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Existing evidence on sex-based differences in safety and effectiveness of COVID-19 vaccines: a narrative review

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Summary. Sex-based differences are expected both in vaccine effectiveness (VE) and adverse events (ADE) for COVID-19 vaccines, with higher levels of humoral immune response and a general higher report of ADEs from females, on the basis of different genetic background and different innate and adaptive immune response. In the EU, COVID-19 vaccines process of approval relied on robust RCTs and disclosed an overall prevalence of non-systemic ADE in female, meanwhile no differences were found for vaccine efficacy. However, rare events and long-term efficacy (effectiveness) can only be detected by studies from the post approval phase, where a general paucity of studies designed to assess sex-based differences is well known. The number of articles generated during the COVID-19 pandemic was impressive but still, we found difficult to draw conclusions about sex-based differences in ADE and VE due to the fragmentation and heterogeneity of studies where only 33.6% had a balanced sex representation, with an overrepresentation of women in 50 studies and an underrepresentation in 25 studies. This review evaluated the existing evidence on sex-based difference in VE and ADEs for COVID-19 vaccines and assessed whether there was an equal representation of females and males and if the outcome of interest for each study was analysed by sex and/or gender.

Keywords. Sex, gender, COVID-19 vaccine, vaccine effectiveness, adverse events.

Introduction

COVID-19 vaccines approval occurred at an unprecedented speed worldwide and in less than 12 months three vaccines were available in the EU and the US.[1-3] Despite the short period of time, approval came with the most rigorous traditional approach supported by large randomized clinical trials (RCTs).[4-6] Albeit not designed to specifically detect sex-based differences, these studies had a good gender balance and sex differences were analysed and submitted to the regulatory authorities for assessment. According to the European Public Assessment Reports (EPARS)[7-9] an overall prevalence of non-systemic adverse events (ADE) was reported for female, meanwhile no differences were found for vaccine efficacy.[7-9] However, even the most comprehensive RCT cannot detect rare events nor can predict long-term effectiveness, such as duration of protection from contagion or disease severity (i.e., hospital and ICU admission or death). Moreover, in a pandemic outbreak, variants might occur and additional evidence need to be constantly generated to verify the initial safety and efficacy claims. After approval, vaccine effectiveness (VE) rather than efficacy is the most appropriate definition.[10,11]

Therefore, important data is expected to be gathered in the post approval phase when the vaccines are used in the general population and studies are carried out including the real-world evidence (RWE).[12] To detect ADEs, a well-developed surveillance system (pharmacovigilance) provides a fast collection of reported ADEs easing identification of safety signals and triggering further evidence generation, guided by the regulatory authorities. Safety re-assessment will enable public health decision where restrictions or recommendations about vaccines usage can be issued.

Differently from the safety assessment, effectiveness does not benefit from a well-established network, nor from a consolidated methodology adequate to fill the knowledge gap remaining after the approval.[13] The approval process addressing efficacy follows stringent methodology and relies on RCTs, meanwhile effectiveness is assessed with different and sometime controversial methodology.[14-18] Typically, VE is generated from studies promoted by the scientific community or by regional authorities.[12] Heterogeneity in the approach is therefore to be expected at any level, study design, outcomes measured, statistical methodology, sample size and sex balance.[12]

Equally, it is well known the general paucity of studies designed to assess sex-based differences.[19] Sex-based differences such genetic background and immune response - both innate and adaptive- have been described as cause for male and female difference in response to vaccines both in terms of VE and ADE,[20-22] with higher levels of humoral immune response and a general higher report of ADEs from females.[23,24] Recently, Vulpis *et al* reported a significant difference in the uptake between males and females of the lipid nanoparticles, a component of the extensively used mRNA COVID-19 vaccine, suggesting possible implication for sex-base differences in VE.[25]

In light of the above, the aims of this study were to evaluate existing evidence on sex-based differences in VE and ADEs for COVID-19 vaccine; to assess whether there was an equal representation of females and males and if the outcome of interest for each study was analysed by sex and/or gender.

Methods

We searched PubMed to collect articles on the safety and effectiveness of COVID-19 vaccines in male as compared to females published between 2020 and 2022. Boolean operators AND/OR were used in the search machine to combine search terms. Medical Subjects headings (MeSH) terms used included (“COVID-19” OR “SARS-CoV-2”) AND (“vaccine” OR “vaccination”). PubMed was searched using the following search string:

(((((sex) OR (male)) OR (female)) OR (gender)) AND (((((efficac*) OR (effectiven*)) OR (toxicity)) OR (safe*)) OR (adverse adj2 event*))) AND (((vaccine) OR (vaccination)) OR (vaccin*))) AND ((SARS-COV-2) OR (COVID-19))

Covid-19	**Efficacy/safety**	**Gender**	**Vaccine**
Sars-cov-2	Effectiveness	Sex	Vaccination
	Safety	Male	Vaccin*
	Toxicity	Female	
	Adverse events		
283,390	3,233,616	12,909,744	482,800
Tot 1,624			

Key parameters of the research

Duplicates were deleted and a first screening by titles and abstracts to assess the relevance of the articles was conducted, followed by full-text review and data extraction. The following inclusion and exclusion criteria were applied. Inclusion criteria were the following: COVID-19 vaccines; articles written only in English; peer reviewed articles; articles with vaccinated subjects aged >12 years old and above; any type of vaccines and vaccine administration (i.e., first, second and/or third doses); articles focused on the general population; articles including both sex and/or gender; articles including healthcare workers. Exclusion criteria were the following: COVID-19 treatments; articles where the vaccinated subjects were aged <12 years old and below or restricted only to specific population such as older population (i.e., articles focusing only on subjects aged 75 and above), pregnant women, people with underlying conditions (i.e., diabetes) or rare diseases (i.e., sclerosis multiple and rheumatoid arthritis); existing reviews, systematic review, case reports; articles where sex and/or gender was adjusted for ~~as~~ a potential bias or risk factor. We decided to include articles where the studied population were healthcare workers in light of three considerations: being the first population to be vaccinated, there were many early studies that enrolled healthcare workers to evaluate safety and effectiveness of COVID-19 vaccines; we expected a more organized setting (e.g. hospitals), hence a better detection of our outcomes of interest through diagnostic tools and robust follow-up; we considered healthcare workers as an heterogeneous group of women and men of different age and possible different underlying conditions, hence a good surrogate sample of the general population.

The terms “sex” and “gender” and “sex and/or gender” were searched considering that studies either used these terms interchangeably or used the term “gender” to identify how many men and women were included in the study population and the term “sex” to identify how many female and male subjects were evaluated and/or to report “sex and/or gender” differences in their findings. Therefore, we included both terms in our research and hereafter refer to sex.

