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Article *in* Drug Safety · May 2024

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ORIGINAL RESEARCH ARTICLE

Long-Term Safety Analysis of the BBV152 Coronavirus Vaccine in Adolescents and Adults: Findings from a 1-Year Prospective Study in North India

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Accepted: 10 April 2024

Abstract

Background and Objective Evidence on the long-term safety of COVID-19 vaccines is scarce. Here, in continuation of our previously published results on short-term safety, we provide data on the long-term safety of the BBV152 vaccine in adolescents and adults.

Methods This was a prospective observational study conducted from January 2022 to August 2023. Adolescents and adults receiving the BBV152 vaccine were interviewed telephonically about long-term adverse events of special interest (AESIs) after 1 year of vaccination. Risk factors of AESIs and AESIs persistent for at least 1 month were identified.

Results Out of 1024 individuals enrolled, 635 adolescents and 291 adults could be contacted during the 1-year follow-up. Viral upper respiratory tract infections were reported by 304 (47.9%) adolescents and 124 (42.6%) adults in this period. New-onset skin and subcutaneous disorders (10.5%), general disorders (10.2%), and nervous system disorders (4.7%) were the common AESIs in adolescents. General disorders (8.9%), musculoskeletal disorders (5.8%), and nervous system disorders (5.5%) were the common AESIs in adults. Menstrual abnormalities were noticed in 4.6% of female participants. Ocular abnormalities and hypothyroidism were observed in 2.7% and 0.6% of participants, respectively. Among serious AESIs (1%), stroke and Guillain–Barre syndrome were identified in 0.3% and 0.1% of participants, respectively. Among adolescents, female individuals, those with a history of allergy and post-vaccination typhoid were respectively at 1.6, 2.8, and 2.8 times higher risk of AESIs. The majority of the AESIs persisted at the 1-year follow-up. Female individuals, adolescents with pre-vaccination COVID-19, those with co-morbidities, and those with post-vaccination typhoid had respectively 1.6, 2, 2.7, and 3.2 times higher odds of persistent AESIs. Adults with co-morbidities had more than 2 times higher odds of AESIs and persistent AESIs.

Conclusions The patterns of AESIs developing after BBV152 differed from those reported with other COVID-19 vaccines as well as between adolescents and adults. With the majority of AESIs persisting for a significant period, extended surveillance of COVID-19-vaccinated individuals is warranted to understand the course and outcomes of late-onset AESIs. Serious AESIs might not be uncommon and necessitate enhanced awareness and larger studies to understand the incidence of immune-mediated phenomena post-COVID-19 vaccination. The relationship of AESIs with sex, co-morbidities, pre-vaccination COVID-19, and non-COVID illnesses should be explored in future studies.

1 Introduction

To limit the impact of COVID-19, various vaccines based on novel and pre-existing technologies were approved for a mass rollout. The COVID-19 vaccination program worldwide was started in December 2020 and early January 2021. The viral vector and mRNA-based COVID-19 vaccines were the vaccines distributed on a large scale worldwide. Vaccines

Key Points

Serious adverse events may occur in 1% of BBV152 recipients.

Extended surveillance is warranted post-BBV152 vaccine.

Female adolescents and those with comorbidities are at higher risk of adverse events.

Extended author information available on the last page of the article

Published online: 13 May 2024

based on inactivated SARS-CoV-2 included SinoVac-CoronaVac (China), Sinopharm-BBIBP-CorV (China), and Bharat BioTech-BBV152 (India). BBV152 was the second most distributed vaccine in India after the adenoviral-vectored AZD1222 (COVISHIELD). Considering the assumed benefits of vaccinating all individuals, the approval of some of the COVID-19 vaccines was later extended to adolescents and children. The mRNA-based vaccines were the first to get the nod for administration in adolescents and children globally [1]. In India, the BBV152 was the only vaccine that was initially granted permission for a mass rollout in adolescents of 15–18 years [2]. The short-term safety of COVID-19 vaccines approved for adolescents was shown to be favorable in controlled settings [3–5]. In this context, we provided the first short-term safety data of BBV152 in adolescents and the comparative safety profile in adults [6]. Despite nearly 2 years having elapsed since the approval of COVID-19 vaccines in adolescents, long-term data on the safety of these vaccines released in the public domain have been minimal. Here, in an extension of our previously published study, we provide data on the long-term safety of the BBV152 vaccine in adolescents and adults.

2 Methodology

2.1 Study Design and Setting

This was a 1-year prospective observational study that started in January 2022 in a tertiary university hospital in North India. The study aimed to provide short-term and long-term safety data of the BBV152 vaccine in adolescents and adults. Participants were initially contacted by telephone after 14 days of receiving the vaccine and the interim safety analysis in the form of adverse events following immunization (AEFIs) was published by us in 2022 [6]. Here, we provide the long-term safety data of BBV152 in the form of adverse events of special interest (AESIs) assessed at the 1-year follow-up in the same study group.

2.2 Study Participants

Adolescents aged 15–18 years and adults aged 19 years and above receiving any dose of BBV152 vaccine constituted the study population.

2.3 Safety Analysis and Outcome Measures

All participants were interviewed telephonically about the occurrence of AESIs. The format used for collecting information on AESIs was guided by the list of AESIs provided by the CEPI-SPEAC-Brighton Collaboration, atypical adverse events published in PubMed/MEDLINE, and our own experience on COVID-19 vaccine-related atypical adverse events reported in our center [7, 8]. Telephonic interviews were conducted by five different observers, including graduate students (pre-final and final year MBBS students) and post-graduate trainees (MD residents). A 3-hour training was given to each by the lead investigators (corresponding authors) and the initial few telephonic interviews were conducted under the supervision of the lead investigators.

