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MAJOR ARTICLE

Effectiveness of Coronavirus Disease 2019 Vaccines in Preventing Infection, Hospital Admission, and Death: A Historical Cohort Study Using Iranian Registration Data During Vaccination Program

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Background. There are some concerns about the effectiveness of the inactivated and vector-based vaccines against severe acute respiratory syndrome coronavirus 2 in real-world settings with the emergence of new mutations, especially variants of concern. Data derived from administrative repositories during mass vaccination campaigns or programs are of interest to study vaccine effectiveness.

Methods. Using 4-repository administrative data linkage, we conducted a historical cohort study on a target population of 1 882 148 inhabitants aged at least 18 years residing in southern Iran.

Results. We estimated a 71.9% [95% confidence interval [CI], 70.7%–73.1%], 81.5% [95% CI, 79.5%–83.4%], 67.5% [95% CI, 59.5%–75.6%], and 86.4% [95% CI, 84.1%–88.8%] hospital admission reduction for those who received the full vaccination schedule of BBIBP-CorV (Sinopharm), ChAdOx1-S/nCoV-19 vaccine (AZD1222, Oxford-AstraZeneca), rAd26-rAd5 (Gam-COVID-Vac, Sputnik V), and BIV1-CovIran (COVIran Barekat) vaccines, respectively. A high reduction in mortality (at least 85%) was observed in all age subgroups of the fully immunized population.

Conclusions. The pragmatic implementation of a vaccination plan including all available vaccine options in the Iranian population was associated with a significant reduction in coronavirus disease 2019 (COVID-19) detected infections as well as hospital admissions and deaths associated with COVID-19.

Keywords. cohort; COVID-19; COVID 19 vaccines; effectiveness; real-world; SARS-CoV-2; vaccine.

Many mass vaccination campaigns or programs are currently underway worldwide to curb the spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In the Islamic Republic of Iran, vaccination was initially started for immunocompromised patients, older people, and healthcare workers on 9 February 2021, with Sputnik V (phase 1). Subsequently, the vaccination program was expanded with the other coronavirus disease 2019 (COVID-19) vaccines authorized by the Iranian Ministry of Health, including Sinopharm and Oxford-AstraZeneca [1–3] with coverage of persons in clinical risk groups (from 21 March 2021; phase 2) and essential nonhealthcare workers (from 22 June 2021; phase 3), followed by the entire population >12 years old (from 18 September 2021; phase 4). As of 22 October 2021, a total of 78 665 265 COVID-19 vaccine doses has been administrated nationally. Controlled clinical trials and real-world clinical studies from some countries have yielded clear evidence of the effectiveness of the aforementioned vaccines [4–6].

However, with the emergence of new mutations, especially variants of concern, there are some debates against the protective effects of the vaccines. Laboratory findings indicate that serum samples from vaccinated persons have been attenuated for the neutralization effects against the B.1.351 (Beta) variant [7, 8]. Moreover, observational data from Qatar showed a modestly reduced effectiveness against symptomatic infection caused by the Beta variant but still high levels of effectiveness against severe, critical, or fatal disease among people vaccinated with the BNT162b2 vaccine (Pfizer-BioNTech) [9]. The B.1.617.2 (Delta) variant is characterized by some new mutation on the spike protein [10]. Some of these mutations might

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affect immune responses focused toward the key antigenic regions of the receptor-binding protein and S1–S2 cleavage site. It appears that strains with mutations at this specific location can increase replication, leading to increased replication transmission and higher viral loads [11]. Therefore, there are some concerns about the effectiveness of the available vaccines in the real-world settings with widespread distribution of the Delta variant. For example, researchers demonstrated an accelerated decline in protection against SARS-CoV infection by the fourth month after vaccination. Additionally, effectiveness has reached low levels of approximately 20% by the seventh month after the second dose of the BNT162b2 vaccine [12].

In this study, we sought to estimate the effectiveness of the 4 most used vaccines in the Iranian national vaccination program against SARS-CoV-2, Sputnik V, Oxford-AstraZeneca, Sinopharm, and COVIran Barekat against infection, hospital admission, and death caused by the circulating variants from February 2021 till late October 2021 in the country.