For each article we extrapolated data regarding the main characteristics of the study population, such as sample size, country, and “male/female ratio”. When sample size was not clearly stated we extrapolated this information from baseline tables/figures or study end points. In addition, we identified the study design, when not clearly stated, and verified whether methodology (i.e., statistical analysis) was used to assess sex-specific difference. Finally, we reported both study limitation identified by the authors and those we assessed.

In terms of outcomes of interest, we assessed efficacy and effectiveness and reclassified as study evaluating vaccine effectiveness (VE) defined either by antibodies titres and/or response, PCR-positivity or positive test, hospital admission and death and/or mortality rate; while those assessing safety described as ‘’vaccine side effects’’, ‘’vaccine adverse events’’, ‘’vaccine adverse effects’’ and ‘’toxicity’’ were reclassified as studies evaluating adverse events (ADEs). After this reclassification, we examined whether studies reported VE and ADEs by sex and whether sex-based differences were found regardless the type of vaccine.

We performed a narrative review and synthetized the collated evidence according to the PICO (Population; Intervention; Comparison, Outcome) framework and the two outcomes of interest were reported by study design.[26]

Results

We found 101 articles meeting our inclusions criteria (Figure 1), of these 41 (40.6%) assessed vaccine effectiveness (VE) and 45 (44.5%) adverse events (ADEs) following administration of one, two or three (booster) doses of any type of COVID-19 vaccines. The remaining 15 articles (14.8%) assessed both VE and ADEs, hence these may appear twice in Tables 1 and 2, based on the reported findings regarding sex-based differences.

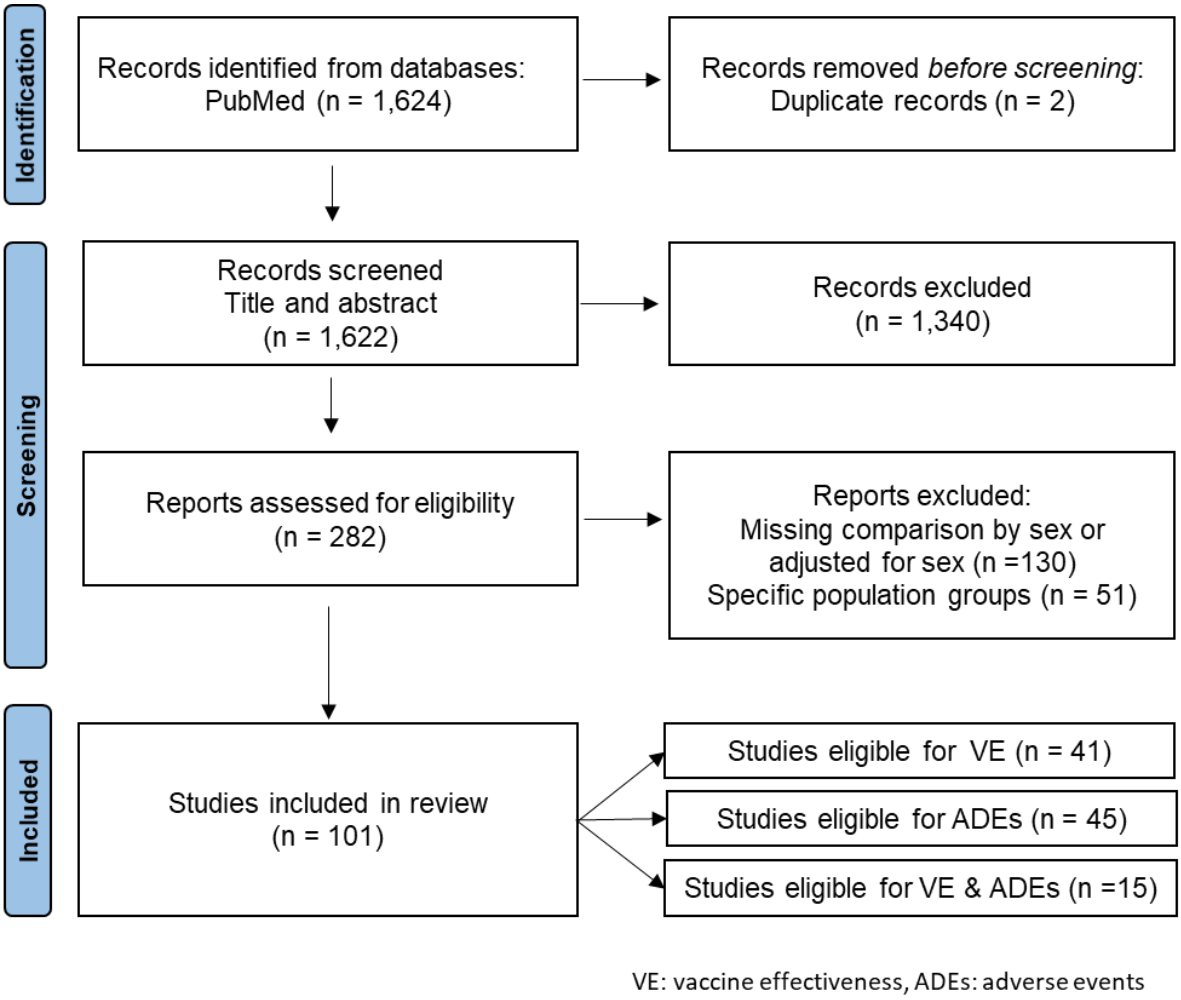

Figure 1. PRISMA flowchart

Adverse events (ADEs)
There were 60 articles evaluating ADEs following first, second or third (booster) dose of any COVID-19 vaccine, these are reported in Table 1.

