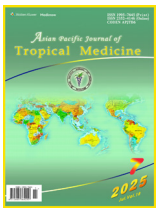

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Safety and immunogenicity of RAZI Cov Pars (RCP) vaccine in children and adolescents aged 5–17 years: An open-label, single arm trial

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ABSTRACT

Objective: To investigate the safety and immunogenicity of the RAZI Cov Pars (RCP) vaccine in children and adolescents aged 5-17 years.

Methods: In this open-label, single arm trial, 26 of the 68 registered volunteers met the inclusion criteria. The participants received RCP vaccine twice intramuscularly (on days 0 and 21) and intranasally on day 51. Safety was assessed up to 6 months after the second dose. Immunogenicity was assessed on days 35, 90, and 180 by measuring neutralizing antibody levels as well as anti-RBD and anti-S_1 IgG antibodies.

Results: Among the 26 volunteers, 22 were in the age group of 5-11 years, and 4 were in the age group of 12-17 years. No grade 3 or higher local or systemic adverse reactions were reported one week after vaccination. Six abnormal laboratory findings were observed after both vaccine doses, none of which were classified as grade 3 or higher. During a total follow-up period of 3875 person-years, 31 adverse events were recorded (incidence rate: 0.008). The seroconversion rates for VNT, anti-RBD and anti-S_1 IgG antibodies two weeks after receiving the second dose were 72.7%, 76.2% and 80.9%, respectively. In the 5-11 year age group, the seroconversion rates for VNT, anti-RBD and anti-S_1 were 78.9%, 83.3% and 88.9%, respectively.

Conclusions: Intramuscular and intranasal administration of the RCP vaccine did not lead to serious adverse events in any of the children or adolescents. The vaccine elicited a robust response in the 5-11 year age group two weeks after the second dose. Considering that this group received half of the adult vaccine dose, these results support the suitability of this dose for the study group.

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KEYWORDS: RAZI Cov Pars vaccine; Trial; Children; Adolescent

Summary

Question: What are the safety and immunogenicity profiles of the RAZI Cov Pars (RCP) vaccine in children and adolescents aged 5–17 years?

Findings: In this single arm clinical trial of 26 participants, no serious adverse events were observed up to 6 months post-vaccination. Seroconversion rates two weeks after the second dose were 72.7% for neutralizing antibodies, 76.2% for anti-RBD IgG, and 80.9% for anti-S_1 IgG, with even higher responses in the 5–11 year age group receiving half the adult dose.

Meaning: Evidence on safety and immunogenicity profile of the RCP vaccine supports its recommendation for use in population aged 5–17 years.

1. Introduction

Since it was first identified in China in December 2019, the COVID-19 pandemic has led to a significant number of infections, illnesses and deaths worldwide. According to the World Health Organization, there have been an estimated 775 million confirmed cases of COVID-19 and nearly 7 million reported deaths in various age groups as of July 2024[1].

While most documented COVID-19 cases in children and adolescents during the pandemic had mild symptoms, severe cases and long-term complications such as multisystem inflammatory syndrome (MIS-C) can occur after infection. There is evidence that school-aged children account for a significant proportion of COVID-19 cases and may play a key role in the transmission of the disease. For example, in September 2021, individuals under the age of 18 accounted for approximately a quarter of the weekly number of COVID-19 cases in the United States, with 1.6% to 4.2% of the cumulative cases in this age group requiring hospitalization[2-4]. Data from the American Academy of Pediatrics on May 4, 2023, show that approximately 15 million cases, or approximately 17% of the total number of COVID-19 cases in the United States, are attributable to children and adolescents. In addition, COVID-19 has an impact on the mental health, education and social-emotional development of children and adolescents, emphasizing the need to protect this population through vaccination[5].

Although morbidity and mortality related to COVID-19 have recently decreased, widespread COVID-19 vaccination remains crucial in the ongoing fight against the disease, especially to prepare for possible future outbreaks. Access to vaccines not only helps to contain the current spread of the virus but also helps to strengthen the immunity of the population to prevent future outbreaks and new variants. By promoting the availability and acceptance of vaccines, communities can strengthen their defences and reduce the risk of a large-scale outbreak.

With these considerations in mind, the Razi Vaccine and Serum Research Institute conducted a clinical trial for the RAZI Cov Pars (RCP) vaccine, a recombinant protein vaccine used to combat COVID-19, in children and adolescents. This follows successful safety, immunogenicity, and efficacy studies of the RCP vaccine conducted in adult participants aged 18 and over, through phase Ⅰ, Ⅱ and Ⅲ clinical trials[6-9]. Therefore, the aim of this study was to evaluate the safety and immunogenicity profiles of the RCP vaccine in children and adolescents aged 5-17 years, in line with the imperative to protect the health and well-being of children and adolescents in the ongoing fight against COVID-19.

2. Methods

2.1. Study design

This study was a single-group open-label clinical trial implemented in two age groups: 5-11 years and 12-17 years. In this study, the 12-17 year-old age group received the full-dose vaccine (the adult-approved dose), whereas the 5-11 year-old age group received the half-dose adult vaccine. This study was conducted by the Clinical Trial Centre of Iran University of Medical Sciences as an Academic Contract Research Organization (CRO) in collaboration with the Razi Vaccine and Serum Research Institute. The trial, along with subsequent amendments, is registered in the clinical trial centre affiliated with Iran University of Medical Sciences at www.irct.ir (IRCT20201214049709N5) on February 9, 2022 (one update on June 20, 2022) and was approved by the country's ethics committee with the number IR.NREC.1401.001.

2.2. Trial procedure

Iranian children aged 5-17 years were enrolled in the research *via* a website. Those who expressed their desire to take part in the study, along with their legal guardians, underwent an initial screening online. If they passed this screening, they were asked to visit the clinical facilities where they and their guardians provided written consent. They underwent eligibility assessments and were examined by a physician. All the data collected were documented in the study's application. The eligibility criteria were outlined in the protocol summary on the Iranian Registry of Clinical Trials (IRCT) Web (www.irct.ir).

