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Safety and immunogenicity of COVID-19 BBIBP-CorV vaccine in children 3-12 years old

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Abstract

Background and Objectives: In the current Covid-19 pandemic, children below the age of 12 could manifest Covid-19 symptoms and serve as a reservoir for the virus in the community. The present study was conducted to evaluate the reactogenicity, and immunogenicity of BBIBP-CorV, prior to involving this age group in the vaccination program in the kingdom of Bahrain.

Subjects and Methods: The study included 582 children from 3 to 12 years old of Bahraini and non-Bahraini nationality, all of which contributed to the reactogenicity study. Of those, 401 contributed to the immunogenicity study. All children received 2 doses of BBIBP-CorV inactivated virus 3 weeks apart. To assess reactogenicity, children were followed up for 5 weeks to evaluate any vaccine-related adverse events (AE). To assess immunogenicity, blood was collected on day 0 and day 35 to assess antibody titer against S, N, and neutralizing antibody.

Results: Of the 582 participants, (45.4%) were female, (54.61%) were male, with 49% in 9-12 age group. Of the 401 children contributing to the immunogenicity study, 274 (68.3%) had no prior exposure to Covid-19. The overall incidence of AE was 27.7%. No significant difference was found among different age groups. The most frequent AE was local (at the injection site) and occurred in 16% of children, followed by fever in 9.3%. No serious adverse events were reported. The Seroconversion rate was 100% among children with no prior exposure to Covid-19. Children with previous Covid-19 exposure had higher averages of anti-S (2379 U/ml compared to 409.1), anti-N (177.6 U/ml compared to 30.9) and neutralizing antibody (93.7 U/ml compared to 77.1) than children with no prior exposure at day 35.

Conclusions: Two doses of COVID-19 BBIBP-CorV on the subjects aged between 3 to 12 has good safety and tolerance and can induce an effective immune response and neutralizing antibody titer.

Key Words: COVID-19; BBIBP-CorV; children 3-12years old; the anti-spike. Anti-nucleocapsid, Neutralizing antibody.

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Introduction

Covid-19 pandemic continues to cause severe morbidity and mortality globally, resulting in more than 5.6 million deaths as of January 2022. In the Kingdom of Bahrain 330,621 cases were reported, of which 1,399 reported dead due to Covid-19 complications [1]. Vaccines approved by the World Health Organization (WHO) have been widely used as an active control measure in the current pandemic. In this respect, SARS-CoV2, BBIBP-CorV is a β-propiolactone-inactivated, aluminum hydroxide-adjuvanted Covid-19 vaccine developed by Beijing Institute of Biological Products of Sinopharm CNBG, China. The vaccine is WHO approved and authorized by 45 countries for adults ≥18 years [2]. In multi-center phase 3 randomized clinical trial performed in 2020, the vaccine provided an efficacy of 78.1% against Covid-19 infection [3].

National Health Regulatory Authority (NHRA) of Bahrain, approved the Covid-19 vaccine (SARS-CoV2, BBIBP-CorV), Beijing strain, for emergency use in adults above 18 years on Dec. 15th, 2020, and in August 2021 for the Age group 12 to 17 years.

In Bahrain, children under 14 years represent 20.1% of the population [4]. Available data on Covid-19 infection suggests that affected children usually present with a mild cough and fever symptoms, with the incidence of Covid-19 in children ranging between 1-2% globally [5-7]. However, this age group remains a potential threat to transmit the disease functioning as a reservoir for the virus in an immunized community, possibly causing breakthrough infection in high-risk groups. The circulation of the virus in children could hypothetically enhance the chance of viral mutations, jeopardizing the value of ongoing vaccination programs. Further, little is known about the chronic complication of Covid-19 infection in children [8].

The current study aimed at exploring the safety and immunogenicity of BBIBP-CorV in children aged 3-12 years in the Kingdom of Bahrain.

