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Review

COVID-19 vaccines: Considering sex differences in efficacy and safety

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ABSTRACT

The development of SARS-CoV-2 vaccines represents a significant breakthrough for managing the COVID-19 pandemic. However, their approval process has exposed a crucial limitation in clinical trial reports—that is, a disregard for sex differences in response to vaccines. Historically, males and females have shown different reactions to vaccines of many kinds, which have become apparent with the arrival of COVID-19 vaccines in late-2020. In this article, we review regulatory data from Phase III vaccine trials as well as peer-reviewed reports from vaccines administered to the general population, many of which failed to stratify results by sex. We also discuss the exclusion of pregnant and lactating persons in drug development and the regulatory guidelines for use of COVID-19 vaccines in such populations. We conclude by proposing some questions to stimulate discussion with the intent of advancing the field toward precision medicine.

1. Introduction

SARS-CoV-2 vaccines represent the most significant breakthrough for managing the COVID-19 pandemic. In this narrative review of the literature, we report the currently available regulatory and peer-reviewed studies on sex differences in vaccines, including safety data and use in pregnancy. We also propose some open questions with the goal of initiating a global discussion on precision medicine in drug development and clinical trials.

1.1. A historical perspective

In 1977, following the tragedy of newborn malformations caused by use of thalidomide during pregnancy, the U.S. Food and Drug Administration (FDA) banned females of childbearing potential from participating in early-phase clinical trials. While originally intended to protect them, excluding females from such early stages of drug development backfired as it generated a knowledge gap, especially on the safety profiles of drugs, with measurable consequences on women's health [43]. Amidst a growing appreciation of sex and gender differences in medicine at large and the emergence of gender-specific medicine, the FDA officially withdrew their 1977 restriction [44]. Today, clinical study guidelines recommend that females be included in drug trials in adequate proportions and that safety and efficacy data analyses of approved drugs be stratified by sex, as one cannot assume that the effects of drugs will be equal between males and females.

1.2. Sex differences in vaccine response

Clear sex differences have been observed within the field of vaccine biology. It is well established that, compared to males, females develop higher antibody responses and report more adverse reactions following vaccination [15]. Between 1990 and 2016, among individuals aged 19 to 49 years, females accounted for 83% of anaphylactic reactions to vaccines [40]. Data from the Centers for Disease Control and Prevention (CDC) showed that, among individuals in the age bracket of 20 to 59 years who received the 2009 H1N1 vaccine, hypersensitive reactions following vaccination were at least four times more common in females than in males (a ratio which increased to 9.5:1 among individuals aged 30–39 years), even though more males received the vaccine [20].

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Table 1
Summary of regulatory safety and efficacy data for approved COVID-19 vaccines.

Vaccine	Regulatory Agency	Total participants (N)	Females (%)	Males (%)	Efficacy subgroup analyses by sex?	Safety subgroup analyses by sex?	Sources
Moderna(mRNA-1273)	EMA[a]	30,351	47.4	52.6	Yes	No	Moderna Assessment Report, EMA Moderna Product Information, EMA
	FDA[a]				Yes	Yes	Moderna VRBPAC[a], FDA
	Health Canada				Yes	No	Moderna Product Information, EMA[1]
Pfizer-BioNTech (BNT162)	EMA	43,651	49.4	50.6	Yes	No	Cominarty Assessment Report, EMA Comirnaty Product Information, EMA
	FDA				Yes	No	Pfizer-BioNTech VRBPAC[a], FDA
	Health Canada				No	No	Pfizer-BioNTech Regulatory Decision Summary, Health Canada
Janssen(Ad26.COV·S)	EMA	44,325	45	55	Yes	Yes	Janssen Assessment Report, EMA Janssen Product Information, EMA
	FDA				Yes	No	Janssen VRBPAC[a], FDA[a]
	Health Canada				Yes	No	Regulatory Decision Summary, Health Canada
AstraZeneca (AZD1222)	EMA	11,636	55.3	44.7	No	No	AstraZeneca Assessment Report, EMA AstraZeneca Product Information, EMA
	Health Canada				No	No	Regulatory Decision Summary, Health Canada
	FDA[2]	–	–	–	–	–	–

