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Research Article

Assessment of long-term adverse events regarding different COVID-19 vaccine regimens within an 18-month follow-up study

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Abstract

Early reports on coronavirus disease 2019 (COVID-19) vaccines presented the short-term adverse events (AEs). This follow-up study investigated a standard regimen based on protein subunit vaccines, PastoCovac and PastoCovac Plus, and the combinational vaccine regimens including AstraZeneca/PastoCovac Plus and Sinopharm/PastoCovac Plus. The participants were followed up to 6 months post the booster shot. All the AEs were collected through in-depth interviews using a valid researcher-made questionnaire and were evaluated regarding the association with the vaccines. Of the 509 individuals, 6.2% of the combinational vaccine participants had late AEs, of whom 3.3% suffered from cutaneous manifestations, followed by 1.1% arthralgia complaints, 1.1% with neurologic disorders, 0.3% ocular problems and 0.3% metabolic complications, with no significant difference between the vaccine regimens. For the standard regimen, 2% of the individuals experienced late AEs as (1%), neurological disorders (0.3%), metabolic problems (0.3%) and involvement of joints (0.3%). Notably, 75% of the AEs were persistent up to the end of the study. A low number of late AEs were captured in 18 months as 12 improbable, 5 unclassifiable, 4 possible and 3 probable associated AEs with the vaccine regimens. The benefits of COVID-19 vaccination far exceed the potential risks and late AEs seem to be uncommon.

Keywords: COVID-19, vaccine, safety, late adverse events, long-term AEs

Background

There have been massive efforts toward vaccine development against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The recent coronavirus disease 2019 (COVID-19) pandemic has hopefully been controlled by quite rapidly well-developed vaccines in a relatively fast time. The well immunogenicity profile of the manufactured vaccines has led to a significant reduction in related COVID-19 death and therefore public trust regarding vaccination (Zhou et al. 2020, Chapin-Bardales et al. 2021, Wu et al. 2021).

Early reports on COVID-19 vaccines described the adverse events (AEs) mostly as local ones at the injection site, as well as some temporary systemic manifestations that lasted from 1 to 10 days, among which fever, fatigue and headache were highlighted (Polack et al. 2020, Kataria et al. 2021, Montalti et al. 2021, Zhang et al. 2021).

The vaccine safety profile is a crucial factor for the distribution process among eligible individuals. Along with the growing range of vaccine applications through different platforms, concerns about the potential side effects over time have come to public attention, as well as the long-term effects of COVID-19 infection (Salehi-Vaziri et al. 2021, Sadat Larijani et al. 2022).

Several reports have been published on the short-term AEs of COVID-19 vaccines (Gras-Champel et al. 2021, Konu et al. 2021, Menni et al. 2021). However, the delayed effects of vaccines are quite neglected. Moreover, case reports cover the delayed vaccine-related effects, including very rare and unsolicited events, have also indicated the importance of long-term studies.

Public trust in terms of COVID-19 vaccines has been affected by several factors, including a relatively rapid release process and a lack of long-term safety data. What is more, booster doses are needed due to new SARS-CoV-2 variants and also because of the decline in induced immunity responses (Papachristodoulou et al. 2020, Dar-Odeh et al. 2022).

Hence, any gap regarding the vaccine safety profile could possibly highlight probable obstacles against the huge effort towards vaccine development by vaccine hesitancy among populations (Lee et al. 2020, Dodd et al. 2021).

The associated data should be clearly provided as an evidence-based and continuous tracking approach. In fact, at this stage of the COVID-19 era, vaccination maintenance among society seems to be a priority. Moreover, valid and sufficient data are needed regarding different vaccine platforms.

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Protein subunit vaccines have been shown to be safe and effective in heterologous platforms in different studies against infectious diseases (Larijani et al. 2020, Mona et al. 2020, Gao 2021). AEs might be late, and newly launched vaccines need to be investigated more (Sadat Larijani et al. 2023, Wu et al. 2023). The effectiveness of a heterologous strategy needs to be more investigated regarding COVID-19 in order to achieve a safe heterologous prime-boost regimen, preferably with the lowest rate of AEs.

