The effectiveness of COVID-19 vaccine in healthcare workers: Does gender matter?

Sağlık çalışanlarında COVID-19 aşı etkililiği: Cinsiyet önemli mi?

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ABSTRACT

Objective: Immunization by vaccination has a crucial role in controlling COVID-19 pandemic. Determination of the factors affecting the effectiveness of the vaccine can increase the success rates. We aimed to investigate the effectiveness of CoronaVac and factors affecting its effectiveness in healthcare workers.

Methods: This retrospective study included healthcare personnel (n=2666) working at a training and research hospital. Logistic regression analysis was used for analyzing the effects of all variables including vaccination status on the development of COVID-19. Adjusted odds ratios calculated by logistic regression analysis were used to determine the vaccine effectiveness. Stratified analyses wre performed for the determination of the interaction/effect modification regarding the vaccine effectiveness.

Results: Mean age of the 2.666 healthcare workers included in this study was 37,3±10,2 and 55,8% (n=1488) were females and %44,2 (n=1178) were males. In this study gender and history of COVID-19 infection was found to be an effect modifier for the vaccine effectiveness by the stratified analysis. The effectiveness of the CoronaVac vaccine in preventing development of

ÖZET

Amaç: COVID-19 aşıları ile bağışıklanma, pandemiden çıkış stratejisi olarak tüm dünyada geniş çapta kabul edilmiştir. Aşının etkililiği ve bunu etkileyen faktörlerin tespit edilmesi, aşı başarısını arttırarak pandeminin kontrolünü sağlayabilir. COVID-19 hastalarının mortalitesinde; düzensiz immünizasyon ve çoklu organ yetmezliği gibi nedenler gösterilse de bunların cinsiyet ile olan ilişkisi aydınlatılmamıştır. Bu çalışmada; sağlık çalışanlarında CoronaVac aşı etkililiğini belirlemek ve etkileyen faktörleri incelemek amaçlanmıştır.

Yöntem: Bu retrospektif çalışmaya Eğitim ve Araştırma Hastanesi'nde çalışan 2.666 sağlık personeli dahil edilmiştir. Çalışmanın bağımlı değişkeni COVID-19 gelişimidir. Bağımsız değişkenler; yaş, cinsiyet, meslek grubu (doktor/hemşire/diğer sağlık çalışanları), çalışılan klinik tipi (YBÜ/YBÜ dışı), COVID-19 kliniğinde çalışma durumu (COVID-19 kliniği/diğer klinikler), COVID-19 geçirme öyküsü (var/yok), aşıdan sonra COVID-19 tanı süresi (gün) ve aşılanma durumu (aşılı/aşısız)'dur. COVID-19 tanısı alan tüm sağlık çalışanlarının klinik takibi Enfeksiyon Hastalıkları ve Klinik Mikrobiyoloji Personel Sağlığı Polikliniği'nde yapılmıştır. Ayrıca klinik sorumluları ile haftalık olarak telefonla görüşülerek veya klinik ziyaretleri yapılarak, COVID-19

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COVID-19 diagnosed by real-time polymerase chain reaction (RT-PCR) in healthcare workers was 84,5% (95%CI: 73,3-91) in women and 47% (95%CI: 1,7-71,4) in men. Being a medical doctor or a registered nurse, working in ICU or a COVID-19 clinic, a positive history of COVID-19 and COVID-19 vaccination were other protective factors against COVID-19 infection.

Conclusion: Determination of the factors affecting the effectiveness of the vaccine can increase the success rates. Vaccination programs may need to be modified if there is a COVID-19 history or gender-related difference in vaccine effectiveness.

Key Words: COVID-19, vaccine, coronavac, gender, effectiveness

gelişimi yönünden tüm sağlık çalışanları izlenmiştir. Aşılama durumu dahil tüm değişkenlerin COVID-19 gelişimi üzerindeki etkilerini analiz etmek için lojistik regresyon analizi kullanılmıştır. Aşı etkililiğine ilişkin etkileşim/etki değişiminin belirlenmesi için tabakalı analizler yapılmıştır. Veriler SPSS versiyon 20.0 paket programı kullanılarak analiz edilmiştir. Tüm istatistiksel testler için önemlilik sınırı 0.05 olarak alınmıştır.

Bulgular: Çalışmaya alınan toplam 2666 sağlık çalışanının yaş ortalaması 37,3±10,2 (n=2556) ve %55,8 (n=1488)'i kadın, %44,2 (n=1178)'si erkektir. CoronaVac aşısının sağlık çalışanlarındaki RT-PCR pozitifliği ile tanı konulan COVID-19'u önlemede etkililiği kadınlarda (%84,5 (%95GA: %73,3-91,0)), erkeklerden (%47,0 (%95GA: %1,7-71,4)) daha yüksek bulunmuştur. Meslek grupları, klinik tipi, COVID-19 kliniğinde çalışma durumu aşı etkililiğini etkilememektedir. Çok değişkenli lojistik regresyon analizinde doktor/hemşire olmak, YBÜ'de çalışmak, COVID-19 kliniğinde çalışmak, COVID-19 geçirmiş olmak ve aşılı olmak koruyucu faktör olarak saptanmıştır. Değişkenler arasında %96,5 ile en yüksek koruyuculuk düzeyi COVID-19 geçirme öyküsünün olmasıdır.

Sonuç: Cinsiyete göre COVID-19 aşı etkililiğinde farklılık, aşılama programlarının revize edilmesini gerektirebilir. Erkekler ve kadınlar için farklı prime-boost aralıkları, özel aşı platformları, farklı dozaj seviyeleri ile sonuçlanan stratejiler COVID-19 eliminasyonu için kullanılabilir. COVID-19 aşısı olan sağlık çalışanlarının belirli aralıklarla, yaklaşık 1 yıl izlenmesi; çeşitli gruplarda aşı etkililiğindeki farklılıkların belirlenmesi; aşılama programları, sürveyans ve klinik takip gibi noktalarda önceliklendirme yapma, rapel doz aşılama, ağır hastalık geçirme riski olan çalışanları koruma, hizmet planlama ve aşı seçimi gibi pek çok konuda büyük fayda sağlayabilir. COVID-19 pandemisinin kontrol altına alınabilmesi için aşı ile immünizasyon anahtar roldedir ve aşı etkililiğini etkileyen faktörleri tespit etmek hedefe giden yolda başarıyı arttırabilir.

