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Influence of epidemiological and clinical factors in the reactogenicity to Comirnaty® vaccine in health care workers of a Spanish university teaching hospital (COVIVAC study)

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ABSTRACT

Introduction. Comirnaty® is an mRNA vaccine against COVID-19 which has been administered to millions of people since the end of 2020. Our aim was to study epidemiological and clinical factors influencing reactogenicity and functional limitation after the first two doses of the vaccine in health care workers (HCWs).

Material and methods. Prospective post-authorization cohort study to monitor safety and effectiveness of the vaccine.

Results. Local side effects were mild and presented both with first and second dose of Comirnaty. Systemic side effects were more frequent after 2nd dose. Nevertheless, previous SARS-CoV-2 infection was associated with systemic effects after the first dose of the vaccine (OR ranging from 2 to 6). No severe adverse effects were reported. According to multivariate analysis, the degree of self-reported functional limitation after the first dose increased with age, female sex, previous COVID-19 contact, previous SARS-CoV-2 infection, and Charlson Comorbidity Index (CCI). After the second dose, the degree of functional limitation observed was lower in those with previous SARS-CoV-2 infection, and it was positively associated to the degree of functional limitation after the first dose.

Conclusion. Systemic adverse effects were more frequent after the second dose of Comirnaty. Previous SARS-CoV-2 infection was associated with systemic effects after the first dose. Age, female sex, previous COVID-19, previous isolation due to COVID-19 contact, and CCI showed to be independent predictors of the degree of functional limitation after the 1st dose of Comirnaty®. After the 2nd dose, the degree of functional limitation was lower in those who previously had SARS-CoV-2 infection.

Keywords: COVID-19, Vaccines, Comirnaty, reactogenicity

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Influencia de factores epidemiológicos y clínicos en la reactogenicidad a la vacuna Comirnaty® en trabajadores sanitarios de un hospital universitario español (estudio COVIVAC)

RESUMEN

Introducción. Comirnaty® es una vacuna de ARNm contra el COVID-19 que se ha administrado a millones de personas desde finales de 2020. Nuestro objetivo fue estudiar los factores epidemiológicos y clínicos que influyen en la reactogenicidad y la limitación funcional asociadas tras las dos primeras dosis de la vacuna en trabajadores de la salud.

Metodología. Estudio de cohorte prospectivo post-autorización para evaluar la seguridad y eficacia de la vacuna.

Resultados. Los efectos secundarios locales fueron leves y se presentaron tanto con la primera como con la segunda dosis de Comirnaty. Los efectos secundarios sistémicos fueron más frecuentes después de la segunda dosis. No obstante, la infección previa por SARS-CoV-2 se asoció con efectos sistémicos tras la primera dosis de la vacuna (OR de 2 a 6). No se informaron efectos adversos graves. El análisis multivariante demostró que el grado de limitación funcional tras la primera dosis aumentó con la edad, el sexo femenino, contacto previo con COVID-19, la infección previa por SARS CoV-2 y el índice de comorbilidad de Charlson (ICC). Tras la segunda dosis, el grado de limitación funcional observado fue menor en aquellos con infección previa por SARS-CoV-2, y se asoció positivamente al grado de limitación funcional tras la primera dosis.

Conclusión. Los efectos adversos sistémicos fueron más frecuentes después de la segunda dosis de Comirnaty. La infección previa por SARS-CoV-2 se asoció con efectos sistémicos después de la primera dosis. La edad, el sexo femenino, infección por COVID-19 previa, el aislamiento previo por contacto de COVID-19 y el ICC se mostraron como predictores inde-

pendientes del grado de limitación funcional tras la 1ª dosis de Comirnaty®. Después de la 2.ª dosis, el grado de limitación funcional fue menor en los que previamente tenían infección por SARS-CoV-2.