Table 1. Summary of studies assessing ADEs following COVID-19 vaccination

Author, year	Study design	Country	Sample size (*n*)	Outcome of interest	Limitations
Abraham et al 2022[27]	cross-sectional study (retrospective)	Canada	1,707	More carditis (myo-peri-carditis) in M than F	F 0.13: M 0.87; retrospective; passive post-marketing surveillance data; reporting bias
Al Khames Aga et al 2021[28]	cross-sectional study	Iraq and Jordan	1,736	no difference in ADE	F 48.4%: M 51.6%; small sample size; no statistical analysis to support results is reported; no follow-up
Alharbi et al 2022*[29]	cohort study (prospective)	Saudi Arabia	18,543	No reports of ADE by sex	F 40%: M 60%; single centre; single dose
Almohaya et al 2022[30]	cross-sectional study (retrospective)	Saudi Arabia	71,221	More ADE (acute unsolicited adverse events following) in F than M	F 44%: M 56%; retrospective; short follow-up
Al Bahrani et al 2021[31]	cross-sectional study	Saudi Arabia	1,592	More ADE ((pain at the site of injection, skin rash and fever) in M than F	F 30%: M 70%; phone call survey risk of recall bias; short follow-up
Arora et al 2022*[32]	cross-sectional study (retrospective)	India	2,051	More ADE in F than M	F 49.63%: M 50.37%; retrospective; online survey;
Baydar et al 2022[33]	cross-sectional study	Turkey	1,628	More ADE in F than M	F 64%: M 36%; small sample size; online questionnaire; healthcare workers
Benjamanukul et al 2022*[34]	cohort study	Thailand	185	No reports of ADE by sex	F 83.2%: M 16.8%; small sample size; no statistical analysis to support results is reported
Borobia et al 2021*[35]	RCT (randomized controlled open-label phase 2, multicentre)	Spain	676	More ADE (local and systemic reactions) in F than M	F 57%: M43%; no statistical analysis to support results is reported; no follow-up; small sample size; interim report
Borroni et al 2021[36]	cross-sectional study (prospective)	Italy	3,659	More ADE (local and systemic reactions) in F than M	F 71%: M 29%; males with more BMI and smokers; self-reported data healthcare workers
Chapin-Bardales et al 2021[37]	cross-sectional study (survey report with follow-up)	US	4,717,908	More ADE in F than M	F >64%: M<31%; reporting bias; no statistical analysis to support results is reported
Chouchana et al 2022[38]	case-control study (observational, retrospective, disproportionality study)	International	26 M reports 2,277 cases	More myocarditis in M than F	F:M balanced; retrospective; pharmacovigilance data base self-reporting data;

Dag Berild et al 2022[39]	case-control study (self-controlled, individual-level data)	Norway, Finland, and Denmark.	265,339	More coronary artery diseases (CV diseases, cerebrovascular and coronary artery diseases) in M	F 43%: M 57%; surveillance data; no statistical analysis to support results is reported; no follow-up
Dar-Odeh et al 2022[40]	cross-sectional study (questionnaire)	Jordan and Saudi Arabia	498	no difference in ADE (long-term)	F 70%: M 30%; small sample size; healthcare workers; no statistical analysis to support results is reported
Ebinger et al 2021[41]	cohort study (prospective)	US	1,632	More ADE (fever, chills, fatigue or malaise, headache, swollen lymph nodes, GI symptoms) in F than M	F 67%: M 33%; medium sample size; self-reported information; survey; healthcare workers
Ella et al 2021*[42]	RCT (Randomised, double-blind, placebo-controlled, multicentre, phase 3 clinical trial, interim report)	India	25,798	No reports of ADE by sex	F 32%: M67%; interim report, short follow-up
Ganczak et al 2022*[43]	cross-sectional study	Poland	200	More ADE in F than M	F84%: M 16%; small sample size; self-reported data; teachers
Ganesan et al 2022[44]	cross-sectional study (based on online survey)	United Arabic Emirates	1878	More Ade in F than M	F28%: M72%; questionnaire on voluntary basis; small sample size to assess ADE
García-Grimshaw et al 2021[45]	cohort study (prospective observational)	Mexico	704,003	More ADE in F than M	F 26%: M74%; no statistical analysis to support results is reported
Gianfredi et al 2021[46]	cross-sectional study	Italy	31,4664	More ADE in F than M	F 48.5%: M 51.5%; administrative data routinely collected
Halperin et al 2022*[47]	RCT (double-blind phase 3 placebo controlled)	international (argenitina, chile, mexico, pakistan, russia)	37,780	No reports of ADE by sex	F 30%: M 70%; short follow-up; interim report only after 1 dose of vaccine
Iguchi et al 2021[48]	cross-sectional study	Japan	181	More ADE (anaphylaxis and anaphylactoid symptoms) in F than M	F 94%: M 6%; small sample size; no statistical analysis to support results is reported
Izak et al 2022*[49]	mixed design, both cross-sectional and cohort study	Israel	61	More ADE ((Injection site pain, fatigue and fever were the most common Symptoms) in F than M	F73.8%: M 26.2%.; small sample size; no follow-up; no statistical analysis to support results is reported; short follow-up; healthcare workers

Izumo et al 2021*[50]	cross-sectional study	Japan	983	More ADE in F than M	F 75%: M 25%; no follow-up; single-centre; healthcare workers
Jarynowski et al 2021[51]	cohort study (retrospective)	Russia	11,515	More ADE (of Sputnik and comparison with ADE of the other COVID-vaccines) in F than M	F59.1%: M 40.9%; Community-based surveillance self-reported data; reporting bias;
Kant et al 2022[52]	cohort study (prospective)	Netherlands	48,236	More ADE in F than M	F>66%: M<28%; no statistical analysis to support results is reported;
Kaplan et al 2022[53]	cohort study	US	113	More ADE (allergic reaction) in F than M	F:M not known; small sample size; no statistical analysis to support results is reported; small sample size;
Kelliher et al 2022*[54]	Cohort study (prospective)	US	149	no difference in ADE	F75.8%: M 24.2%; small sample size; self-reporting survey; recall bias
Klein et al 2021[55]	cohort study	US	11.8M	More ADE (to evaluate association with Vaccination and 23 selected ADE) anaphylaxis in F and more carditis in M	F46%: M 54%; no statistical analysis to support results is reported
Lai et at 2022[56]	case-control study	Hong Kong	2.3 M vaccine 1 3.5M vaccine 2 controls 1,693 cases 160	More M had carditis than F	37.5F%: M 62.5%; main analysis stratified for sex; risk of underreporting of carditis
Le Vu et al 2022[57]	case-control study (matched)	France	Case 1,612 controls 16,120	More M had myocarditis; more F had pericarditis	F 20.5%: M 79.5% (cases), F 38.7%: M 61.3% (controls); short follow-up; risk of underreporting due to nature of report
Mahallawi et al 2021*[58]	cross-sectional study	Saudi Arabia	365	More ADE in F than M	F16.2%: M 83.8%; small sample size; online self-reported questionnaires; adjusted for sex in the logistic regression model
Manomaipiboon et al* 2022[59]	cohort study (prospective, observational)	Thailand	60	No reports of ADE by sex	F 35.2%: M 64.8%; single-centre; interim analysis small sample size; healthcare workers

