

Impact of gender difference towards coronavirus disease 2019 (COVID-19) vaccine antibody response: systematic review



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Introduction: There are several factors contributing to antibody response towards COVID-19 vaccination. Age, infection history, virus mutation, nutritional status, body mass index, gut microbiota, host polymorphism, and immune system have been accounted for variations in antibody development due to COVID-19 vaccination in several studies. Sex differences are also included in the list. Therefore, this study aims to determine the impact of gender differences on antibody development after COVID-19 vaccination on general populations.

Methods: We conducted a systematic review based on the PRISMA statement. Searching for clinical trials was conducted in PubMed, Scopus, EBSCOHost, and ProQuest using selected keywords. Inclusion and exclusion criteria were applied to filter the study. Filtered studies were appraised using The Joanna-Briggs Institute tools for critical appraisal to determine the studies' eligibility for inclusion. Included studies were extracted for study and subjects' characteristics. Study outcomes were analyzed qualitatively and reported.

Results: Eight prospective cohort studies involving 3,381 subjects were included after searching and selection. Appraisal of studies found that studies were considered good enough for inclusion. We found that multiple studies reported higher COVID-19 vaccination antibodies in females compared to males. However, several studies doubted long-term differences due to antibody waning. These doubts were clarified by a study that stated that even though has been adjusted to various demographic factors, females showed significantly higher IgG levels up to 40 weeks. Another finding stated that antibody titer waned much softer in females compared to males.

Conclusion: Antibody towards COVID-19 vaccination was higher in females compared to males as initial response up to several weeks. However, long-term differences should be studied and investigated further.

Keywords: antibody, COVID-19, gender identity, sex, vaccine.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which is highly contagious and causing a lot of burden. It was known that COVID-19 has been responsible for more than 6 million deaths around the world.¹ To prevent transmission of COVID-19, various vaccines have been developed. To date, there have been various vaccines that have been approved by the World Health Organization (WHO) to be applied as emergency use authorization (EUA)-qualified vaccines. They consisted of adenoviral-vectored vaccines, inactivated coronavirus vaccines, and other messenger RNA (mRNA) vaccines.²

COVID-19 vaccines have been proven effective in various settings. A systematic review of 30 studies has determined that COVID-19 vaccines have efficacy of 80–90% towards both symptomatic and asymptomatic COVID-19 infections when administered in full dose.³ A clinical trial found that vaccines by Pfizer-BioNTech, Moderna, and Sputnik V have better efficacy when compared to Oxford-AstraZeneca and Janssen with efficacy of 95%, 94%, 92% versus 80%, and 54–72%, respectively.⁴ However, in general, COVID-19 vaccines protected against COVID-19 infection. This is possible as COVID-19 vaccines work by eliciting neutralizing antibodies (NAbs) against spike protein of SARS-CoV-2.⁵ Antibodies which elicited by vaccine wanes over time,

hence booster is needed for continuous protection.^{6,7}

There are several factors contributing to antibody response towards COVID-19 vaccination. Age, infection history, virus mutation, nutritional status, body mass index, gut microbiota, host polymorphism, and immune system have been accounted for variation in antibody development due to COVID-19 vaccination in several studies.^{8,9} Sex differences are also included in the list.⁸ It is known that males are more at risk of severe COVID-19 infection with more risk of mortality.¹⁰ Two studies exploring response towards hepatitis vaccinations found that women are more likely to develop better immune responses compared to men.^{11,12} Even though sex differences seem to alter immune response

towards vaccination, the impact on COVID-19 antibody development is still controversial. Therefore, we conducted a

systematic review to determine the impact of gender on antibody development in COVID-19-vaccinated populations.