Palabras clave: COVID-19, Vacunas, Comirnaty, reactogenicidad

INTRODUCTION

Since December 2019 more than 295 million COVID-19 cases and almost 5.5 million deaths have been reported worldwide [1]. The magnitude of the health problem has driven the focus of public health efforts to the development of effective and safe vaccines with an unprecedented celerity [2]. Comirnaty®, an mRNA BNT162b2 vaccine, developed by Pfizer-BIONTech, has been one of the first vaccines in being approved by EMA (European Medicines Agency) and FDA (USA Food and Drug Administration) [3,4]. This vaccine showed to be reasonable safe, and evidenced a high efficacy in preventing symptomatic (over 90%) and severe COVID-19 (over 95 %) in clinical trials conducted in adults, younger people (from 12-15 years old) and lately, in children (from 5 to 11 years) [5-8]. In different post-authorization studies conducted in Israel, the vaccine showed an effectiveness over 95% in preventing symptomatic COVID-19, and even higher in preventing severe illness or death [9,10]

In the different clinical trials conducted (adult people, adolescents, children), the safety profile of the vaccine showed to be acceptable, reporting mild to moderate side effects, such as injection site pain, fatigue, and headache, though some serious allergic reactions were observed [5,7,8]. In other post-authorization studies, less frequent side effects, (with around 1 per 10,000 incidence rate) such as myocarditis, and pericarditis, more common in young male people, have been reported [11,12]. Other possible less frequent side effects are under study. Further observational post-emergency use authorization studies are needed in order to more precisely define the safety profile of these new vaccines [13].

The COVIVAC-1 is a prospective cohort investigation on the safety and effectiveness of Comirnaty® vaccine in health care workers of a university teaching Spanish hospital who received two doses of the vaccine, taking into account epidemiological and clinical variables such as age, sex, ethnicity, blood group, comorbidities, previous COVID-19 infection, or previous exposure to COVID-19.

MATERIAL AND METHODS

COVIVAC-1 is a prospective cohort study about safety and effectiveness of mRNA BNT162b2 vaccine (Comirnaty®). This investigation was conducted in health care workers (HCW) of the HM Sanchinarro, a university teaching hospital in Madrid (Spain), who had received two doses of the vaccine. The first phase of the study, concerning safety, was carried out after reception of both doses of the vaccine. In this phase, which was focused on safety issues of the vaccine, the health care workers answered an online questionnaire about previous health conditions (including comorbidities, previous exposure to COVID-19 at home or at work, previous COVID-19 infection, or previous isolation due to COVID-19 contact), age, sex, ethnicity, blood group, date of administration of each dose, and possible adverse effects, from mild to severe. All participants agreed to enter the study (informed consent) at the time of receiving the second dose of vaccine. The study was approved by the Ethics Advisory Board of HM hospitals.

Quantitative data were presented with mean and standard deviation, or median and interquartile range in case of non-parametric data. Qualitative data were presented with proportions and percentages. Association was studied with Pearson coefficient for normal quantitative data, and chi square test in case of parametric qualitative data. In non-parametric data, Spearman coefficient and Fisher's exact test were applied, respectively. Logistic regression was applied to study the association of the different secondary effects to previous COVID-19 infection or exposure, and linear regression (multivariate) was used to study the association of clinical and epidemiological factors to the degree of functional limitation with each dose of the vaccine. Data analysis was performed with STATA software version 16.1.

RESULTS

Up to 278 HCW answered the questionnaire (85 male, 193 female). The mean age was 39.34 years in men, and 36.31 years in women ($p<0.05$). The complete description of the characteristics of participants is presented in Table 1.

Regarding previous exposure to SARS-CoV-2, more than 60% of HCW reported previous exposure to COVID-19 patients without adequate protection in the laboral environment, around 15% at home, and around 15% had been isolated before the vaccination due to COVID-19 contact. 19 per cent of them reported previous SARS-CoV-2 infection The list of symptoms in those with previous COVID-19, as well as other more concrete data about previous exposure to COVID-19 might be consulted in Table 2.

The most frequent adverse effect was local pain, significantly slightly more common after first dose (83 vs 78%, $p<0.05$). On the other hand, systemic symptoms including fever (from mild to severe), dysthermia, use of antipyretic, headache, cough, vomiting, diarrhoea, adenopathy, myalgia, arthralgia, and work absenteeism, were significantly more frequent after the second dose of the vaccine ($p<0.05$). More concrete details might be consulted in Table 3. The degree of post-vaccine limitation was significatively higher after the second dose of the vaccine (Figure 1).