Marchevsky et al 2022*[60]	mixed design, RCT (single-blind randomised controlled, to assess VE) and cross-sectional study (ADE)	Brazil – UK	788 ADE	More ADE in F than M	F 55.7%: M 44.3% no limitation section; health and social care workers
Maruyama et al 2022[61]	cross-sectional study (prospective)	Japan	374	More ADE in F than M (general fatigue, chills, muscle and joint pain, headache, skin pain, erythema)	F 60%: M 40%; small sample size; healthcare workers
Massari et al 2022[62]	cohort study (observational, multiregional)	Italy	2,861,809	More carditis in M than F with mRNA-1273, no difference in carditis with BNT162b2	F33%: M 67%; short follow-up; different age profile
Matzuzaki et al 2022[63]	cross-sectional study	Japan	581 27 cases	More ADE (haematuria) in F than	F 18%: M 82%; questionnaire on web-based survey; small sample size
Mazur et al 2021[64]	cross-sectional study	multicentre; multi-country	223	More M presented earlier with ADE (orofacial) than F (1+2 dose), F had longer duration of ADE	F 74%: M 26%; small sample size; short follow-up; web-based questionnaire; preliminary results
Menni et al 2021[65]	cross-sectional study (prospective)	UK, US, Sweden	627 383	More ADE in F than M	F 61%: M 38%; observational collider bias; assessed only short-term ADE
Mohakuda et al 2021[66]	cohort study (multicentre, observational)	India	268	More ADE (incidence or systematic effect within 7 days post vaccination) in M than F	F 25.4%: M 74.6%; observational; small sample size; short follow-up; healthcare workers
Nachtigall et al 2022[67]	cohort study	Germany	8,375	More ADE (and loss of working day (reactogenicity) in F than M	F 74%: M 26% voluntary self-reporting; healthcare workers
Namiki et al 2022[68]	cross-sectional study	Japan	1,756	More ADE in F than M	F:M balanced; survey-based; single-centre; healthcare workers
Poudel et al 2022[69]	cross-sectional study	Nepal	637	More ADE in F than M	F 30.4%:M 69.6%; small sample size; high risk and healthcare workers
Presby et al 2022[70]	cross-sectional study (retrospective)	US	69,619	More ADE in F than M	F:M not known; retrospective; lack placebo control; not adjusted for 95%CI around estimated marginal means

Quiroga et al 2021[71]	cross-sectional study	Spain	708	no difference in ADE	F 65%: M 36%; survey-based analysis; self-reported; specific population (nephrologist)
Ripabelli et al 2022[72]	cross-sectional study	Italy	404	More ADE in F than M	F 61.5%: M 38.5%; small sample size; self-reported data not inference of casuality for short-term analysis; healthcare workers
Rolfes et al 2022[73]	cohort study (prospective)	Netherlands	22,184	More ADE in F than M	F:M balanced: web-based; selection bias; data only on vaccinate people
Rosenblum et al 2021[74]	cross-sectional study (surveillance data)	US	12.6 M	More ADE ((Guillain Barre syndrome, thrombosis with thrombocytopenia syndrome and myocarditis) in M than F	F 53%; M 47%; report on surveillance data; no correlation measurement; no statistical analysis to support results is reported
Sachdeva et al 2022[75]	cross-sectional study	India	1,145	More ADE in F than M	F 75%: M 25%; small sample size; anonymous survey via questionnaire self-reported data; no follow-up; limited statistical analysis
Saita et al 2022[76]	cross-sectional study	Japan	3,254 dose 1 3,165 dose 2	More ADE in F than M	F65%: M 35%; online survey; self-reported; single-centre
Shasha et al 2022[77]	cohort study (observational)	Israel	729,851	More ADE (Bell's palsy, Guillain Barre syndrome, herpes zoster and symptoms of numbness or tingling sensation) in F than M	F:M balanced; short follow-up; observational historical
Tawinprai et al 2022*[78]	cohort study (prospective)	Thailand	796	No reports of ADE by sex	F 65%: M 35%; observational; single-centred; timing of anti-RBD antibodies measurement in each participant was different

Terentes-Printzios et al 2022[79]	RCT (Sequence-randomized sham-controlled assessor-blinded 2period crossover design study)	Greece	32	no difference in ADE (FMD (brachial artery flow-mediated dilatation and), PWV (carotid-femoral pulse wave velocity) to assess myocardial function), aortic augmentation index corrected for a heart rate of 75 beats per minute (AIx@75)	F35%: M65%; very small sample size; no statistical analysis to support results is reported
Ughi et al 2021[80]	cross-sectional study	Italy	7014	More ADE in F than M	F 61%: M 39%; retrospective; short follow-up
Undugodage et al 2021[81]	cross-sectional study (observational, multicentre)	Sri Lanka	4,478	More ADE in F than M	F 67%: M 33%; observational; self-reports; healthcare workers
Vigezzi et al 2021[82]	cross-sectional study	Italy	2,659	More ADE in F than M	F 72.9%: M 27.1%; survey-based, reporting bias; single-centre; missing long-term surveillance
Warkentin et al 2022[83]	cohort study (comparative observational)	Germany	9,146	More ADE (short- (14-19 days) and long- (40-56 days) term effects after boost vaccine) in F than M	F>M (multiple surveys); observational; self-reporting bias; web-based survey
Yap et al 2022[84]	cross-sectional study (retrospective)	Singapore	34 cases 7,183,889 doses (1,298,117 one dose 2,942,886 two doses)	More M had myocarditis than F	F:M not known; surveillance registry, potential for underreporting
Zhang R. et al 2022*[85]	non-RCT (Open label)	Hong Kong	189	More ADE ((headache, nausea, muscle pain, joint pain, injection site pain) in F than M	F 64.2%: M 35.8%; small sample size; not randomized; no statistical analysis to support results is reported;
Zhang M.X. et al 2021[86]	cross-sectional study	Hong Kong	1526	More ADE in F than M	F 79.3%: M 20.7%; self-administered online survey, reporting bias; single-centre;

RCT: randomized clinical trial; non-RCT: non-randomized CT; ADEs: adverse events; F:M: Females-Males ratio when balanced means it was evenly matched F 50%: M 50%; *these studies evaluated both ADEs and VE, in this table only findings on VE are reported.

There were six CTs evaluating ADEs, five of these were RCTs, one was a non-randomised CTs. Marchevsky *et al* in a single-blind RCTs found females participants were twice as likely as males to report any systemic reaction after a first dose (OR 1.95; 95%CI 1.37-2.77).[60] The remaining trials did not report evidence of difference by sex in ADEs.