[1] EMA and Health Canada publish clinical data used to support their authorisations of the Moderna COVID-19 vaccine. For source of Health Canada Moderna vaccine information, see EMA documents above.
[2] The AstraZeneca vaccine has not yet been approved by the U.S. FDA.
[a] EMA = European Medicines Agency, FDA = Food and Drug Administration, VRBPAC = Vaccine and Related Biological Products Advisory Committee.

Table 2
Summary of non-regulatory study data for approved COVID-19 vaccines.

Vaccine	References	Total participants (N)	Females (%)	Males (%)	Efficacy subgroup analyses by sex?	Efficacy in women (vs men)	Safety subgroup analyses by sex?	Reported ARs (N)	Reported ARs in women (%)
Moderna (mRNA-1273)	*[2]*	28,207	47.4	52.6	Yes	93.1% (vs 95.4%)	No	7340	Not reported
Pfizer-BioNTech (BNT162)	*[29]*	37,706	49	51	Yes	93.7% (vs 96.4%)	No	8408	Not reported
Janssen (Ad26.COV·S)	*[32]*	39,321	45	54.9	Yes	Not reported	Yes	6736	Not reported
AstraZeneca (AZD1222)	*[47]*	11,636	55.3	44.7	No	Not reported	No	Not reported	Not reported
Sputnik V (Gam-COVID-Vac)	*[23]*	19,866	38.8	61.2	Yes	87.5% (vs 94.2%)	No	122	Not reported

Note. ARs = Adverse Reactions.

An interplay between several biological mechanisms has been proposed to underlie the sex differences in vaccine response. Females are known to mount stronger and more rapid innate and adaptive immune responses compared to males, which render them more susceptible to autoimmune diseases and may also explain the higher frequency of adverse reactions to vaccines in this group [13,16]. Importantly, age has been shown to interact with sex to predict vaccine response: while some vaccines are more effective in older females compared to males, the sex dimorphism in adverse reactions to certain vaccines does not necessarily narrow with age (for a review, see [12]). Additionally, the immune response can be modulated by both hormonal and genetic factors, depending on sex. For instance, while higher concentrations of estrogen may contribute to a heightened vaccine response in females, testosterone has been associated with an attenuated vaccine response [42]. Genetic factors and their interaction with sex hormones are also linked to this sex dimorphism in immunological response. There are approximately 10 times more genes on the X chromosome than on the Y chromosome, including a large proportion of genes that code for immune-related proteins [14]. Females, who carry two X chromosomes, therefore have a higher expression of these immune-related genes and proteins [4,31], which may interact with sex hormones to strengthen the immune response. For a more comprehensive review of the mechanisms underlying sex differences in vaccine response, see Ciarambino et al. [4].

2. Materials and methods

Two searches were conducted for this narrative review. First, we searched the FDA, European Medicines Agency (EMA), and Health Canada websites for publicly available Phase III COVID-19 clinical trial reports on vaccines approved for emergency use by these agencies. We then extracted data on vaccine efficacy and safety from these regulatory documents (see Table 1 for specific data sources) as well as the specific recommendations regarding vaccine use in pregnant and lactating persons issued by these regulatory agencies (see Table 3). Second, we searched PubMed for peer-reviewed studies published until May 31st, 2021, reporting on safety and/or efficacy data from Phase III vaccine trials. Five articles were found that fit these criteria, and their findings are summarized in Table 2. Additionally, several other studies analyzing safety data from real-world vaccine rollout in the general population are included in our discussion.