Methods

Study design and participants

The study is an observational cohort study, carried out between August – October 2021, to assess the immunogenetic and reactogenicity effects of participants vaccinated with two doses of BBIBP-CorV. The study was approved by National Health Regulatory Authority (NHRA) (Approval Code: CRT-COVID2021-154). After obtaining informed consent from the legal guardians, 582 participants were recruited from the age 3-12 years of both sex who had no history of positive PCR

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Covid-19 test or manifestations suggestive of Covid-19 symptoms. Children with a history of bleeding diathesis or conditions associated with prolonged bleeding were excluded. The participants were followed for 35 days after receiving the first dose of BBIBP-CorV for adverse events through regular interviews and phone calls.

Procedures

The potential participants were first screened for eligibility criteria (age 3-12, no history of positive PCR test, no No bleeding diathesis or conditions causing prolonged bleeding). Eligible subjects underwent physical examination, including cardiac and respiratory check-ups. Blood samples were collected for the immunogenicity base line evaluation at day 0.

The vaccine was then prepared and administered intramuscularly into the deltoid muscle of the upper arm (4μg/0.5 ml). All subjects were observed for 20 minutes in the healthcare facility for any immediate adverse event following immunization. All participants were instructed to report any side effects through a dedicated electronic system. On days 1,5, and 14, the research team conducted a follow-up call to investigate the presence of adverse events (AE). The second dose was administered on day 21, prior to which all subjects underwent face to face interviews for any side effects. On day 22 and day 28, other phone calls were conducted to follow up any AE after the second dose. Face-to-face interviews were conducted again on day 35 during collecting the second blood sample for evaluation of the antibody responses to vaccination.

Immunogenicity:

The antigen-specific humoral immune response was analyzed using one commercial immunoassay (S, N) and one pseudo virus neutralization assay (sVNT) before the receipt of the first dose and 14 days after the reception of the second dose (day 35). S and N antigen-specific humoral immune response were analyzed using The Elecsys® Anti-SARS-CoV-2 S assay (Roche Diagnostics GmbH, Mannheim, Germany), which is an electrochemiluminescence immunoassay (ECLIA) that detects IgG antibodies to the SARS-CoV-2 spike protein receptor-binding domain (RBD) on the Cobas e411 module. According to the manufacturer, the measuring range spanned from 0.4 U/ml to 25,000 U/ml (up to 250 U/ml with onboard 1:10 dilution and more than 2,500 with onboard 1:100 dilution). Values higher than 0.8 BAU/ml were considered positive. U/ml and BAU

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(International OMS standard) correlation are U=0.972 BAU. The pseudovirus sVNT neutralization was analyzed using cPass™ SARS-CoV-2 Neutralization Antibody Detection Kit (Genscript Biotech Corporation, China); neutralizing antibodies were calculated as 30% inhibitory dose (neutralizing titer 30, NT30).

Outcomes

The primary outcome for safety was the occurrence of adverse reactions within 35 days after the first dose of vaccination. The intensity of adverse events was graded according to a 4-grade scale: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), and Grade 4 (life-threatening). An adverse reaction included local (hardness, itch, pain, warmth, redness, swelling) and systemic (chills, fatigue, fever, feverish, headache, joint pain, malaise, muscle aches, nausea, vomiting, diarrhea, turbid or red urine) reactogenicity symptoms.

The secondary outcome for this study was to evaluate the humoral immunogenicity of the vaccine. Samples from participants were tested for SARS-CoV-2 Anti S, Anti N (on days 0 and 35). The SARS-CoV-2 neutralizing assay was measured on day 35, flowing the 2 doses of BBIBP-CorV, and the mean titers and seroconversion rates were measured.