All symptoms were labeled using the low-level terms and system organ class (SOC) as per the MedDRA® terminology [9]. The severity of AESIs was rated using the US Food and Drug Administration-AEFI Severity Assessment Scale [10]. AESIs were labeled as 'serious' depending upon the World Health Organization Scale of Seriousness of AEFIs [11]. Depending upon improvement, outcomes of AESIs were rated as 'improved' if no symptoms were present at the time of follow-up or the participant was off therapy required initially for the management of AESIs and 'partially improved' if symptoms were persisting at the 1-year follow-up or were controlled only on medication. Additionally, we enquired about "persistent AESIs" pre-defined as "any symptoms persisting for a minimum period of 4 weeks at the time of one year follow up" [7].

The final list of AESIs selected for the present study is provided in Table 1 of the Electronic Supplementary Material (ESM). Briefly, we enquired about the occurrence of infections such as upper respiratory tract infections, laboratory-confirmed COVID-19, and dengue, among others. Among AESIs, detailed information was sought on new-onset rheumatologic disorders, cardiac disorders such as heart failure, myocardial infarction or myocarditis, metabolic disorders such as diabetes mellitus, endocrinal disorders such as thyroid abnormalities, nervous system disorders such as headaches, attention deficits, stroke and weakness in limbs, hematologic disorders such as anemia and thrombocytopenia, skin disorders such as alopecia, reproductive disorders such as menstrual disturbances and flares of underlying diseases such as diabetes, hypertension, and arthropathy. The causality assessment of 'serious' AESIs was performed using the 2005 World Health Organization Scale of Assessment of AEFIs [12].

2.4 Sample Size

The sample size estimation of our 1-year follow-up study was based on primary outcomes of rates of AEFIs following the BBV152 vaccine. Details are provided in the published interim analysis [6].

2.5 Statistical Analysis

Dichotomous data were analyzed as frequencies and percentages and depending upon the normality, mean or median values were chosen for quantitative variables. The chi-square test was separately applied to assess the association of independent variables such as demographic factors, co-morbidities, and pre-vaccination COVID-19 and post-vaccination non-COVID-19 illnesses with the two dependent variables, namely "AESIs" and "persistent AESIs". The variables with a p-value <0.05 in the bivariate analysis and those presumed to be clinically significant were incorporated in the final logistic regression model to determine the risk factors. Separate logistic regression analyses were performed for the two dependent variables, "AESIs" and "persistent AESIs", and for adolescents and adults separately. Hence, altogether four different regression analyses were performed. SPSS version 16 (SPSS Inc., Chicago, IL, USA) was used to perform the statistical tests.

3 Results

A total of 1024 participants (698 adolescents and 326 adults) receiving BBV152 were enrolled in the study in January 2022. The initial short-term AEFIs noticed within 14 days of receiving the vaccine have already been published [6]. Data on long-term safety at the 1-year follow-up could be procured for 635 adolescents and 291 adults. Information about the total number of vaccine doses was not known for 58 adolescents and 66 adults. Thus, the association between the number of doses and AESIs could be analyzed for 577 adolescents and 225 adults. Four deaths were reported in adults. There were 635 adolescents and 287 adults subsequently assessed for persistent AESIs at 1 year. The details of the participants recruited and analyzed are depicted in Fig. 1. Details of infections and AESIs reported in adolescents and adults are described subsequently.

3.1 Infections

3.1.1 Infections in Adolescents

A total of 304 adolescents (47.9%) reported viral upper respiratory tract infections (URTIs) and all except one were moderate in severity. The majority of these infections were reported after June 2022. Among these 304, recurrent viral URTIs (defined as three or more episodes in a year) were cited by 26. As laboratory tests for COVID-19 were not being opted for by patients during this period, no case of viral URTI could be labeled as COVID-19. Laboratory-confirmed and symptomatic dengue occurred in 22 (3.5%). Eight cases (36.4%) of dengue were 'severe' or 'serious' cases and three among them required hospitalization. Laboratory-confirmed typhoid was the third most common infection reported in 17 (2.7%) and was 'severe' in four cases. Details are provided in Table 2 of the ESM.

3.1.2 Infections in Adults

Among 291 adults, viral URTIs were reported by 124 (42.6%) and the majority were moderate in severity. Similar to adolescents, laboratory tests for COVID-19 were not conducted in the cases of URTIs. Laboratory-confirmed typhoid and symptomatic dengue were observed in seven and six cases, respectively. Severity wise, one case of viral URTI was 'severe' and one case each of typhoid and dengue was 'serious'. Details are provided in Table 2 of the ESM.

3.2 AESIs in Adolescents

Among 635 adolescents, AESIs were recorded in 214 (33.7%). Skin and subcutaneous disorders, such as alopecia ($n = 67$, 10.5%), general disorders ($n = 65$, 10.2%) such as undiagnosed fever and weakness, and nervous system disorders ($n = 30$, 4.7%) such as headache and attention difficulty were the three most common SOCs affected by AESIs in adolescents. Other common disorders included eye disorders ($n = 23$, 3.6%) such as refractive error and musculoskeletal disorders ($n = 18$, 2.8%). Around 5.7% ($n = 36$) of adolescents reported a flare of underlying disease. Cutaneous disturbances in the form of increased hair fall, eye disturbances such as an increase in refractive error, and nervous system disturbances such as an aggravation of headache were the common flares. Details are provided in Table 2 of the ESM.

3.2.1 Persistent AESIs in Adolescents

Among 214 adolescents with AESIs, 142 (66.3%) had persistent AESIs. Alopecia ($n = 47$), refractive errors ($n = 26$), headache ($n = 20$), menstrual abnormalities ($n = 17$), and increased symptoms of allergy ($n = 16$) were the five common persistent AESIs. With regard to SOCs, all cases of psychiatric disorders, 91.3% of eye disorders, 88.2% of reproductive disorders, 83.3% each of musculoskeletal and immune system disorders, 80% of nervous system disorders, and 64.2% of skin disorders were persisting till the last follow-up with an approximate time of persistence of 5.5 months, 3.5 months, 10.5 months. 11.5 months, 6.5 months, 9.5 months, and 8.5 months, respectively. Details of SOCs of persistent AESIs and the approximate times of persistence are mentioned in Tables 3 and 4 of the ESM, and depicted in Fig. 2.