2.1. SARS-Cov-2 vaccines and sex differences: the regulatory data

Based on the existing knowledge about sex differences in vaccine response, sex-specific reporting of vaccine efficacy and safety data appears to be crucial for the development and approval of COVID-19 vaccines. Since mid-2020, thirteen vaccines have been approved for

emergency use for COVID-19—including, but not limited to, Moderna, AstraZeneca, Janssen (Johnson & Johnson), Pfizer-BioNTech, and Sputnik V. The FDA, EMA, and Health Canada published official regulatory data for Phase III vaccine trials. Below we investigate the safety and efficacy outcomes of the COVID-19 vaccines reported by these regulatory agencies.

A summary of regulatory data for each approved vaccine is reported in Table 1. All pivotal trials were large, enrolling tens of thousands of individuals, with equal representation of both sexes. We accessed the regulatory reports and data published in support of vaccine approval to assess whether efficacy and safety data were analyzed by sex. Specific subgroup efficacy analyses by sex were reported for Moderna, Pfizer-BioNTech, and Janssen vaccines, with no statistically significant differences between males and females. Specifically, the EMA reported the general results of their vaccine efficacy analyses by subgroup for the Janssen and Pfizer-BioNTech vaccines by mentioning that efficacy rates were similar between the sexes. However, tables reporting sex-disaggregated data were not included in their reports. In contrast, we found that sex-specific vaccine safety results were only available in the FDA reports for Moderna, which suggested that the safety profiles of these vaccines were similar between the sexes, and in the EMA reports for the Janssen vaccine, which reported that the frequency of both local and systemic solicited adverse events was higher among females compared to males.

These regulatory sources were last consulted on October 20th, 2021. Hyperlinks to specific regulatory documents are included in Table 1. It should be noted that some of the reports in question have been updated during this article's review process and may still be subject to change; therefore, the information reported here may not always match the information reported in these regulatory documents.

3. Results

3.1. SARS-Cov-2 vaccines and sex differences: additional data

In addition to the data used for regulatory approval, several peer-reviewed papers have been published on interim and real-world data since initiation of the vaccine rollout. A summary of vaccine-related data from peer-reviewed Phase III studies is reported in Table 2.

In reviewing interim safety and efficacy trial studies, we found that efficacy data were in most cases stratified by age and sex. In those studies reporting sex-specific efficacy data for the first shot of the vaccine, vaccine efficacy was consistently found to be higher in males than in females (see Table 2). However, in the same studies, safety data were only stratified by age. These analyses revealed a generally higher number of solicited injection-site and systemic adverse events in younger individuals (aged 18–65 years) for the Moderna vaccine [2]. On the other hand, safety analyses for the Pfizer-BioNTech vaccine indicated that local reactions (e.g., pain) were reported more frequently among older participants (aged >55 years) than younger participants (aged 16–55 years), while systemic adverse events (e.g., headache, fatigue) were more common among younger than older vaccine recipients [29]. For the AstraZeneca jab, no stratification was reported. Indeed, 'gender' was indicated as an additional, but not primary, subgroup of interest in their statistical analysis plan [47]. A more recent report on the Janssen vaccine also reported sex-specific efficacy results; however, out of all safety analyses (i.e., solicited and unsolicited local and systemic adverse events), only descriptions of grade 3 unsolicited adverse events post-vaccination were reported separately for males and females [32]. Similarly, only Phase III Sputnik V vaccine efficacy, and not safety, data was disaggregated by sex [23]. Based on the strong real-world evidence demonstrating that sex differences exist in the safety profiles of many vaccines, an a priori stratification of the data by sex is important to establish the distribution of adverse events within male and female populations not only in phase III, but also in phases I and II when studying vaccine dose, pharmacokinetics, and pharmacodynamics.