There were 18 cohort studies assessing ADEs, seven of these found females more likely to report ADEs such as general fatigue, chills, fever, shallowness of site of injection than their males' counterparts following vaccination.[41,45,51,67,73,77,83] For example, a large cohort from the US reported female sex to be associated with greater odds of appreciable symptoms such as fevers or chills, fatigue, after both dose 1 (OR 1.75, 95% CI 1.19-2.51) and dose 2 (OR 1.76, 1.28-2.42) than males.[41] While a large cohort from Israel found higher odds for females in developing mild non-specific neurological complains of numbness and tingling than males (OR 0.48, 95%CI 0.45-0.52, p <0.001).[77] There were two small sample sized studies reporting more ADEs in males than females (Kaplan *et al* reported higher incidence of dermatologic non-urticarial reactions in men p = 0 .004 and Mohakuda *et al* reported the odds for men to develop systemic effects were 2.08 times higher than women 95%CI 1.170-3.710, p = 0.013).[53,66] Massari *et al* found increased risk in males after both dose 1 and 2 with 3.8 and 8.8 excessive cases per 100,000 vaccinated, respectively in a subgroup analysis by sex, and a risk of excessive cases of myo- or peri-carditis being the same between male and females after 7 days following second dose of vaccination.[62] The remaining nine studies did not report evidence of difference by sex in ADEs.

ADEs were also assessed through four case-control studies, three evaluated the risk for carditis, either myo- or peri-carditis,[38,56,57] two of which showed a significant increased risk to develop myocarditis in young males compared to females (Chouchana *et al* reported males had an increased risk of myocarditis reporting ROR 9.4, 95%CI 8.3-10.6 and of pericarditis reporting ROR 3.7, 95% CI 3.2-4.2 and Lai *et al* reported OR was 4.68, 95% CI 2.25 to 9.71 for males and OR 2.22, 95% CI 0.57 to 8.69 for females).[38,56] Dag Berlind *et al* found an increased risk for coronary artery disease in males, while coagulation disorders and cerebrovascular disease were more evenly balanced across the sexes.[39]

There were 32 cross-sectional studies, of these 20 found females more likely than males to report ADEs following vaccination mainly through online/telephone-based surveys; these studies varied in sample size and different statistical analysis but reached the same conclusion. On the contrary, two studies found males to be more likely to report reactions than females, one reported more ADE (76.7% vs 23.3%; p = 0.001)[31] and one reported an increased risk of developing myocarditis and/or pericarditis in males aged 18-29 than females while assessing two types of vaccines (RR 4.72, 95% CI 3.09-7.39, p <0.001 vs Female RR 2.67, 95% CI 1.28-5.78, p = 0.01).[27] There was one study reporting surveillance data for the US showing a higher case incidence of Guillain-Barré Syndrome and myo-carditis in males, whist a higher case incidence for thrombosis with thrombocytopenia in females.[74] The remaining eight studies did not report evidence of differences in ADEs based on sex.

To summarise, there were 29 studies reporting higher ADEs in females than males (one RCTs, seven cohort, one case-control and 20 cross-sectional); eight studies reported higher ADEs in males than females (zero RCTs, three cohort, three case-control and four cross-sectional); one case-control reported no difference and 22 did not report evidence of sex-based differences (five RCTs, nine cohort, zero case-control and eight cross-sectional). Sex representation were balanced in 13 studies (21.6%), females were overrepresented in 28 studies and underrepresented in 16, three studies did not report F/M ratio.

Vaccine effectiveness (VE)

A total of 56 studies evaluated VE either through antibodies response or antibodies titres or specific antibodies such as neutralizing and anti-Spike protein or via PCR-test or evaluating breakthrough infection, hospitalization admission or mortality rate (Table 2).

Table 2. Summary of studies assessing VE following COVID-19 vaccination

Author, year	Study design	Country	Sample size (n)	Outcome of interest	Measure	Limitations
Abu Jabal et al 2021[87]	cohort study	Israel	514	no statistically significant difference in VE	antibodies titres anti-spike IgG levels after 1 dose	F 65%: M 35%; no statistical analysis to support results is reported; short follow-up
Ai et al 2022[88]	non-RCT (open-label single centre, non-randomized)	China	103	no difference in VE	neutralizing antibodies titres (RBD) of booster dose	F 60%: M 40% in both booster and control; non randomized, preliminary report small sample size
Alharbi et al 2022*[29]	cohort study (prospective)	Saudi Arabia	18,543	VE higher in F than M	breakthrough infection	F 40%: M 60%; single centre; single dose
Arora et al 2022*[32]	cross-sectional study (retrospective)	India	2,051	VE higher in F than M	breakthrough infection	F 49.63%: M 50.37%; retrospective; online survey; no statistical analysis to support results is reported
Barda et al 2021[89]	ecological study (observational simulation of a target trial)	Israel	1.158,269	no difference in VE	III dose of vaccine via hospital admission and COVID-19-related death	F51%:M49%; Exclusion of young individuals (<40 years)
Behera et al 2022[90]	case-control study (test-negative)	India	670	no statistically significant difference in VE	PCR-confirmed SARS-COVID-19 infection	F <45%: M >55%; single-centre; no measure of antibodies titres
Benjamanukul et al 2022*[34]	cohort study (longitudinal prospective)	Thailand	185	no difference in VE	antibodies titres seroconversion following 1 and 2 vaccine doses	F 83.2%: M 16.8%; small sample size; no statistical analysis to support results is reported
Björk et al 2022[91]	cohort study	Sweden	805.741	no difference in VE	estimated incidence rates of COVID-19	F 80%: M 20% vaccinated vs F52%: M 48% unvaccinated; main analysis adjusted for sex
Borobia et al 2021*[35]	RCT (controlled open-label phase 2, multicentre)	Spain	676	VE higher in F than M	Antibodies titres (first anti-spike, then neutralizing)	F 57%: M43%; no statistical analysis to support results reported; no follow-up; small sample size; interim report

Braeye et al 2022[92]	cohort study	Belgium	931.518	VE higher in M than F	estimates transmission of infection	F:M not known; transmission evaluated via model and contact tracing
Brehm et al 2021[93]	cross-sectional study (longitudinal)	Germany	872	no difference in VE	antibodies titres	F 78%: M 22%; single-centre; healthcare workers
Butt et al 2021[94]	case-control study (test-negative)	US	54.360	no difference in VE	prevention of infection	F 16.4%: M 83.6%; short follow-up; no statistical analysis to support results reported
Chiarella et al 2022[95]	cohort study (observational)	US	805	VE higher in F than M	antibodies response	F 52.9%: M 47.1%; main analysis adjusted for sex; no assessment of neutralizing antibodies; single-centre
Chodick et al 2021[96]	cohort study (comparative observational)	Israel	503.875	no statisticall y significant difference in VE	PCR-confirmed SARS-COVID infection	F:M balanced; short follow-up;
Choi et al 2022[97]	cohort study (prospective)	South Chorea	249	VE higher in F than M	neutralizing antibody and spike protein-IgG antibody titres	F 58%: M 42%; single-centre; healthcare workers;
Dashdorj et al 2021[98]	cohort study (retrospective, observational)	Mongolia	196	VE higher in F than M	antibodies response	F:M balanced retrospective, limited analysis to assess sex as a risk factor, small sample size
Ella et al 2021*[42]	RCT (double-blind, placebo-controlled, multicentre, phase 3 clinical trial, interim report)	India	25,798	No difference in VE	laboratory confirmed RT-PCR-positive; symptomatic COVID-19 (any severity) at least 14 days after the second dose	F 32%; M67%; interim report, short follow-up
Fabiani et al 2022[99]	cohort study (retrospective)	Italy	33.250,34 4	no difference in VE	infection and severe covid-19 (admission to hospital or death)	F:M balanced; main analysis adjusted for sex; limited analysis to assess sex as a risk factor
Ferenci et al 2022[100]	cohort study	Hungary	497	no statisticall y significant difference in VE	neutralizing antibodies titres (RBD-specific Ab)	F:M not known; no statistical analysis to support results is reported