Anahtar Kelimeler: COVID-19, aşı, coronavac, cinsiyet, etkililik

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected millions of people and led to hundreds of thousands of deaths since its emergence in December 2019 (1). Although precautions including wearing masks, compliance with hygiene procedures, and social isolation were taken to control the pandemic, they were not enough to stop the pandemic. Immunization by vaccination has been accepted as the solution strategy for returning to pre-pandemic work, school, and social life worldwide. Vaccination is the most important and effective means of protecting child and adult health and preventing disease transmission since the 20th century (2). The main target of immunization services is the reduction of infectious disease-related morbidity and mortality (3). Therefore, the permanent prevention of COVID-19 (i.e., Coronavirus disease-2019) spread can only be possible by vaccinating most of the world population with an effective and safe vaccine. Surprisingly, since the end of 2019, approximately 200 vaccines were tested in phase 1 and phase 2 trials (i.e., preclinical trials), and some inactivated vaccines, nucleic acid-based vaccines, and vector vaccines were tested in clinical trials (4).

Inactivated vaccines are prepared by chemical (i.e., formaldehyde) or physical (i.e., ultraviolet or heat) methods using killed pathogenic strains. Until today, purified inactivated viruses were usually used for preparing vaccines, and these vaccines were reported to be safe and effective against influenza and poliovirus (5). The candidate vaccine CoronaVac produced by the Chinese company Sinovac was tested in a clinical trial including 743 healthy volunteers aged between 18 and 59, and neutralizing antibodies were detected 14 days after vaccination (6). The phase 3 trial of this candidate vaccine was initiated at the end of July 2020 in Brasil, and it was approved for clinical use in Turkey in September 2020 (7). Thus, the first COVID-19 vaccine introduced to clinical use in Turkey is Coronavac. Since they were at high risk due to close contact with patients, healthcare workers were in the first vaccination group (8).

On the other hand, people who were vaccinated by CoronaVac draw attention regarding serum antibody levels, effectiveness of the vaccine in protection against COVID-19, and factors affecting its effectiveness. The answers to these questions are critical in preventing the spread of COVID-19 and controlling the pandemic. Therefore, in this study, we aimed to investigate the effectiveness of CoronaVac and the factors affecting its effectiveness in healthcare workers.

MATERIAL and METHOD

Study group

This retrospective study included medical doctors, nurses, and allied health personnel (n=3.550) working at a training and research hospital. The hospital had 770 beds, 90 of which were located at adult intensive care units, and the bed occupancy rate was 93% during the study period. The minimum sample size was calculated as 2097 (1.677 vaccinated, 420 unvaccinated) with a 95% confidence interval and 0.9 power. The vaccine effectiveness, vaccination rate, and the risk of acquiring COVID-19 in unvaccinated were presumed as 0.5, 0.75, and 0.1. The Epi Info (Centers for Disease Control and Prevention, Atlanta, USA) software was used for this analysis. No participant selection was carried out, and all the healthcare worker population (n=2.666) was included in the study. The study was initiated on the 1st of March, 2021, which corresponds to the earliest time after completing a 14-day interval following administration of the 2nd Coronovac dose to all healthcare workers. In addition, the study period corresponds to the third and the most severe wave of the countrywide epidemic of COVID-19 (Figure 1).

The study was approved by the University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinic Research Ethics Committee (Date: 31.05.2021 and Number: 112/07).

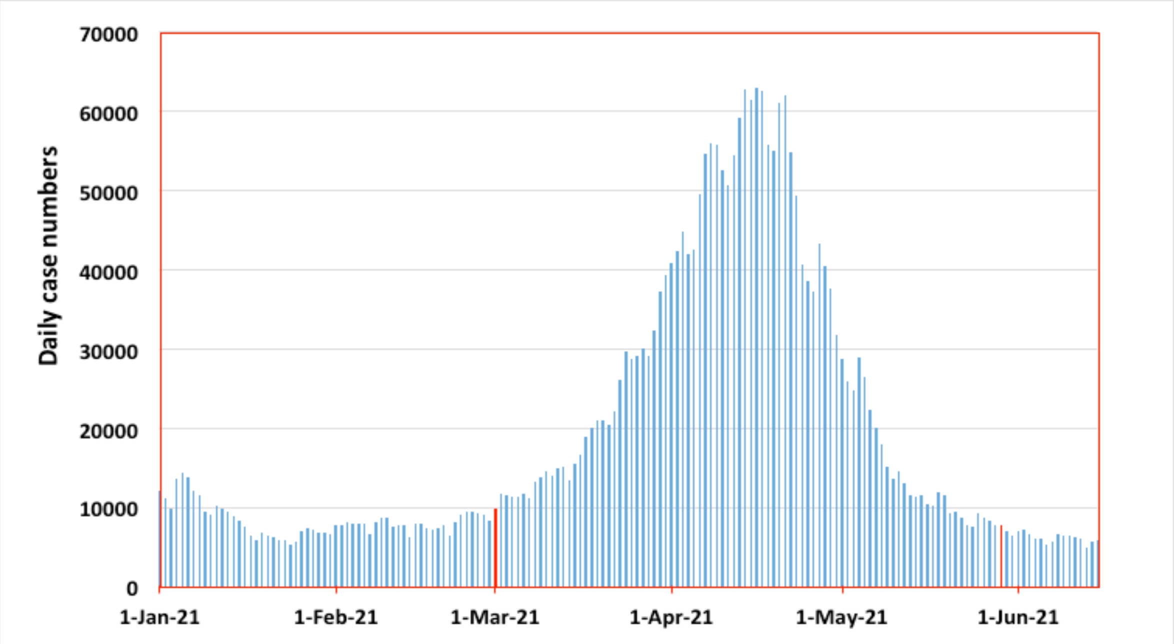


Figure 1. Distribution of daily diagnosed COVID-19 case numbers in Turkey, 01.01.2021 – 15.06.2021 (9).

Variables

The dependent variable was the development of COVID-19. Microbiological confirmation was performed using nasopharyngeal and oropharyngeal sampling according to World Health Organization (WHO) guidelines (1). Viral nucleic acids were isolated from the samples using Bio-Speedy vNAT viral nucleic acid buffer (Bio-Rad CFX Connect Real-Time PCR Detectıon System, USA). The COVID-19 RT PCR kit (DS CORONEX COVID-19 Multıplex Real-Time qPCR, GENSUTEK Ltd., Ankara, Turkey) used in this study was designed to detect SARS-CoV-2 causing COVID-19. The COVID-19 diagnosis was made by COVID-19 RT-PCR test positivity during the three months between 1st of March and 31st of May, 2021. All healthcare workers diagnosed with were followed by the occupational health clinic of the Department of Infectious Diseases and Clinical Microbiology. In addition, all participants were either examined or called by phone on a weekly basis for follow-up.

The independent variables were age, gender, occupation (medical doctor/nurse/assistant health personnel), department type (ICU/other), working environment (COVID-19 clinic/other), history of COVID-19 (present/absent), the time interval between vaccination and diagnosis of COVID-19 (days), and vaccination status (vaccinated/unvaccinated). In addition, data of the patients regarding the period between 01.03.2021 and 31.05.2021 were retrospectively reviewed between 01.06.2021 and 15.06.2021.