In the past months, peer-reviewed studies examining the safety and efficacy of the COVID-19 vaccines in the general population have allowed the implementation of pharmacovigilance steps and the identification of rare side effects that were not detected during clinical trials. Importantly, such studies indicated clinically-relevant sex differences in vaccine safety profiles. Among the first 13.7 million COVID-19 vaccine doses administered to Americans, a report from the CDC found that, while females represented only 61.2% (or 8,436,863) of all 13,794,904 vaccine dose recipients, 79.1% (or 5413) of the 6994 reported adverse events concerned females [17]. In another study, following the administration of the mRNA COVID-19 vaccines in the U.S. between December 14th, 2020 and January 18th, 2021, all 19 individuals who experienced adverse reactions to the Moderna vaccine were females, as were 44 of the 47 individuals who reported anaphylactic reactions to the Pfizer-BioNTech vaccine [37,38].

Similarly, Swissmedic evaluated 1953 reports of adverse reactions to the Moderna and Pfizer-BioNTech vaccines out of approximately 2.8 million doses administered in Switzerland (as of May 4th, 2021). They reported that 69.2% of adverse side effects were experienced by females, whereas only 27.8% were experienced by males, with severity ranging from mild (e.g., injection site erythema) to serious (e.g., death) [41].

3.2. Thrombotic events with thrombocytopenia

A unique safety signal associated with the SARS-CoV-2 vaccines is represented by thrombotic events including cerebral venous sinus thrombosis (CVST) and thrombocytopenia. Out of the first 34 million doses administered in Europe and the United Kingdom as of April 4th, 2021, the EMA has reported 169 cases of CVST and 53 cases of splanchnic vein thrombosis following the first dose of the AstraZeneca vaccine, the majority of which occurred in females below 60 years of age [10,11]. All cases were spontaneous reports to EudraVigilance, the European Union drug safety database, which collects electronic reports of adverse events to medicines from clinical trial sponsors. Although these numbers might seem large, it is important to note that the rate of occurrence of thrombosis with thrombocytopenia is less than 1 in 10,000 people [10,11]. In addition, 28 confirmed cases of thrombosis with thrombocytopenia (out of approximately 8.7 million doses administered as of May 7th, 2021) have been reported to the CDC's Vaccine Adverse Events Reporting System (VAERS) following the Janssen vaccine in the U.S., most (22 out of 28) occurring in females between 30 and 49 years of age [36]. It should be noted, however, that specific sex-stratified vaccination rates were not available at the time these adverse events were published. On April 13th, 2021, the CDC and FDA published a joint statement wherein they recommended to pause the Janssen vaccine rollout in the U.S. in response to the aforementioned concerns [45]. On April 23rd, this halt was lifted and a warning of rare clotting events is now being included with use of the Janssen vaccine in individuals aged 18–49 years [50]. Furthermore, the EMA has officially acknowledged a possible causal link between thrombotic events and the AstraZeneca and Janssen vaccines. Such events are now listed as very rare side effects for these vaccines.

An aberrant immune response, with high levels of antibodies to platelet factor 4 reminescent of heparin-induced thrombocytopenia, has been proposed as a mechanism underlying thrombotic events as adverse side effects to the COVID-19 vaccine [19,27,34]. As females tend to have higher prevalence of autoimmune reactions compared to males [22], it is possible that such side effects affect females more often than males. It should also be noted that females, especially those using oral contraceptives, have been shown to be more at risk of CVST than males in the general population [6,21,28]. However, a detailed analysis by sex including a comparison in prevalence of CVST in the general young female population versus the vaccinated female young population is currently lacking, but is much needed. It would also be important to evaluate concomitant risk factors such as hormonal treatment, immune system disorders, and other conditions that may show sex differences.

Table 3
Advice on all market authorized COVID-19 vaccines for pregnant and lactating persons by selected regulatory bodies.