Statistical analysis

The data was analyzed using the Statistical Package for the Social Sciences (SPSS) version 28 (IBM SPSS Statistics, version 28 (IBM Corp., Armonk, N.Y., USA)). Descriptive statistics were used for qualitative parameters (gender, frequency of physical examination findings, and frequency of adverse events. Chi-square ($\chi 2$) test was used to assess the association between categorical variables. The secondary outcome of IgG concentrations of S, N, and neutralising antibodies in children with or without previous Covid-19 exposure was reported as means and 95% confidence intervals. Two independent samples t-test and Analysis of Variance (ANOVA) were used to test the significant differences in the mean of quantitative variables. For all statistical results, $p<0.05$ was considered statistically significant

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Results

The study took place from August to October 2021, and 582 eligible participants were enrolled. Out of this group, 401 participants completed the serological testing on day 0 and day 35. All participants received 2 doses of 0.5 ml of BBIBP-CorV at days 0 and 21. Table1 summarizes the demographics of participants in the study.

Table 1. The age and sex of participants

		Reactogenicity		**Immunogenicity**	
		No.	%	No.	%
Gender	Female	264	45.4	188	46.9
	Male	318	54.6	213	53.1
Age	3 - < 6	93	16.0	60	15.0
	6 - < 9	204	35.1	147	36.6
	9 - < 12	285	49.0	194	48.4
Total		582	100.0	401	100.0

A total of 256 Adverse events (AE) were reported in 161 subjects (27.7%). The main AE was related to pain in the injection site (16%), followed by fever (9.3%). No severe adverse events were reported across the study duration. Overall, the most AE were reported in participants aged 6-9 years, however this was not statistically significant. There was no statistical difference regarding AE in different age groups or sex.

Table 2 summarizes the incidence of different AE by age, with no statistically significant difference in AE observed by age.

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Table 2: Analysis of the incidence of Adverse Reaction after the two doses vaccination

Items	Age Group	Total No.	Events	No. Subjects	Incidence %	Chi-Square P Value
Local adverse effect (injection site)	3 - < 6	93	11	10	10.8	
	6 - < 9	204	39	34	16.7	0.320
	9 - < 12	285	60	49	17.2	
Total		582	110	93	16.0	
Systemic Adverse effects	3 - < 6	93	5	5	5.4	
	6 - < 9	204	11	11	5.4	0.892
	9 - < 12	285	20	18	6.3	
Total		582	36	34	5.8	
Fever	3 - < 6	93	14	13	14.0	
	6 - < 9	204	28	20	9.8	0.194
	9 - < 12	285	30	21	7.4	
Total		582	72	54	9.3	
Other Adverse Effects	3 - < 6	93	7	7	7.5	
	6 - < 9	204	19	16	7.8	0.199
	9 - < 12	285	12	12	4.2	
Total		582	38	35	6.0	
Overall AE	3 - < 6	93	37	23	24.7	
	6 - < 9	204	97	62	30.4	0.522
	9 - < 12	285	122	76	26.7	
Total		582	256	161	27.7	

The majority of AE were reported one day following vaccination. This was observed for both doses (Table 3).

Table 3: Adverse Reactions after the 2 doses

	Visit Related Dose		Total
	Dose 1	Dose 2	
Day 0	2	0	2
Day 1	82	0	82
Day 7	15	0	15
Day 14	8	0	8
Day 21	6	2	8
Day 22	0	79	79
Day 28	0	36	36
Day 35	0	26	26
Total	**113**	**143**	**256**

No statistically significant difference was found with adverse events in subjects with previous Covid-19 exposure compared to non-exposed subjects, as in table 4.