Previous COVID-19 was significantly associated with higher incidence of low-grade fever (OR 2.96), asthenia (OR 2.48), headache (OR 2.8), dysthermia (OR 4.36), myalgia (OR 5.69), use of antipyretic (OR 3.46), and post-vaccine functional limitation, after the first dose of Comirnaty®. On the other hand, after the second dose of Comirnaty®, previous COVID-19 was

Table 1 Descriptive summary of Health Care Workers fully vaccinated with Comirnaty

Sex n (%)	Men 85 (30.58)	Women 193 (69.42)		
Age mean (IC 95%)	39.34 (36.58-42.10)	36.31 (34.93-37.70)		p = 0.031
BMI mean (IC 95%)	25.37 (24.69-26.09)	22.63 (22.10-23.17)		p < 0.0001
Ethnicity n (%)	Caucasian 76 (89.41)	Caucasian 166 (86.01)		
	Asian 0 (0)	Asian 2 (1.04)		
	Latin 9 (10.59)	Latin 23 (11.92)		
	Black 0 (0)	Black 1 (0.52)		
	Other 0 (0)	Other 1 (0.52)		p=0.749
Blood Group n (%)	0- 8 (12.12)	0- 12 (7.55)		
	0+ 23 (34.85)	0+ 53 (33.33)		
	A+ 31 (46.97)	A+ 76 (47.80)		
	B+ 4 (6.06)	B+ 18 (11.32)		p=0.483
Comorbidities n (%)				
COPD- Asthma	3 (3.53)	14 (7.25)		p=0.234
Acute Myocardial Infarction	0 (0)	0 (0)		p=0.606
Cardiac Failure	0 (0)	0 (0)		p=0.182
Vascular Peripheric Disease	4 (2.07)	2 (1.18)		p=0.0325
Stroke	0 (0)	0 (0)		p=0.0325
Dementia	0 (0)	0 (0)		p=0.883
Rheumatologic Disease	4 (2.07)	0 (0)		p=0.808
Ulcus	0 (0)	2 (2.35)		
Hepatic steatosis	0 (0)	2 (2.35)		
Hepatic Cirrhosis	0 (0)	0 (0)		
DM with target organ damage	0 (0)	0 (0)		
DM without target organ damage	4 (2.07)	2 (2.35)		
Hemiplegia	0 (0)	0 (0)		
Kidney Chronic Disease	0 (0)	0 (0)		
Tumour	3 (1.55)	1 (1.18)		
Leukaemia	0 (0)	0 (0)		
Lymphoma	0 (0)	0 (0)		
Metastasis	0 (0)	0 (0)		
AIDS	0 (0)	0 (0)		
Charlson Index n (%)	0	75 (88.24)	167 (86.53)	p=0.896
	1	8 (9.41)	21 (10.08)	
	2	2 (2.35)	4 (2.07)	
	3	0 (0)	1 (0.52)	

associated with lower incidence of moderate fever (OR 0.13) and cough (OR 0.16), and, as with the first dose, with greater incidence of asthenia (OR 2.48). The rest of adverse effects studied did not show significative association with previous COVID-19 (Table 4).

Finally, we employed linear regression analysis to study the predictive capacity of different factors and covariables in the degree of self-reported (from 0 to 5) functional limitation after each dose of the vaccine. Neither ethnicity, blood group, or body mass index revealed themselves as significant predic-

Table 2 Previous exposure to SARS-CoV2 in HCWs receptors of COVID-19 mRNA BNT162b2 (n =278)