European Medicines Agency (EMA)	
COVID-19 vaccines – conditional market authorisation granted	Pfizer-BioNTech, Janssen, Moderna, and AstraZeneca
• Animal studies do not show any harmful effects in pregnancy; however, data on the use during pregnancy are very limited. • Although there are no studies on breast-feeding, no risk for breast-feeding is expected. • The decision on whether to use the vaccine in pregnant persons should be made in close consultation with a healthcare professional after considering the benefits and risks.	
U.S. Food and Drug Administration (FDA)	
COVID-19 vaccines – conditional market authorisation granted	Pfizer-BioNTech, Janssen, and Moderna
• Clinical trials that look at the safety and how well the COVID-19 vaccines work in pregnant people are underway or planned. Vaccine manufacturers are also monitoring data from people in the clinical trials who received vaccine and became pregnant. • Studies in animals receiving Moderna, Pfizer-BioNTech, or Janssen (Johnson & Johnson) COVID-19 vaccines before or during pregnancy found no safety concerns. • If you are pregnant, you may choose to receive a COVID-19 vaccine. While a conversation with your healthcare provider may be helpful, it is not required prior to vaccination. • Any pregnant woman who has had vaccine is advised to enrol into the v-safe health checker to monitor their side effects. • Most reports to the Vaccine Adverse Event Reporting System (VAERS) among pregnant women (73%) involved non-pregnancy-specific adverse events (e.g., local and systemic reactions). Miscarriage was the most frequently reported pregnancy-specific adverse event to VAERS, but the number was not concerning considering the expected background rate. • Safety monitoring in pregnant women is ongoing in v-safe, Vaccine Safety Datalink (VSD), and Clinical Immunization Safety Assessment (CISA).	
Medicines & Healthcare products Regulatory Agency (MHRA) and Joint Committee on Vaccination and Immunization (JCVI)	
COVID-19 vaccines – conditional market authorisation granted	Pfizer-BioNTech, Moderna, and AstraZeneca
• There is no evidence the COVID-19 vaccine is unsafe if you're pregnant. More evidence is needed before you can routinely be offered the vaccine. • The JCVI has updated its advice to recommend you may be able to have the vaccine if you're pregnant and at high risk of getting COVID-19 because of where you work, or have a health condition that means you're at high risk of serious complications of COVID-19. • You can get the COVID-19 vaccine if you're breastfeeding. • Speak to a healthcare professional before you get the vaccine. They will discuss the benefits and risks with you. • There's no evidence that the COVID-19 vaccine has any effect on your chances of becoming pregnant. There's no need to avoid pregnancy after vaccination. • The vaccine cannot give you or your baby COVID-19.	
Health Canada & National Advisory Committee on Immunization (NACI)	
COVID-19 vaccines – conditional market authorisation granted	Pfizer-BioNTech, Moderna, and AstraZeneca
• For some specific populations (including pregnant and lactating persons) who were either excluded from, or were represented by small numbers of participants in clinical trials, the NACI recommends that a complete vaccine series with a currently authorized COVID-19 vaccine may be offered, if a risk assessment deems that the benefits of vaccination outweigh the potential risks for the individual (e.g., where the risk of severe outcomes of COVID-19 and/or risk of exposure to SARS-CoV-2 is high) or for the foetus/infant (in the case of pregnancy/breastfeeding) and if informed consent includes discussion about the insufficient evidence in these populations. These recommendations may change as more evidence on safety and/or efficacy/effectiveness in these populations becomes available. • Clinical trials assessing COVID-19 vaccines should continue to be encouraged to include individuals with potential vulnerabilities to disease related to biological (e.g., pre-existing medical conditions, frailty, pregnancy and breastfeeding, immunocompromised), and social (e.g., residence in long term care facilities or crowded/remote locations, belonging to a racialized population, occupation) factors to ensure that vaccine options are informed by robust safety, immunogenicity, and efficacy data as outlined in the NACI's guidance on Research Priorities for COVID-19 Vaccines to Support Public Health Decisions. Furthermore, NACI recommends the continuation of clinical trials and ongoing follow-up of participants for as long as it is ethically feasible to determine the level of immunity needed to prevent disease, duration of protection, efficacy in different sub-populations, and medium- and long-term safety. • In addition to ongoing vaccine pharmacovigilance activities in Canada with Phase 4 clinical trials and post-marketing studies, additional research and surveillance of COVID-19 vaccination, particularly in populations not currently included in clinical trials (e.g., pregnant, breastfeeding, immunosuppressed, seniors living in congregate care settings, children and adolescents), is recommended.	