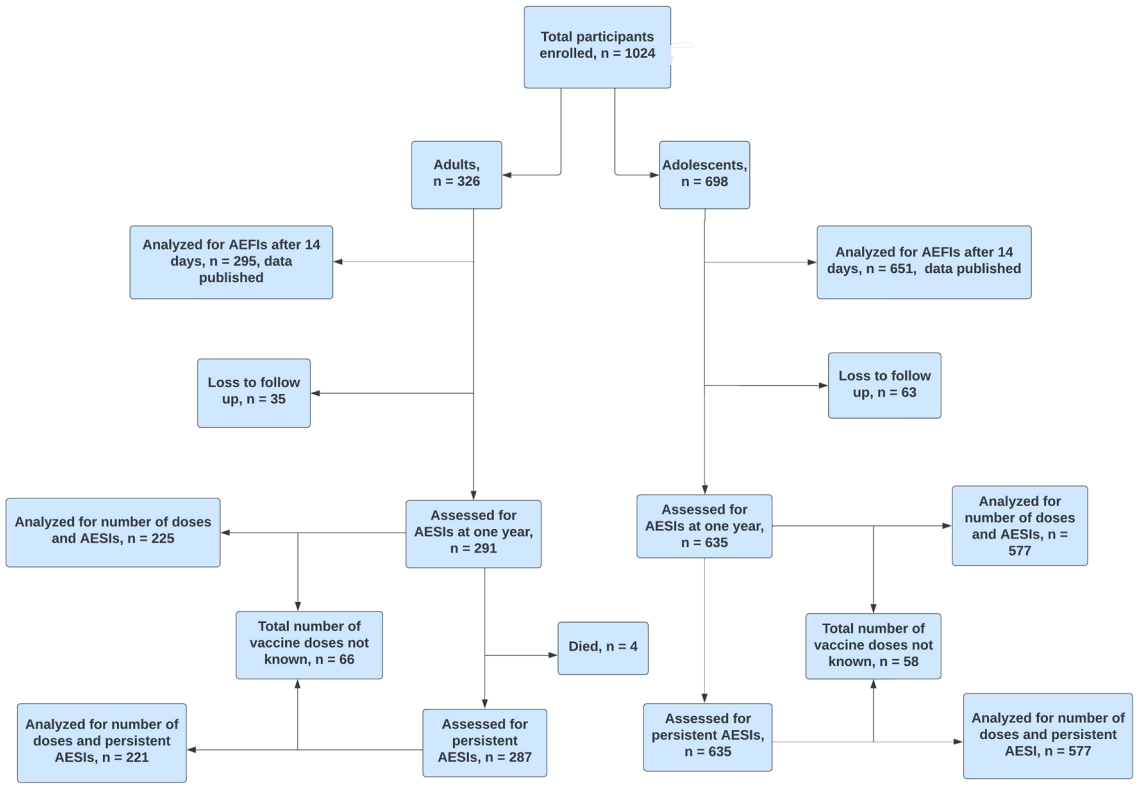

Fig. 1 STROBE flow diagram of the study. *AESIs* adverse events of special interest

3.2.2 Risk Factors of AESIs and Persistent AESIs in Adolescents

A bivariate analysis showed a statistically significant association of AESIs in adolescents with sex ($p = 0.006$), history of allergy ($p < 0.001$), and the presence of any co-morbidity especially asthma ($p = 0.007$). Though not statistically significant, a marginal association of AESIs was also observed with post-vaccination typhoid ($p = 0.09$) (Table 1a). As typhoid can influence the occurrence of clinical symptoms such as musculoskeletal and subcutaneous disorders, it was incorporated in the logistic regression model along with variables sharing a statistically significant association ($p < 0.05$) with AESIs in the bivariate analysis. After adjusting for confounders, female individuals were observed to have a 1.57 times higher odds of AESIs compared with male individuals ($p = 0.009$), and a history of allergy to any stimulus was associated with a 2.81 times higher odds of AESIs ($p = 0.004$) (Table 1b). A nearly similar odds (adjusted odds ratio 2.76) of AESIs was observed with post-vaccination typhoid ($p = 0.042$).

For persistent AESIs, a statistically significant association was noted with sex ($p = 0.016$) and the presence of a co-morbidity such as asthma ($p = 0.007$). With marginal statistical significance, persistent AESIs were also more common in adolescents with a history of allergy, a pre-vaccination history of COVID-19, and post-vaccination typhoid ($p = 0.07$ for each) (Table 2a). All these factors were included in the regression analysis, which showed a 1.61 times higher risk of persistent AESIs in female individuals ($p = 0.018$) and a 2.71 times higher risk in adolescents with co-morbidities ($p = 0.011$). Pre-vaccination COVID-19 increased the odds of persistent AESIs by around 2 times ($p = 0.047$) and a close to 3.2 times higher risk of persistent AESIs was observed with post-vaccination typhoid ($p = 0.023$) (Table 2b). No association of persistent AESIs was observed with a history of allergy.

3.3 AESIs in Adults

Among 291 adults, AESIs were recorded in 83 (28.5%). General disorders were the most common SOC affected by AESIs ($n = 26$, 8.9%). This was followed by musculoskeletal disorders ($n = 17$, 5.8%) and nervous system disorders ($n = 16$, 5.5%). Other common disorders were gastrointestinal disturbances and skin and subcutaneous disorders, each seen in ten (3.4%) cases. A flare of underlying disease was reported by ten adults (3.4%). Details are provided in Table 2 of the ESM.