PastoCovac (Soberana 02) is a recombinant protein vaccine composed of an immunogenic region of SARS-CoV-2 RBD conjugated to the tetanus toxin (Toledo-Romani et al. 2021). PastoCovac Plus (Soberana Plus) is based on dimerized RBD (d-RBD) (Gorry 2020, Toledo-Romani et al. 2021, SOBERANA). Both vaccines have been administrated in the Iranian population as the standard protein vaccine regimen (Mostafavi et al. 2023) and also as the combinational regimen with inactivated virus-based (Ramezani et al. 2023) and Adenovirus-based vaccines (data under review).

In the present study, COVID-19 vaccine platforms through standard and combinational regimens were investigated in one-year and half follow-ups to assess the unsolicited AEs, as well as the safety comparison between the vaccine regimens.

Methods

Study population

This study was conducted from April 2021 to October 2022 and included COVID-19 vaccine study participants under different standard and combinational regimens who responded to the 18-month follow-up. Combinational regimens included three categories as: (a) two doses of Sinopharm and one dose of PastoCovac Plus (BBIP/Plus); (b) two doses of Sinopharm and one dose of PastoCovac (BBIP/PCovac); and (c) two doses of AstraZeneca (ChAdOx1 nCoV-19) and one dose of PastoCovac Plus (ChAd/Plus). Two doses of PastoCovac and one dose of PastoCovac Plus (PCovac/Plus) was the standard regimen. Fig. 1 presents the study design.

All the individuals provided informed consent prior to enrolment and the protocol was performed according to the Declaration of Helsinki (Fortaleza, 13 October 2013). The study protocol was approved by the Pasteur Institute of Iran National Committee for Ethics (ethics code numbers: IR.PII.REC.1400.077 [standard vaccine regimen study] and IR.PII.REC.1400.076 [combinational vaccine regimen study]).

Data collection

Information regarding AEs during an 18-month period (6 months after the booster dose) was collected through an in-depth interview using a researcher-made, valid and reliable questionnaire. This included any complications, disorders, new onsets or worsening of a previous medical condition after each dose of vaccination.

For the identified AEs, injection of extra doses/other vaccines and COVID-19 infection/hospitalisations, the start and end dates were recorded. The dates were then aligned with the dates of original COVID-19 vaccine injections in order to determine the temporality of events, and to identify the duration of identified complication(s). The data regarding the temporality of AEs were used to infer the causal association between the vaccine and the identified complication. For every reported complication, a complementary causal assessment form was also completed by the physician.

A full medical history of all the identified cases was investigated by the AEs assessment committee, based upon which causal inference about the association of (Adverse drug reactions) with the vaccine was made by committee members, who were expert in different topics such as immunology, infectious diseases, internal medicine, medical biotechnology, epidemiology and clinical pharmacology. Case-based consultations with other specialists were carried out where needed.

Descriptive statistics are reported as means (SD) for quantitative variables and as frequency (percentage) for categorical variables. Chi-square was used to evaluate associations between qualitative demographic and clinical variables and the vaccination regimens. The difference in the frequency of AEs between different vaccination regimens was assessed using the Kruskal–Wallis test. All statistical analyses were performed with an alpha level of 0.05 in Stata software (version 17).

Results

Demographic characteristics

In total, 509 individuals were included in this study; 271 individuals received combinational vaccine regimens as BBIP/PCovac Plus recipients (n = 110), ChAd/Plus recipients (n = 71) and BBIP/PCovac (n = 90). The standard group, the PCovac/Plus recipients, accounted for 288 individuals.

There was no significant difference between the groups regarding age, gender and comorbidities (Table 1). Hyperthyroidism (6.6%), hypertension (4.4%) and hyperlipidaemia (3.6%) were the most common comorbidities among the participants.

Data collection

COVID-19 history was recorded in four different periods and showed that there was a significant difference between COVID-19 incidence after the first dose between the regimens ($P < 0.001$), among which the BBIP/PCovac group did not develop the infection post first dose (Table 1). Furthermore, all the COVID-19 infections were recorded before the booster dose.