Such information, collected but not examined, might have a considerable impact on the current halt or restrictions to vaccinations in many countries. For instance, the AstraZeneca vaccine is not recommended for use in Denmark, Cameroon, and Norway, or has age restrictions (ranging from 50 to 65 years) in Australia, Britain, Canada, France, Italy, and Spain, among other nations. These modifications have led several countries to alter their planned vaccination program timelines. However, if the risk is confined to females, this would not impact the rollout in half the population under 50 years of age. As many studies have noted, the risk of death from COVID-19 is more common than the risk from the rare complications of current vaccines, and even more so for males who have a higher risk of severe infection and death due to COVID-19 than females [7]. In fact, early data described above suggest that males have a lower risk of adverse outcomes following COVID-19 vaccination than females. The lack of sex-specific advice on this issue is therefore causing considerable limitations on vaccine programs across the globe.

3.3. SARS-CoV-2 vaccines in pregnant and lactating females

An additional aspect related to sex differences in the safety and efficacy profile of the vaccines is their use in specific periods across the female reproductive life course, such as pregnancy and post-partum lactation. As illustrated in Table 3, and in line with clinical research programs, pregnant and lactating females have been excluded from all initial COVID-19 vaccine trials due to the required safety standards for these populations [8,39,46]. Consequently, at the time of regulatory approval, it was unknown whether the SARS-CoV-2 vaccines would be safe to administer in pregnant or lactating females; thus, public and medical debates ensued on the use of these vaccines in these groups. Several regulatory bodies issued specific recommendations for such groups (summarized in Table 3), most of them allowing the use in pregnant females at high risk of infection, also considering that pregnancy has been associated with an increased risk for experiencing severe illness and death due to COVID-19 [26,48].

While the literature is currently in its infancy, several researchers have begun to explore the pregnancy and lactation outcomes of COVID-19 vaccines in the general population. For instance, a team of researchers at the CDC has recently published their preliminary findings on the safety of mRNA COVID-19 vaccines in 3958 pregnant individuals across all three trimesters of pregnancy who were enrolled using the v-safe COVID-19 Vaccine Pregnancy Registry [37,38]. Reports of adverse events in pregnant persons received by the Vaccine Adverse Event Reporting System (VAERS) were also analyzed. These researchers found

Table 4
Summary of data from peer-reviewed studies on pregnant and lactating persons.

Study	Vaccine(s)	Total vaccinated (N)	Pregnant (N)	Lactating (N)	Main findings
[18]	Pfizer-BioNTech (BNT162b2), Moderna (mRNA-1273)	131	84	31	• Pregnant women showed antibody response to the vaccines • Antibodies present in all umbilical cord blood and breastmilk
[51]	Pfizer-BioNTech (BNT162b2)	16	16	0	• Antibodies present in umbilical cord blood in all participants
[5]	Pfizer-BioNTech (BNT162b2), Moderna (mRNA-1273)	103	30	16	• Pregnant, lactating, and nonpregnant vaccinated participants showed antibody responses • Antibodies present in umbilical cord blood and breastmilk
[35]	Pfizer-BioNTech (BNT162b2), Moderna (mRNA-1273)	84	84	0	• Vaccinated women more likely to deliver vaginally and showed robust immune response • No evidence of vaccines causing placental lesions
[37,38]	Pfizer-BioNTech (BNT162b2), Moderna (mRNA-1273)	3958	3958	0	• Reported adverse events in pregnant women receiving COVID-19 vaccines similar to data pre-COVID • Miscarriage most commonly reported adverse outcome in vaccinated pregnant persons
[3]	Pfizer-BioNTech (BNT162b2)	92	92	N/A	• Vaccine causes strong antibody response in pregnant mothers • Antibodies transfer to foetus within 15 days of vaccine (first dose)

no evidence of safety signals, such that reported adverse outcomes were similar between groups of pregnant and nonpregnant females, and comparable to those in studies conducted prior to the COVID-19 pandemic. The most common adverse event reported to the VAERS among vaccinated pregnant females was miscarriage. Interestingly, compared to nonpregnant individuals, pregnant participants more frequently reported injection-site pain and, less frequently, headache, myalgia, chills, and fever.