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Table 4 Comparison of the Adverse Reactions with exposure

Item			Female		Male		Total		Chi-Square P value
	Age	No	Non exposed	Exposed	Non exposed	Exposed	Non exposed	Exposed	
Local Adverse Effect (injection site)	3- < 6 Year	**10**	5	3	1	1	6	4	0.920
	6- < 9 Year	**31**	14	4	6	7	20	11	
	9- < 12 Year	**45**	13	4	17	11	30	15	
	Total	**86**	**32**	**11**	**24**	**19**	**56**	**30**	
Systemic Adverse Effects	3- < 6 Year	**4**	1	0	3	0	4	0	NA
	6- < 9 Year	**6**	4	0	1	1	5	1	
	9- < 12 Year	**14**	5	0	5	4	10	4	
	Total	**24**	**10**	**0**	**9**	**5**	**19**	**5**	
Fever	3- < 6 Year	**11**	2	2	4	3	6	5	0.476
	6- < 9 Year	**17**	5	1	8	3	13	4	
	9- < 12 Year	**16**	5	3	6	2	11	5	
	Total	**44**	**12**	**6**	**18**	**8**	**30**	**14**	
Other Adverse Effects	3- < 6 Year	**1**	0	0	1	0	1	0	NA
	6- < 9 Year	**9**	2	0	3	4	5	4	
	9- < 12 Year	**9**	2	1	4	2	6	3	
	Total	**19**	**4**	**1**	**8**	**6**	**12**	**7**	
Overall AE	3- < 6 Year	**22**	7	4	7	4	14	8	0.965
	6- < 9 Year	**59**	23	5	17	14	40	19	
	9- < 12 Year	**75**	22	6	29	18	51	24	
	Total	**156**	**52**	**15**	**53**	**36**	**105**	**51**	

Immunogenicity:

Of the 401 individuals who completed the immunogenicity study, 127 were found to have anti-S and anti-N levels indicative of a prior history of COVID-19 even though with no history of symptoms or positive PCR test. None of the cases with prior Covid-19 exposure had any symptoms related to the disease, and the exposure was incidentally discovered during the study. All covid naïve cases with negative Anti-S and Anti-N (274) were seroconverted (100%) at day 35.

The mean Anti S increased across the whole age groups with overall 6 folds increase for all age groups, while the mean anti N increased by 2.8 folds at D 35 after vaccination.

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Table 5 shows the antibody response for the overall tested participants stratified by sex for all age groups.

Table 5. Antibody response in males and females in different age groups

	Age (Years)							
	3 to < 6 Year		6 to < 9 Year		9 to < 12 Year		Total	
	Female	Male	Female	Male	Female	Male	Female	Male
Number (%)	28 (46.7)	22 (53.3)	74 (50.3)	73 (49.7)	86 (44.3)	108 (55.7)	188	213
Seroconversion rate	22 (100%)	20 (100%)	49 (100%)	49 (100%)	62 (100%)	72 (100%)	133	141
Mean value (95% C.I) D0 Anti- S	85.57 (8.98-208.04)	169.73 (71.91-293.60)	197.87 (121.41-277.73)	163.84 (101.59-242.68)	186.20 (94.88-310.35)	172.51 (108.80-246.13)	175.81 (119.65-241.67)	169.12 (126.11-213.98)
Mean value (95% C.I) D35 Anti- S	866.89 (519.96-1320.12)	1183.81 (862.35-1539.74)	1171.04 (859.02-1498.37)	1245.22 (906.66-1647.42)	898.13 (645.19-1198.56)	919.99 (726.58-1129.98)	1000.9 (819.66-1191.69)	1071.09 (907.74-1252.13)
Mean value (95% C.I) D0 Anti-N	22.99 (1.03-50.11)	27.74 (10.25-49.11)	29.48 (15.87-45.13)	28.50 (14.68-47.44)	21.83 (10.13-35.01)	30.72(18.81-43.77)	25.01 (16.70-33.72)	29.51 (21.38-38.76)
Mean value (95% C.I) D35 Anti-N	64.69 (41.58-90.66)	90.75 (65.53-118.75)	89.79 (73.33-107.03)	80.55(72.23-86.89)	64.94 (49.06-82.34)	81.74 (72.81-88.69)	74.69 (63.26-84.86)	80.53 (70.19-92.09)
Mean value (95% C.I) Neutralizing Ab	82.74 (77.80-87.56)	87.49 (84.11-90.60)	82.37 (78.75-85.79)	85.09 (81.85-88.16)	78.51 (74.22-82.30)	82.13 (79.2-84.82)	80.66 (78.05-82.91)	83.95 (81.99-85.90)