MATERIALS AND METHODS

Study Design, Population, Vaccines, and Data Repositories

As a potential spin-off of administrative data linkage, we conducted a historical cohort study on the individual data of inhabitants aged at least 18 years, residing in the regions under cover of the Shiraz University of Medical Sciences (SUMS), Fars province, southern Iran. Out of the total population of 4 943 933, 3 628 857 were aged 18 years and older from the start of the vaccination program (9 February 2021).

The 4 study vaccines against COVID-19 were (1) the BBIBP-CorV (Sinopharm) vaccine, which is a monovalent Vero cell vaccine composed of the inactivated 19nCoV-CDC-Tan-HB02 strain of SARS-CoV-2 virus antigens [13]; (2) the ChAdOx1-S/nCoV-19 (AZD1222, Oxford-AstraZeneca) vaccine, which is a modified recombinant replication-deficient adenovirus (rAd) vector (ChAdOx1), containing the full-length codon-optimized coding sequence of the spike protein of SARS-CoV-2 (Oxford-AstraZeneca), with a tissue plasminogen activator leader sequence [14]; (3) the rAd26-rAd5 (Gam-COVID-Vac, Sputnik V) vaccine, which is an rAd-based vaccine, containing rAd type 26 (rAd26) and rAd type 5 (rAd5) vectors, both of which carry the gene for SARS-CoV-2 full-length glycoprotein S (rAd26-S and rAd5-S) [2]; and (4) the BIV1-CovIran (COVIran Barekat) vaccine, which is an inactivated whole-virus SARS-CoV-2 vaccine [15]. The first 2 vaccines have been authorized for emergency use by the World Health Organization (WHO), while the other 2 vaccines have been listed for emergency use, regionally, so far.

By using recoded national ID as the join variable, 4 data repositories were combined. All data were limited to the population under cover of SUMS, which is in charge of the vaccination program, COVID-19 reverse-transcription polymerase chain reaction (RT-PCR) tests, COVID-19 hospital admissions, COVID-19 outcome registry, and health data documentation.

1. The first repository was the Integrated Health System (in Persian: "Samaneh Yekparche-ye Behdashti")—an electronic health record system established 5 years ago—that by the start of the vaccination program was introduced with the vaccination data. This repository includes demographic characteristics (ie, sex and age), address, type of dose, and data of the administered vaccine.
2. The second repository was CORONALAB, which contains the data of all people who underwent a COVID-19 RT-PCR test in public or private centers by the beginning of the COVID-19 pandemic. Through this dataset, definite cases of COVID-19 infection were identified. This repository includes demographic characteristics, RT-PCR sampling date (equivalent to date of COVID-19 infection, if positive) and result, occupation (especially being a health worker), underlying medical condition (ie, pregnancy, diabetes mellitus, malignancy, hypertension, cardiovascular disease, chronic kidney disease, and pulmonary disease), presenting sign and symptoms (ie, nausea, diarrhea, generalized body pain, dyspnea, cough, and fever), and if a subject was hospitalized or not.
3. The third repository was hospitals' medical care monitoring center (MCMC). When the COVID-19 pandemic began, the country introduced recording data about all clinically suspected hospital admissions ("gray zone" admissions) due to COVID-19 as well as between-ward and between-hospital transfers and hospital deaths. The acquired dataset includes admission data, underlying medical condition, presenting sign and symptoms, inpatient RT-PCR result, ward and hospital transfer dates, and hospital outcome with its date.
4. The last repository was the Department of Health's Registry of Deaths, which served to recheck the MCMC outcome data. In addition, this was used as an adjacent dataset to add people who died within 30 days of an admission related to COVID-19 diagnosis but whose data were missed in the MCMC dataset. To these ends, unofficial monthly datasets were made available with a 10-day delay for research purposes, and we specifically searched for *International Classification of Diseases, Tenth Revision* codes U07.1 (denoting COVID-19, virus identified) and U07.2 (denoting COVID-19, virus not identified) with date of death [16]. Moreover, several other overlapping variables were rechecked using the just-mentioned repositories, including (1) demographics (using all 4 repositories), (2) hospital admission (using CORONALAB and MCMC), and (3) RT-PCR result (using CORONALAB and MCMC).