Ferrari et al 2021[101]	cohort study (multicentre prospective)	Italy	4.290	VE decreasing more rapidly in M than F	antibodies response	F >60%: M <40%; short follow-up;
Flego et al 2022[102]	cohort study (prospective)	Italy	11	differences in F and M	Features of the platelet-immune crosstalk	F 54%: M 46%; short follow-up; small sample size
Florea et al 2022[103]	cohort study (observational prospective 5-year)	US	1.854,008	no difference in VE	infection and severe disease	F 54.5%: M 45.5%; interim report; follow-up stopped before omicron variant
Fraley et al 2021[104]	ecological study (prospective)	US	194	no difference in VE	antibody response (neutralizing, spike IgG) in seropositive and seronegative	F: M not known; no statistical analysis to support results is reported; small sample size
Fujigaki et al 2022[105]	cohort study	Japan	219	VE higher in F than M	neutralizing antibodies response (RBD-IgG)	F 68.5%: M 31.5%; small sample size
Ganczak et al 2022*[43]	cross-sectional study	Poland	200	No reports of VE by sex	antibodies response (anti-RDB)	F84%: M 16%; small sample size; self-reported data; teachers
Glampson et al 2021[106]	cohort study (retrospective)	UK	2.183,939	no difference in VE	positive swab	F:M balanced; lack of robust control groups; evaluated only first dose (early study); test might lack sensitivity/specificity
Halperin et al 2022*[47]	RCT (double-blind phase 3 placebo controlled)	international (argenitina, chile, mexico, pakistan, russia)	37,780	VE higher in M than F	prevention of symptomatic real-time PCR positive within 28 days post 1 dose of vaccine	F 30%: M 70%; short follow-up; interim report only after 1 dose of vaccine
Hu et al 2022[107]	cross-sectional study	China	476	no statistically significant difference in VE	severe illness in Delta variant-infected patients	F >50%: M <50%; amin analysis adjusted for sex; no statistical analysis to support results is reported

Izak et al 2022*[49]	mixed design, both cross-sectional and cohort study	Israel	61	no difference in VE	anti-SARS-CoV-2 antibody levels after being 2 doses of vaccination	F73.8%: M 26.2%.; small sample size; no follow-up; no statistical analysis to support results is reported; short follow-up; healthcare workers
Izumo et al 2021*[50]	cross-sectional study	Japan	983	no reports of VE by sex	antibodies titres	F 75%: M 25%; no follow-up; single-centre; healthcare workers
Kelliher et al 2022*[54]	Cohort study (prospective)	US	149	no difference in VE	antibodies response, total antibody assay difference between 2 vaccines (Pfizer and Moderna)	F75.8%: M 24.2%; small sample size; self-reporting survey; recall bias
Kondo et al 2022[108]	cross-sectional study	Japan	996	VE higher in F than M	antibodies response	F:M balanced; short follow-up
Levin et al 2021[109]	cohort study (6-month longitudinal prospective)	Israel	4,868	VE higher in F than M	antibodies titres (anti-spike IgG and neutralizing)	F:M balanced; single-centre; healthcare workers
Li et al 2021[110]	case-control study (test-negative)	China	366	VE higher in F than M	PCR- test	F:60.8%: M 39.2% in both groups; main analysis stratified by sex; disproportion between cases and controls
Liu et al 2022[111]	cohort study (observational retrospective, six cohort)	US	11. 156	VE higher in F	breakthrough infection rate to evaluate risk factors	F<49%: M>51%; single-centre in NYC; higher rate of comorbidities and older age
Lo Sasso et al 2022[112]	Cohort study (observational)	Italy	1,013	VE higher in F than M	antibodies response (anti-spike protein) after booster	F55.3%: M 44.7%; single-centre; no neutralizing antibody testing
Lopera et al 2022[113]	cohort study (prospective longitudinal with 6 months follow-up)	Colombia	60	VE higher in F than M	antibodies titres (neutralizing)	F:M balanced; no statistical analysis to support results is reported; small sample size
Lusvarghi et al 2022[114]	cohort study (prospective)	US	39	no difference in VE	antibodies titres (neutralizing)	F 64.1%: M 35.9%; short follow-up; no statistical analysis to support results is reported; small sample size; healthcare workers

Mahallawi et a2021*[58]	cross-sectional study	Saudi Arabia	365	No reports of VE by sex	antibodies titres (anti-S protein)	F16.2%: M 83.8%; small sample size; online self-reported questionnaires; adjusted for sex in the logistic regression model
Mallow et al 2022[115]	cohort study (retrospective)	US	13,203	no difference in VE	PCR-test & acute respiratory infections symptoms identified via ICD-10 code hospital	F 51.5%: M 48.5%; retrospective; no statistical analysis to support results is reported
Manomaipiboon et al 2022*[59]	cohort study (prospective, observational)	Thailand	60	no difference in VE	antibodies response	F 35.2%: M 64.8%; single-centre; interim analysis small sample size; healthcare workers
Marchevsky et al 2022*[60]	mixed design, RCT (single-blind controlled, to assess VE) and cross-sectional study (ADE)	Brazil - UK	15,169 VE	no statisticall y significant difference in VE	via nucleic acid amplification test (NAAT)-positive symptomatic SARS-CoV-2 infection	F 55.7%: M 44.3% no limitation section; health- and social-care workers
Mediu et al 2022[116]	case-control study (randomly assigned)	Albania	187	no difference in VE	antibodies titres (IgG)	F 60.5%: M 39.5% (cases) F 68%: M 32% (controls); small sample size
Nordstrom et al 2022[117]	cohort study (retrospective, total population)	Sweden	842,974	no difference in VE	reinfection with positive test hospitalization due to COVID	F:M balanced; retrospective; follow-up completed before omicron variant
Otsuka et al 2022[118]	cross-sectional study	Japan	401	VE higher in F than M	antibodies titres	F 70%: M 30%; single-centre; no follow-up; limited statistical analysis assessing sex reported; small sample size
Pani et al 2022[119]	cohort study (prospective longitudinal observational)	Italy	1,738	No difference in VE	antibodies titres (increase of anti-RBD IgG between basal, pre-booster and after 14 days	F 67%: M 33%; lack of neutralizing antibodies measure; healthcare workers
Saciuk et al 2022[120]	cohort study retrospective observational)	Israel	1.6 M	not statisticall y significant difference in VE	hospitalization and mortality and infection via positive PCR cases	F 52%: M 47%; PCR upon request risk of underreporting;

