveillance and monitoring

Post-marketing surveillance and pharmacovigilance data on safety and adverse events must be collected by sex and age, and ideally by other markers to capture potential differential effects. Designated pregnancy registries must collect data on the adverse events and other impacts on pregnancy outcome. Data and monitoring systems should be developed with these considerations in mind to facilitate collection and timely analysis and reporting of disaggregated data to identify (or rule out) any notable discrepancies. Gender-sensitive indicators must be developed to monitor progress in terms of access and uptake to ensure equitable access to COVID-19 vaccines. Research (including qualitative research), and assessment of acceptability and uptake of the vaccine among adults can identify gender-related barriers to vaccination and improve coverage. COVID-19 vaccination programmes must continuously collect, analyse and monitor indicators by sex and age, and other relevant indicators in order to adjust programmes to overcome gender-related and equity barriers.

Recommendation 6: Inclusive decision-making

Successful vaccine implementation will depend on engaging women in the health workforce, as they make up the majority yet are under-represented in leadership and decision-making positions. Gender imbalances in the management and decision-making cadres of the health sector must be addressed to define conscious and flexible policies and plans that do not undermine the safety and resilience of the health workforce. Women must also be engaged at all levels of decision-making, from research and development to policymaking, programme design, and decisions about vaccine roll-out and delivery.

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