Data Processing and Outcomes

The assessed outcomes were the incidence density (event count/100 000 person-days) of (1) COVID-19 detected

infections confirmed by RT-PCR, (2) COVID-19 hospital admissions lasting >24 hours, and (3) COVID-19 death in hospital. Of note, event for second and third outcomes was defined in 2 different ways, including RT-PCR–confirmed event associated to COVID-19 infection and clinically suspicious event associated with COVID-19 infection. To be more precise, an individual was suspected to have COVID-19 if he/she had been registered in MCMC but the result of RT-PCR against COVID-19 was negative or missed.

Subjects who had several RT-PCR test records were treated in 2 different ways: (1) In a subject who had "consecutive (serial)" records (eg, subjects who required a negative result to return to a workplace), date of the first positive test was extracted for vaccine effectiveness (VE) assessment; (2) in a subject who had several test records that were not apparently related (separate records), dates of all positive tests were recorded. Furthermore, hospital admissions with length of stay <24 hours as well as hospital readmissions within 30 days after discharge were ignored.

The first day of follow-up for VE was defined as the index date. For vaccinated subjects, the index date was a day 14 days after the second dose date. For unvaccinated subjects, the index date was set to 23 March 2021, that is, 42 days after the start of the vaccination program (assuming 4 weeks of between-doses interval + 14 days after second dose was injected). Importantly, according to the Iranian nationwide vaccination program, Sinopharm, Sputnik V, and COVIran Barekat vaccines required 2 doses separated by an interval of at least 4 weeks, but this interval was 3 months for the Oxford-AstraZeneca vaccine. Hence, for assessing the effectiveness of these vaccines, the index date of unvaccinated cohort was set to 24 May 2021 (matched risk period).

A subject was excluded if (1) aged <18 years at initiation of vaccination program (n = 1 315 076); (2) had previous COVID-19 infection (either positive RT-PCR test or being symptomatic), hospital admission, or death prior to the index date (n = 81 069); (3) their index date would be beyond the end of follow-up (22 October 2021) (n = 955 393); (4) did not receive the second dose of vaccine (n = 585 608); (5) was not vaccinated with 2 doses of an identical vaccine (n = 11 226); (6) was vaccinated with other vaccines, for example, Soberana, Moderna, Pfizer-BioNTech, Bharat Biotech (n = 2304); and (7) received the third dose of a vaccine (n = 3908). It should be noticed that 107 201 subjects were also excluded due to unreliable data—that is, follow-up for <28 days till the censoring date, missing or misleading vaccination date, or duplicated data. By and large, data records of 1 882 148 inhabitants were linked to assess the VE.

Subjects were defined as vaccinated if they received 2 doses of an identical vaccine and their index date was before the end of follow-up (22 October 2021).

In each vaccinated subject, person-days was calculated by subtracting the index date from the date of censoring day, which was the occurrence date of any of the aforementioned events or, if no event was developed, the last day of follow-up (22 October 2021).

In unvaccinated people, person-days was calculated by subtracting index date from the occurrence date of any of the aforementioned events. Similar to the vaccinated group, unvaccinated people who did not develop any event were assumed to be alive and the date of data censoring was set as 22 October 2021.

Statistical Analysis

The R programing language (version 4.0.4 for MacOS) was used for statistical analysis, and the package "tidyverse" was utilized for data combination and data cleaning to yield an analysis-ready dataset. Quantitative variables were reported using median with interquartile range (IQR).

VE was calculated for each vaccine, separately. To calculate VE, relative risk (RR) values (with 95% confidence interval [CI]) were subtracted from 1. We utilized the aggregated person-days as denominator of the RR calculation fraction, which is expected to correct for differences in exposure (follow-up) times, adjusted for heterogenous "risk periods" (varying dynamic of a pandemic, change in dominant variants, as well as the fact of more vaccinated people, less burden of disease), and considered the time intervals for those who developed an event, which were censored before the end of study. The CI of each RR value was calculated based on the approximate procedures proposed by Ederer and Mantel [17] (Table 1).