Eligible participants aged 12-17 years received their first dose of 10 μg/200 μL RCP vaccine *via* deep intramuscular injection within the deltoid muscle, whereas participants aged 5-11 years received a half dose of the vaccine *via* the same method as the first dose. The

second intramuscular dose was delivered three weeks later on day 21 in the same way. The third dose was delivered on day 51 *via* an intranasal mucosal atomization device containing 10 μg/200 μL of RCP vaccine for the participants aged 12-17 years and a half-dose for the participants aged 5-11 years.

The participants were closely observed for half an hour after each vaccine dose, and their vital signs and immediate allergic reactions were monitored. Subsequent follow-ups of all participants were managed through an integrated mobile application installed on their smartphones. They were asked to record their daily local and systemic adverse reactions for seven days after vaccination. A centralized follow-up centre with round-the-clock resident physicians was set up to provide consultation and support for the study participants. They could also report any adverse events, including symptoms suspicious of COVID-19 disease, a medical visit, or medication use at any time *via* the application triggering an active follow-up at the centre until complete resolution. The participants were actively followed six months to find the occurrence of any adverse event (AE) through weekly telephone calls if they failed to report a no-AE status *via* the mobile application.

2.3. Outcome

2.3.1. Safety

In this study, four outcomes were considered to demonstrate the safety of the vaccine, as outlined below: abnormal vital signs and anaphylactic reactions immediately after vaccination, local and systemic adverse reactions, abnormal laboratory findings in addition to severe adverse events (SAEs), suspected unexpected serious adverse reactions (SUARs) and medically attended adverse events (MAAEs). Notably, with the exception of the latest mentioned safety outcomes, the remaining outcomes were considered primary outcomes. Local and systemic adverse reactions were classified according to FDA Toxicity Grading Scale. Abnormal laboratory findings were classified according to Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events[10,11].

2.3.2. Immunogenicity

In addition to safety outcomes, we determined 3 outcomes related to the immunogenicity of the vaccine: measurement of neutralizing antibody titres; measurement of serum levels of specific IgG antibodies against S_1 and RBD components of the SARS-CoV-2 spike protein antigen(s); and evaluation of cell-mediated immunity by counting the numbers of CD3, CD4 and CD8 T cell. IFN-γ, TNF-α, and interleukins 2, 4, 6, and 17 will also be measured following the stimulation of peripheral blood mononuclear cells with the COVID-19 antigen. It should be noted that among the immunogenicity outcomes, neutralizing antibody titres were considered as the primary outcome.

2.4. Statistical method

The data collected were analysed following sorting using Stata statistical software. Initially, a descriptive analysis of basic variables, including demographic information, baseline vital signs, baseline laboratory findings and baseline specific antibody levels, was conducted. Frequency and percentage were used to analyse safety data and express vaccine safety results. Immunological results were reported by converting the measured titres into a geometric mean (GM) and geometric mean fold titre increase (GMFI) with a confidence interval of 95%. Additionally, the seroconversion rate was utilized to interpret immunological findings. The definition of the seroconversion rate is the proportion of those whose serum levels of IgG, S_1 and VNT have increased by four-fold or more compared to the baseline value using the ELISA method.

3. Results

3.1. Participant flow

In this research, a total of 68 individuals were registered online. Among them, 13, 6, and 15 individuals were excluded from the study for reasons related to incomplete information during registration, ineligibility in the online screening process, and failure to attend an in-person visit, respectively. A total of 34 individuals subsequently underwent in-person screening, with 5 deemed ineligible for study participation and 3 preferred not to continue. Ultimately, 26 eligible participants, divided into two age groups (5-11 years and 12-17 years), received the RCP vaccine. Indeed, 22 participants were in the 5-11 years age group, whereas 4 were in the 12-17 years age group. All 26 individuals received the first and second doses, but only 10 individuals received the third dose.

3.2. Participant's baseline characteristics

The results regarding the demographic information of the participants revealed that most of the participants were male (57.7%). The mean age of the participants and its standard deviation was (9.88±2.35) years.

The results related to the basic vital signs of the participants showed that the average body temperature was 36.9 ℃, the average heart rate was 89.15 per minute, and the average respiratory rate was 17.11 per minute. Additionally, the average systolic blood pressure was 103.42 mm Hg, and the average diastolic blood pressure was 64.11 mm Hg.

The ELISA results related to the levels of specific antibodies against the S_1 antigen and RBD of the virus revealed that the geometric mean (GM) of the serum levels of specific antibodies

against the S_1 antigen and RBD were 135 670.7 (95% *CI* 75 052.4-245 249.1) and 126 334.4 (95% *CI* 67 373.8-236 893.1) according to the AUC, respectively. Additionally, the average neutralizing antibody level was 11.6 (95% *CI* 3.7-36.5). The completed results due to participant's baseline characteristics are shown in Table 1.

3.3. Safety outcomes

To evaluate the safety outcomes, as shown in Figure 1, all of 26 participants received the first and second doses of the vaccine, and therefore they were included in the safety analysis after the first and second doses of the vaccine. Only ten people received the third dose of the vaccine and were considered for safety analysis after the third dose of the vaccine.

The results regarding abnormal vital signs and anaphylaxis revealed that immediately (half an hour) after receiving the first and third dose of vaccine, no abnormal vital signs were found, and no cases of anaphylaxis were recorded. Immediately (half an hour) after receiving the second dose of vaccine, 3 cases developed abnormal heart rate grade 1, and one case developed grade 1 diastolic blood pressure.