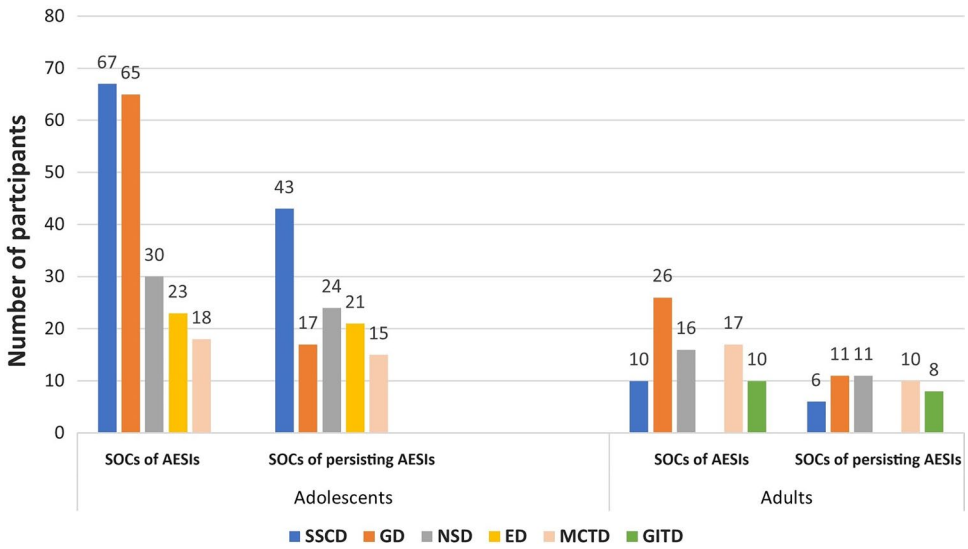

Fig. 2 System organ classes (SOCs) affected by adverse events of special interest (AESIs) and their persistence in BBV152 vaccinated adolescents and adults. (Out of 635 adolescents and 291 adults for AESIs; out of 635 adolescents and 287 adults for persistent AESIs) [eye disorders (ED), general disorders (GD), gastrointestinal disorders (GITD), musculoskeletal and connective tissue disorders (MCTD), nervous system disorders (NSD), skin and subcutaneous tissue disorders (SSCD)]

3.3.1 Persistent AESIs in Adults

Among 83 adults with AESIs, 54 (65.1%) had persistent AESIs. Joint pain ($n = 12$), weakness ($n = 8$), alopecia ($n = 8$), headache ($n = 6$), and dyspepsia ($n = 4$) were the common five AESIs that were persistent in adults at the 1-year follow-up. Regarding SOCs, 80% of gastrointestinal disorders, 75% of cardiac disorders, 68.7% of nervous system disorders, and 60% each of skin and reproductive disorders persisted at the 1-year follow-up with an approximate time of persistence of 5.25 months, 9.5 months, 9 months, 12 months, and 10.3 months, respectively. Details are described in Tables 3 and 4 of the ESM, and Fig. 2.

3.3.2 Risk Factors of AESIs and Persistent AESIs in Adults

With statistical significance, AESIs were more common in adults aged 45 years and above ($p = 0.035$), those with co-morbidities such as hypertension ($p = 0.009$), and those receiving three doses of BBV152 ($p = 0.001$) (Table 3a). Upon adjusting for confounders, the regression analysis showed a 2.23 times higher risk of AESIs in adults with co-morbidities ($p = 0.04$). Individuals receiving three doses and those receiving a single dose of BBV152 were respectively at 4.03 times and 2.16 times higher risk of AESIs compared with those receiving two doses. The difference was not significant between individuals receiving one and three doses of BBV152 (Table 3b).

For persistent AESIs, the unadjusted analysis showed a marginally significant association with age ($p = 0.056$) and a significant association with the presence of co-morbidities ($p = 0.004$) (Table 4a). In the regression analysis, the effect of age was nullified and only the presence of co-morbidities remained a significant determinant, increasing the odds of persistent AESIs by 2.26 times ($p = 0.025$) (Table 4b). Among co-morbidities, the risk of persistent AESIs was attributed to hypertension. This was confirmed in a separate regression analysis based on age groups and hypertension as independent variables (results not shown).

3.4 Serious AESIs in Adolescents and Adults

A total of 11 (1.2%) participants (ten adults and one adolescent) developed serious AESIs. A case of hematemesis (upper gastrointestinal bleed) was reported in a 15-year-old female individual. Stroke events were reported in three adults and one adult in his 20s was hospitalized for Guillain–Barré syndrome (GBS). Using the World Health Organization Scale of Causality Assessment, the latter was attributed a 'probable' association with the vaccine. Details of all serious AESIs are given in Table 5 of the ESM. Four deaths were reported in adults. A history of COVID-19 before receiving the vaccine was present in two of these. Three deaths occurred in female individuals with stroke as the main contributor in two. One among these had a history of diabetes and hypertension and was in her late 60s and the other in her late 50s had a history of diabetes. The cause of death in the third woman could not be identified but the woman in her early 70s had diabetes and hypertension and had a history of multiple episodes of unconsciousness after receiving the vaccine whose etiology could not be identified. The fourth mortality was recorded in a diabetic male individual in his 40s with a history of post-COVID-19 rhinocerebral mucormycosis before receiving the vaccine. The concerned participant succumbed to the illness around 2.5 months after receiving the vaccine. Three of these fatalities shared a 'possible' association with the vaccine while the fourth was 'unclassifiable'.

Table 1 Unadjusted (1a) and adjusted (1b) analysis of risk factors of AESIs in BBV152 vaccinated adolescents