COVID-19 vaccination

In Turkey, mass immunization was targeted by four-staged COVID-19 vaccination based on the Turkish COVID-19 National Vaccination Strategy. People were categorized into groups based on the risk of exposure, severe disease, and transmitting the virus. These groups were vaccinated in an order. In this categorization, healthcare workers were included in the first group (i.e., Group A) (8, 9). The first shipment of the CoronaVac vaccine has arrived in Turkey on 30.12.2020. The CoronaVac vaccine (Sinovac Life Sciences, Peking, China) includes 3 µg/0.5 mL (600 SU per dose) inactivated SARS-CoV-2 and aluminum hydroxide as an adjuvant. It should be transported in cold boxes at 2–8 °C (36–46 °F) and is administered intramuscularly. It was given emergency use approval by the Turkish Medicines and Medical Devices Agency, and the healthcare workers were started to be vaccinated in 14.01.2021, and vaccinations of the healthcare workers of our hospital were completed in 15.02.2021. A two-dose vaccination schedule was completed in 28 days on a voluntary basis.

Antibody testing

Anti-SARS-CoV-2 nucleocapsid (i.e., Anti-N) protein immunoglobulin (Ig) M and IgG total antibody (Anti N) tests were performed in the adult vaccination clinic to the healthcare workers who received the 2nd dose of the vaccination at least 14 days ago and unvaccinated healthcare workers. Anti-N antibodies were detected by the Elecsys® Anti-SARS-Cov-2 (Roche Diagnostics, ABD) and electrochemiluminescence immunoassay (ECLIA) method. The test was performed in the Roche Cobas E601 (Roche Diagnostics, ABD) automated analyzer. The results were given qualitatively as non-reactive or reactive based on the cut-off index (COI) values (i.e., COI<1,0 non-reactive, COI>1.0 reactive). In this study only Anti-N antibody was evaluated and healthcare workers were categorized into two groups as positive and negative as per antibody testing results.

Statistical analysis

Categorical variables were given as numbers or percentages with a 95% confidence interval, and the Chi-square test was used for comparisons. The age variable was given as means, standard deviations, minimums, and maximums, and the Student's t-test was used to compare the independent groups.

Odds ratios (OR) were calculated with 95% confidence intervals during the analysis of the COVID-19 risk factors. The vaccine protection rate was calculated by the formula: (1-OR) x100. The protection rate shows the effectiveness of the vaccine (10). Logistic regression analysis was used for analyzing the effects of all variables, including vaccination status, on the development of COVID-19. Adjusted odds ratios calculated by logistic regression analysis were used to determine the vaccine's protection rate and effectiveness.

Layered analyses were performed to determine the "interactions" or "effect modifications" regarding the effectiveness of the vaccine. First, the homogeneity of the odds ratios between different layers was analyzed by the Breslow-Day test. Next, the term "interaction" was added to the logistic regression model if odds ratios were found to be heterogeneous between the layers and interactions/effect modifications were analyzed. Finally, adjusted vaccine effectiveness was calculated separately in different layers of the variables, which were determined as effect modifiers by logistic regression analysis (11–13).

The Statistical Package for Social Sciences (SPSS v20.0, SPSS Inc., USA) software was used for statistical analysis. The p value was considered significant if it was lower than 0.05.

RESULTS

Mean age of the 2.666 healthcare workers included in this study was 37.3±10.2. Among these patients, 55.8% (n=1488) were females and %44.2 (n=1178) were males. While 20.1% (n=536) of the participants were medical doctors, 31.4% (n=836) were registered nurses and 48.5% (n=1294) were allied health personnel. The rates of the participants working in ICU and COVID-19 clinics were 16.5% (n=439) and 20.4% (n=545). In total, 836 (31.4%) patients had history of COVID-19. Among these patients, 36 (1.4%) were hospitalized and 12 (0.05%) were admitted to ICU. While vaccination data were unavailable in 30 (1.1%) cases, 2035 (77.2%) study participants were vaccinated and 601 (22.8%) were unvaccinated (Figure 2). The Anti-N antibody levels were analyzed in 68.9% (n=1381) of the vaccinated. Among those who were unvaccinated, 68.1% (n=409) underwent Anti-N antibody testing. In total, 69% (n=1.813) of the study participants were tested for Anti-N antibodies and 72.2% (n=1.301) of the subjects had a positive result. Among the participants who underwent Anti-N antibody testing, 74.9% (n=1.034) of the vaccinated and 62.1% (n=254) of the unvaccinated were positive ($p<0.001$). Vaccination data of thirteen (0.1%) subjects with a positive antibody result were unavailable. Before vaccinated; while 26.3% (n=536) of the vaccinated participants had a history of COVID-19 and 47.8% (n=287) of the unvaccinated participants had past medical history of COVID-19 ($p<0.001$).

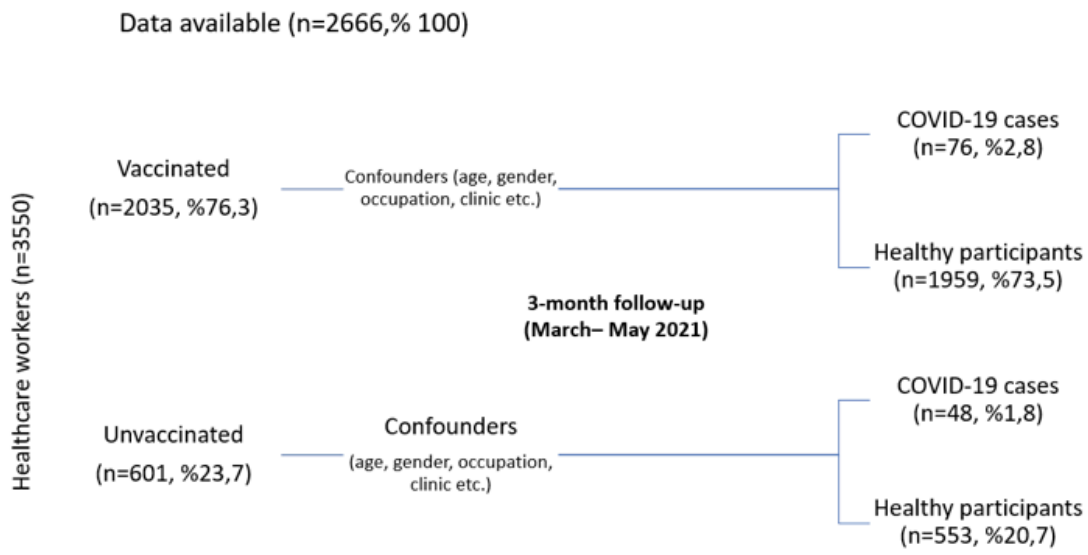


Figure 2. The distribution of participants in terms of vaccination status

During the study period, 124 (4.7%) patients were diagnosed with COVID-19. While most (70.2%) of these cases were diagnosed in April, 9.2% and 20.2% were diagnosed in March and June, respectively (Figure 3). Our review revealed that 61.3% (n=76) of the participants with a history of COVID-19 and 78% (n=1.959) of those without a history of COVID-19 were vaccinated ($p<0.001$). Healthcare workers with anti-N antibodies (n=61) were evaluated and while 41% (n=25) of the subjects who were diagnosed with COVID-19 had a positive antibody result, this figure was 72.8% (n=1276) in the other group ($p<0.001$). None of these cases were hospitalized or admitted to ICU.