Soegiarto et al 2022[121]	mixed design, cohort study (prospective for antibodies response and retrospective breakthrough infection)	Indonesia	101 (for the first study) 2,714 (for second study)	No difference in VE	antibody response and breakthrough infection	F40.6%: M 59.4%; self-reported data online-questionnaire; healthcare workers with underlying conditions and comorbidities
Tawinprai et al 2022*[78]	cohort study (prospective)	Thailand	796	VE higher in F than M	antibodies titres (RBD antibodies)	F 65%: M 35%; observational; single-centred; timing of anti-RBD antibodies measurement in each participant was different
Vietri et al 2022[122]	cohort study	Italy	52	no difference in VE	neutralizing antibodies titres following one and two vaccine doses	F:M balanced; limited statistical analysis to support their results; small sample size
Wang et al 2022[123]	cohort study (retrospective observational)	UK	2,784	VE higher in F than M	via antibodies response	F 84.9%: M15.1%; healthcare workers
Wu et al 2021[124]	RCT (open-label, phase 1)	China	130	no difference in VE	antibodies response (neutralizing antibody)	F:M balanced; phase 1; single-centre; small sample size;
Xu et al 2021[125]	cohort study (observational)	US	~11M	no difference in VE	mortality risk	F 54%: M 46%; individual-level confounders that might affect mortality risk
Yamamoto et al 2022[126]	cross-sectional study	Japan	2,435	VE higher in F than M	association of BMI and antibodies titres	F 70%: M 30%; restricted population by BMI; no assessment of neutralizing antibodies
Young-Xu et al 2021[127]	case-control study (test-negative)	US	667,733	no difference in VE	positive PCR or antigen test for SARS-CoV-2 2	F 10%: M 90%; no statistical analysis to support results is reported;
Zhang et al 2022*[85]	non-RCT (Open label)	Hong Kong	189	no statisticall y significant difference in VE	antibodies neutralizing response in 3 times points	F 64.2%: M 35.8%; small sample size; not randomized; no statistical analysis to support results is reported;

RCT: randomized clinical trial; non-RCT: non-randomized CT; RBD: receptor binding domain PCR: polymerase chain reaction; VE: vaccine effectiveness; F:M: Females-Males ratio when balanced means it was evenly matched F 50%: M 50%; *these studies evaluated both ADEs and VE, in this table only findings on VE are reported.

Looking at study design, there were seven CT, five were RCT and two were non-randomized CTs. Only one large sample size double blind phase 3 placebo-controlled CT interim report found a significantly higher VE in males compared to females (males VE 65·8% 95%CI 46.1 to 78.3% vs women VE 40·0% 95%CI-4.9 to 65.7) based on symptomatic infection (PCR positivity within 28 days post vaccination dose 1).[47] Whilst Wu *et al* in a phase 1 RCT reported similar neutralising antibodies response in both sexes (p = 0.031)[124] and Marchevsky *et al* found no statistically significant difference in VE through positive nucleic acid amplification test (p = 0.3359).[60] The remaining four RCT did not report evidence of VE difference by sex, regardless the outcome measured.

There were 32 cohort studies assessing VE, of these 11 found statistically significant higher VE in females than males, with two large studies, one cohort from Saudi Arabia (aOR 1.167 95%CI 1.039-1.311 p = 0.0091)[29] and a multicohort from the US (incidence rate risk = 1.47, 95%CI 1.11-1.94, p = 0.1)[111] both assessing VE via breakthrough infection rates; seven studies assessed VE through antibodies response and one through platelet surface receptor expression all in small sample size.[102] There was one large cohort from Belgium modelling estimation of transmission of infection reporting higher VE in males than females (susceptibility-VEs, males had lower odds of infection after vaccination compared to females OR 0.83 95%CI 0.84-0.93).[92] There were three large cohorts reporting no difference in VE according to sex (51-53). Chodick *et al* reported a relative risk reduction (RRR) of infection in women of 50.0%; 95%CI 13.5%-71.0% vs in men of RRR 52.1 (95%CI 17.3%-72.2%);[96] Florea *et al.* reported adjusted VE (assessed by positive molecular test) in females 82.4%, 95%CI 81.7-83.1 vs in males 83.1 (95%CI 82.3-83.9);[103] and Xu *et al* reported similar adjusted relative risk of mortality for vaccinated individuals with three different vaccines.[125] The remaining 18 studies did not find strong evidence to support statistical difference in VE by sex.

Li *et al* was the only case-control (test-negative) study out of a total of five, presenting with a statistically significant higher VE in females than males (assessed by PCR test) following two doses of vaccine (aOR 70.4%, 95% CI: 18.4% to 91.0%).[110] However, this observational study had a small sample size with a disproportion between cases and controls. Behera *et al*[90] reported similar infection risk between female and male participants via PCR test (aOR 0.94, 95% CI: 0.61-1.43). The other three studies did not report strong evidence of sex-related differences in VE.

Out of the nine cross-sectional studies, only two found a statistically significant higher VE in females than males, the first by breakthrough infection (OR 1.71, 95% CI 1.20-2.43, p = 0.003)[32] and the second via antibodies titres (p = 0.028).[118] The remaining seven studies did not find any difference by sex.

Finally, there were two ecological studies, one found VE similar between females and males against admission to hospital (males 1-risk ratio 92%, 95%CI 85-97 and females 1-risk ratio 96% 95% CI 93-99) and severe disease (males 1-risk ratio 89%, 95%CI 73-98 and females 1- risk ratio 97%, 95% CI 93-99),[89] while Fraley *et al* did not report any statistical difference.[104]

To summarise, there were 14 studies reporting higher ADEs in females than males (zero RCTs, 11 cohort, zero case-control and two cross-sectional); two studies reported higher ADEs in males than females (one RCTs, one cohort); seven reported no difference (two RCT, three cohort, one case-control, zero cross-sectional and one ecological) and 33 did not report evidence of sex-based differences (four RCTs, 17 cohort, one case-control and seven cross-sectional, one ecological). Sex representation were balanced in 21 studies (37%), females were overrepresented in 22 studies, underrepresented in nine and four studies did not report F/M ratio.