N = 635 (1a)				*N* = 635 (1b)		
Tentative risk factors	*N*	AESIs, *n* (%)	*P*-value	Tentative risk factors	aOR (CI)	*P*-value
Sex			**0.006**	**Sex**		
Female	337	130 (38.6)		Female	**1.57 (1.12–2.21)**	**0.009**
Male	298	84 (28.2)		Male (reference)		
Body mass index (kg/m^2)			0.32			
< 25	584	200 (34.2)				
≥ 25	51	14 (27.5)				
Pre-vaccination COVID-19			0.14			
Yes	38	17 (44.7)				
No	597	197 (33)				
Comorbidities[a]			**0.011**	Comorbidities[a]		
Yes	31	17 (54.8)		Yes	1.87 (0.87–4.03)	0.11
No	604	197 (32.6)		No (reference)		
Asthma[a]			**0.007**			
Yes	7	6 (85.7)				
No	628	208 (33.1)				
Hypothyroidism			0.60			
Yes	4	2 (50)				
No	631	212 (33.6)				
Allergy			**<0.001**	Allergy		
Yes	38	23 (60.5)		Yes	**2.81 (1.40–5.65)**	**0.004**
No	597	191 (32)		No (reference)		
Post-vaccination dengue			0.85			
Yes	22	7 (31.8)				
No	613	207 (33.8)				
Post-vaccination typhoid			0.09	Post-vaccination typhoid		
Yes	17	9 (52.9)		Yes	**2.76 (1.04–7.34)**	**0.042**
No	618	205 (33.2)		No (reference)		
Viral upper respiratory tract infection			0.56			
Yes	304	99 (32.6)				
No	331	115 (34.7)				
Number of doses[b]			0.49			
1	79	24 (30.4)				
2	490	169 (34.5)				
3	8	4 (50)				

AESIs adverse events of special interest, *aOR* adjusted odds ratio, *CI* confidence interval

[a]Major co-morbidities in adolescents were asthma and hypothyroidism. Considering a small number of individual co-morbidities such as asthma and to prevent multicollinearity in the analysis, 'co-morbidities' and not 'asthma' were included in the regression model. In a separate regression model including 'sex,' 'asthma,' 'typhoid,' and 'allergy' as risk factors, similar trends and statistical significance were observed for 'sex,' 'typhoid,' and 'allergy'. High risk was observed with 'asthma' but with varying CIs and marginal statistical significance (results not shown)

[b]Out of *N* = 635, total number of vaccine doses not known for *n* = 58

Bold values denote statistical significance

Table 2 Unadjusted (2a) and adjusted (2b) analysis of risk factors of persistent AESIs in BBV152 vaccinated adolescents ($N = 635$)

Tentative risk factors (2a)	*N*	Persistent AESIs, *n* (%)	*P*-value	Tentative risk factors (2b)	aOR (CI)	*P*-value
Sex				Sex		
Female	337	88 (26.1%)	**0.016**	Female	**1.61 (1.09–2.37)**	**0.018**
Male	298	54 (18.1%)		Male (reference)		
BMI (kg/m^2)						
< 25	584	133 (22.8)	0.39			
≥ 25	51	9 (17.6)				
Pre-vaccination COVID-19				Pre-vaccination COVID-19		
Yes	38	13 (34.2)	**0.07**	Yes	**2.06 (1.01–4.19)**	**0.047**
No	597	129 (21.6)		No (reference)		
Comorbidities[a]				Comorbidities[a]		
Yes	31	14 (45.2)	**0.002**	Yes	**2.71 (1.25–5.86)**	**0.011**
No	604	128 (21.2)		No (reference)		
Asthma[a]						
Yes	7	5 (71.4)	**0.007**			
No	628	137 (21.8)				
Hypothyroidism						
Yes	4	2 (50)	0.22			
No	631	140 (22.2)				
Allergy				Allergy		
Yes	38	13 (34.2)	**0.07**	Yes	1.47 (0.69–3.11)	0.31
No	597	129 (21.6)		No (reference)		
Post-vaccination dengue						
Yes	22	4 (18.2)	0.79			
No	613	138 (22.5)				
Post-vaccination typhoid				Post-vaccination typhoid		
Yes	17	7 (41.2)	**0.07**	Yes	**3.19 (1.17–8.67)**	**0.023**
No	618	135 (21.8)		No (reference)		
Post-vaccination viral upper respiratory tract infection						
Yes	304	69 (22.7)	0.85			
No	331	73 (22.1)				
Number of doses of vaccine (***N* = 577**[b])						
1	79	18 (22.8)	0.98			
2	490	110 (22.4)				
3	8	2 (25)				

AESIs adverse events of special interest, *aOR* adjusted odds ratio, *CI* confidence interval

[a]Major co-morbidities in adolescents were asthma and hypothyroidism. Considering a small number of individual co-morbidities such as asthma and to prevent multicollinearity in the analysis, 'co-morbidities' and not 'asthma' were included in the regression model. In a separate regression model including 'sex,' 'asthma,' 'typhoid,' 'pre-vaccination COVID-19,' and 'allergy' as risk factors, similar trends and statistical significance were observed for all risk factors (results not shown)

[b]Total number of vaccine doses not known for $n = 58$

Bold values denote statistical significance or marginal statistical significance

3.5 Symptoms with Reduced Frequency and Severity

Though not included in the study format, some study participants self-reported the health benefits they observed after receiving the BBV152 vaccine. Around 6.3% ($n = 40$) of adolescents and 5.5% ($n = 16$) of adults mentioned a reduced frequency or severity of health issues that they had had before vaccination. Among these, reduced frequency and/or severity of URTIs was the most common health benefit observed, being reported by 37 adolescents and 13 adults.

Table 3 Unadjusted (3a) and adjusted (3b) analysis of risk factors of AESIs in BBV152 vaccinated adults