COVID-19 Laboral contact n (%)	167 (60.07)
COVID-19 Cohabiting Contact n (%)	40 (14.39)
Isolation due to COVID-19 contact n (%)	42 (15.11)
N. isolations due to COVID-19 contact	
1 isolation n (%)	29 (70.73)
2 isolations n (%)	9 (21.95)
3 isolations n (%)	3 (7.32)
Previous COVID-19 diagnose n (%)	53 (19.06)
PCR n (%)	31 (11.15)
Ag test n (%)	3 (1.08)
Serology n (%)	19 (6.83)
Hospitalization due to COVID-19	1 (0.36)
ICU admission due to COVID-19	1 (0.36)
Symptoms in previous COVID-19 cases in vaccinated health care workers n (%)	
Fever	24 (45.28)
Cough	21 (39.62)
Dyspnoea	9 (16.98)
Diarrhoea	10 (18.87)
Headache	33 (62.26)
Dysgeusia	28 (52.83)
Anosmia	33 (62.26)
Asthenia	44 (83.02)
Myalgia	26 (49.06)
Odynophagia	8 (15.09)
Chest tightness	9 (16.98)
Extreme weakness	1 (1.89)
Rash	2 (3.77)

tors of functional limitation after the first or second dose of Comirnaty®. After the first dose of Comirnaty®, in the multivariate model, we found a positive independent association between degree of functional limitation and age (years), female sex, previous SARS-CoV-2 infection, previous isolation due to COVID-19 contact, and Charlson Comorbidity Index Punctuation. By contrast, after the second dose of the vaccine, in the multivariate model, the degree of functional limitation was positively associated with the degree of functional limitation (0 to 5) after the first dose of vaccine ($p<0.001$), and it was significatively lower in people with previous COVID-19 (Table 5)

DISCUSSION

In our group of health care workers fully vaccinated with Comirnaty®, around 90% did experience at least one side effect. Most of the self-reported side effects were mild to moderate. The main adverse effect observed after the first and second dose of Comirnaty® was local pain. In general, systemic side effects were significatively more intense after the second dose of the vaccine. The degree of self-reported functional limitation (from 0 to 5) after vaccination was also significantly higher after the second dose of the vaccine ($p<0.05$).

This echoes the results of the clinical trial conducted by Polack [5], and the cohort study by Chapin-Bardales [14], with over three and half million participants, using the V-safe Active Surveillance System, in USA.

On the contrary, another evidence from our study was that in those with previous SARS-CoV-2 infection, systemic side effects were more intense after first dose of Comirnaty®. These findings were in congruence with those reported by Me-

Table 3 Adverse effects after 1st and 2nd dose of COVID-19 mRNA BNT162b2 vaccine (n =278)

Adverse effect	1st Dose n (%)	2nd Dose n (%)	P
None	31 (11.15)	27(9.71)	0.48
Local erythema	35 (12.59)	30 (10.79)	0.25
Local swelling	51 (18.35)	51 (18.35)	1
Local pain	232 (83.45)	217 (78.06)	0.025
Low grade fever (under 38ºC)	18 (6.47)	62 (22.30)	<0.0001
Fever >38ºC & < 39ºC	6 (2.16)	31 (11.15)	<0.0001
Fever >39ºC	0 (0)	7 (2.52)	<0.01
Asthenia	72(25.90)	72 (25.90)	1
Headache	60 (21.58)	104 (37.41)	<0.0001
Dysthermia	39 (14.03)	97 (34.89)	<0.0001
Cough	13 (4.68)	46 (16.55)	<0.0001
Vomiting	1 (0.36)	16 (5.76)	<0.001
Diarrhoea	6 (2.16)	20 (7.19)	0.002
Adenopathy	11 (3.96)	27 (9.71)	0.002
Myalgia	23 (8.27)	80 (28.78)	<0.0001
Arthralgia	16 (5.76)	46 (16.55)	<0.0001
Antipyretic use	44 (15.83)	95 (34.17)	<0.0001
Urgent care need	0 (0)	0 (0)	
Work absenteeism	4 (1.44)	16 (5.76)	0.003
Post-vaccine limitation			
None (0)	182 (65.70)	122 (43.88)	< 0.001
Very Mild (1)	45 (16.25)	38 (13.67)	
Mild (2)	22 (7.94)	34 (12.23)	
Moderate (3)	12 (4.33)	38 (13.67)	
Severe (4)	13 (4.69)	34 (12.23)	
Very Severe (5)	3 (1.08)	12 (4.32)	

ni [15] in the British COVID Symptom Study and D'Arminio [16] on HCW in Italy.