Evaluation of AEs

The incidence of AEs including the defined duration of the first 7 days was fully investigated. Pain at the injection site was the only local AE and it accounted for 44.5%, 58.8% and 23.9% among BBIP/Plus, BBIP/PastoCovac and ChAd/Plus, respectively. Notably, among the participants who had this local reaction, one case experienced it for nearly 1 month after the PastoCovac booster shot, before it was then resolved without requiring medical care.

Systemic AEs among the BBIP/Plus and BBIP/PCovac Plus recipients mostly included headache and fatigue. Nevertheless, ChAd/Plus led to higher rates of AEs including fever (57.7%), body pain (50.7%), chill (33.8%) and headache (30.2%), mostly caused by priming vaccine shots.

Long-term assessment of unsolicited AEs

The long-term assessment after the vaccination included any late unsolicited AEs that occurred 7 days post vaccination. After each dose of vaccine, the participants were followed to record any disorder. This schedule included any complaint post day 7 of injections up to at least 6 months after the booster shot. The relation of each recorded disorder to the administrated vaccine/regimen was carefully discussed by an independent committee based on the cases' medical history, COVID-19 history and complementary clinical and preclinical assessments.

The results showed that almost 3% of the total population experienced late AEs during the 18-month follow-up. Notably, of 308 females who participated in the follow-up, 7.1% reported men-