Local adverse reactions were measured after the first and second

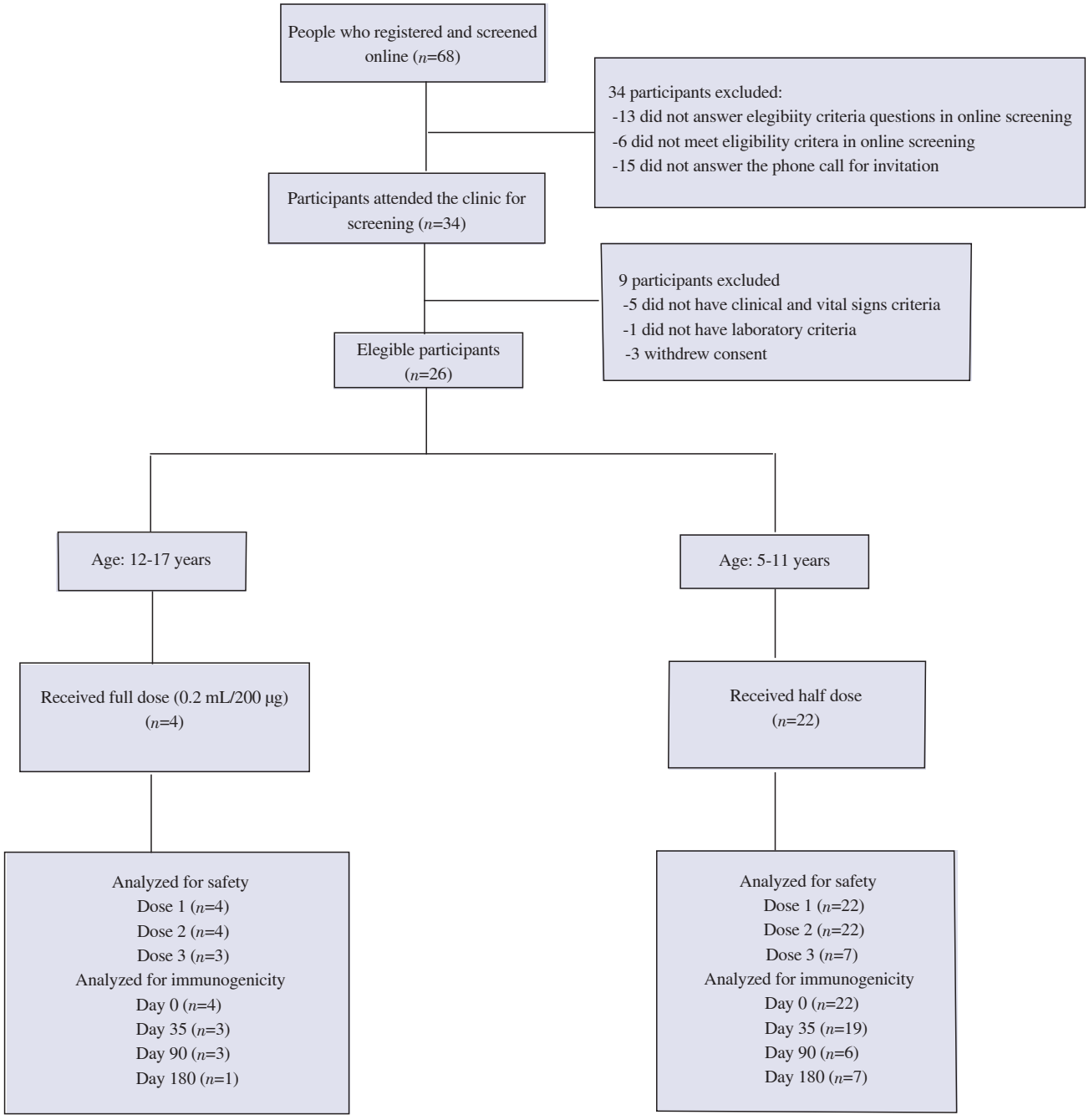

Figure 1. Flowchart of this study.

Table 1. Description of participant's baseline characteristics.