Currently, several studies have been published exploring the effects of COVID-19 vaccines (i.e., the Moderna and Pfizer-BioNTech vaccines) in pregnant females (See Table 4). Overall, preliminary evidence indicates safe use in pregnant individuals and their offspring [3,5,18,24,25,30,35,37,38,51]. A recent study preprint reported that pregnant ($N = 84$) and lactating ($N = 31$) females who received one of the mRNA vaccines generated an immune response to SARS-CoV-2, with immunogenicity and reactogenicity comparable to that in nonpregnant participants ($N = 16$). This study also found that SARS-CoV-2 antibodies were present in the placenta and could be passed to newborns through breastmilk [18]. Similarly, Collier et al. found vaccine-elicited SARS-CoV-2 antibodies in umbilical cord blood as well as in the breast milk of vaccinated mothers in their sample of 103 females (including 30 pregnant and 16 lactating persons) [5]. Furthermore, a recent study found that the mRNA vaccines provide immunogenicity in pregnant persons and do not cause certain placental lesions which have come to be associated with SARS-CoV-2 infection [35]. Although these findings might seem promising, it should be noted that the sample sizes employed in all three of these studies were not sufficiently large to accurately estimate vaccine efficacy rates. Further high-powered studies are therefore needed to systematically assess vaccine efficacy and safety in pregnant and lactating persons.

The first randomized controlled trial examining the safety of the Pfizer-BioNTech and Moderna vaccines in pregnant females will soon be launching, and will enrol approximately 235 females across the United Kingdom. Moreover, two Canadian studies on pregnant and lactating females have recently begun, one of which is collecting information on the health of pregnant, vaccinated individuals, as well as examining women's attitudes toward the vaccines, and the other is collecting safety data from vaccinated, pregnant mothers. Such studies should provide pregnant and lactating persons with the necessary evidence to make an informed decision about getting the COVID-19 jab, as well as much needed reassurance about vaccine safety, which, up until now, have been largely lacking in this population.

4. Discussion and open questions

In this narrative review, we explored sex differences in COVID-19 vaccine response using the currently available data from vaccine safety and efficacy studies. We found that, while most studies included sex-disaggregated efficacy data, very few safety analyses were reported by sex. This was true for both reports from regulatory bodies (i.e., FDA, EMA, and Health Canada) and clinical trials. On the other hand, peer-reviewed studies investigating vaccine safety and efficacy outcomes in the general population reported overall higher rates of adverse reactions to the vaccines in females compared to males. Thrombotic events were also more common among female recipients of the AstraZeneca and Janssen vaccines. Finally, despite pregnant individuals not being originally included as participants in vaccine trials, evidence from recent peer-reviewed studies points toward the COVID-19 vaccines having similar effects in pregnant and lactating persons as in nonpregnant vaccine recipients. More high-powered, systematic studies are needed to further assess vaccine efficacy and safety outcomes in these populations.

The COVID-19 vaccine approval process has exposed a number of fundamental issues in drug development and clinical trials related to a disregard of individual patient characteristics, such as sex differences, in biological responses to drugs. It is important to note that the collection of such information would not delay the availability of medications at the bedside, as both sex and side effect data have already been collected—they have just not been reported. A vast body of evidence has indicated that a "one-size-fits-all" approach in medicine, which has informed most clinical research conducted in the past decades, is failing to address the heterogeneity in patient populations and the specific needs of patient subgroups [33]. The presence of clinical differences between males and females, which are well-established in several fields including vaccine biology, is a very clear example of patient heterogeneity that needs to be addressed.