Also, VE was reported in different age groups (18–44, 45–64, and ≥65 years), separately, for both vaccinated and unvaccinated cohorts. Finally, the incidence density per each 100 000

Table 1. Relative Risk Formulas of Incidence Densities

(1)	$RR = \frac{Event_{vaccinated}/Aggregated\ \ persons\text{-}day_{vaccinated}}{Event_{unvaccinated}/Aggregated\ persons\text{-}day_{unvaccinated}}$
(2)	$95\ \%\quad CI = \text{Lower limit} = \left[\frac{P_L}{1-P_L}\right] \times \frac{L_2}{L_1}$; $\text{Upper limit} = \left[\frac{P_U}{1-P_U}\right] \times \frac{L_2}{L_1}$
O_1 = events in vaccinated people	
O_2 = events in unvaccinated people	
L_1 = persons-day in vaccinated people	
L_2 = persons-day in unvaccinated people	
R_1 = event rate in vaccinated people (O_1/L_1)	
R_2 = event rate in unvaccinated people (O_2/L_2)	
$\hat{P}$ = set limits on the ratio of events in vaccinated people $= O_1/O_1 + O_2$	
Lower (P_L) limits of the 95 % CI $= P_L = \hat{P} - \left[1.96 \times \sqrt{\frac{\hat{P}(1-\hat{P})}{O_1+O_2}}\right]$;	
Upper (P_U) limits of the 95 % CI $= P_U = \hat{P} + \left[1.96 \times \sqrt{\frac{\hat{P}(1-\hat{P})}{O_1+O_2}}\right]$	

Source: Szklo and Nieto [18].

Abbreviations: CI, confidence interval; RR, relative risk.

person-days of follow-up was reported. For this purpose, the PersonTime1 module of Open Source Epidemiologic Statistics for Public Health (Open Epi) was used to calculate person-days (95% CI) through Mid-P exact test with Miettinen modification [19].

RESULTS

Among 1 882 148 adults (median age, 44 [IQR, 33–60] years; 916 904 [48.72%] female) who composed the analysis-ready dataset, 881 638 (46.84%) were vaccinated with 2 doses and considered immunized, from 9 February 2021 to 22 October 2021. In the vaccinated and unvaccinated cohorts, respectively, the median ages were 55 (IQR, 41–65) years and 36 (IQR, 29–48) years, and 369 274 (41.88%) and 547 630 (54.74%) were female. The vaccine composition was 75.33% for Sinopharm (n = 664 101), 14.87% for Oxford-AstraZeneca (n = 131 102), 1.62% for Sputnik V (n = 14 273), and 8.18% for COVIran Barekat (n = 72 162).

Among 948 230 people aged 18–44 years, 259 949 (27.41%) received 2 doses of a vaccine; among 585 166 people aged 45–64 years, 393 994 (67.33%) received 2 doses of a vaccine; and among 348 752 people aged 65 years and older, 227 695 (65.29%) received 2 doses of a vaccine.

The incidence density of confirmed COVID-19 was 20.5 (95% CI, 20.3–20.7) cases/100 000 person-days among the unvaccinated, and 4.12 (95% CI, 4.02–4.22), 3.49 (95% CI, 3.30–3.70), 5.19 (95% CI, 4.47–5.99), and 2.64 (95% CI, 2.41–2.88) cases/100 000 person-days among those who were fully immunized with Sinopharm, Oxford-AstraZeneca, Sputnik V, and COVIran Barekat vaccines, respectively. These yielded 79.9% (95% CI, 79.4%–80.4%), 84.4% (95% CI, 83.5%–85.3%), 74.7% (95% CI, 71.0%–78.4%), and 87.1% (95% CI, 86.0%–88.3%) positive RT-PCR test reduction rates for those who received the full vaccination schedule of the Sinopharm, Oxford-AstraZeneca, Sputnik V, and COVIran Barekat vaccines, respectively (Table 2).