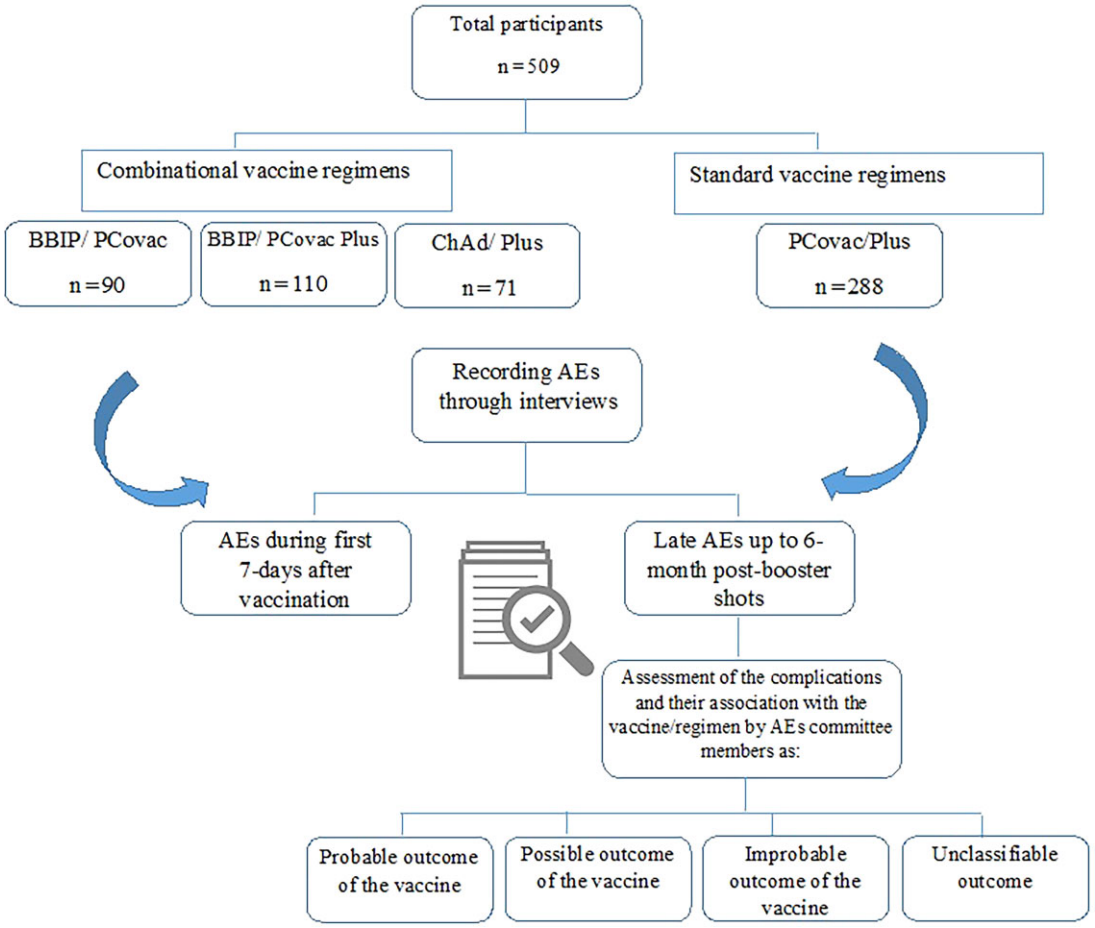

Figure 1. Summary of the follow-up study.

strual abnormalities, which are fully discussed elsewhere and the associated data are excluded from this study (paper under review). In order to compare the vaccine regimens, the AEs in the long-term schedule are presented for the combinational vaccine regimens versus the standard one in Tables 2 and 3.

Combinational vaccine regimens

According to Table 2, 17 cases (6.2%) of the combinational vaccine regimens experienced long-term unsolicited AEs. Skin was the most affected organ, accounting for 52.9% (nine cases), particularly in the form of hair loss, which in total occurred in 2% of combinational vaccine regimen recipients. There was no significant difference between the vaccine regimens regarding hair loss frequency ($P = 0.66$). Other captured incidences were joints involvement in three cases (1.1%), neurological disorder in three individuals (1.1%), ocular involvement in one case (0.3%) and metabolic complications in one person (0.3%), with no significant difference between the vaccine regimens ($P > 0.05$). Notably, 70% of AEs were persistent up to the end of the study (6 months after the booster shot). Furthermore, other AEs resolved after at least 3 months post onset.

The assessment of correlation between the vaccine regimens to the unsolicited AEs was also investigated according to the existence of comorbidities, COVID-19 history or co-incidence, previous history of similar problems and other demographics. More than one-half of the AEs (64.7%) were evaluated as an improbable outcome of the vaccine/regimen. Four (23.5%) incidences were evaluated as possible and only one event was a probable outcome of the vaccine/regimen (5.8%). There was also an unclassified AE related to optic which is being investigated for diagnosis.

Standard vaccine regimens recipients

In total, six (2%) individuals who received PCovac/Plus vaccines experienced late AEs, among whom one case had two different disorders (Table 3). Cutaneous problems were seen in three individuals (1.04%), from which two incidences of skin rashes were assessed as probable vaccine consequences that required medical treatment. Most of the unsolicited AEs occurred post booster shot. Four incidences required additional follow-up and thus the unclassifiable reported AEs are still being investigated or have been resolved after treatment.

Discussion

Several studies have reported acute AEs of COVID-19 vaccines, mostly in short-term follow-ups post vaccination. As the number of vaccinated individuals increases over time, the late unsolicited AEs come to attention. Thus, investigating the late onset of disorders which are potentially vaccine outcomes seems to be a critical issue. There is no clear vision of future SARS-CoV-2 trends and so booster vaccines might be required as an annual programme.

The present study addressed some unsolicited AEs that were mostly persistent during the 18-month follow-up. In total, unsolicited AEs were reported for 3% of the study population in the

Table 1. Demographic characteristics of the study participants.