METHODS

We conducted a systematic review based on the Preferred Reporting Items for

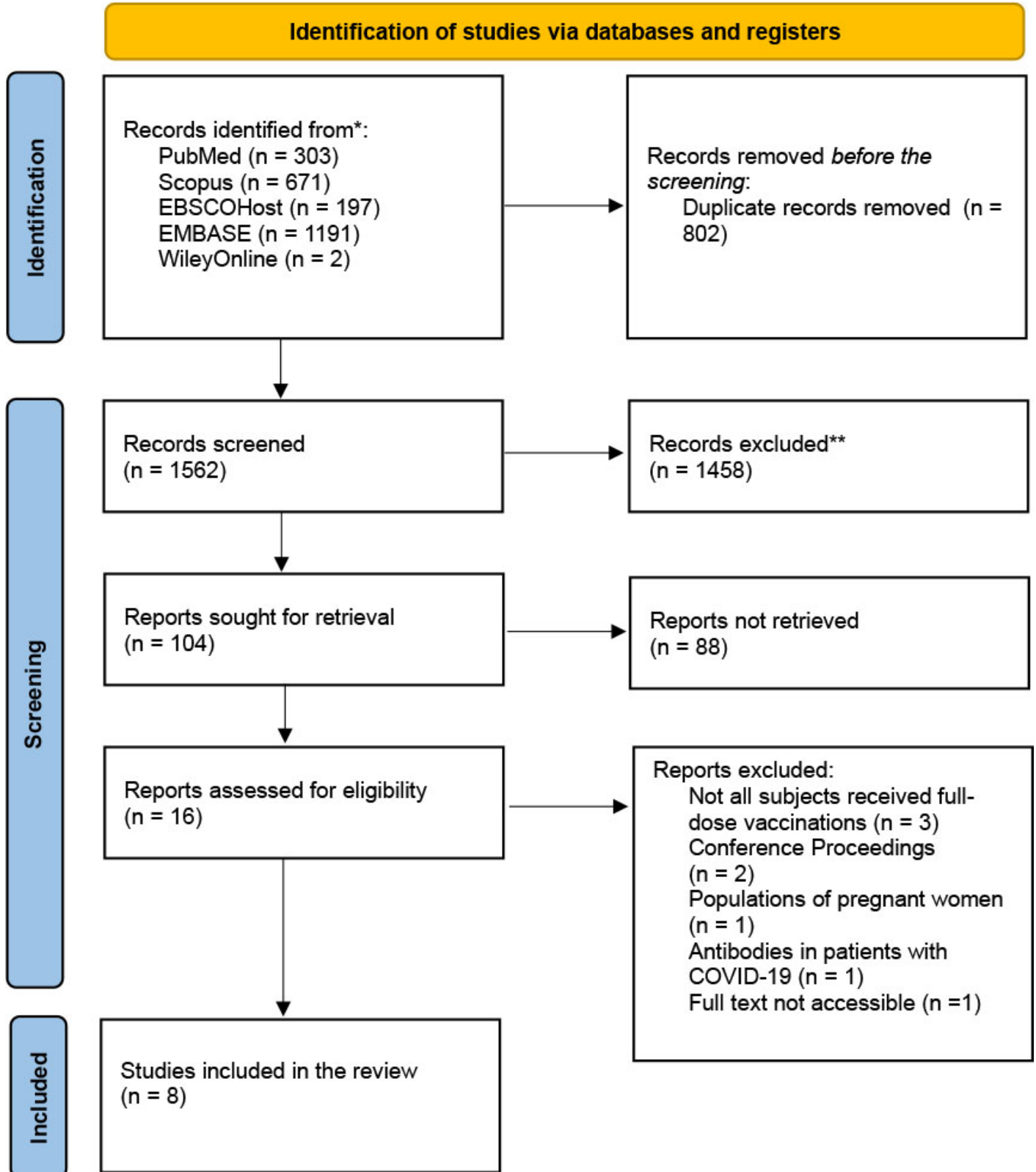


Figure 1. Inclusion processes of selected studies.¹³

Table 1. Critical appraisal of selected studies

Studies	Appraisal questions ¹⁴											Conclusion
	1	2	3	4	5	6	7	8	9	10	11	
Anastassopoulou et al ¹⁵	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Included
Jalkanen et al ¹⁶	Y	Y	Y	UC	UC	Y	Y	Y	Y	NA	Y	Included
Heriyanto et al ¹⁷	Y	Y	Y	UC	UC	Y	Y	Y	UC	UC	Y	Included
Nam et al ¹⁸	Y	Y	Y	Y	Y	Y	Y	Y	UC	UC	Y	Included
Ebinger et al ¹⁹	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Included
Wheeler et al ²⁰	Y	Y	Y	UC	UC	Y	Y	Y	Y	NA	Y	Included
Farid et al ²¹	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Included
Chen et al ²²	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Included

Abbreviations: Y = yes; N = no; UC = unclear; NA = not applicable

Systematic Review and Meta-Analysis (PRISMA) statement.¹³ Searching was conducted on PubMed, Scopus, EBSCOHost, EMBASE, and WileyOnline databases. We determine the population of COVID-19-vaccinated population, indicator of gender (male/female), no control, and outcome of COVID-19 antibody titer. We used keywords “(“COVID-19 Vaccines”[Mesh]) AND (“sex” OR “gender”) AND (“Antibodies”[Mesh])” in PubMed and “(“SARS-CoV-2 vaccine” OR “COVID-19 vaccine” OR “Coronavirus vaccine”) AND (“sex” or “gender”) AND (“antibody” OR “immunoglobulin”)” in other databases.