N = 291 (3a)				*N* = 225 (3b)		
Tentative risk factors	*N*	AESI, *n* (%)	*P*-value	Tentative risk Factors[a]	aOR (CI)	*P*-value
Age (years)			**0.035**	Age (years)	1.01 (0.49–2.10)	0.98
19–44	230	59 (25.7)		≥ 45		
≥ 45	61	24 (39.3)		19–44 (reference)		
Sex			0.78			
Female	144	40 (27.8)				
Male	147	43 (29.3)				
Body mass index (kg/m^2)			0.62			
< 25	233	68 (29.2)				
≥ 25	58	15 (25.9)				
Pre-vaccination COVID-19			0.18			
Yes	25	10 (40)				
No	266	73 (27.4)				
Comorbidity[b]			**0.011**	Comorbidity[b]	2.23 (1.04–4.75)	**0.04**
Yes	60	25 (41.7)		Yes		
No	231	58 (25.1)		No (reference)		
Hypothyroidism			1.0			
Yes	6	2 (33.3)				
No	285	81 (28.4)				
Diabetes mellitus			0.31			
Yes	18	7 (38.9)				
No	273	76 (27.8)				
Hypertension			**0.009**			
Yes	18	10 (55.6)				
No	273	73 (26.7)				
Allergy			0.38			
Yes	24	5 (20.8)				
No	267	78 (29.2)				
Post-vaccination dengue			0.68			
Yes	6	1 (16.7)				
No	285	82 (28.8)				
Post-vaccination typhoid			0.41			
Yes	7	3 (42.9)				
No	284	80 (28.2)				
Post-vaccination viral upper respiratory tract infection			0.053			
Yes	124	28 (22.6)				
No	167	55 (32.9)				
Number of doses[c] (*N* = 225)			**0.001**	**Number of doses**		
1	40	17 (42.5)		3 dose group 2 dose group (reference)	**4.03 (1.51–10.77)**	**0.005**
2	164	42 (25.6)		1 dose group 2 dose group (reference)	**2.16 (1.04–4.48)**	**0.039**
3	21	13 (61.9)		1 dose group 3 dose (reference)	0.53 (0.17–1.65)	0.27

*AESIs a*dverse events of special interest, *aOR* adjusted odds ratio, *CI* confidence interval

[a]In *N* = 225 adults, the bivariate analysis showed 'comorbidity' and 'number of doses' to share a significant association with AESIs

[b]Only 'comorbidity' and not 'hypertension' was included in regression model because of small sample size of individual comorbidity as well as to prevent multicollinearity in analysis. In a separate regression done including 'age,' 'number of doses,' and 'hypertension' as independent variables, similar trends and statistical significance was observed with 'number of doses' and 'age'. Hypertension did not emerge as an independent risk factor of AESIs (results not shown)

[c]Out of *N* =291, total number of vaccine doses not known for 66 adults

Bold values denote statistical significance

Table 4 Unadjusted (4a) and adjusted (4b) analysis of risk factors of persistent AESIs in BBV152 vaccinated adults ($N = 287$, after removing 4 adults who died)

Tentative risk factors (4a)	*N*	Persistent AESIs, *n* (%)	*P*-value	Tentative risk factors (4b)	aOR (CI)	*P*-value
Age (years)			**0.056**	Age (years)		
≥ 45	58	16 (27.6)		≥ 45	1.43 (0.69–2.98)	0.33
19–44	229	38 (16.6)		19–44 (reference)		
Sex						
Female	141	29 (20.6)	0.45			
Male	146	25 (17.1)				
Body mass index (kg/m^2)						
< 25	229	47 (20.5)	0.14			
≥ 25	58	7 (12.1)				
Pre-vaccination COVID-19						
Yes	23	6 (26.1)	0.40			
No	264	48 (18.2)				
Comorbidities[a]				Comorbidities[a]		
Yes	56	18 (32.1)	**0.004**	Yes	**2.26 (1.11–4.62)**	**0.025**
No	231	36 (15.6)		No (reference)		
Hypothyroidism						
Yes	6	2 (33.3%)	0.31			
No	281	52 (18.5%)				
Diabetes mellitus						
Yes	14	4 (28.6)	0.31			
No	273	50 (18.3)				
Hypertension[a]						
Yes	15	7 (46.7)	**0.011**			
No	272	47 (17.3)				
Allergy						
Yes	23	3 (13)	0.59			
No	264	51 (19.3)				
Post-vaccination dengue						
Yes	6	1 (16.7)	1.0			
No	281	53 (18.9)				
Post-vaccination typhoid						
Yes	7	2 (28.6)	0.62			
No	280	52 (18.6)				
Post-vaccination viral upper respiratory tract infection						
Yes	124	22 (17.7)	0.68			
No	163	32 (19.6)				
Number of doses[b] ($n = 221$)						
1	39	12 (30.8)	0.13			
2	162	29 (17.9)				
3	20	6 (30)				

AESIs adverse events of special interest, *aOR* adjusted odds ratio, *CI* confidence interval

[a]Only 'co-morbidities' and not 'hypertension' were included in the regression model because of the small sample size of individual co-morbidity as well as to prevent multicollinearity in the analysis. In a separate regression done with 'hypertension' and 'age' as independent variables, similar trends and statistical significance were observed (results not shown)

[b]Total number of vaccine doses not known for 66 adults

Bold values denote statistical significance or marginal statistical significance

Details of the symptoms in which improvement was noticed after BBV152 are mentioned in Table 6 of the ESM.

4 Discussion

In the absence of long-term safety data of COVID-19 vaccines, the main aim of the present study was to highlight the safety issues in recipients of the BBV152 vaccine, particularly among adolescents, at the 1-year follow-up. Nearly 50% of study participants complained of infections during the follow-up period, predominated by viral URTIs. Close to one third of the individuals developed AESIs. New-onset skin and subcutaneous disorders, general disorders, and nervous system disorders were the three most common disorders observed in adolescents after receiving the vaccine. More than 10% of adolescents complained of skin conditions, mainly in the form of alopecia and a similar percentage had general disorders such as weakness. While the majority of general disorders had recovered, skin disorders were present in the majority during the final follow-up with a median time of persistence of 8.5 months. General disorders and musculoskeletal disorders were the common long-term AESIs in adults. General disorders had recovered in more than 50% but symptoms of musculoskeletal disorders were persisting in the majority for almost 6 months at the final follow-up. Close to 5% of adolescents and adults complained of nervous system disorders such as headaches, which were persisting in the majority for around 9 months at the final follow-up. Among other atypical and persistent AESIs, eye disorders such as new-onset refractive error were reported in 3.6% of adolescents and 5% of adolescent female individuals complained of new-onset menstrual abnormalities. Hypothyroidism was reported by around 0.6% of adolescents and adults, each.