The incidence density of hospital admission with confirmed COVID-19 diagnosis was 5.34 (95% CI, 5.24–5.45) cases/100 000 person-days among the unvaccinated, and 1.50 (95% CI, 1.44–1.56), 1.10 (95% CI, .99–1.22), 1.74 (95% CI, 1.35–2.21), and 0.73 (95% CI, .61–.86) cases/100 000 person-days among those who were fully immunized with the Sinopharm, Oxford-AstraZeneca, Sputnik V, and COVIran Barekat vaccines, respectively. These yielded 71.9% (95% CI, 70.7%–73.1%), 81.5% (95% CI, 79.5%–83.4%), 67.5% (95% CI, 59.5%–75.6%), and 86.4% (95% CI, 84.1%–88.8%) reduction in hospital admission for those who received the full vaccination schedule of Sinopharm, Oxford-AstraZeneca, Sputnik V, and COVIran Barekat vaccines, respectively. In addition, considering all clinically suspicious hospital admissions due to COVID-19, VE values were 72.6% (95% CI, 71.7%–73.6%), 79.4% (95% CI, 77.8%–81.1%), 63.8% (95% CI, 57.0%–70.6%), and 85.5% (95% CI, 83.6%–87.4%), respectively (Table 2).

The incidence density of death with confirmed COVID-19 diagnosis was 0.95 (95% CI, .91–1.00) cases/100 000 person-days among the unvaccinated, and 0.13 (95% CI, .12–.15), 0.06 (95% CI, .04–.09), 0.00, and 0.02 (95% CI, .00–.04) cases/100 000 person-days among those who were fully immunized with Sinopharm, Oxford-AstraZeneca, Sputnik V, and COVIran Barekat vaccines, respectively. These values represented 86.1%

Table 2. Incidence Density per 100 000 Person-Days and Severe Acute Respiratory Syndrome Coronavirus 2 Vaccine Effectiveness Regarding Coronavirus Disease 2019 Detected Infection, Hospital Admission, and Death in the Historical Cohorts of Fully Vaccinated and Unvaccinated People, Iran

Vaccine	Detected Infection (Positive RT-PCR)	Hospital Admission Suspicious/ Definite[a])	Hospital Admission (Definite)	Death (Suspicious/ Definite)	Death (Definite)
Incidence density per 100 000 person-days (95% CI)					
Sinopharm	4.12 (4.02–4.22)	2.27 (2.20–2.35)	1.50 (1.44–1.56)	0.17 (.15–.19)	0.13 (.12–.15)
Oxford-AstraZeneca	3.49 (3.30–3.70)	1.90 (1.76–2.05)	1.10 (.99–1.22)	0.10 (.07–.13)	0.06 (.04–.09)
Sputnik V	5.19 (4.47–5.99)	3.01 (2.48–3.61)	1.74 (1.35–2.21)	0.03 (.00–.13)	0.00 (…)[c]
COVIran Barekat	2.64 (2.41–2.88)	1.20 (1.05–1.37)	0.73 (.61–.86)	0.03 (.00–.06)	0.02 (.00–.04)
Unvaccinated[b]	20.5 (20.3–20.7)	8.31 (8.19–8.44)	5.34 (5.24–5.45)	1.81 (1.14–1.23)	0.95 (.91–1.00)
Effectiveness, % (95% CI)					
Sinopharm	79.9 (79.4–80.4)	72.6 (71.7–73.6)	71.9 (70.7–73.1)	85.3 (83.5–87.1)	86.1 (84.1–88.0)
Oxford-AstraZeneca	84.4 (83.5–85.3)	79.4 (77.8–81.1)	81.5 (79.5–83.4)	89.5 (85.8–93.2)	91.8 (88.2–95.4)
Sputnik V	74.7 (71.0–78.4)	63.8 (57.0–70.6)	67.5 (59.5–75.6)	97.7 (93.1–100)	100 (…)[c]
COVIran Barekat	87.1 (86.0–88.3)	85.5 (83.6–87.4)	86.4 (84.1–88.8)	97.7 (95.7–99.7)	98.3 (96.3–100)

Abbreviations: CI, confidence interval; RT-PCR, reverse-transcription polymerase chain reaction.

[a]Suspicious: negative RT-PCR but clinically in favor of coronavirus disease 2019 (COVID-19) infection; definite: positive RT-PCR and clinically in favor of COVID-19 infection.