We applied inclusion and exclusion criteria to select studies. Inclusion criteria were applied as follows: (1) studying populations receiving at least full dose COVID-19 vaccinations; (2) studying outcome of COVID-19 antibody titer; (3) studying differences of outcome within sex; (4) clinical trial; (5) full paper available. These exclusion criteria were applied: (1) studies not written in the English language; (2) clinical register; (3) special populations. The included studies were appraised using critical appraisal tools by The Joanna-Briggs Institute.¹⁴ Studies were extracted for characteristics (authors, location, design, vaccine type, doses received, subject size, gender, age, and any others applicable). Studies outcomes were extracted and analyzed qualitatively to synthesize conclusions about outcomes. All processes were conducted by 3 reviewers (MEP, GS, LW) with any discrepancies between searching, appraisal, and synthesis were discussed further to conclude.

RESULTS

We included eight studies after thorough processes of searching, selection, and appraisal (Figure 1).^{15–22} All studies were considered good enough to be included in the study after appraisal using The Joanna-Briggs Institute critical appraisal tools (Table 1).¹⁴ Therefore, the final studies which were included consisted of eight retrospective studies from around the world.^{15–22}

Studies were all retrospective in design and conducted in Europe, Asia, and America, involving a total of 3,381 subjects who were naïve towards COVID-19 vaccination. Most of the studies were dominated by females with only one study having a bigger male-to-female proportion. There were six studies administered Pfizer BioNTech (BNT162b2) vaccine, one study each administered Moderna (mRNA-1273) and Sinovac vaccine, and one study administered various vaccines (Chinese hamster ovary cells-based, vero cells-based, and adenovirus vector). All studies were involving adults with the oldest mean age of 49.29 years old (Table 2).^{15–22}

We found that multiple studies reported significantly higher COVID-19 vaccination antibodies in females compared to males (Table 3).^{15–17,20–22} However, multiple studies also reported doubts about long-term effects. A study by Jalkanen et al could not determine the difference in IgG between groups.¹⁶ A study by Anastassopoulou et al could not determine any significant difference after 12 weeks of administration and beyond.¹⁵ Study by Wheeler and Farid

could not find any significant difference in antibodies after 45 days and 14–31 days of administration, respectively.^{20,21} Study by Chen which was conducted for 25 weeks could not determine the difference of IgM between groups after 8 weeks of administration and the difference of IgG within the whole study period.²² However, a study by Ebinger which was conducted for 40 weeks stated that, even though has been adjusted to various demographic factors, females showed significantly higher IgG levels until the end of the study period.¹⁹ Study by Anastassopoulou also supported this finding, stating that antibody titer waned much softer in females compared to males.¹⁵

DISCUSSION

COVID-19 vaccinations were proven to elicit a greater antibody response in females compared to males. This was suspected to be caused by the nature of the immune systems of females and males which are different. A study by Flanagan et al has shown that female tends to show better antibody response towards any type of vaccine compared to male.¹² However it was also reflected as an excessive response toward vaccination. A study conducted between 1990 and 2016 found that 83% of anaphylactic patients aged 19 to 49 years old due to vaccines were female.²³ Another report by the Centers for Disease Control and Prevention (CDC) stated that females were four times more likely to experience hypersensitive reactions due to H1N1 vaccination in populations aged 20 to 59 years old.²⁴

Several biomechanisms have been

Table 2. Characteristics of selected studies

Authors	Year	Location	Design	Vaccine used	Doses received	Measurement week	Subject size	Females (%)	Age (years)
Anastassopoulou et al ¹⁵	2022	Greece	PC	BNT162b2	2	3-4, 12	439	65.8	48.6 (9.51)
Jalkanen et al ¹⁶	2021	Finland	PC	BNT162b2	2	3, 6	180	83.0	43 (20-65)
Heriyanto et al ¹⁷	2021	Indonesia	PC	Sinovac	2	4, 8, 12	350	70.0	22 (19-28)
Nam et al ¹⁸	2022	South Korea	PC	BNT162b2	2	8, 16, 24	50	80.0	34.7 (9.4)
Ebinger et al ¹⁹	2022	United States	PC	BNT162b2	2	1-3, 8, 16, 24, 32, 40	843	69.6	41.66 (35.19-52.80)
Wheeler et al ²⁰	2021	United States	PC	BNT162b2/ mRNA-1273	2	6, 11	47	70.0	49.29 (12.81)
Farid et al ²¹	2022	Bahrain	PC	BNT162b2	2	2-4	379	43.0	> 18
Chen et al ²²	2022	China	PC	CHO cells/ Vero cells/ adenovirus vector (local brand varies)	2-3	1, 2, 3, 4, 5-6, 7-8, 9-10, 11-25	1093	58.6	> 18

Abbreviations: PC = prospective cohort; BNT162b2 = The Pfizer BioNTech COVID-19 vaccine; mRNA-1273 = The Moderna COVID-19 vaccine; CHO = Chinese hamster ovary