No difference was found in the anti-S response between males and females. However, the antibody response was higher in the group with the previous exposure, and the difference was statistically significant (P=< 0.001). Further, the age group 6-9 years had a higher antibody response compared to 9-12 years, and the difference was statically significant (P=<0.05) (Table 6.a)

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Table 6a The comparison of the mean value of Anti-S according to age, sex, and exposure

Variable's	Delta Mean (post-pre)	Statistics	P. Value
Mean value Anti- S			
Gender Male (n=213)	901.97 ± 1112.67	T=0.718	0.473[a]
Female (n=188)	825.09 ± 1017.72		
Age 3 to < 6 (n=60)	905.46 ± 872.22	F=3.276	P < **0.05**[b]
6 to < 9 (n=147)	1026.91 ± 1283.83		
9 to < 12 (n=194)	865.93 ± 1068.57		
Exposure Negative (n=274)	408.74 ± 413.35	T=16.018	P < **0.001**[a]
Positive (n=127)	1841.10 ± 1350.13		

a: Independent Sample T-test b: Analysis of Variance (ANOVA)

There was no statistically significant difference antibody response with sex or age group regarding anti-N. However, the antibody response was higher in the group with the previous exposure, and the difference was statistically significant (Table 6 b)

Table 6 b The Comparison of the mean value of Anti N according to age and sex

Variable's	Delta mean (post-pre)	Statistics	P. Value
GMT Anti N			
Gender Male (n=213)	51.02 ± 64.63	T=0.216	0.829[a]
Female (n=188)	49.67 ± 59.77		
Age 3 to < 6 (n=60)	53.07 ± 57.99	F=2.425	0.090[b]
6 to < 9 (n=147)	58.30 ± 66.07		
9 to < 12 (n=194)	43.57 ± 60.02		
Exposure Negative (n=274)	30.83 ± 36.97	T=10.331	P < **0.001**[a]
Positive (n=127)	92.09 ± 81.84		

a: Independent Sample T-test b: Analysis of Variance (ANOVA)

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Similarly, neutralizing antibody response with exposure showed a statistically significant difference favoring higher response in subjects with earlier exposure Table 6c.

Table 6 c The Comparison of the mean value of Neutralizing Antibody with Exposure (at day 35)

Variable's	Mean	Statistics	P. Value
Neutralizing Antibody			
Exposure Negative (n=274)	77.11 ± 15.8	T=11.507	P < **0.001**[a]
Positive (n=127)	93.70 ± 5.79		

a: Independent Sample T-test

Discussion

Coronavirus (SARS-CoV2), causing the severe acute respiratory syndrome, established itself as the worst pandemic in the 21st century [9].

The virus affected the current way of life across the globe. The disease morbidity in terms of its negative impact on the quality of life is as deleterious as its mortality toll that exceeded 5 million lives lost over about 2 years (reference; WHO dashboard is a good reference to use here). Widespread vaccination programs utilizing vaccines with proven safety and efficacy is essential to reduce virus transmission and minimize disease-associated morbidity and mortality. Covid-19 morbidity and mortality were age-dependent and exponentially increased with age, among other risk factors such as the presence of comorbid conditions and obesity [10].

BBIBP-CorV is a product of Sinopharm's of HB02 strain [11] The vaccine is manufactured by isolating and propagating the strain in a Vero cell line followed by inactivation utilizing β-propiolactone. The inactivated viral particles were then adsorbed to aluminum adjuvant and administered as 2 intramuscular injections every 3 weeks. The kingdom of Bahrain contributed to the multinational study that proved the safety and efficacy of the vaccine in a study involving 40382 adult participants [3]. The vaccine showed an efficacy of 78.1% and was well-tolerated in

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the tested population. In May 2021, the WHO Advisory Group of Experts on Immunization (SAGE) recommended using the vaccine as one of the WHO recognized SARS- CoV-2 recommended vaccines [12].