Participant's baseline characteristics		5-11 years (*n*=22)	12-17 years (*n*=4)	Total (*n*=26)
Demographic characteristics	Sex, *n* (%)			
	Male	13 (59.1)	2 (50.0)	15 (57.7)
	Female	9 (40.9)	2 (50.0)	11 (42.3)
	Age, years, Mean±SD	9.18±1.76	13.75±0.95	9.88±2.35
	Body-mass index, Mean±SD	18.45±4.56	20.11±3.67	18.70±4.41
	Education, *n* (%)			
	Preschool	1 (4.5)	0 (0.0)	1 (3.9)
	School, grade 1 to 3	11 (50.0)	0 (0.0)	11 (42.3)
	School, grade 4 to 6	10 (45.5)	0 (0.0)	10 (38.5)
	School, grade 7 and above	0 (0.0)	4 (100.0)	4 (15.4)
Baseline vital sign*	Body temperature, ℃	36.9 (35.5-37.9)	37.1 (36.7-37.6)	36.9 (35.5-37.9)
	Heart rate per minute	90.68 (61.00-110.00)	80.75 (68.00-90.00)	89.15 (61.00-110.00)
	Respiratory rate per minute	17.18 (11.00-23.00)	16.75 (14.00-20.00)	17.11 (11.00-23.00)
	Systolic BP, mmHg	103.18 (80.00-120.00)	104.75 (100.00-109.00)	103.42 (80.00-120.00)
	Diastolic BP, mmHg	64.22 (50.00 -80.00)	63.50 (54.00-70.00)	64.11 (50.00-80.00)
Baseline laboratory finding#	Hemoglobin, g/dL	13.9 (10.8-15.4)	14.3 (13.3-15.1)	14.0 (10.8-15.4)
	WBC, $\times 10^4$ cell/mm^3	7.1 (3.5-11.6)	7.4 (6.0-8.3)	7.1 (3.5-11.6)
	Lymphocytes, cell/mm^3	2.9 (1.2-5.2)	2.9 (2.3-3.6)	2.9 (1.2-5.2)
	Neutrophils, cell/mm^3	3.4 (2.4-5.2)	3.8 (2.4-5.2)	3.4 (2.4-5.2)
	Eosinophil, cell/mm^3	0.18 (0.03-0.45)	0.15 (0.08-0.31)	0.17 (0.03-0.45)
	Platelets, cell/mm^3	308.32 (171.00-450.00)	290.25 (258.00-315.00)	305.54 (171.00-450.00)
	Erythrocyte sedimentation rate (ESR)	7.73 (1.00-37.00)	10.25 (3.00-25.00)	8.12 (1.00-37.00)
	C-reactive protein (CRP)	1.85 (1.00-5.00)	1.25 (1.00-2.00)	1.75 (1.00-5.00)
	Blood urea nitrogen (BUN), mg/dL	11.98 (7.50-21.40)	10.28 (7.90-14.50)	11.72 (7.50-21.40)
	Creatinine,mg/dL	0.59 (0.40-0.90)	0.83 (0.60-1.20)	0.63 (0.40-1.20)
	Alkaline phosphatase, IU/L	664.1 (401.0-918.0)	657.3 (307.0-932.0)	663.0 (307.0-932.0)
	Aspartate transaminase (AST), IU/L	26.73 (2.00-38.00)	24.75 (18.00-29.00)	26.42 (2.00-38.00)
	Alanine transaminase (ALT), IU/L	14.45 (10.00-25.00)	18.75 (10.00-32.00)	15.17 (10.00-32.00)
	Total bilirubin	0.55 (0.50-0.70)	0.57 (0.50-0.60)	0.56 (0.50-0.70)
	Protein, U/A	All negative	All negative	All negative
	Glucose, U/A	All negative	All negative	All negative
	RBC, U/A	All negative	All negative	All negative
	HIV test	All negative	All negative	All negative
	Polymerase chain reaction (PCR) test	All negative	All negative	All negative
Baseline specific antibody levels&	Antibody for S_1 Ag, AUC	6.6 (2.1-20.9)	271.9 (15.8-4681.6)	11.6 (3.7-36.5)
	Antibody for RBD Ag, AUC	110 035.8 (58 309.8-207 647.4)	762 268.0 (110 753.1-5 246 379.0)	148 201.7 (79 199.3-277 322.4)
	Antibody for VNT titer	92 991.6 (49 121.2-176 042.8)	681 478.6 (118 493.5-3 919 314.0)	126 334.4 (67 373.8-236 893.1)

*Baseline vital sign were reported as mean (Min-Max); #Baseline laboratory finding were reported as mean (Min-Max); &Baseline specific antibody levels were reported as geometric mean (95% *CI*).

Table 2. Safety of RAZI Cov Pars vaccine among children and adolescent 5–17 years.

Safety criteria		5-11 years			12-17 years			Total		
		First dose (*n*=22)	Second dose (*n*=22)	Third dose (*n*=7)	First dose (*n*=4)	Second dose (*n*=4)	Third dose (*n*=3)	First dose (*n*=26)	Second dose (*n*=26)	Third dose (*n*=10)
Vital sign	Body temperature, ℃	36.8 (36.0-37.0)	36.8 (36.0-37.0)	36.8 (36.0-37.0)	37 (37.0-37.0)	36.2 (36.0-37.0)	37.0 (37.0- 37.0)	36.8 (36.0-37.0)	36.8 (36.0-37.0)	36.9 (36.0-37.0)
	Heart rate per minute	92.5 (77.0-108.0)	97.0 (84.0-120.0)	89.3 (81.0-98.0)	89.2 (84.0-94.0)	89.2 (87.0-94.0)	87.0 (77.0-93.0)	92.0 (84.0-94.0)	95.8 (87.0-94.0)	88.6 (77.0-98.0)
	Respiratory rate per minute	16.8 (15.0-24.0)	16.2 (16.0-19.0)	16.0 (15.0-19.0)	17.0 (15.0-19.0)	18.0 (16.0-19.0)	16.7 (15.0-19.0)	16.8 (15.0-24.0)	16.5 (14.0-19.0)	16.2 (15.0-19.0)
	Systolic BP, mmHg	95.1 (60.0-100.0)	98.0 (75.0-120.0)	99.3 (90.0-110.0)	103.7 (90.0-110.0)	88.5 (75.0-100.0)	91.7 (65.0-110.0)	96.4 (60.0-110.0)	96.6 (75.0-100.0)	97.0 (65.0-110.0)
	Diastolic BP, mmHg	63.1 (40.0-80.0)	65.7 (45.0-80.0)	67.8 (60.0-75.0)	70.2 (53.0-80.0)	55.2 (50.0-60.0)	63.3 (45.0-80.0)	64.2 (40.0-80.0)	64.1 (45.0-80.0)	66.5 (45.0-80.0)
Local adverse reaction, *n* (%)	Pain									
	Grade 1	2 (9.1)	4 (18.2)	-	0 (0.0)	0 (0.0)	-	2 (7.7)	4 (15.4)	-
	Tenderness									
	Grade 1	1 (4.5)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	1 (3.8)	0 (0.0)	-
	Grade 2	1 (4.5)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	1 (3.8)	0 (0.0)	-
	Redness									
	Grade 1	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-
	Swelling									
	Grade 1	0 (0.0)	1 (4.5)	-	0 (0.0)	0 (0.0)	-	0 (0.0)	1 (4.5)	-
	Nausea									
	Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Diarrhea									
	Grade 1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Headache									
	Grade 1	0 (0.0)	2 (9.1)	0 (0.0)	1 (25.0)	1 (25.0)	0 (0.0)	1 (3.8)	3 (11.5)	0 (0.0)
	Grade 2	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)	0 (0.0)
	Fatigue									
	Grade 1	2 (9.1)	2 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (7.7)	2 (7.7)	0 (0.0)
	Myalgia									
	Grade 1	1 (4.5)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	2 (7.7 %)	0 (0.0)	0 (0.0)
	Grade 2	0 (0.0)	2 (9.1)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	3 (11.5)	0 (0.0)
Abnormal laboratory findings*	Grade 2 (Decrease) Hemoglobin, g/dL	-	1	-	-	-	-	-	1	-
	Grade 2 (Increase), WBC, cell/mm^3	-	1	-	-	-	-	-	1	-
	Grade 2 (Increase) Eosinophils, cell/mm^3	-	1	-	-	-	-	-	1	-
	Grade 1 (Increase) AST IU/L	-	1	-	-	-	-	-	1	-
	Grade 1, U/A protein	1	1	-	-	-	-	1	1	-
Adverse event#	Not related		25			2			27	
	Unlikely related		0			0			0	
	Suspected/ possible related		4			0			4	
	Probable related		0			0			0	
	Not assessable		0			0			0	
	Total		29			2			31	