A mutant variant of coronavirus was detected in 25 (20.2%) cases. Among these cases, 14 (11.2%) had the English variant, while 11 (8.9%) were detected to have the South African/Brazilian variant. Three cases had a second episode of COVID-19 infection. In these subjects, the re-infection was diagnosed 126, 147, and 230 days after the first infection. All of these three cases were unvaccinated, and they did not undergo Anti-N testing.

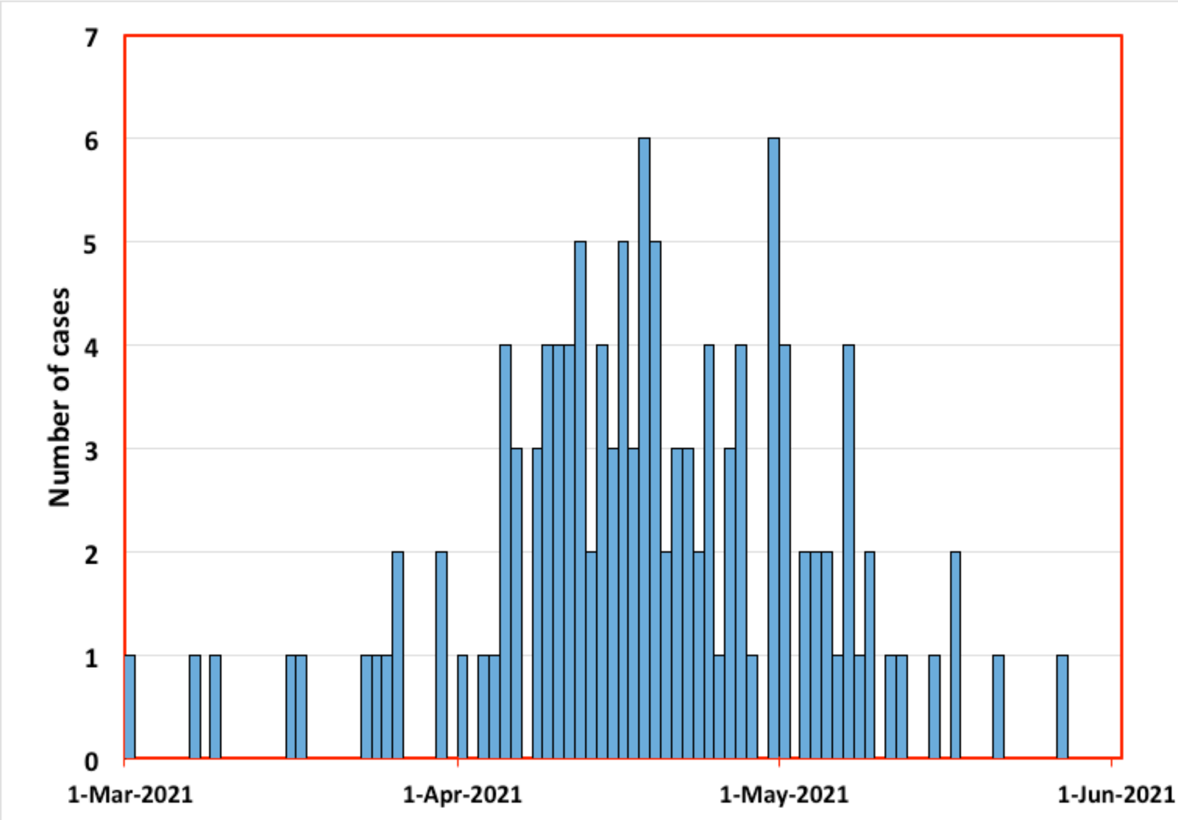


Figure 3. Distribution of cases as per PCR testing dates

Univariate analysis revealed working in ICU, a positive history of COVID-19, COVID-19 vaccination, and a positive antibody test result as protective factors while age, gender, occupation, and working environment (COVID-19 clinic/other) did not have a significant effect. Effectiveness of the vaccine was calculated as 55.3% (95% CI: 34.7-69.2%). Among those who were vaccinated, a positive Anti-N antibody result was found to be more protective than a negative result (Table 1).

Multivariate logistic regression analysis showed that being a medical doctor or a registered nurse, working in ICU or a COVID-19 clinic, a positive history of COVID-19 and COVID-19 vaccination were protective factors against COVID-19 infection. Age and gender were not included in this model. Effectiveness of the vaccine was determined as 72.5% (95% CI: 59.2-81.2%). Among all variables, the strongest protective factor was a history of COVID-19 infection (Table 2).

In the gender layer of the layered analyses, the rough (i.e., unadjusted) and adjusted (i.e., Mantel-Haenszel) odds ratios regarding the effect of the vaccination status on the development of COVID-19 were found to be similar (Unadjusted OR: 0.447; 95% CI:0.308-0.649 and adjusted OR: 0.443; 95% CI: 0.305-0.644). While the OR was calculated as 0.264 (95% CI:0.157- 0.441) for women, it was determined as 0.837 (95% CI:0.466-1.569) for men. These odds