[b]Incidence densities (95% CIs) of the unvaccinated cohort for Oxford-AstraZeneca vaccine were 22.36 (22.11–22.60), 9.25 (9.10–9.41), 5.94 (5.81–6.06), 0.92 (.87–.97), and 0.73 (.69–.78), respectively.

[c]No death reported.

(95% CI, 84.1%–88.0%), 91.8% (95% CI, 88.2%–95.4%), 100%, and 98.3% (95% CI, 96.3%–100%) reductions in mortality for the Sinopharm, Oxford-AstraZeneca, Sputnik V, and COVIran Barekat vaccines, respectively. Moreover, considering all clinically suspicious deaths due to COVID-19, VE values were 85.3% (95% CI, 83.5%–87.1%), 89.5% (95% CI, 85.8%–93.2%), 97.7% (95% CI, 93.1%–100%), and 97.7% (95% CI, 95.7%–99.7%), respectively (Table 2).

In those who were fully immunized with a vaccine, a high reduction in mortality (>95%) was observed in all age subgroups, except for those aged 18–44 and ≥65 years who received Sinopharm vaccine (87.3% [95% CI, 79.5%–94.8%] and 86.3% [95% CI, 84.1%–88.4%], respectively). In addition, the rate of reduction in hospital admission was noticeably lower in elderly persons (≥65 years); that is, a full vaccination schedule with the Sinopharm, Oxford–AstraZeneca, Sputnik V, and COVIran Barekat vaccines reduced hospital admission for 45.7% (95% CI, 42.1%–49.2%), 76.0% (95% CI, 73.0%–78.9%), 45.5% (95% CI, 4.9%–85.8%), and 80.3% (95% CI, 72.8%–87.8%), respectively. Furthermore, specifically, for people aged ≥65 years, the full schedule by the Sinopharm, Oxford–AstraZeneca, Sputnik V, and COVIran Barekat vaccines was associated with 29.1% (95% CI, 25.3%–32.8%), 62.4% (95% CI, 59.0%–65.6%), 76.3% (95% CI, 53.1%–99.5%), and 67.0% (95% CI, 58.5%–75.4%) reductions in detected infections (Table 3).

Total and age-specific frequency of events, as well as age-specific incidence density per 100 000 person-days, are shown in Supplementary Tables 1–3.

DISCUSSION

Besides proving vaccine efficacy in clinical trials, demonstrating VE in real-world settings has an essential role in strategic planning and controlling infectious diseases in the community. For various COVID-19 vaccines, there are a lot of data about efficacy [20–23]. There is, to our knowledge, no VE assessment conducted on the real-world big data of the inactivated and vector-based vaccines that are utilized in the Islamic Republic of Iran.

In a context of vaccine shortages for our country, related to many factors (ie, supply delays, sanctions), this study found that the mass vaccination program implementing a group of vaccines that, even for some of them (Sputnik V, and COVIran Barekat vaccines), have limited information for effectiveness and impact, has been associated with a dramatic reduction in COVID-19 detected infections, as well as in hospital admissions and deaths related to the COVID-19 diagnosis. This information is of health relevance and encourages health authorities to rapidly reach a critical mass of vaccinated population to control the disease around the country.

In our analysis of approximately 13 987 hospital admissions of adults with laboratory-confirmed COVID-19 during 17 February–22 October 2021, receipt of 2 doses of any type of authorized vaccine was effective in preventing laboratory-confirmed COVID-19 hospital admissions among patients who were elderly (VE range, 45.5%–80.3%) and those who were in younger age groups (VE range, 60.1%–94.4% for age 18–44 years, 76%–95.2% for age 45–64 years). Nonetheless, the elderly were largely less protected from severe COVID-19 outcomes

Table 3. Severe Acute Respiratory Syndrome Coronavirus 2 Vaccine Effectiveness in Different Age Groups