	Combinational regimens			Standard regimen	P-value
Vaccine groups	**BBIP/PCovac Plus[1]**	**ChAd/Plus[2]**	**BBIP/PCovac[3]**	**PastoCovac/Plus[4]**	
Population (n)	110	71	90	288	
Gender n (%)					0.043
Male	61 (55.4)	26 (36.6)	41 (54.4)	190 (66.0)	
Female	49 (44.5)	45 (63.3)	49 (45.5)	98 (34.0)	
Age					
Mean (SD)	42.2 (13.1)	42.7 (11.15)	39.3 (12.7)	39.2 (11.3)	0.951
Min, Max	19, 77	25, 70	18, 81	19, 71	-
< 50	85 (77.2)	55 (77.4)	71 (78.8)	225 (80.1)	0.959
≥ 50	25 (22.2)	16 (22.5)	19 (21.1)	56 (19.9)	
BMI					
Mean (SD)	26.26 (6.6)	22.62 (9.3)	26.7 (4.7)	26.3 (3.9)	0.021
≤ 25	40 (36.3)	32 (66.1)	38 (42.2)	118 (42.0)	0.755
25–30	47 (42.7)	24 (45.0)	33 (33.6)	117 (41.6)	
≥ 30	23 (20.9)	15 (21.1)	19 (21.1)	46 (16.4)	
COVID-19 history n (%)					
Before vaccine	39 (35.45)	25 (35.21)	35 (38.88)	94 (32.6)	0.850
After the first dose	1 (9.09)	6 (8.45)	0	25 (8.6)	0.001
After the second dose	12 (10.90)	7 (9.85)	17 (18.88)	3 (1.0)	0.015
After the third dose	-	-	-	-	-
Comorbidity n (%)	33 (Aquino et al. 2022)	22 (32.3)	20 (22.2)	49 (17.4)	0.364

[1]BBIP/Plus: Two doses of Sinopharm (inactivated virus-based vaccine) and a booster dose of PastoCovac Plus (protein subunit-based vaccine).
[2]BBIP/PCovac: Two doses of Sinopharm (inactivated virus-based vaccine) and a booster dose of PastoCovac (subunit protein-based vaccine).
[3]ChAd/Plus: Two doses of AstraZeneca (Adenovirus-based vaccine) and a booster dose of PastoCovac Plus (protein subunit-based vaccine).
[4]PCovac/Plus: Two doses of PastoCovac and a booster dose of PastoCovac Plus (protein subunit-based vaccines).

Table 2. Unsolicited AEs regarding combinational vaccine regimens (of the 271 total population).

Organ involved	Disorder type	Regimen	Time of disorder onset	Status	Association with the vaccine
Skin	Hair loss	BBIP/PCovac*	After the booster shot	Persistent	Improbable
		BBIP/PCovac	After each dose	Persistent	Improbable
		BBIP/Plus#	After the booster shot	Resolved after few months	Improbable
		ChAd/Plus$	After the booster shot	Persistent	Improbable
		ChAd/Plus	After each dose	Persistent	Improbable
		ChAd/Plus	After the booster shot	Resolved after 9 months	Possible
	Rash	BBIP/Plus	After the booster shot	Persistent	Possible
		BBIP/Plus	After the booster shot	Persistent	Improbable
	Morphea onset	BBIP/Plus	After the booster shot	Persistent	Possible
Joints	Pelvic pain	ChAd/Plus	After the booster shot	Resolved after 3 months	Improbable
	Upper extremity pain	BBIP/Plus	After each dose	Persistent	Improbable
	Aggravation of backache and arthralgia	BBIP/Plus	After the booster shot	Persistent	Improbable
Neurological system	Headache	BBIP/PCovac	After the booster shot	Persistent	Possible
	Neuritis	BBIP/Plus	After the booster shot	Persistent	Probable
	Dizziness, sleepiness and headache	ChAd/Plus	After each dose	Resolved after 6 months	Improbable
Eyes	Blurred vision	BBIP/PCovac	After the booster shot	Persistent	Unclassifiable
Endocrine system	Aggravation of hypothyroidism	BBIP/PCovac	After the booster shot	Persistent	Improbable

*BBIP/PCovac: Two doses of Sinopharm (inactivated virus-based vaccine) and a booster dose of PastoCovac (subunit protein-based vaccine).
#BBIP/Plus: Two doses of Sinopharm (inactivated virus-based vaccine) and a booster dose of PastoCovac Plus (protein subunit-based vaccine).
$ChAd/Plus: Two doses of AstraZeneca (Adenovirus-based vaccine) and a booster dose of PastoCovac Plus (protein subunit-based vaccine).

Table 3. Unsolicited AEs regarding the standard vaccine regimen (of the 288 total population).