Table 1. Univariate analysis results regarding COVID-19 risk

Variable	Category	CASES (n=124)	CONTROLS (n=2542)	OR (Odds Ratio)	%95 CI	*p* value	Protection rate (%)*	%95 CI
Age (year). mean±SD		36.7±11.1	37.4±10.1	-	-	0.507	-	-
Gender	Male	61(49.2)	1117(43.9)	1.235	0.861-1.772	0.250	-	-
	Female	63(50.8)	1425(56.1)					
Occupation	Other	54(43.5)	1240(48.8)	Reference		0.433	-	-
	Medical doctor	25(20.2)	511(20.1)	1.123	0.682-1.814			
	Nurse	45(36.3)	791(31.1)	1.306	0.673-1.960			
Department type	ICU	10 (8.1)	429(16.9)	0.432	0.213-0.803	**0.010**	56.8	19.7 - 78.7
	Non-ICU	114(91.9)	2113(83.1)					
Working environment	Other clinics	94(75.8)	2027(79.7)	0.796	0.522-1.214	0.289	-20.4	-21.4 - 47.8
	COVID-19 Clinic	30(24.2)	515(20.3)					
History of COVID-19	Present	3(2.4)	833(32.8)	0.051	0.016-0.160	**<0.001**	94.9	0.84 - 98.4
	Absent	121(97.6)	1709(67.2)					
Vaccination status	Vaccinated	76(61.3)	1959(78.0)	0.447	0.308-0.653	**<0.002**	55.3	34.7 - 69.2
	Unvaccinated	48(38.7)	553(22.0)					
Anti-N antibody	Positive	25(41.0)	1276(72.8)	0.259	0.152-0.436	**<0.001**	74.1	56.4 - 84.8
	Negative	36(59.0)	476(27.2)					
Vaccinated healthcare workers	Antibody positive	24(94.8)	1010(97.7)	0.435	0.233-0.823	**0.007**	56.5	17.7 - 76.7
	Antibody negative	18(5.2)	329(2.3)					

Protection rate: (%)=(1 - OR) x 100
SD: Standard deviation
CI: Confidence interval

Table 2. Multivariate logistic regression analysis results regarding COVID-19 risk

Variable	Category	B	Standard error	*p* value	Odds Ratio	%95 CI	Protection rate (%)*	%95 CI
Intercept	-	-0.813	0.273	0.005	-	-	-	-
Occupation	Other	Reference						
	Medical doctor/ Nurse	-0.443	0.196	0.023	0.642	0.439-0.940	35.8	6.0-56.1
Department type	Non-ICU	Reference						
	ICU	-1.221	0.357	0.001	0.295	0.146-0.594	70.5	40.6-85.4
Working environment	Other clinics	Reference						
	COVID-19 Clinic	-0.649	0.233	0.005	0.523	0.331-0.826	47.7	17.4-66.9
History of COVID-19	Absent	Reference						
	Present	-3.364	0.592	<0.001	0.035	0.011-0.110	96.5	89.0-98.9
Vaccination status	Unvaccinated	Reference						
	Vaccinated	-1.289	0.201	<0.001	0.275	0.186-0.408	72.5	59.2-81.4

Hosmer Lemeshow Test p=0.693; Nagelkere R^2=0.148; Omnibus Test p=<0.001
*Protection rate (%) =(1-OR) x100

ratios were significantly different (*p*: 0.004). Since the OR confidence interval included 1 in the analysis of male participants, the logistic regression analysis was repeated for the male participants, female participants, and subsequently for the entire cohort by adding the term 'interaction' (gender*vaccination status) with the assumption that gender was an effect modifier. The effectiveness of the vaccine was found as 84.5% (95% CI:73.3-91) in women and 47% (95% CI:1.7-71.4) in men (Table 3).

Table 3. Results of the logistic regression analysis repeated due to effect modifiers

Analyzed group	Other variables included in the model	Vaccination status	B	Standard error	*p* value	Odds Ratio	%95 CI	Protection rate (%)	%95 CI
WOMEN[1] (n=1468)	History of COVID-19, occupation, department type, working environment	Unvaccinated	Reference						
		Vaccinated	-0.930	0.323	<0.001	0.155	0.090-0.267	84.5	73.3-91.0
MEN[2] (n=1158)	History of COVID-19	Unvaccinated	Reference						
		Vaccinated	-0.635	0.315	0.044	0.530	0.286-0.983	47.0	1.7-71.4
ENTIRE GROUP[3] (n=2636)	History of COVID-19, occupation, department type, working environment, gender	Gender*Vaccination status (interaction term)	-1.049	0.416	0.012	0.350	0.155-0.792	-	-

[1] Hosmer Lemeshow Test p=0.735; Nagelkere R2=0.210; Omnibus Test p=<0.001

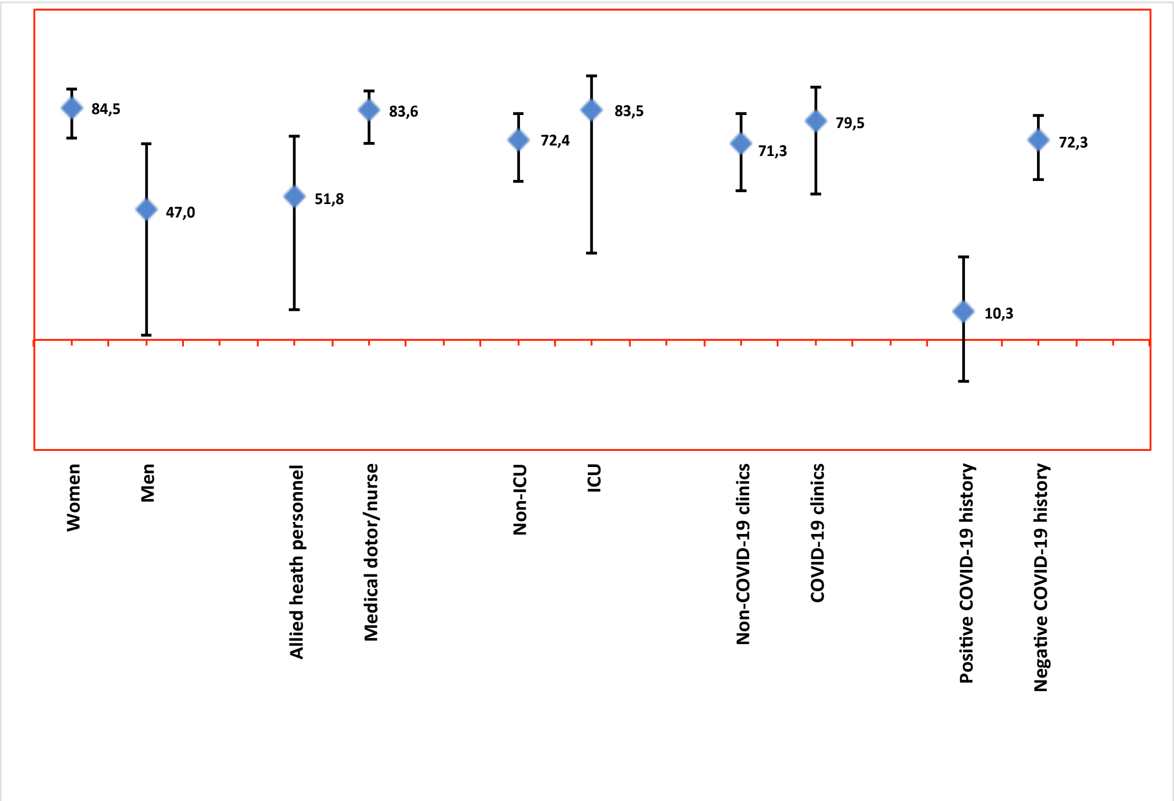
[2] Hosmer Lemeshow Test p=0.613; Nagelkere R2=0.105; Omnibus Test p=<0.001

[3] Hosmer Lemeshow Test p=0.213; Nagelkere R2=0.159; Omnibus Test p=<0.001

In layered analyses, the odds ratios were similar in occupation, working environment (COVID-19 clinic/other), department type (ICU/non-ICU), and history of COVID-19 layers (*p*>0.05). The effectiveness of the vaccine adjusted by the logistic regression model as per different variables with a confidence interval of 95% is shown in Figure 4. The vaccine's effectiveness was not found significant in the study participants with a history of COVID-19 (p=0.394). Considering the confidence intervals, a positive history of COVID-19 was also an effect modifier.