A very rare adverse effect attributed to mRNA vaccines (Pfizer and Moderna) has been the development of myocarditis and/or pericarditis, mainly in the first week after the second dose, as reported by Kim [17], Montgomery [18], Marshall [19] or Boehmer [20]. No events of pericarditis or myocarditis post-vaccination with Comirnaty® were reported in our series of 278 HCW. No deaths or other serious adverse events were reported in our study.

A strength of our study is the attention paid to different epidemiological and clinical factors and their influence in the reactogenicity to Comirnaty®. In this way, in the multivariate linear regression analysis we found that age, female sex, Charlson Comorbidity Index Punctuation, previous SARS CoV-2 infection, and previous isolation due to COVID-19 contact

Table 4 OR of previous COVID-19 and adverse effects after mRNA BNT162b2 vaccine (n =278)

Adverse effect*	Dose 1 OR (IC 95%)	p	Dose 2 OR (IC 95%)	p
Low grade fever (<38ºC)	**2.96 (1.08-8.04)**	**0.033**	0.66 (0.30-1.45)	0.303
Fever >38ºC & < 39ºC	0.85 (0.10-7.40)	0.880	**0.13 (0.02-0.94)**	**0.043**
Asthenia	**2.48 (1.32-4.67)**	**0.005**	**2.48 (1.32-4.67)**	**0.005**
Headache	**2.80 (1.46-5.38)**	**0.002**	0.83 (0.44-1.56)	0.565
Dysthermia	**4.36 (2.11-9.00)**	**<0.0001**	0.77 (0.40-1.47)	0.425
Cough	1.29 (0.34-4.86)	0.71	**0.16 (0.04-0.69)**	**0.014**
Myalgia	**5.69 (2.35-13.78)**	**<0.0001**	0.97 (0.50-1.88)	0.932
Arthralgia	**4.82 (1.72-13.52)**	**0.003**	1.04 (0.47-2.31)	0.925
Antipyretic use	3.46 (1.71-6.99)	**0.001**	0.89 (0.47-1.69)	0.721
Post-vaccine limitation				
None (0)	1		1	
Very Mild (1)	**2.28 (1.04-5.01)**	**0.039**	0.63 (0.24-1.66)	0.349
Mild (2)	2.35 (0.84-6.59)	0.103	0.45 (0.15-1.38)	0.162
Moderate (3)	**6.28 (1.88-21.01)**	**0.003**	1.20 (0.52-2.77)	0.671
Severe (4)	2.80 (0.80-9.75)	0.108	0.32 (0.09-1.14)	0.080
Very Severe (5)			0.67 (0.14-3.24)	0.620

*The rest of adverse effects did not show significant association (OR) with previous COVID-19, nor with 1st dose, neither with 2nd dose.