Table 3. Outcome of included studies

Studies	Findings
Anastassopoulou et al ¹⁵	- Significantly higher antibody in females after 3-4 weeks (60.97 vs 54.33; p = 0.012) but not after 12 weeks (22.21 vs 21.46, p = 0.50) - Softer elimination titer rate in females compared to males (p < 0.05)
Jalkanen et al ¹⁶	- Females had significantly higher neutralization antibody titer compared to males after 6 weeks (p = 0.04) - Anti-S1 IgG antibody level was not different between genders
Heriyanto et al ¹⁷	Significantly higher neutralizing antibody in the female after 4 weeks (43 vs 29; p = 0.001), 8 weeks (42 vs 39; p = 0.002), and 12 weeks (39 vs 29; p = 0.03)
Nam et al ¹⁸	Sex did not give a significant difference in antibody level after being adjusted to demographic characteristics after six months of vaccination
Ebinger et al ¹⁹	Female sex was associated with significantly higher IgG-S levels during the study period (40 weeks) after being accounted for age, race, ethnicity, hypertension, obesity, and the Charlson comorbidity burden index
Wheeler et al ²⁰	- Significantly higher anti-S2 antibodies in females after vaccination (55.93 vs 28.91; p < 0.05) - No statistically significant difference of anti-S2 antibodies in females 45 days and 75 days after vaccination (41.31 vs 19.60 and 19.00 vs 13.00, respectively)
Farid et al ²¹	- Slightly higher seropositivity in males compared to females (94.9% vs 92.0%) after 14-31 days of vaccination
Chen et al ²²	- No significant difference in S antibody levels between males and females (p = 0.51) after 14-31 days of vaccination - Significantly higher IgM in the female after one week, two weeks, and eight weeks after vaccination (2.06 vs 0.67, 2.13 vs 1.21, 0.80 vs 0.33, respectively; p < 0.05) - No significant difference in IgG during the study period (25 weeks)

proposed as the underlying theory behind this phenomenon. Females have more innate and adaptive immune responses in terms of quantity and quality compared to males. Therefore, females were more prone to adverse reactions after vaccination, but also more potential for vaccine responses.^{25,26} Estrogen, which is abundantly produced in females, has also proven important in the mechanism. A high concentration of estrogen was subjected to a better immune response towards vaccinations, while testosterone, which is rich in males, was subjected to an attenuated response towards vaccinations.²⁷ Besides hormonal factors, genetic factors are also impactful in females. The x chromosome, which was found more in women, contains more and greater genes which responsible for immune-related protein-coding. It was known that there could be up to 10-fold differences in the gene contained by the X chromosome when compared to the Y chromosome.²⁸ Therefore, females who have one more X chromosome than males have greater potential to develop an immune response.^{29,30}

However, the greater immune response towards the COVID-19 vaccine in women is yet to be supported by findings of its longevity. It was known that vaccine response wane over time. A study of BNT162b2, ChAdOx1 nCoV-19, and mRNA-1273 vaccines has shown that antibody response wanes after five months of administration regardless of age, sex, and body mass index. Antibody titer decreases even faster and greater in those with comorbidities. Therefore, booster administration is necessary.³¹ A study in Malaysia that administered either BNT162b2 or CoronaVac vaccines found that there was a waning and reduction of effectiveness against intensive care unit (ICU) admission after approximately six months of administration regardless of sex. However, their effectiveness against death remained.³² Development of newer variants is also responsible for the COVID-19 vaccine waning regardless of sex. A report in Thailand showed that Omicron's appearance waned antibody response towards the COVID-19 vaccine after considering sex as one of its factors.³³

This was the initial systematic review

to determine the impact of sex towards antibody response to COVID-19 vaccination. However, this study could not precisely determine the long-term response to COVID-19 vaccination. Therefore, we recommended high-quality longitudinal studies to be conducted so that outcomes over time in this field of study could be gathered. In addition, meta-analysis concerning this topic should be conducted to determine pool estimates of antibody responses and their details over time.

Our study has several limitations. First, the number of participants and they are limited to the Asian race. Second, the form of steroid used was different in the two studies.

CONCLUSION

Antibody response due to COVID-19 vaccination was higher in females compared to males after initial assessment up to a few weeks after administration. However, long-term differences remain unclear. Therefore, further long-term longitudinal studies should be conducted to provide more information on this field in terms of time.

CONFLICT OF INTEREST

The authors declare no conflict of interest in the making of this manuscript.

ETHICAL CONSIDERATION

No ethical clearance is needed as we conduct a study of the literature.

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AUTHOR CONTRIBUTION

MEP was involved in writing the manuscript. GS and LW supervised and revised all manuscripts. All authors prepare the manuscript and agree for this final version of the manuscript to be submitted to this journal.

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