In univariate analysis, investigation of the differences between women and men revealed that the mean age of the female participants was lower than male participants; female subjects had a higher rate of working in ICU and positive antibody test results. The same analysis also showed a higher rate of male participants than female subjects in the allied health personnel group (Table 4).

Analysis of all variables by logistic regression analysis for investigating the differences between women and men elucidated that mean age was higher in men while the rates of a positive history of COVID-19 and antibody positivity were higher in women. The same analysis also confirmed that the male gender was significantly predominant in the allied health personnel group (Table 5).



*Error bars represent 95% confidence interval

Figure 4. Vaccine effectiveness adjusted by logistic regression analysis as per variable categories

Table 4. Comparison of women and men by univariate analysis

Variable	Category	Women	Men	*p* value
Age (mean±SD)	-	36.3±10.1	38.6±10.2	**<0.001**
Occupation	Other	602(40.5)	692(58.7)	**<0.001**
	Medical doctor/nurse	886(59.5)	486(41.3)	
Department type	Non-ICU	1220(82.0)	1007(85.5)	**0.016**
	ICU	268(18.0)	171(14.5)	
Working environment	Other clinics	1168(78.5)	953(80.9)	0.126
	COVID clinic	320(21.5)	225(19.1)	
History of COVID-19	Present	468(31.5)	368(31.2)	0.907
	Absent	1020(68.5)	810(68.8)	
Vaccination status	Vaccinated	1124(76.3)	911(78.4)	0.193
	Unvaccinated	350(23.7)	251(21.6)	
Anti-N antibody	Positive	794(73.7)	507(68.9)	**<0.001**
	Negative	283(26.3)	229(31.1)	
COVID-19 Diagnosis	Case	63(4.2)	61(5.2)	0.250
	Control	1425(95.8)	1117(94.8)	

Table 5. Results of the multivariate logistic regression analysis regarding the differences of female and male study participants in terms of variables

Variable	Category	B	Standard error	p value	Odds Ratio	%95 CI
Intercept	-	-0.886	0.347	0.011	-	-
Age	-	0.015	0.005	0.003	1.015	1005-1.026
Occupation	Other	Reference				
	Medical doctor/nurse	0.603	0.104	<0.001	1.828	1.490-2.242
ICU	Non-ICU	Reference				
	ICU	-0.166	0.148	0.264	0.847	0.634-1.133
Working environment	Other clinics	Reference				
	COVID-19 Clinic	-0.174	0.145	0.230	0.840	0.633-1.116
History of COVID-19	Absent	Reference				
	Present	0.290	0.116	0.013	1.336	1.064-1.678
Vaccination status	Unvaccinated	Reference				
	Vaccinated	0.176	0.126	0.161	1.193	0.932-1.526
Antibody	Positive	Reference				
	Negative	-0.246	0.121	0.042	0.782	0.616-0.991
COVID-19 diagnosis	Present	Reference				
	Absent	-0.261	0.274	0.341	0.77	0.450-1.318

[1] Hosmer Lemeshow Test p=0.724; Nagelkere R2=0.055; Omnibus Test p=<0.001

DISCUSSION

In this study, we determined that the effectiveness of the CoronaVac vaccine in preventing the development of COVID-19 diagnosed by real-time polymerase chain reaction (RT-PCR) in healthcare workers was 84.5% (95% CI:73.3-91) in women and 47% (95% CI:1.7-71.4) in men. As per our analysis, occupation (i.e., medical doctor/nurse/allied health personnel), department type (ICU/non-ICU), and the working environment (COVID-19 clinic/other) did not affect the effectiveness of the vaccine. However, the vaccine was not effective in those with a positive history of COVID-19. This finding may be because the risk of COVID-19 is relatively low in these subjects. We also found that working in ICU, being a medical doctor or a nurse, and working in a COVID-19 clinic was associated with a relatively lower risk of COVID-19. This result may be because these healthcare workers are aware of the high risk of disease transmission and take precautions for their safety.

In a study including 20787 healthcare workers in England, Hall et al. noted that 83% of the patients who recovered from COVID-19 were protected against re-infection during the first five months after the primary episode (14). Furthermore, Abu Raddad L. et al. determined that the re-infection rate was 0.01% (95% CI:0.01-0.02) in patients with a positive history of COVID-19 and the incidence rate was 0.36 per 10000 person-week (95% CI:0.28-0.47) (15). In line with this, a positive history of COVID-19 was found as the most potent protective factor among all variables analyzed.

It is known that accuracy, rapidity, simplicity, convenience, workforce need, and logistics are considered while using antigen and antibody kits (16). In this study, we could analyze the Anti-N antibody titers only because of financial restrictions. K. Oved et al. reported that the specificity and sensitivity of the Roche antibody kit were 100% and 89%, respectively (17). Lumley et al. analyzed the effect of antibodies on the re-infection rates in healthcare workers, and they reported that the rate ratios were similar between those who were tested only for anti-nucleocapsid IgG and those who were also tested for anti-spike IgG (18). Chen et al. determined a strong correlation between Anti-S and Anti-N antibodies (19). In this case-control study, the researchers could test 49.2% of the cases and 69% of the controls for Anti-N antibodies. The univariate regression analysis showed that antibody positivity was protective against COVID-19, and patients with positive Anti-N antibody tests were protected better than those with negative results. This finding shows the significance of antibody response after vaccination.