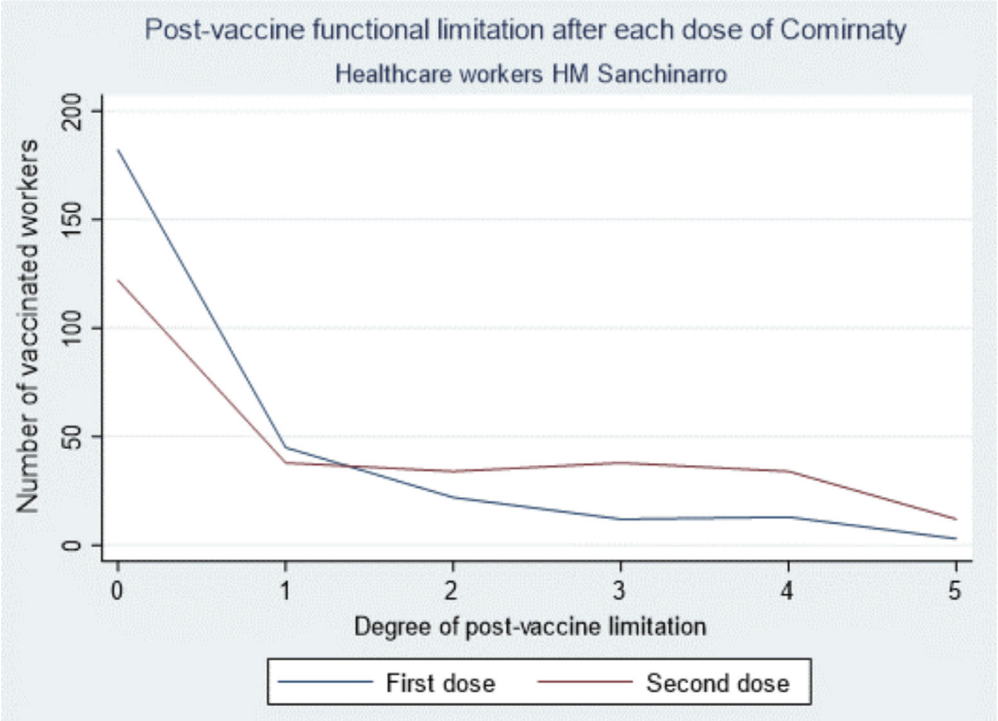

Figure 1 Degree of functional limitation (0 to 5) in HCWs after 1st & 2nd dose of Comirnaty

Table 5 Multivariate Linear regression model of post-vaccine limitation after 1st & 2nd dose of Comirnaty®

	Model after 1st dose		
	Coef.	CI 95%	P Wald
Age (each year)	0.0016	0.001 to 0.002	<0.001
Male Sex	-0.34	-0.62 to - 0.05	0.021
Charlson Index	0.35	0.05 to 0.65	0.020
Previous COVID-19	0.61	0.27 to 0.95	<0.001
Isolation due to COVID-19 contact	0.47	0.09 - 0.84	0.015
	Model after 2nd dose		
	Coef.	CI 95%	P Wald
Age (each year)	0.00003	-0.001 to 0.001	0.963
Male Sex	-0.20	-0.60 to 0.20	0.332
Charlson Index	-0.04	-0.45 to 0.38	0.859
Previous COVID-19	-0.55	-1.03 to -0.06	0.027
Isolation due to COVID-19 contact	-0.11	-0.64 to 0.42	0.687
Functional limitation after 1st dose (0 to 5)	0.48	0.31 to 0.64	<0.001

were independent predictors of a higher degree of functional limitation after the first dose of Comirnaty®. After the second dose, previous COVID-19 was associated with a lower functional limitation, and only the degree of functional limitation after the first dose revealed itself as an independent predictor of greater impairment. Other evidences from our analyses not published in previous works include that no differences in functional limitation post-vaccination were observed according to body mass index, ethnicity, or blood group.

A limitation of our study was the limited number of participants, though this could be counterbalanced with the higher degree of precision in the answer to the questionnaire due to the fact that all of them were HCW. Although this limitation, we obtained results in congruence with much greater studies, such as the ones conducted by Chapin Bardales or Menni [14,15].

CONCLUSION

In conclusion, in the same way as other studies, globally we found a higher incidence of systemic side effects with the second dose of Comirnaty® than with the first dose, while in those previously infected by SARS-CoV-2 systemic adverse effects were more intense after the first dose. No events of myocarditis neither pericarditis were reported in our HCW population. No deaths or major severe adverse events were reported. The degree of functional limitation after the first dose was independently associated with age, female sex, previous COVID-19 isolation, previous SARS-CoV-2 infection, and punctuation in the Charlson Comorbidity Index. The degree of functional limitation after the first dose showed to be an independent predictor of a higher degree of functional limitation after the second dose, while previous SARS-CoV-2 infection was associated with a lower functional limitation after the second dose. Further post-emergency use authorization studies are still needed in order to define more precisely the safety profile of these new vaccines against COVID-19.

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None to declare.

CONFLICT OF INTEREST

Authors declare no have conflict of interest

REFERENCES

1. WHO, COVID-19 Dashboard, 4th January 2022, from https://covid19.who.int/. Last access 5th february 2022
2. Our World in Data. "Coronavirus (COVID-19) Vaccinations." from https://ourworldindata.org/covid-vaccinations. last access 5th January 2022
3. EMA Comirnaty authorization for Emergency Authorized Use, 21st December 2020, available at https://www.ema.europa.eu/en/news/ema-recommends-first-covid-19-vaccine-authorisation-eu, last access 5th January 2022

4. FDA full approval in people of sixteen years or older for Comirnaty vaccine, 23rd August 2021. Available at https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/comirnaty-and-pfizer-biontech-covid-19-vaccine, last access 5th January 2022

5. Polack FP, Thomas SJ, Kitchin N, et al; C4591001 Clinical Trial Group. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med. 2020 Dec 31; 383(27):2603-2615. doi: 10.1056/NEJMoa2034577.