-: case not found. *Abnormal laboratory findings were reported as number; #Adverse events were reported as number; adverse events were recorded from different channels (weekly contact of experts with the volunteer, contact of the volunteer with the experts or on-call physician, registration in the application by the volunteer).

Table 3. Number of adverse events suspected/possible related to vaccine.

ICD code	ICD description	5-11 years	12-17 years	Total
R23.8	Other and unspecified skin changes	2	0	2
R05	Cough	1	0	1
J30.3	Other allergic rhinitis	1	0	1

doses of the vaccine were given up to 6 days. A total of 9 local adverse reactions were recorded, none of which were grade 3 or 4. Systemic adverse reactions were measured after receiving the first, second and third doses of the vaccine up to 6 days. A total of 14 abnormal reactions were recorded, none of which were grade 3 or higher.

In terms of laboratory safety, at least one sample related to laboratory safety after the vaccine has been obtained from all individuals in addition to laboratory screening. This number was equal to 16 after the first dose of the vaccine and 17 after the second dose of the vaccine. The results of the abnormal laboratory findings revealed that a total of 6 abnormal findings were found, none of which were grade 3 or higher.

Considering that all 26 volunteers received their first and second doses of the vaccine, all these 26 people were followed up for six months after the second dose of the vaccine to evaluate adverse events (14 people were followed up for six months, and 12 people were followed up for less than six months). During the follow-up after receiving the second dose of the vaccine, a total of 39 adverse events were recorded after receiving the vaccine from different channels (weekly contact of experts with the volunteer, contact of the volunteer with the experts or on-call physician, registration in the application by the volunteer). Among these 39 recorded adverse events, 8 cases were diagnosed as "repetitive reporting of an event", and finally 31 recorded adverse events were followed up by the on-call physician. None of these recorded adverse events were considered SAEs or SUSARs. Until the end of the study, the total person-time of the participants in the study was 3 875 days, so the incidence rate of adverse events until the end of the study was 0.008 (incidence rate: 0.008, 95% *CI* 0.005-0.011). The results related to the 31 recorded adverse events in terms of evaluating the relationship with the vaccine are shown in the Table 2. Among these 31 recorded adverse events, 4 cases were evaluated as suspected cases. Of the 4 cases mentioned, 2 were considered under code R23.8, 1 case under code R05, and another case under code J30.3 according to ICD-10. Detailed information provided on Table 2 and 3.

3.4. Immunogenicity outcomes

The data on neutralizing antibody activity were collected from 26, 22, 9, and 8 individuals on days 0, 35, 90, and 180, respectively. These findings revealed that the geometric mean antibody level on day 35, compared with that on day zero, increased by 121.9 and 4.6 times in the 5-11 year-old and 12-17 year-old age groups, respectively. Furthermore, the seroconversion rates on day 35 for the 5-11 and 12-17 age groups were 78.9% and 33.3%, respectively. The detailed results for days 90 and 180 can be found in Table 4 and Figure 2.

The serum levels of a specific antibody against the S_1 antigen of the virus were assessed *via* ELISA in 26, 21, 9, and 8 individuals on days 0, 35, 90, and 180, respectively. These findings indicated that the geometric mean of the serum antibody levels increased by 17 and 2.8 times in the 5-11 years and 12-17 years age groups, respectively, on day 35 compared with day 0. Furthermore, the seroconversion rates on day 35 for the 5-11-year-old and 12-17 year-old age groups were 88.9% and 33.3%, respectively. The detailed results for days 90 and 180 can be found in Table 4 and Figure 2.

Data related to the serum level of specific antibody against the RBD antigen of the virus were measured by ELISA method for 26, 22, 9 and 8 individuals on days 0, 35, 90 and 180, respectively. These results showed that the geometric mean serum level of this antibody increased by 15.5 and 3 times in the age groups of 5-11 years and 12-17 years, respectively, on day 35 compared with day zero. Additionally, the seroconversion rates on day 35 for the 5-11 year-old and 12-17 year-old age groups were 83.3% and 33.3%, respectively. The results related to days 90 and 180 can be found in Table 4 and Figure 2.