Organ involved	Disorder type	Regimen	Time of disorder onset	Status	Association with the vaccine
Skin	Rash	PCovac/Plus*	After the first dose	Persistent	Probable
			After the booster shot	Persistent	Probable
	Canker sores (on and off)		After the first dose	Partial improvement	Unclassifiable
Joints	Aggravation of arthralgia		After the booster shot	Persistent	Unclassifiable
Neurological system	Neuropathy		After the booster shot	Persistent	Unclassifiable
Gastrointestinal system	Pain at right upper side of the abdomen		After the booster shot	Partial improvement	Unclassifiable
Endocrine system	Worsening of hypothyroidism		After the second booster shot	Persistent	Improbable

*PCovac/Plus: Two doses of PastoCovac and a booster dose of PastoCovac Plus (protein subunit-based vaccines).

form of cutaneous disorders, musculoskeletal pain and aggravation of metabolic disorder, neuropathy and ocular difficulty. The most important point might be the persistency of the AEs, apart from those which were transient. The exact mechanism by which late AEs appear is not clear yet. Further studies are required in the same context to identify the possible relation of late incidences to COVID-19 vaccines.

Fundamentally, vaccinations are applied to prevent an infection or to decrease its burden. Adjuvants that are usually incorporated in the vaccine formula could possibly trigger inflammatory or autoimmune responses, as well as immunity stimulation (Ng et al. 2021). One of the possible mechanisms through which an acute autoimmune response could be stimulated is molecular mimicry between the spike proteins and the host's antigens (Akinosoglou et al. 2021).

In a study conducted by Dar-Odeh et al., the long-term AEs of COVID-19 vaccines were explored among 498 practitioners who were vaccinated with Pfizer-BioNTech, Sinopharm and AstraZeneca through a survey. In total, 16.0% of the included population experienced late AEs that lasted for more than 1 month. Similar to our study, the short-term AEs included fatigue, dizziness, myalgia, arthralgia and headache (Dar-Odeh et al. 2022). Menstrual disturbances in females accounted for 4.8% as the most frequently reported vaccine outcome in females, in agreement with our data, which showed that 7.1% of the females had a similar complaint.

A comparative cross-sectional study was conducted on 606 vaccinated healthcare professionals in Nepal with ChAdOx1 and BBIBP-CorV vaccines. The rate of AEs was slightly higher after the first dose of both vaccine types (Rayamajhi et al. 2022). The present study indicates that late disorders could be triggered after injection of each dose, although almost 74% of all detected AEs were set after receiving the booster shot.

According to recent review data, most delayed reactions to applied vaccines included cutaneous involvements, which could present from local nodules to systemic rashes. Although the manifestation is usually within a few days, some delayed ones have also been captured (Aquino et al. 2022). We found hair loss and skin rashes to be the most frequent cutaneous disorders, which might seem unimportant, although their persistence could result in serious concerns. In addition to hair loss, persistent skin rashes in the form of rash and a case with morphea were identified. Morphea, as a serious systemic unsolicited AE, manifested 1 month after the booster shot in a healthy 52-year-old man. Environmental factors including COVID-19 vaccination can cause immune system dysregulation and consequently the pathogenesis of morphea. Other vaccines against SARS-CoV-2, including BNT162b2, mRNA-1273 and AstraZeneca, have also been reported as associated with morphea (Antoñanzas et al. 2022, Aryanian et al. 2022).

The other identified serious AE in this study was an ocular complication, which the 38-year-old man described as blurred vision that had no previous medical history. In fact, visual impairment was not detected in this case after optical examination. Thus he has been followed up. In a study by Nyankerh CAN, of 55 313 reported AEs, 26.69% and 19.77% were classified as blurred vision and visual impairment, respectively (Nyankerh et al. 2022). Ad26.COV2.S, Sinopharm, Pfizer-BioNTech and AstraZeneca vaccines have also led to ocular complications (Elnahry et al. 2021, García-Estrada et al. 2022, Raxwal et al. 2022). A specific monoclonal antigen in response to the vaccination could be the probable response of this complication, as well as a pro-inflammatory condition or post viral inflammatory syndrome (Raxwal et al. 2022).