6. Chagla Z. The BNT162b2 (BioNTech/Pfizer) vaccine had 95% efficacy against COVID-19 ≥7 days after the 2nd dose. Ann Intern Med. 2021 Feb;174(2):JC15. Doi: 10.7326/ACPJ202102160-015.

7. Frenck RW Jr, Klein NP, Kitchin N, et al; Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents. N Engl J Med. 2021;385(3):239-250. doi: 10.1056/NEJMoa2107456.

8. Walter EB, Talaat KR, Sabharwal C, et al; C4591007 Clinical Trial Group. Evaluation of the BNT162b2 Covid-19 Vaccine in Children 5 to 11 Years of Age. N Engl J Med. 2022;386(1):35-46. doi: 10.1056/NEJMoa2116298.

9. Haas EJ, Angulo FJ, McLaughlin JM, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. Lancet. 2021 May 15;397(10287):1819-1829. doi:: 10.1016/S0140-6736(21)00947-8.

10. Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting, New England Journal of Medicine 2021;384(15):1412-1423. doi:

11. EMA update on safety profile of Comirnaty, December 2021, from https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/covid-19-vaccine-safety-update-comirnaty-9-december-2021_en.pdf, last access 5th January 2022

12. Rathore SS, Rojas GA, Sondhi M, et al. Myocarditis associated with Covid-19 disease: a systematic review of published case reports and case series. Int J Clin Pract . 2021;75(11):e14470. doi: 10.1111/ijcp.14470

13. Patel, M. K., Bergeri, I., Bresee, J. S et al. Evaluation of post-introduction COVID-19 vaccine effectiveness: Summary of interim guidance of the World Health Organization. Vaccine, S0264-410X(21)00707-6. doi: 10.1016/j.vaccine.2021.05.099.

14. Chapin-Bardales J, Gee J, Myers T. Reactogenicity Following Receipt of mRNA-Based COVID-19 Vaccines. JAMA. 2021 Jun 1;325(21):2201-2202. doi: 10.1001/jama.2021.5374.

15. Menni, C., Klaser, K., May, A., et al (2021). Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID Symptom Study app in the UK: a prospective observational study. The Lancet Infectious Diseases, 21(7). 00224-3. doi: 10.1016/S1473-3099(21)00224-3

16. D'Arminio Monforte, A; Tavelli, A; Perrone, PM., et al. Association between previous infection with SARS CoV-2 and the risk of self-reported symptoms after mRNA BNT162b2 vaccination: Data from 3,078 health care workers, EClinicalMedicine, 2021;36:100914. doi: 10.1016/j.eclinm.2021.100914.

17. Kim HW, Jenista ER, Wendell DC et al. Patients With Acute Myocarditis Following mRNA COVID-19 Vaccination. JAMA Cardiol. 2021;6(10):1196-1201. doi: 10.1001/jamacardio.2021.2828.

18. Montgomery J, RyanM, Engler R, et al. Myocarditis following immunization with mRNA COVID-19 vaccines in members of the US military. JAMA Cardiol. 2021;6(10):1202-1206 19. Marshall M, Ferguson ID, Lewis P, et al. Symptomatic acute myocarditis in seven adolescents following Pfizer-BioNTech COVID-19 vaccination. Pediatrics. Published online June 4, 2021. doi: 10.1001/jamacardio.2021.2833

20. Boehmer TK, Kompaniyets L, Lavery AM, et al. Association Between COVID-19 and Myocarditis Using Hospital-Based Administrative Data — United States, March 2020–January 2021. MMWR Morb Mortal Wkly Rep 2021;70:1228–1232. doi: 10.15585/mmwr.mm7035e5.