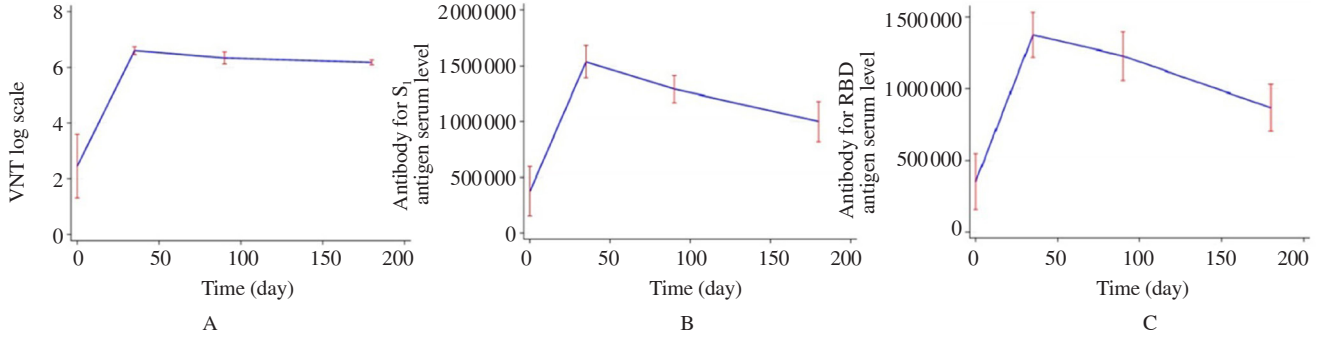

Figure 2. Immunogenicity of RAZI Cov Pars vaccine among children and adolescents aged 5-17 years. A: Mean VNT titer, B: Mean antibody for S_1 antigen level, C: Mean antibody for RBD antigen level.

Table 4. Immunogenicity of RAZI Cov Pars vaccine among children and adolescent 5-17 years.

Immunogenicity criteria		5-11 years	12-17 years	Total
VNT titers	Mean* (95% *CI*)			
	Baseline (*n*=26)	6.6 (2.1-20.9)	271.9 (15.8-4681.6)	11.6 (3.7-36.5)
	Day 35 (*n*=22)	721.2 (611.5-850.5)	834.0 (596.3-1166.6)	735.6 (637.3-849.1)
	Day 90 (*n*=9)	618.5 (455.8-839.1)	474.1 (291.8-770.3)	566.0 (455.4-703.5)
	Day 180 (*n*=8)	487.6 (440.8-539.4)	447[&]	482.3 (441.6-526.9)
	GMFI[#], (95% *CI*)			
	Baseline	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
	Day 35	121.9 (32.0-464.3)	4.6 (0.0-720.9)	78.0 (21.7-280.1)
	Day 90	131.8 (7.1-2440.6)	2.6 (0.0-208.7)	35.7 (3.4-379.1)
	Day 180	138.4 (15.1-1265.0)	-	72.6 (6.6-799.6)
	Sero-conversion a, *n*/N (%)			
	Day 35	15/19 (78.9)	1/3 (33.33)	16/22 (72.7)
	Day 90	5/6 (83.3)	1/3 (33.33)	6/9 (66.7)
	Day 180	6/7 (85.7)	-	6/8 (75.0)
Anti-S_1 IgG antibodies	Mean (95% *CI*)			
	Baseline (*n*=26)	98083.1 (55778.5-172473.2)	807963.3 (111894.9-5834087.0)	135670.7 (75052.4-245249.1)
	Day 35 (*n*=21)	1465906.0 (1320444.0-1627392.0)	1757208.0 (950698.3-3247909.0)	1504359.0 (1361743.0-1661910.0)
	Day 90 (*n*=9)	1285530.0 (1118444.0-1477577.0)	1276508.0 (930805.2-1750604.0)	1282515.0 (1167084.0-1409363.0)
	Day 180 (*n*=8)	1342023.0 (579217.5-1609411.0)	1100000[&]	1309073.0 (646395.3-1651122.0)
	GMFI (95% *CI*)			
	Baseline (*n*=26)	1.0 (1.00-1.00)	1.0 (1.00-1.00)	1.0 (1.00-1.00)
	Day 35 (*n*=21)	17.0 (9.1-31.6)	2.8 (0.2-49.0)	13.1 (7.0-24.4)
	Day 90 (*n*=9)	19.5 (3.2-118.8)	2.0 (0.1-48.9)	9.1 (2.1-38.9)
	Day 180 (*n*=8)	22.0 (4.9-98.9)		14.5 (2.9-71.8)
	Sero-conversion a , *n*/N (%)			
	Day 35 (*n*=21)	16/18 (88.9%)	1/3 (33.3%)	17/21 (80.9%)
	Day 90 (*n*=9)	5/6 (83.3%)	1/3 (33.3%)	6/9 (66.7%)
	Day 180 (*n*=8)	6/7 (85.7%)	0 (0.0%)	6/8 (75.0%)
Anti-RBD antibodies	Mean (95% *CI*)			
	Baseline (*n*=26)	92991.6 (49121.2-176042.8)	681478.6 (118493.5-3919314.0)	126334.4 (67373.8-236893.1)
	Day 35 (*n*=21)	1287778.0 (1134829.0-1461341.0)	1643776.0 (878029.4-3077346.0)	1333473.0 (1183215.0-1502812.0)
	Day 90 (*n*=9)	1174181.0 (956736.4-1441047.0)	1288117.0 (904561.8-1834307.0)	1210994.0 (1057687.0-1386522.0)
	Day 180 (*n*=8)	834453.7 (676509.8-1029273.0)	951357[&]	848242.3 (708630.0-1015361.0)
	GMFI (95% *CI*)			
	Baseline (*n*=26)	1.0 (Re)	1.0 (1.0-1.0)	1.0 (Re)
	Day 35 (*n*=21)	15.5 (7.4-32.3)	3.0 (0.3-34.5)	12.2 (6.1-24.4)
	Day 90 (*n*=9)	20.7 (3.2-131.5)	2.4 (0.2-35.8)	10.0 (2.4-41.5)
	Day 180 (*n*=8)	15.9 (3.5-72.4)		10.9 (2.3-51.5)
	Sero-conversion a , *n*/N (%)			
	Day 35 (*n*=21)	15/18 (83.3%)	1/3 (33.3%)	16/21 (76.2%)
	Day 90 (*n*=9)	5/6 (83.3%)	1/3 (33.3%)	6/9 (66.7%)
	Day 180 (*n*=8)	6/7 (85.7%)	0 (0.0%)	6/8 (75.0%)

*We used all samples available on each day to calculate the mean (geometric mean). #GMFI: geometric mean fold titer increase; to calculating GMFI, we compared all the samples available on each day (35, 90 and 180) with the corresponding samples on day zero. -: data not avaliable; &: one sample was analyzed. Number of samples to evaluate VNT were 22, 19, 6 and 7 for 5-11 years group on day 0, 35, 90 and 180; the corresponding number were 4, 3, 3, and 1 for the 12-17 years group. Number of samples to evaluate S_1 and RBD were 22, 18, 6 and 7 for 5-11 years group on day 0, 35, 90 and 180; the corresponding number were 4, 3, 3, and 1 for the 12-17 years group.