The patterns and incidence of AESIs differ with respect to the type of vaccine and study population. In a predominantly adult-based population receiving the ChAdOx1-nCov-19 vaccine, nearly 14% developed AESIs contrary to the one-third rates of AESIs observed in the present study. Musculoskeletal disorders, general disorders, and cardiovascular disorders were the common AESIs in that study, but the incidence reported was low, being 3.7%, 2.1%, and 1.4%, respectively. Reproductive system disturbances and ocular disturbances were less common and were documented in 0.7% (2% of female individuals) and 0.26% of participants, respectively [7]. Three out of five mortalities reported with ChAdOx1-nCoV-19 happened because of cardiac causes in contrast with the neurological events such as stroke reported in the present study. Another 18-month long study commented upon the late AESIs after the protein subunit-based PastoCovac vaccine in Iran. Cutaneous disturbances (3.3%), musculoskeletal disorders (1.1%), and neurological events (1.1%) were the common AESIs with PastoCovac given in heterogeneous regimens with the AstraZeneca or Sinopharm vaccine. The rates were further low with the standard regimen of the PastoCovac vaccine in which neurological, musculoskeletal, and metabolic disturbances were the common events, each witnessed in 0.3% of individuals [13]. Apart from the type of vaccine and study population, the system affected and the incidence of AESIs are strongly influenced by reporting rates and awareness regarding AESIs.

Among adolescents, the occurrence of AESIs and persistent AESIs was higher in female individuals, those with co-morbidities, those with a history of allergy to any stimulus, and those developing typhoid after receiving the vaccine. Some association of persistent AESIs was also observed with a pre-vaccination history of COVID-19. The adjusted analysis showed female individuals to have a 1.6 times higher odds of AESIs. Adolescents with a history of allergy and those developing typhoid after receiving the vaccine, each, were independently at a 2.8 times higher risk of AESIs. Considering the persistence of AESIs, female individuals were at a 1.6 times higher risk, and adolescents with co-morbidities were at a 2.7 times higher risk compared respectively with male individuals and adolescents without co-morbidities. The pre-vaccination history of COVID-19 and post-vaccination occurrence of typhoid increased the odds of persistent AESIs by 2 and 3.2 times, respectively. In our previous work, the pre-vaccination history of COVID-19 was shown as an independent risk factor for long COVID-19, AESIs, and persistent AESIs in recipients of the ChAdOx1-nCoV-19 vaccine [7, 14]. Female individuals were also the common victims of AESIs and persistent AESIs after ChAdOx1-nCoV-19, similar to the findings of the present study. These findings, which have been consistent across our several studies, emphasize the need for more stringent vigilance in female recipients of COVID-19 vaccines and also suggest revisiting the guidelines for vaccinating those who have recovered from natural COVID-19.

The association of AESIs with post-vaccination typhoid needs to be explored in future research. In the opinion of consultants involved in the present study, many patients showing seropositivity for typhoid during the second and third wave of the pandemic were diagnosed eventually with COVID-19. The false cross-reactivity of Salmonella typhi antibodies in patients of COVID-19 has also been highlighted in some studies [15]. Thus, the possibility of observed AESIs being determined actually by COVID-19 cannot be ruled out. Notwithstanding the above limitation, AESIs were not associated with respiratory tract infections in adolescents or adults.

Interestingly, adults receiving three doses and those receiving one dose of BBV152 were respectively at four and two times higher risk of AESIs compared with adults receiving two doses of BBV152. A booster dose mechanistically enhances the production of anti-Spike antibodies above that produced by the second dose. Significant cross-reactivity has been shown between anti-SARS-CoV-2 antibodies and diverse human antigens and this can explain the multi-system AESIs witnessed in the study participants [16]. Reasons behind the high risk of AESIs in one dose group are elusive but aberrant biochemical and immunological signatures have been observed in recipients of a SARS-CoV-2 inactivated vaccine within the first few months of the first dose. Such changes include an increase in blood sugar, a decline in renal function, an abnormal coagulation profile, increased nuclear factor-κB signaling, decreased CD4+ regulatory T cells, and upregulation of inflammatory response signaling in monocytes [17].

In one of our previous works on COVID-19 vaccine effectiveness, a rather higher rate of COVID-19 was observed in one dose group compared with unvaccinated individuals, and transient immune suppression after the first dose was cited as a possible reason in line with the post-vaccine immunomodulation observed in the study by Liu et al. [14, 17] However, whether the one-dose group is more vulnerable to AESIs also is worth exploring. The results concerning the boosters need corroboration from larger studies owing to the limited number of adults receiving the third dose of vaccine. Among adults, those with co-morbidities such as hypertension were at more than 2 times higher risk of AESIs and persistent AESIs. It has often been emphasized that adults with comorbidities are more at risk of adverse COVID-19 outcomes and hence should be prioritized for vaccination. Our findings emphasize the need for balancing these risks against those of higher AESIs in these groups.

Among serious AESIs, GBS occurred in one adult following the booster dose and shared a 'probable' association with the vaccine. The concerned adult however had a history of GBS 15 years previously and hence might have been more vulnerable to develop the syndrome after known immunologic insults such as infection or vaccination. However, considering the global annual incidence of GBS (one to two cases/100,000 people), the observed rate of one case of GBS in 926 vaccinated individuals demands larger studies and increased awareness to comment on the incidence of immune-mediated phenomena post-COVID-19 vaccination [18].

Four deaths (three female individuals, one male individual) were reported in adults. All of them had diabetes while hypertension and a history of pre-vaccination COVID-19 were present in three and two individuals, respectively. Stroke was the main contributor in two fatalities and one fatality was due to post-COVID-19 rhinocerebral mucormycosis, which supposedly disseminated after vaccination as reported by the caregivers. The fourth death happened in a woman with multiple episodes of unconsciousness post-vaccination, the etiology of which remained unidentified till death. In the absence of a definite causality association, no conclusions can be drawn from these events. Still, it is noteworthy that more deaths in our ChAdOx1 long-term safety study were reported due to cardiac events whereas with BBV152, more stroke deaths were reported.