After completion of the CoronaVac Phase 3 trials, the vaccine's efficacy was reported as 84% in Turkey and 65% in Indonesia (20). While only 10% of the 13000 study participants were healthcare professionals, 1620 subjects included in the study conducted in Indonesia were all selected from the general population. According to WHO reports, in a study conducted in Chile including 10.5 million participants selected from the general population and in another study including 12688 health professionals from Brasil, the vaccine's effectiveness was reported as 67% and 50%, respectively (20). In our study, the effectiveness of CoronaVac was 72.5% (95% CI:59.2-81.2), and it was found to be effective in preventing COVID-19. Although these rates were similar to those reported in other studies, it can be suggested that the differences in the study populations, high risk of COVID-19 exposure in our study population, differences in the follow-up periods, differences in the case densities during different study periods, and differences in mass immunity levels could have led to different outcomes.

Although potential etiologies such as dysregulated inflammation and multi-organ failure were accused of COVID-19-related mortality, the relationship of these factors with the patients' gender was not fully clarified (21). Previously published studies reported that COVID-19 had a more severe and mortal course in men than women (22,23). It is widely accepted that sex hormones, sex chromosomes, genomic and epigenetic differences can lead to the difference in the immune responses of women and men (24,25). Studies investigating the effects of gender on the immune system reported that women develop more potent natural and adaptive immunity responses than men, and this feature provides an advantage in viral clearance and infection control (26,27). It is known that gender-related biological differences can also affect the post-vaccination humoral and cellular immunity (28). Engler et al. worked on 1.114 individuals aged between 18 and 64 to assess the trivalent inactivated influenza vaccine in a randomized prospective trial setting. They concluded that women had more potent humoral immune responses and produced a higher amount of protective antibodies than men (29). These authors also stated that half the dose of a vaccine in women had the same effect as the total dose of the same vaccine in men. Dominguez et al. investigated the efficacy of the measles-mumps-rubella (MMR) vaccine in 2.619 individuals older than 15 years (30). They determined that serum IgG antibody prevalence was higher in women than men.

Similarly, some studies detected relatively higher antibody levels in female children and adult women after hepatitis B vaccination (31,32). In our study, the vaccine's effectiveness was determined to be higher in women than in men. Although the mean age of men was significantly higher than women, this difference was not sufficient to affect the vaccination response. However, the rate of men was higher in the allied health personnel group, and this finding may be the reason for the higher COVID-19 risk. While the rates of a positive history of COVID-19 and subjects with positive antibody testing results were higher in women, the difference between men and women was not significant in this regard. We suggest that we found gender as an effect modifier on vaccine effectiveness may be due to other variables not analyzed in this study. This study was conducted on a group mainly consisting of young and healthy individuals. Vaccine effectiveness can be different based on gender in elderly patient populations. However, this statistical effect modification can also indicate a biological interaction. Although a significant difference is not anticipated between women and men in the general patient population regarding vaccine effectiveness, there may be a significant difference between the two genders in healthcare professionals.

Eyre et al. worked on 3.610 healthcare workers for analyzing the Anti-Spike IgG responses after Pfizer-BioNTech and Oxford-AstraZeneca vaccinations (33). These researchers determined that -after the first dose of vaccination- the seropositivity rate was higher in the young participants who had a history of COVID-19, and these findings were not affected by gender and ethnicity. However, they stated that further studies were needed for analyzing the factors affecting the vaccination response. Vaccines produced for preventing COVID-19 have different immune mechanisms of action (4). In this study, only CoronaVac vaccine outcomes were evaluated with the expectation that its findings can be used for guiding future vaccination programs. Different prime-boost intervals, specific vaccine platforms, and strategies leading to different dosage levels can be applied to men and women and can all be used to eliminate COVID-19.

Since our study is a single-center study, our results may not be generalized to the entire population. However, it should be considered that we had a homogeneous study group regarding virus exposure with the help of this feature. Also, the previously-calculated minimum sample size was exceeded in both vaccinated and unvaccinated groups, and the effectiveness of the vaccine was calculated by a power higher than 90%. Although the fact that only patients with the suspicion of COVID-19 underwent diagnostic testing can be considered a weakness of the study, it should be noted that vaccine effectiveness was calculated based on the prevention of symptomatic disease. Also, the results should have been affected by the sensitivity of the RT-PCR test. However, this influence should be similar in vaccinated and unvaccinated groups. Symptomatology, severity, and duration of symptoms were not analyzed in our study. Since none of the cases were hospitalized or admitted to ICU during the study period, the vaccine's effectiveness could not be assessed in this regard. Potential confounders such as off-duty times, comorbidities, medications, duration of working, night duty, and day shift conditions of the participants were not included in the analysis. However, the most critical factors were analyzed by multivariable analysis. Since a national barcode system was used for the determination of the vaccination status of the participants, there was no risk of bias. Nevertheless, 75% of the target population could be included in the study. The remaining 25% may be a source of selection bias.

Immunization by vaccination has a crucial role in controlling the COVID-19 pandemic. Determination of the factors affecting the effectiveness of the vaccine can increase the success rates. For example, vaccination programs may need to be modified if there is a gender-related difference in vaccine effectiveness. In addition, periodic follow-up of the healthcare workers who were vaccinated for COVID-19 at least for one year can help in the determination of the differences in vaccine effectiveness between various groups, organizing prioritization schedules in vaccination, surveillance, clinical follow-up programs and booster vaccination programs, protection of high-risk of workers, planning of healthcare services and vaccine selections.

ETHICS COMITTEE APPROVAL

* The study was approved by the University of Health Sciences, Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinic Research Ethics Committee (Date: 31.05.2021 and Number: 112/07).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

KAYNAKLAR

1. WHO. Coronavirus disease (COVID-19) - World Health Organization https://www.who.int/emergencies/diseases/novel-coronavirus-2019. Accessed 01 June 2021.
2. CDC. Vaccines and Immunizations-CDC. https://www.cdc.gov/vaccines/index.html. Accessed 01 June 2021.
3. WHO. Immunization coverage. https://www.who.int/news-room/fact-sheets/detail/immunization-coverage. Accessed 20 June 2021.
4. WHO. Draft landscape and tracker of COVID-19 candidate vaccines .https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines. Accessed 1 July 2021.
5. Vellozzi C, Burwen DR, Dobardzic A, Ball R, Walton K, Haber P. Safety of trivalent inactivated influenza vaccines in adults: background for pandemic influenza vaccine safety monitoring. Vaccine 27(15):2114-20. https://doi.org/10.1016/j.vaccine.2009.01.125.

6. Xia S, Duan K, Zhang Y, Zhao D, Zhang H, Xie Z, et al. Effect of an Inactivated Vaccine Against SARS-CoV-2 on Safety and Immunogenicity Outcomes: Interim Analysis of 2 Randomized Clinical Trials. JAMA 324(10):951-60 https://doi.org/10.1001/jama.2020.15543.

7. Staff R. China's CNBG, Sinovac find more countries to test coronavirus vaccines. Reuters https://www.reuters.com/article/us-health-coronavirus-vaccine-china. Accessed 1 July 2021.