Aggregated reports indicate that the lower infection rate, and decreased occurrence of Covid-19-associated hospitalization to be associated with young age groups; however, severe disease still occurs in all age groups [13]. Furthermore, infected children at a young age can serve as a reservoir for the virus in an otherwise vaccinated population. In addition, the circulation of the unmanifested viral infection may play a role in the possible emergence of new variants of the virus. Hence, it is important to consider younger age groups in assessments of Covid-19 spread and consequently incorporating these ages in strategies and policies targeting Covid-19 spread.

In this study, we performed a cohort observational study on 582 volunteers to assess the safety and immunogenicity of BBIBP-CorV in participants aged 3-12 years. All participants received 4 mcg of inactivated particles on day 0 and 21. As shown in Table 2., the most frequent vaccine-related AE were correlated to pain at the injection site followed by fever. All AE were mild and resolved spontaneously. Most of the participants (72.3%) did not demonstrate any AE. AEs were reported amongst the cohort for both dose administrations, with more AE reported after the second dose. Most of the reported AE emerged on the first day following vaccination, which was observed for both doses. No serious adverse effects were reported in any subject in this study. The inactivated vaccine BBIBP-CorV resulted in 100% seroconversion rate in all subjects with no prior exposure to SARS- CoV2 and augmented the anti-S, anti-N and neutralizing antibodies in those with previous Covid-19 exposure. All age groups showed significant antibody response (S, N, and neutralizing antibody), with the age group 6-9 years showing a significantly higher antibody response against S antigen (anti-S). The AEs were comparable in those with previous infection and virus naive children.

Inactivated BBIBP-CorV vaccine utilizes the same technology known for decades in the management of influenza, polio, and measles [11]. Common to all vaccines in this group, the predominant side effects are the results of local reactions at the injection site as pain, tenderness, swelling, and mild fever attributed to the presence of adjuvants in the vaccine. Optimal dosage requires fractionation of the dose to reduce the vaccine's unwanted reactions and boost the immune response [14].

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In this study, the dose of the vaccine used was the same dose that was administered to an adult patient (4μg/0.5 ml). Different dosages of BBIBP-CorV had been tested earlier with the dosage of 2,4 and 8 μg in children 3-17 years old in China [15]. The 2 μg dose showed a lower antibody level than the 4 and 8 μg. Between 4 and 8 μg, 4 μg was recommended as it was associated with less adverse effects and comparable immunogenic response Our results show similar findings to the results reported; namely, the seroconversion rate was 100%, and the vaccine was well tolerated at 4 mg dose. There are several limitations of our study including short duration of the follow up. Longer duration of observation would allow for assessment of the protective effect of the vaccine and allow for the evaluation of the duration of the antibody response. The extension of vaccination programs to involve younger age groups is being extensively studied with a wide variety of other vaccines. Previous work has shown acceptable safety and 100% efficacy with Pfizer BNT162b2 in the age group of 12-25 years old [16]. Similarly, Moderna mRNA-1273 was reported to have 100% efficacy after 2 doses in 12-17 years [17]. Given all reported data on vaccine safety and efficacy in children, it seems plausible that targeting this age group in ongoing SARS-CoV2 vaccination programs could prove highly beneficial with limited or negligible risk when proven and tested vaccines are utilized in this age group. The continuous emergence of new virus variants further highlights the significance of achieving this.

Though the current study sheds light on the safety and immunogenicity of the BBIBP-CorV in children, the study had its limitations given the short follow-up period of 35 days. A longer follow-up is perceived to determine the vaccine's efficacy and the duration of antibody response. This study was not a randomized trial and hence representations of the general population could have been better accomplished. Further, the study did not assess the cellular response to the vaccine, which may prove beneficial in illuminating the role of BBIBP-CorV in combating the emerging Omicron variant which is causing a global concern. A recent preliminary study on the role of BBIBP-CorV against the hypermutated Omicron was conducted by studying the produced neutralizing antibodies after 2 doses and after 3 doses [18]. In 80% of the vaccinated population the antibody titer against Omicron variants was below detection limit after the second dose. However, the entire study population showed naturalizing antibody presence after the booster dose.