Vaccine	Detected Infection (Positive RT-PCR)	Hospital Admission (Suspicious/Definite[a])	Hospital Admission (Definite)	Death (Suspicious/Definite)	Death (Definite)
Sinopharm					
18–44 y	84.6 (83.8–85.3)	90.5 (89.3–91.6)	86.2 (84.4–87.9)	88.7 (82.1–95.1)	87.3 (79.5–94.8)
45–64 y	86.6 (86.0–87.2)	91.0 (90.4–91.6)	89.9 (89.1–90.7)	97.2 (96.4–98.0)	97.9 (97.1–98.7)
≥65 y	29.1 (25.3–32.8)	55.4 (52.9–57.7)	45.7 (42.1–49.2)	86.1 (84.2–88.0)	86.3 (84.1–88.4)
Oxford-AstraZeneca					
18–44 y	74.6 (71.6–77.5)	92.5 (89.5–95.4)	93.5 (90.0–96.9)	100 (…)[b]	100 (…)[b]
45–64 y	89.5 (87.9–91.2)	94.6 (93.1–96.1)	95.2 (93.4–97)	99.1 (97.3–100)	98.9 (96.7–100)
≥65 y	62.4 (59.0–65.6)	77.0 (74.8–79.1)	76.0 (73.0–78.9)	95.6 (93.9–97.1)	96.4 (94.7–98.0)
Sputnik V					
18–44 y	74.5 (70.0–78.9)	58.4 (47.5–69.2)	60.1 (46.9–73.4)	100 (…)[b]	100 (…)[b]
45–64 y	78.2 (72.1–84.3)	72.1 (63.1–81.1)	76.0 (65.7–86.3)	94.9 (84.9–100)	100 (…)[b]
≥65 y	76.3 (53.1–99.5)	28.7 (–7.5 to 64.8)	45.5 (4.9–85.8)	100 (…)[b]	100 (…)[b]
COVIran Barekat					
18–44 y	89.7 (87.9–91.5)	92.2 (89.2–95.2)	94.4 (91.2–97.6)	100 (…)[b]	100 (…)[b]
45–64 y	88.2 (86.8–89.6)	89.8 (88.1–91.4)	90.0 (87.9–92.0)	98.6 (97.0–100)	98.6 (97.3–100)
≥65 y	67.0 (58.5–75.4)	78.4 (72.2–84.4)	80.3 (72.8–87.8)	97.6 (94.2–100)	98.5 (95.5–100)

Data are presented as % (95% confidence interval).

Abbreviation: RT-PCR, reverse-transcription polymerase chain reaction.

[a]Suspicious: negative RT-PCR but clinically in favor of coronavirus disease 2019 (COVID-19) infection; definite: positive RT-PCR and clinically in favor of COVID-19 infection.

[b]No death reported.

than younger age groups, supporting the WHO's recommendation for administering the booster dose of a vaccine to enhance further protection, especially in elderly persons, against severe COVID-19 outcomes [24].

The analysis found significant protection associated with 2 doses of any of the vaccines used to prevent death from any cause. However, compared with the other used vaccines, the Sinopharm vaccine was associated with a higher mortality risk during follow-up. The reasons why 2 doses of Sinopharm were associated with lower protection against death than other studied vaccines remain obscure. One can surmise that the low effectiveness found in people who received inactivated whole-virus vaccines should not be surprising, since the process of treatment used to eliminate infectivity may be effectively damaging to modify immunogenicity, especially of the antigens needed to induce cell-mediated immune responses. Additionally, it should be emphasized that although there was no large difference in the mortality among the populations who received the different types of vaccines in our study, this should be evaluated in the future studies, involving more numbers of cases—especially the other 3 vaccines—and other parts of the country to confirm if there is different effectiveness among these vaccines.

Our findings demonstrated high VE against laboratory-confirmed COVID-19 detected infections after receiving the second doses of all used vaccines. The VE point estimates reached 87.1% with COVIran Barekat, and at least around 75% with Sputnik V. Similar to the vaccine efficacy results published by original vaccine research groups as well as VE results by other researchers, generally, our results consistently indicate that a high level of protection, with little variability, has been provided by all available vaccines against COVID-19 after the second dose of vaccine in the Islamic Republic of Iran. Noticeably, the VE estimations in this study are different with published in-line studies of fully immunized cohorts from other middle-income countries [25, 26]. In a prospective cohort of adult subjects in Chile, Jara et al [25] assessed VE of CoronaVac, an inactivated SARS-CoV-2 vaccine. They found 65.9% effectiveness against COVID-19 infection, 87.5% against hospital admission, and 86.3% for the prevention of death. Additionally, Macchia et al [26] retrospectively investigated VE of Sinopharm, Oxford-AstraZeneca and Sputnik V vaccines among adults aged ≥60 years in Argentina. They reported 88.1% effectiveness against COVID-19 infection and 98.3% in preventing COVID-19–associated deaths. Differences on population characteristics, study design, study timeline, type of vaccines, and VE calculation method as well as presence of VE adjustment, health system capacities, etc, could drastically influence the study. Hence, VE values should be interpreted exclusively.