8. MOH, Turkey. COVID-19 Vaccine National Implementation Strategy https://covid19asi.saglik.gov.tr/TR-77706/covid-19-asisi-ulusal-uygulama-stratejisi.html. Accessed 5 July 2021.

9. General Coronavirus Table. https://covid19.saglik.gov.tr/TR-66935/genel-koronavirus-tablosu.html. Accessed 2 July 2021.

10. Hekimoğlu CH. Vaccine Epidemiology: Epidemiologic Measures of the Effects of a Vaccine and Vaccination. Turk Bull Hyg Exp Biol. 2016;73(1):55-70. https://doi.org/ 10.5505/TurkHijyen.2016.90377.

11. Corraini P, Olsen M, Pedersen L, Dekkers OM, Vandenbroucke JP. Vandenbroucke JP. Effect modification, interaction and mediation: an overview of theoretical insights for clinical investigators. Clin Epidemiol. 2017;9:331-8. https://doi.org/10.2147/CLEP.S129728.

12. Knol MJ, VanderWeele TJ. Recommendations for presenting analyses of effect modification and interaction. Int J Epidemiol 41(2):514-20. https://doi.org/10.1093/ije/dyr218.

13. VanderWeele TJ. On the distinction between interaction and effect modification. Epidemiol Camb Mass. 20(6):863-71. https://doi.org/10.1097/EDE.0b013e3181ba333c.

14. Hall V, Foulkes S, Charlett A, Atti A, Monk EJM, Simmons R, et al. Simmons R, vd. Do antibody positive healthcare workers have lower SARS-CoV-2 infection rates than antibody negative healthcare workers? Large multi-centre prospective cohort study (the SIREN study), England: June to November 2020. https://www.medrxiv.org/content/10.1101/2021.01.13.21249642.

15. Abu Raddad LJ, Chemaitelly H, Malek JA, Ahmed AA, Mohamoud YA, Younuskunju S, et al. Assessment of the risk of SARS-CoV-2 reinfection in an intense re-exposure setting. Epidemiology. http://medrxiv.org/lookup/doi/10.1101/2020.08.24.20179457.

16. CDC. Coronavirus Disease 2019 (COVID-19). Centers for Disease Control and Prevention. 2020 https://www.cdc.gov/coronavirus/2019-ncov/index.html Accessed 5 July 2021.

17. Oved K, Olmer L, Shemer-Avni Y, Wolf T, Supino-Rosin L et al. Multi-center nationwide comparison of seven serology assays reveals a SARS-CoV-2 non-responding seronegative subpopulation. EClinicalMedicine 29-30:100651. https://doi.org/10.1016/j.eclinm.2020.100651.

18. Lumley SF, O'Donnell D, Stoesser NE, Matthews PC, Howarth A et al. Antibodies to SARS-CoV-2 are associated with protection against reinfection https://www.medrxiv.org/content/10.1101/2020.11.18.20234369.

19. Chen Y, Zuiani A, Fischinger S, Mullur J, Atyeo C , Travers M, et al. Quick COVID-19 Healers Sustain Anti-SARS-CoV-2 Antibody Production. Cell 183(6):1496-1507 https://doi.org/10.1016/j.cell.2020.10.051.

20. Strategic Advisory Group of Experts on Immunization https://www.who.int/groups/strategic-advisory-group-of-experts-on-immunization/working-groups/cholera. Accessed 4 July 2021.

21. Scully EP, Haverfield J, Ursin RL, Tannenbaum C, Klein SL. Considering how biological sex impacts immune responses and COVID-19 outcomes. Nat Rev Immunol. 20(7):442-7 https://doi.org/10.1038/s41577-020-0348-8.

22. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA 323(13):1239-42 https://doi.org/10.1001/jama.2020.2648.

23. Dudley JP, Lee NT. Disparities in Age-specific Morbidity and Mortality From SARS-CoV-2 in China and the Republic of Korea. Clin Infect Dis Off Publ Infect Dis Soc Am. 71(15):863-5 https://doi.org/10.1093/cid/ciaa354.

24. Ghosh S, Klein RS. Sex Drives Dimorphic Immune Responses to Viral Infections. J Immunol 198(5):1782-90 https://doi.org/10.4049/jimmunol.1601166.

25. Piasecka B, Duffy D, Urrutia A, Quach H, Patin E , Posseme C, et al. Distinctive roles of age, sex, and genetics in shaping transcriptional variation of human immune responses to microbial challenges. Proc Natl Acad Sci. 115(3):488-97 https://doi.org/10.1073/pnas.1714765115.

26. Flanagan KL, Fink AL, Plebanski M, Klein SL. Sex and Gender Differences in the Outcomes of Vaccination over the Life Course. Annu Rev Cell Dev Biol.33:577-99 https://doi.org/10.1146/annurev-cellbio-100616-060718.

27. Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol 16(10):626-38 https://doi.org/10.1038/nri.2016.90.

28. Klein SL, Jedlicka A, Pekosz A. The Xs and Y of immune responses to viral vaccines. Lancet Infect Dis. 10(5):338-49 https://doi.org/10.1016/S1473-3099(10)70049-9.

29. Engler RJM, Nelson MR, Klote MM, VanRaden MJ, Huang C-Y, Cox NJ, et al. Half- vs full-dose trivalent inactivated influenza vaccine (2004-2005): age, dose, and sex effects on immune responses. Arch Intern Med. 168(22):2405-14 https://doi.org/10.1001/archinternmed.2008.513.

30. Domínguez A, Plans P, Costa J, Torner N, Cardenosa N, Batalla J et al. Seroprevalence of measles, rubella, and mumps antibodies in Catalonia, Spain: results of a cross-sectional study. Eur J Clin Microbiol Infect Dis Off Publ Eur Soc Clin Microbiol 25(5):310-7 https://doi.org/10.1007/s10096-006-0133-z.

31. Fang JW, Lai CL, Chung HT, Wu PC, Lau JY. Female children respond to recombinant hepatitis B vaccine with a higher titre than male. J Trop Pediatr 40(2):104-7 https://doi.org/10.1093/tropej/40.2.104.

32. Bock HL, Kruppenbacher J, Sänger R, Höbel W, Clemens R, Jilg W, et al. Immunogenicity of a recombinant hepatitis B vaccine in adults. Arch Intern Med. 156(19):2226-31 https://doi.org/10.1001/archinte.1996.00440180088011.

33. Eyre DW, Lumley SF, Wei J, Cox S, James T, Justice A et al. Quantitative SARS-CoV-2 anti-spike responses to Pfizer-BioNTech and Oxford-AstraZeneca vaccines by previous infection status. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis. 21;S1198-743X(21)00289-5. https://doi.org/10.1016/j.cmi.2021.05.041.