5 Limitations

The study enrols individuals vaccinated with BBV152. To understand the link of AESIs with COVID-19 vaccines, a control arm of unvaccinated individuals is needed to compare the rates of AESIs between the two groups. In the absence of data on background rates of the observed AESIs, no comments can be made on changes in the incidence of the observed events in the post-vaccination period. The findings of our study are confined to BBV152 and should not be extrapolated to viral vector or mRNA vaccines. The study primarily involved adolescents and the sample size of adults was relatively small. Larger adult-based studies are needed to understand the long-term safety of BBV152 in adults. The study participants belonged to the northern belt of India and ethnicity-related differences in vaccine tolerability should be explored. The sample size was decided based on the primary outcome of AEFIs and not based on AESIs as no study on the incidence of AESIs was available when the present study was started. However, considering the high observed rates of overall AESIs, the study seems to be well powered for detecting AESIs. The observed rates of serious AESIs such as stroke and GBS however will need confirmation from vaccine-specific larger multicentric studies. The final follow-up being at 1 year, the study is subject to recall bias at certain points. For example, the exact time of onset of AESIs was not available but the approximate time of persistence of AESIs was obtained. For the same reason, the time of improvement of AESIs was not recorded. To reduce contamination by recall bias and in line with the protocol of our previous study on the long-term safety of the ChAdOx1-nCoV-19 vaccine, the health issues confirmed by participants to be present for at least 1 month during the final follow-up were considered "persistent AESIs" [7]. However, some of the AESIs not persisting during the final follow-up but which lasted for a significant period at any time since vaccination might have gone unreported. Further, as the reporting rates of COVID-19 went down in India after May 2022 (end of the third wave), routine testing for SARS-CoV-2 was not performed in individuals developing viral URTIs, and it was voluntary on the part of those having any symptoms. The possibility of COVID-19 cannot be excluded

in these individuals. Importantly, however, no association was observed between AESIs and respiratory infections. The relationship of AESIs with typhoid and pre-vaccination COVID-19 needs corroboration from larger studies owing to the smaller representation of these subsets. The specific laboratory test used for the diagnosis of typhoid was not enquired. Furthermore, in the experience of the study researchers (UK, SSC, KP, VJ, and SK), findings concerned with seropositivity for typhoid should be interpreted cautiously as the test was commonly found to be co-positive in patients of COVID-19 during the second and third wave of the pandemic. The possibility of sera of patients with COVID-19 showing cross-reactivity in the serological tests designed for typhoid needs to be determined. For the same reason, the high rates of AESIs observed in the study should be interpreted cautiously as the likelihood of typhoid cases actually being COVID-19 cannot be excluded. Although all interviews were conducted by medical students and residents, the possibility of inter-observer bias in collecting AESIs cannot be eliminated. More than 5% of participants self-reported reduced viral URTIs. The percentage might be falsely low as symptoms improving after vaccination were not a part of the designed questionnaire used in the present study.

6 Conclusions

Nearly one third of participants receiving the BBV152 vaccination reported AESIs. Female adolescents and those with a history of allergy are at a higher risk of AESIs after the BBV152 vaccine. Vaccinated adolescents developing typhoid after BBV152 might also be at a higher risk of AESIs, but the finding of seropositivity for typhoid needs to be viewed cautiously. Adolescent female individuals and those with co-morbidities are at a higher risk of persistent AESIs. Focussed monitoring for persistent AESIs is warranted for individuals with a pre-vaccination history of COVID-19. Adults with co-morbidities, especially hypertension, are at a higher risk of AESIs and persistent AESIs after BBV152 administration. The patterns of AESIs developing after BBV152 differ from those seen after ChAdOx1-nCoV-19 as well as among different age groups. Vigilance is advised in adolescents for alopecia, headache, and menstrual abnormalities and in adults for musculoskeletal and nervous system disorders. Serious AESIs including stroke and GBS should be actively investigated to determine their actual incidence post-vaccination and to identify the persons vulnerable to them. With the majority of the AESIs persisting for a significant period, extended surveillance is suggested for COVID-19-vaccinated individuals to understand the course and outcomes of late-onset AESIs. The relationship of AESIs with sex, co-morbidities, pre-vaccination COVID-19, and non-COVID illnesses should be explored in future studies.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40264-024-01432-6.

Acknowledgments Upinder Kaur and Sankha Shubhra Chakrabarti thank the Institutions of Eminence Scheme in the Banaras Hindu University for research support. Sankha Shubhra Chakrabarti thanks the Indian Council of Medical Research for research support.

Declarations

Funding No funding was received for the conduct of this study or the preparation of this article.

Conflicts of Interest/Competing Interests Upinder Kaur, Aakanksha Jaiswal, Ayushi Jaiswal, Kunal Singh, Aditi Pandey, Mayank Chauhan, Mahek Rai, Sangeeta Kansal, Kishor Patwardhan, Vaibhav Jaisawal, and Sankha Shubhra Chakrabarti have no conflicts of interest that are directly relevant to the content of this article.

Ethics Approval The study was conducted after permission from the Institute Ethics Committee of the Institute of Medical Sciences, Banaras Hindu University. No human experimentation was performed. All procedures were performed as per the Declaration of Helsinki and its subsequent modifications (Ethical Approval number: Dean/2022/EC/3210 and Dean/2021/EC/2526).

Consent to Participate Written informed consent/assent to participate was obtained from each participant in the study.

Consent for Publication Written informed consent/assent for publication was obtained from all participants.

Availability of Data and Material All data produced in the present study are available upon reasonable request to the corresponding authors, as per institutional and national legal norms and procedures.

Code Availability Not applicable.

Authors' Contributions Conceptualization: UK, SSC, SK, VJ, KP. Methodology: UK, SSC, VJ. Formal analysis and investigation: UK, VJ, AJ, AJ, KS, AP, MC, MR. Writing, original draft preparation: UK, AJ AJ, KS, MR. Writing, review and editing: UK, SSC. Funding acquisition: none. Resources: none. Supervision: UK, VJ. All authors read and approved the final version.

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