Obtained VE values for the COVIran Barekat vaccine should be interpreted with caution. First, results of the phase 3 clinical trial on this vaccine are not yet published. Second, the vast majority of COVIran Barekat vaccine doses have been given during phases 3 and 4 of the vaccination program. Therefore, compared to the other 3 vaccines, the recipients of the COVIran Barekat vaccine might have a shorter follow-up period and be in better health condition. Third, similar to Sputnik V vaccine, due to lower numbers of people vaccinated with these 2 vaccines, VE values might not be robust. Wider precision of analysis (95% CI) around the point estimates confirm our claim.

The findings in our study are subject to several limitations. First, vaccination status and outcome misclassifications might be plausible, comparing the vaccine efficacy studies, despite the high specificity of the COVID-19 vaccination status from our data repositories. Worth noting, we performed a number of data-recheck plans. Second, while our study covered a long follow-up period of 35 weeks, VE data with longer follow-up are warranted. Third, the historical cohort design for VE studies cannot inherently detect the true rate of infections, while rates of hospital admissions and deaths are more accurate. In other words, we could not assess VE on total infections: There is a potential underdetection of COVID-19 infection among the study population due to the underuse of RT-PCR tests for all patients with suspected COVID-19 in the community, unacceptable test sensitivity, asymptomatic patients, patients' ignorance of symptoms, and "ostrich effect" (less concern among vaccinated people regarding symptoms). Fourth, noncomprehensive data entry—specifically, the COVID-19–related administrative data registries were not intended to collect the unvaccinated population data—for comorbidities and other confounding factors did not allow us to introduce these variables into the analysis. Fifth, different phases of the vaccination program (different risk groups) may affect VE values. For example, in our study, most healthcare workers received Sputnik V vaccine; however, we were not able to perform multivariable analysis to take control of this effect. Sixth, VE in reducing COVID-19 deaths was limited to the hospitals' events. We could not include COVID-19 deaths occurring in other settings, especially deaths at home, since the detailed "Registry of Deaths" repository is available by about 1 year of delay (detailed data were available till 21 March 2021, equivalent to the first day of the solar Hijri calendar). As we mentioned, our dataset was unofficial and only for research purposes.

CONCLUSIONS

The present study shows that the pragmatic implementation of a vaccination plan including all different vaccine options in the Iranian population was associated with a significant reduction in COVID-19 detected infections, hospital admissions, and deaths associated with COVID-19. These results suggest implementing mass vaccination strategies with these available vaccines in the shortest possible time. Also, our findings are the first actual world report for an Iranian vaccine, COVIran Barekat, with noticeable results and role in mass immunization goals.

Notes

Author contributions. Conceptualization: A. M., A. H., K. B. L., M. M. Data curation: M. S., M. H. Formal analysis: A. M., O. E. Methodology: A. H., A. M. Project administration: A. H., F. H., M. M. Software: A. H., F. H. Supervision: A. M., K. B. L., M. M. Validation: A. M., M. S., M. H. Writing—original draft: A. H., M. M. Writing—review and editing: K. B. L., O. E.

Data sharing. The data repositories generated during the current study are not publicly available, but can be available from the corresponding author on reasonable request to the Shiraz University of Medical Sciences, Vice Chancellor of Research.

Patient consent. The design of the work was approved by Biomedical Research Ethics Committees of Shiraz University of Medical Sciences (code = IR.SUMS.REC.1400.486). The present study does not include factors necessitating patient consent. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Potential conflicts of interest. All authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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