New onset of neuropathic symptoms was captured through an observational study by Safavi et al., who showed neuropathic manifestations within 1 month after COVID-19 vaccination in 23 cases. The symptoms included serious paresthesia, heat intolerance, palpitations and orthostasis (Safavi et al. 2022). Anti-spike immune responses might be linked to post vaccine syndromes because all COVID-19 vaccines encode or include spike protein. In addition to spike protein, which can directly interact with neurons, the related anti-idiotypic antibodies might bind to the ACE-2 receptor as well (Arthur et al. 2021). Furthermore, autoantibody generation stemming from molecular mimicry and independent immune-dysregulation may both contribute (Dutta et al. 2022).

Hereby, the crucial finding is quite uncommon late AEs, as a total incidence of 24 among 509 individuals (the menstrual disorders in females are discussed elsewhere and so the associated data are excluded). In total, 6.2% of the combinational vaccine regimens participants had late AEs, of whom 3.3% suffered from cutaneous manifestations, followed by 1.1% arthralgia complaints, 1.1% with neurologic disorders, 0.3% with an ocular problem and 0.3% with a metabolic complication, with no significant differences between the vaccine regimens ($P > 0.05$). Of the standard vaccine recipients, 2% of individuals experienced late AEs in the form of cutaneous manifestation (1%), neurological disorders (0.3%), a metabolic problem (0.3%) and involving joints (0.3). Notably, 75% of the AEs were persistent up to the end of the study.

The association between the unsolicited consequences and the vaccine/regimen were as 12, 5, 4, improbable, unclassifiable, possible and 3 probable ones, respectively. Considering the number in the study population, 7 of 288 standard vaccine regimen participants experienced late AEs, of whom 2 individuals achieved partial improvement, while the other 5 cases had a persistent con-

dition. Seventeen of the combinational vaccine regimen participants complained of an AE: 5 improved, while the other 12 still suffer from AEs. Therefore, from a comparative point of view, the standard vaccine regimen, of PCovac/Plus based on a protein subunit vaccine regimen, resulted in a lower rate of late AEs. Nevertheless, there were no significant differences between the combinational vaccine regimens regarding the triggering of AEs. COVID-19 infection/re-infection and also vaccinations still require to be investigated due to their possible effect on immune system activity and responses.

The next step of this study is following up the cases with possible and probable associated AEs. In addition, individuals with underlying diseases will be assessed regarding COVID-19 vaccine immunogenicity and AEs.

Conclusions

There are limited and insufficient immunological data on unsolicited AEs and their association with COVID-19 vaccines, particularly in long-term follow-ups. Hence, large-scale epidemiological studies regarding late unsolicited AEs are necessary to confirm or deny the causal relations between immune-mediated complications and COVID-19 vaccination. Currently, it is clear that every SARS-CoV-2 vaccine combination could lead to late outcomes, even after booster doses. Nevertheless, the protein-based vaccine that was mainly administered in this study population led to a lower rate of serious events compared with other studies of different vaccine types. COVID-19 vaccination benefits far exceed the potential risks and the late AEs appear to be uncommon conditions ,which confirms vaccination pbeing a riority in communities.

Author contributions

Mona Sadat Larijani (data curation, methodology, writing – original draft, writing – review and editing), Rahim Sorouri (project administration, validation, visualisation), Sana Eybpoosh (formal analysis, investigation, methodology, writing – review and editing), Delaram Doroud (data curation, validation), Ladan Moradi (data curation), Mozhgan Ahmadinezhad (formal analysis), Anahita Bavand (data curation, methodology), Fatemeh Ashrafian (data curation), Parinaz Tajmehrabi Namini (data curation), Mahsan Zali (data curation) and Amitis Ramezani (conceptualisation, investigation, resources, writing – review and editing).

Ethics approval and consent to participate

The study protocol was approved by the Pasteur Institute of Iran National Committee for Ethics (ethics code numbers: IR.PII.REC.1400.077 [standard vaccine regimen study] and IR.PII.REC.1400.076 [combinational vaccine regimen study]).

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Supplementary data

Supplementary data are available at *FEMSPD* online.

Conflict of interest statement. The authors declare no competing financial interest.

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Data availability

The data that support the findings of this study are available from the corresponding author upon request.

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