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Future work may provide further insight on the role of BBIBP-CorV in protecting emerging variants of SARS -CoV2 through the ongoing surveillance program as the landscape of virus's variants evolves.

Conclusion

In conclusion, this study demonstrated the value of BBIBP-CorV in providing a favorable immunogenic response in 100% of tested subjects involving both S, N antigens, and neutralizing antibodies, while the reported adverse effects were all tolerated. The current study can provide insight for large-scale use of BBIBP-CorV in children aged 3-12 years old.

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References

1. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real-time. Lancet Infect Dis. 2020;20(5):533-4.
2. Evidence Assessment: Sinopharm/BBIBP COVID-19 vaccine: https://cdn.who.int/media/docs/default-source/immunization/sage/2021/april/2_sage29apr2021_critical-evidence_sinopharm.pdf accessed on Nov 29, 2021.
3. Al Kaabi N, Zhang Y, Xia S, Yang Y, Al Qahtani MM, Abdulrazzaq N, et al. Effect of 2 Inactivated SARS-CoV-2 Vaccines on Symptomatic COVID-19 Infection in Adults: A Randomised Clinical Trial. JAMA. 2021;326(1):35-45.
4. Bahrain society demography. https://www.data.gov.bh/en/ResourceCenter/DownloadFile?id=3582 . accessed on Nov 29, 2021.
5. Roossen LM, Branum AM, Ahmad FB, Sutton P, Anderson RN. Excess Deaths Associated with COVID-19, by Age and Race and Ethnicity - United States, January 26-October 3, 2020. MMWR Morb Mortal Wkly Rep. 2020;69(42):1522-7.
6. Wu Z, McGoogan JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239-42.
7. Rapid risk assessment: Pediatric inflammatory, multisystem syndrome and SARS -CoV-2 infection in children. https://www.ecdc.europa.eu/en/publications-data/paediatric-inflammatory-multisystem-syndrome-and-sars-cov-2-rapid-risk-assessment : accessed on Nov 29, 2021.
8. Laskar R, Ali S. Differential mutation profile of SARS-CoV-2 proteins across deceased and asymptomatic patients. Chem Biol Interact. 2021;347:109598.

9. Feehan J, Apostolopoulos V. Is COVID-19 the worst pandemic? Maturitas. 2021;149:56-8.
10. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;584(7821):430-6.
11. Wang H, Zhang Y, Huang B, Deng W, Quan Y, Wang W, et al. Development of an Inactivated Vaccine Candidate, BBIBP-CorV, with Potent Protection against SARS-CoV-2. Cell. 2020;182(3):713-21 e9.
12. WHO Interim recommendations for using the inactivated COVID-19 vaccine BIBP developed by China National Biotec Group (CNBG), Sinopharm. https://apps.who.int/iris/handle/10665/341251. It was accessed on Nov 29, 2021.
13. Shekerdemian LS, Mahmood NR, Wolfe KK, et al. Characteristics and Outcomes of Children with Coronavirus Disease 2019 (COVID-19) Infection Admitted to US and Canadian Pediatric Intensive Care Units. *JAMA Pediatr.* 2020;174(9):868–873. doi:10.1001/jamapediatrics.2020.1948
14. Stern PL. Key steps in vaccine development. Ann Allergy Asthma Immunol. 2020;125(1):17-27.
15. Xia S, Zhang Y, Wang Y, Wang H, Yang Y, Gao GF, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial. Lancet Infect Dis. 2021;21(1):39-51.
16. 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: 239–50.
17. Moderna. Moderna announces TeenCOVE Study of its COVID-19 vaccine in adolescents meets primary endpoint and plans to submit data to regulators in early June. 2021. https://investors.modernatx.com/news-releases/news-release-details/moderna-announcesteencove-study-its-covid-19-vaccine (accessed Nov 29th, 2021).
18. Ai J, Zhang H, Zhang Y, Lin K, Zhang Y, Wu J, et al. Omicron variant showed lower neutralizing sensitivity than other SARS-CoV-2 variants to immune sera elicited by vaccines after boost. Emerg Microbes Infect. 2021:1-24.