4. Discussion

Numerous COVID-19 vaccines have been shown to be effective and safe in individuals aged 6 months to 18 years; however, there remains a lack of research data for those under 18 years[12-20]. In this clinical trial involving children and adolescents aged 5-17 years, 68 individuals were initially screened, with 26 receiving the RCP vaccine. All 26 participants completed both the first and second doses, but only 10 individuals received the third dose as the intranasal dose.

The participants' demographic data revealed that males participated slightly more than females did, with the majority falling into the 5-11 age group (85%) and a smaller proportion falling into the 12-17 age group (15%). Of note, participants aged 12-17 years had significantly higher baseline levels of neutralizing antibodies, S_1 and RBD antigens compared to the 5-11 age group, which is likely due to previous exposure to the virus in some individuals in this age group.

Post vaccination safety evaluations for expected adverse reactions revealed only some mild abnormalities, such as abnormal vital signs, local/systemic adverse reactions and abnormal laboratory results, after receiving the second dose of the vaccine. None of these cases exceeded mild or moderate severity, indicating that administration of the RCP vaccine in children and adolescents aged 5 to 17 years did not result in severe expected adverse reactions according to the predefined criteria.

In addition, our results indicated that no serious adverse events (SAEs) or suspected unexpected serious adverse reactions (SUSARs) were reported in the study. Out of the 31 nonrecurring adverse events identified from different channels mentioned in the text, such as the weekly contact of experts with the volunteer, most were classified as unrelated to the vaccine, and only 4 cases were considered suspected and monitored until they were fully resolved. Notably, contrary to reports in global studies among children and adolescents, no cases of myocarditis or pericarditis were observed after the second dose of vaccine in this study, which predominantly affected males[20].

Immunological results demonstrated a favorable seroconversion rate for neutralizing antibodies and antibodies against S_1 and RBD antigens in the 5-11 year age group, surpassing the rate observed in adults receiving the RCP vaccine two weeks after receiving the second dose of the vaccine. The study suggested non-inferiority of the immune response due to neutralizing antibodies in children aged 5-11 compared with adults two weeks after receiving second doses of the vaccine according to non-inferiority margins recommended by the World Health Organization[8,14]. However, for the 12-17 year-old participants, relatively low seroconversion rates were attributed to elevated baseline antibody levels, although the limited sample size hinders definitive conclusions for this older group. Replicating experiments with a larger sample size is essential for accurate evaluation.

Despite the study's significant findings, limitations such as a small participant pool were noted, potentially influenced by prior vaccination among older children, reduced disease severity, and decreased community willingness to vaccinate at the study time. Addressing these limitations through larger-scale studies is crucial to validate and expand upon the current findings and enhance the understanding of vaccine efficacy and safety profiles in children and adolescents.

In summary, the results of this study show that the RCP vaccine given intramuscularly and intranasally did not lead to severe adverse events in volunteers aged 5-11 years or 12-17 years. The vaccine appears safe for both age groups. In terms of the immune response, administering the vaccine to 5-11 year-olds elicited a strong response two weeks after the second dose, with neutralizing antibodies, S_1 antigens, and RBD antibodies. Since the 5-11 year-old participants received half the adult dose; these findings support the appropriateness of this dosage for their age group.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: As an academic CRO, the Iran University of medical sciences clinical trial center (IUMS-CTC) contributed to the conduct of the trial. MHFM, MN, MHR, AE, ARM, SHR, MH, FSF, LM, MT, MB, EG, MRD and SRB are Razi Vaccine and Serum Research Institute, employees. SRB is the inventor of the RCP vaccine.

The study was supported by the Razi Vaccine and Serum Research Institute (RVSRI). The institute contributed to the study design and conducted the immunogenicity tests, but did not participate in other activities. These activities such as data collection, data management, analysis, interpretation, and writing the report, were carried out by the Iran University of Medical Sciences (IUMS) clinical trial center. It should be noted that the immunology laboratory was blinded to the participants' identities for all blood samples.

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Ethic approval

The study was approved by Iran National Committee for Ethics in Biomedical Research (IR.NREC.1401.001) on 6 February, 2022 and performed in accordance with the Declaration of Helsinki and Good Clinical Practice. The trial protocol is registered in www.irct.ir (IRCT20201214049709N5).

Data availability statement

We are committed to sharing the individual participant data. The de-identified individual participant data (including text, tables, figures, and appendices) that form the basis of the results reported in this article will be made available.

Authors' contributions

MHR, MSD, SRB, MHFM and MN conceived and deigned the trial, and SK is the chief investigator. MHFM, SK, AE, and SRB led the implementation of the study. MHR, MSD, and SM did the statistical analysis and verified the underlying data. MHR, SRB and MSD wrote the first draft of the manuscript. MN, MHR, ARM, FSF, LM, EB, EG, MRD, RG, RM, NG and VM have made substantial contributions to the conduct and data collection. SRB, MHM, SHR, MB and MT were responsible for laboratory analyses. All authors reviewed and approved the fnal report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors read and approved the final manuscript.