Still, despite the efforts of numerous federal organizations calling for sex difference data to be reported (e.g., [9,44]), it has proven difficult to properly integrate considerations of sex differences in drug development. The emergence of rare side effects in young females and the lack of evidence-based medicine for pregnant and lactating persons, both experienced during the COVID-19 vaccine campaign, exemplify the need for a new approach.

The world has shown an incredible capacity for an accelerated COVID-19 vaccine development process. Even with this fast-tracked approach, the data on sex, therapeutic interventions, and side effects were all collected. We argue that this experience should be used as an opportunity to reiterate the importance of implementing regulatory mandates to report sex differences in both the safety and efficacy of new drugs and vaccines, with the goal of moving the field toward precision medicine. Some important aspects that must be considered include:

The Women's Brain Project is a non-profit organization studying sex and gender determinants of brain and mental health. Since 2016, WBP is fostering a global, multidisciplinary discussion on the topic of sex and gender considerations in clinical trials. A series of regulatory roundtables on women's health and precision medicine was launched by WBP in 2019. For more information: www.womensbrainproject.com

1. **Careful characterization of safety profile of drugs by sex during drug development**. Is a drug equally safe, in terms of frequency and types of events, in males and females? How does the frequency of adverse events compare with that in the general population (i.e., comparing frequency among young, vaccinated females with that of young females in the general population)? How should we make sure that female-specific risk factors (such as hormonal contraceptive or hormone therapy use) are factored into the analysis? Considering the well-known stronger effect of vaccines in females (e.g., higher frequency of adverse reactions), should the dosage of vaccines be tested separately in each sex?
2. **Regulatory analysis of safety and efficacy data by sex**. How can we increase the ability of the regulatory bodies to identify critical sex differences in efficacy and safety before they emerge in the pharmacovigilance stage (e.g., Zolpidem; [43])? What is the best approach to characterize rare events in subgroups (e.g., females)? Should sex-stratification of data be mandatory for drug approval?
3. **Ad hoc solutions for pregnant and lactating females**. Should these special populations be included in pivotal clinical trials? Alternatively, could specific studies or registries be designed for such populations?

By addressing the previous points, we can provide policy makers, regulators, and drug developers with tools to address and possibly prevent issues such as those that have emerged during the COVID-19 vaccination campaign.

5. Conclusion

It is well known that females generally respond differently than males to many vaccines and experience more side effects, which may be due in part to their heightened immune response. In this review, we show that this trend is also true for the novel SARS-CoV-2 vaccines. However, despite numerous calls for the reporting of sex-disaggregated data in clinical trials, considerations of sex differences in drug development have generally been overlooked. In writing this review, we hope to spark a discussion in the field surrounding the systematic incorporation of sex-based analyses in drug development, reporting of sex-disaggregated clinical data by regulatory bodies, and inclusion of pregnant and lactating individuals in clinical trials, with the overarching goal of achieving precision medicine.

CRediT authorship contribution statement

Adelaide Jensen: Investigation, Writing – original draft, Writing – review & editing, Visualization. **Masha Stromme:** Writing – review & editing. **Shayda Moyassari:** Investigation, Writing – review & editing, Visualization. **Antonella Santuccione Chadha:** Writing – review & editing. **Maria Carmela Tartaglia:** Writing – review & editing. **Cassandra Szoeke:** Writing – review & editing. **Maria Teresa Ferretti:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing, Project administration.

Declaration of Competing Interest

M.T.F is the Chief Scientific Officer of the Women's Brain Project and receives consulting fees from Eli Lilly and Company; however, the latter does not interfere with her involvement in the current project.

A.S.C. is the Chief Executive Officer of the Women's Brain Project and is also currently an employee of Biogen International. Any opinions expressed within the content of this article are solely the author's and do not reflect the opinions and beliefs of her employer.

The authors declare no other competing interests.

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