Discussion

COVID-19 pandemic generated a huge number of studies and data. Major journals provided additional space and published extra issues on regular bases to allow for timely sharing of all updated findings. Despite this impressive effort to speed up research and improve knowledge we found difficult to draw strong conclusions about sex-based differences in ADE and VE. Out of more than 1,600 articles initially retrieved, we could only select 101 full-filling our inclusion/exclusion criteria. Disappointingly, 22 out of 60 evaluating ADE and 33 out 56 assessing VE were inconclusive (total exceeds 101, since few studies concerned both ADEs and VE).

Regarding equal representation of females and males, we found that the majority of the studies selected did not have a balanced representation of the sexes even if they reported a statistical analysis by sex. Historically, women have been both over- and under-represented in clinical studies[128,129] and this is confirmed by our findings were only 33.6% of the studies had a balanced sex representation, with an overrepresentation of women in 50 studies and an underrepresentation in 25 studies.

Our study presents with some limitations and some strengths. We chose to perform an unsystematic narrative review focused on how the existing literature generated and evaluated sex-based differences. We have partially applied the PRISMA checklist for systematic reviews to our methodology and three different reviewers assessed independently the studies using a set of predefined inclusion/exclusion criteria and evidence synthesis was performed with a critical approach rather than an established methodology. We decided to exclude previous reviews assessing the same issue, wanting to evaluate original articles, and we only searched articles published in PubMed, given it is one of the largest known databases. Though, in doing so we might have missed identification of certain preprints or specific studies published in different databases or conclusion derived from previous reviews. Furthermore, we excluded studies focusing only on specific population (i.e., sclerosis multiple, cancer or diabetes) and/or those looking only at specific cut off ages (i.e., >75 years) because we wanted a population that could be representative of the general population, however these might have excluded studies reporting of very rare ADE or sex-based difference in VE due to the nature of an underlying conditions. Moreover, we included studies with healthcare workers with the rational provided in methods, being aware that a possible overrepresentation of females in healthcare settings could affects our findings.[130] Finally, our review identified whether each article presented with a statistical analysis assessing sex-based differences, rather than evaluating the quality of the methodology presented. Overall, the above did not preclude us to reach several important findings.

Almost half of the studies included in our review reported more ADE in females than males (28/60 studies), and the majority of these were cross-sectional, baring the limitation of gathering data through survey instead of performing a clinical assessment. However, eight studies investigated specific rare events, most likely driven by signals emerged when mass vaccination started.[27,38,39,48,57,62,84] These studies evaluated whether exposure to a given vaccine potentially increased the risk for thrombosis/thrombocytopenia in young females and for myo- peri-carditis in young males. They all used post-marketing national surveillance systems/registries, given the large sample size needed to detect rare events. From our review we could identify two trends regarding safety, firstly females are more likely to both report and suffer from generic and mild ADE - which is in line with existing evidence, of females being both more likely to report their symptoms and to experience post-vaccination reaction than males;[24,131-133] secondly, young males have increased risk of myo- and peri-carditis whereas coagulative problems appear to be more frequently observed in females.

About VE, we find more than half of the studies (33/56) were inconclusive about sex-based differences. Two articles reported increased VE in males, 14 in females and six with no difference. Taken together these studies can only support a trend toward a possible increased VE in females. Even though it was not the scope of this review to rank the measure of outcomes, we noticed the reported higher VE in females was mostly assessed by antibodies titres rather than clinical outcomes.

We found studies heterogeneity and fragmentation were the two major obstacles precluding conclusive assessment of sex-based VE differences. Heterogeneity emerged in the study design and methodology (i.e., statistical analysis) and in the choice of the outcome measures (i.e., antibodies response, number of infections ascertained by different tests, hospital admission and mortality rate). Additional variables include type of vaccine and the time of data collection (different follow-up time after vaccination, exposure to different variants). Moreover, it is not possible to directly compare immune response to clinical outcomes. A good example is provided by three studies evaluating VE through PCR test and reporting three different outcomes with three different study design on three different vaccine type. Halperin *et al*,[47] reported a RCT with higher VE in males than females, Liu *et al*[125] reported a cohort study finding higher VE in females than males and Behera *et al*[90] reported a case-control study finding no sex-based VE difference.

Fragmentation and the heterogeneity of VE studies was expected since no authorities are in charge of coordinating studies after approval nor to issue guidance or to promote a robust methodology.[134] As reported the major regulatory authorities, EMA and FDA, are more keen to foster generation of evidence of both safety and efficacy and therefore to reach gender balance and detect sex-based differences before a vaccine is approved, however after the approval they can encourage or even impose additional evidence generation only when a safety signal emerge from ADEs reports.[135,136] Two clear examples are the findings about carditis in young men and thrombosis/thrombocytopenia in women, substantially detected by exploiting the official data collected by surveillance systems.

Regarding VE post-approval evaluation, we speculate whether the lack of similar authorities could be the cause for the fragmentation and inconclusiveness of too many studies. A need for coordination has been flagged as the most urgent action to fill the knowledge gap in the shortest possible time frame without wasting resources.[15] Attempts to address uncoordinated clinical research are in place[137] and suggestion were also provided on how to mitigate the inefficiency by the creation of CTs platforms and consortia in order to reduce the number of small studies and to promote bigger trials properly designed.[18,138,139]

Overall, studies are very seldom designed to identify sex-based differences[140] as also confirmed by our data and more recently by six articles investigating waning VE over time against different SARS-CoV-2 variants, none of which evaluated sex-based differences, even though all had the potential (e.g., large sample size and adequate study design) to draw robust conclusion on VE difference by sex.[141-146] Moreover, we wonder if along with coordination a cultural change is needed to reach equal representation of females and male's individual in research and to detect sex-based differences by design in any study.

Key messages

Sex-based differences in VE and ADEs are still poorly addressed as emerged by reviewing COVID-19 vaccines literature.

There is general trend of both increased reporting and experiencing of ADEs from females compared with males.

An increased risk for thrombosis in young females and for carditis in young males was evidenced.

Full assessment of VE was not possible due to the contradictory and heterogeneity of the measures of outcomes (i.e., different way of measuring VE).

Fragmentation and heterogeneity of studies are the two major obstacles, identified to preclude full assess on sex-based differences for both VE and ADEs.

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