References

[1] World Health Organization. *WHO coronavirus (COVID-19) data: WHO; 2023.* [Online]. Available from: https://data.who.int/dashboards/covid19/cases. [Accessed on 30 March 2023].

[2] Tsabouri S, Makis A, Kosmeri C, Siomou E. Risk factors for severity in children with coronavirus disease 2019: A comprehensive literature review. *Pediatr Clin North Am* 2021; **68**(1): 321-338.

[3] Szablewski CM, Chang KT, Brown MM, Chu VT, Yousaf AR, Anyalechi N, et al. SARS-CoV-2 transmission and infection among attendees of an overnight camp-Georgia, June 2020. *MMWR Morb Mortal Wkly Rep* 2020; **69**(31):1023-1025.

[4] Rumain B, Schneiderman M, Geliebter A. Prevalence of COVID-19 in adolescents and youth compared with older adults in states experiencing surges. *PLoS One* 2021; **16**(3): e0242587.

[5] Pediatrics AAO. *Children and COVID-19: State-level data report US: American Academy of Pediatrics; 2023.* [Online]. Available from: https://www.aap.org. [Accessed on 11 May 2023].

[6] Banihashemi SR, Es-haghi A, Fallah Mehrabadi MH, Nofeli M, Mokarram AR, Ranjbar A, et al. Safety and efficacy of combined intramuscular/intranasal RAZI-COV PARS vaccine candidate against SARS-CoV-2: A preclinical study in several animal models. *Front Immunol* 2022; **13**: 836745. doi: 10.3389/fimmu.2022.836745. eCollection 2022.

[7] Erfanpoor S, Banihashemi SR, Mokhbaeralsafa L, Kalantari S, Es-haghi A, Nofeli M, et al. Immunogenicity and safety of RAZI recombinant spike protein vaccine (RCP) as a booster dose after priming with BBIBP-CorV: A parallel two groups, randomized, double blind trial. *BMC Med* 2024; **22**(1): 78.

[8] Mohazzab A, Fallah Mehrabadi MH, Es-haghi A, Kalantari S, Mokhberalsafa L, Setarehdan SA, et al. Phase ||, safety and immunogenicity of RAZI Cov Pars (RCP) SARS CoV-2 vaccine in adults aged 18-70 years: A randomized, double-blind clinical trial. *J Pharm Sci* 2023; **112**(12): 3012-3021.

[9] Solaymani-Dodaran M, Kalantari S, Banihashemi SR, Es-haghi A, Nofeli M, Mohazzab A, et al. Safety and efficacy of RCP recombinant spike protein covid-19 vaccine compared to Sinopharm BBIBP: A phase |||, non-inferiority trial. *Heliyon* 2024; **10**(5): e27370.

[10]Food and Drug Administration. *Guidance for industry toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials: Food and Drug Administration. U.S. Department of Health and Human Services 2007.* [Online]. Available from: http://www.fda.gov/cber/guidelines.htm. [Accessed on 11 May 2023].

[11]DAIDS. *Table for grading the severity of adult and pediatric adverse events: Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, US Department of Health and Human Services; 2017.* [Online]. Available from: https://rsc.niaid.nih.gov/. [Accessed on 11 May 2023].

[12]Ali K, Berman G, Zhou H, Deng W, Faughnan V, Coronado-Voges M, et al. Evaluation of mRNA-1273 SARS-CoV-2 vaccine in adolescents. *N Engl J Med* 2021; **385**(24): 2241-2251.

[13]Creech CB, Anderson E, Berthaud V, Yildirim I, Atz AM, Melendez Baez I, et al. Evaluation of mRNA-1273 Covid-19 vaccine in children 6 to 11 years of age. *N Engl J Med* 2022; **386**(21): 2011-2023.

[14]Gunale B, Kapse D, Kar S, Bavdekar A, Kohli S, Lalwani S, et al. Safety and immunogenicity of SARS-CoV-2 recombinant spike protein vaccine in children and adolescents in India: A phase 2-3 randomized clinical trial. *JAMA Pediatr* 2023; **177**(9): 911-920.

[15]Muñoz FM, Sher LD, Sabharwal C, Gurtman A, Xu X, Kitchin N, et al.

Evaluation of BNT162b2 Covid-19 vaccine in children younger than 5 years of age. *N Engl J Med* 2023; **388**(7): 621-634.

[16]Walter EB, Talaat KR, Sabharwal C, Gurtman A, Lockhart S, Paulsen GC, et al. Evaluation of the BNT162b2 COVID-19 vaccine in children 5 to 11 years of age. *N Engl J Med* 2021; **386**(1): 35-46.

[17]Xia S, Zhang Y, Wang Y, Wang H, Yang Y, Gao GF, et al. Safety and immunogenicity of an inactivated COVID-19 vaccine, BBIBP-CorV, in people younger than 18 years: A randomised, double-blind, controlled, phase 1/2 trial. *Lancet Infect Dis* 2022; **22**(2): 196-208.

[18]Sabu JM, Zahid I, Jacob N, Alele FO, Malau-Aduli BS. Effectiveness of the BNT162b2 (Pfizer-BioNTech) vaccine in children and adolescents: A systematic review and meta-analysis. *Vaccines (Basel)* 2022; **10**(11): 1880. doi: 10.3390/vaccines10111880.

[19]Piechotta V, Siemens W, Thielemann I, Toews M, Koch J, Vygen-Bonnet S, et al. Safety and effectiveness of vaccines against COVID-19 in children aged 5-11 years: A systematic review and meta-analysis. *Lancet Child Adolescent Health* 2023; **7**(6): 379-391.

[20]Lv M, Luo XF, Shen Q, Lei RB, Liu X, Liu E, et al. Safety, immunogenicity, and efficacy of COVID-19 vaccines in children and adolescents: A systematic review. *Vaccines* 2021; **9**(10): 1102.

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