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Appendix (extra tables)

Table S1a: Incidence of Adverse events after the first dose of vaccination

Items	Age Group	Total No	Events	No. Subjects	Incidence %
Local adverse effect (injection site)	3 - < 6	93	5	5	5.4
	6 - < 9	204	20	19	9.3
	9 - < 12	285	25	24	8.4
Total		582	50	48	8.2
Systemic Adverse effects	3 - < 6	93	1	1	1.1
	6 - < 9	204	7	7	3.4
	9 - < 12	285	11	11	3.9
Total		582	19	19	3.3
Fever	3 - < 6	93	10	9	9.7
	6 - < 9	204	12	10	4.9
	9 - < 12	285	11	11	3.9
Total		582	33	30	5.2
Other Adverse Effects	3 - < 6	93	2	2	2.2
	6 - < 9	204	6	5	2.5
	9 - < 12	285	3	3	1.1
Total		582	11	10	1.7
Overall AE	3 - < 6	93	18	13	14.0
	6 - < 9	204	45	33	16.2
	9 - < 12	285	50	40	14.0
Total		582	113	86	14.8

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Table S1b: Incidence of Adverse events after the second dose of vaccination

Items	Age Group	Total No	Events	No. Subjects	Incidence %
Local adverse effect (injection site)	3 - < 6	93	6	5	5.4
	6 - < 9	204	19	18	8.8
	9 - < 12	285	35	33	11.6
Total		582	60	56	9.6
Systemic Adverse effects	3 - < 6	93	4	4	4.3
	6 - < 9	204	4	4	2.0
	9 - < 12	285	9	8	2.8
Total		582	17	16	2.7
Fever	3 - < 6	93	4	4	4.3
	6 - < 9	204	16	14	6.9
	9 - < 12	285	19	13	4.6
Total		582	39	31	5.3
Other Adverse Effects	3 - < 6	93	5	5	5.4
	6 - < 9	204	13	11	5.4
	9 - < 12	285	9	9	3.2
Total		582	27	25	4.3
Overall AE	3 - < 6	93	19	11	11.8
	6 - < 9	204	52	37	18.1
	9 - < 12	285	72	51	17.9
Total		582	143	99	17.0

Table S2a: Adverse events incidence after the first dose stratified by sex

Items	Females (n= 264)			Males (n= 318)			Total (n=582)	
cases	Events	No. Subjects	Incidence %	Events	No. Subjects	Incidence %	No.	%
Local AE	21	21	8.0	29	27	8.5	48	8.2
Systematic AE	6	6	2.3	13	13	4.1	19	3.3
Fever	12	11	4.2	21	19	6.0	30	5.2
Other AE	5	4	1.5	6	6	1.9	10	1.7
Total	44	42	15.9	69	65	20.4	107	18.4

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Table S2b: Adverse events incidence after the second dose stratified by sex

Items	Females (n= 264)			Males (n= 318)			Total (n=582)	
cases	Events	No. Subjects	Incidence %	Events	No. Subjects	Incidence %	No.	%
Local AE	29	27	10.2	31	29	9.1	56	9.6
Systematic AE	10	10	3.8	7	6	1.9	16	2.7
Fever	16	12	4.5	23	19	6.0	31	5.3
Other AE	8	7	2.7	19	18	5.7	25	4.3
Total	63	56	21.2	80	72	22.6	128	22.0