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Effectiveness of Heterologous Coronavirus Disease 2019 (COVID-19) Vaccine Booster Dosing in Brazilian Healthcare Workers, 2021

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Background. Little is currently known about vaccine effectiveness (VE) for either 2 doses of Oxford-AstraZeneca (ChAdOx1) viral vector vaccine or CoronaVac (Instituto Butantan) inactivated viral vaccine followed by a third dose of mRNA vaccine (Pfizer/BioNTech) among healthcare workers (HCWs).

Methods. We conducted a retrospective cohort study among HCWs (aged ≥18 years) working in a private healthcare system in Brazil from January to December 2021. VE was defined as 1 – incidence rate ratio (IRR), with IRR determined using Poisson models with the occurrence of laboratory-confirmed coronavirus disease 2019 (COVID-19) infection as the outcome, adjusting for age, sex, and job type. We compared those receiving viral vector or inactivated viral primary series (2 doses) with those who received an mRNA booster.

Results. A total of 11 427 HCWs met the inclusion criteria. COVID-19 was confirmed in 31.5% of HCWs receiving 2 doses of CoronaVac vaccine versus 0.9% of HCWs receiving 2 doses of CoronaVac vaccine with mRNA booster ($P < .001$) and 9.8% of HCWs receiving 2 doses of ChAdOx1 vaccine versus 1% among HCWs receiving 2 doses of ChAdOx1 vaccine with mRNA booster ($P < .001$). In the adjusted analyses, the estimated VE was 92.0% for 2 CoronaVac vaccines plus mRNA booster and 60.2% for 2 ChAdOx1 vaccines plus mRNA booster, when compared with those with no mRNA booster. Of 246 samples screened for mutations, 191 (77.6%) were Delta variants.

Conclusions. While 2 doses of ChAdOx1 or CoronaVac vaccines prevent COVID-19, the addition of a Pfizer/BioNTech booster provided significantly more protection.

Keywords. COVID-19 vaccine; effectiveness; CoronaVac; Oxford-AstraZeneca; Pfizer/BioNTech booster.

In the third year of the coronavirus disease 2019 (COVID-19) pandemic, individuals are still at risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection even with vaccines available [1, 2]. During 2021, infection and hospitalization rates among unvaccinated individuals were higher than in vaccinated individuals [3, 4]. Healthcare workers (HCWs) remain at risk of COVID-19 because of a high frequency of exposure [5]. In several settings, frontline HCWs had a higher risk of COVID-19 when compared with the general population; the risk was higher in areas with inadequate access to personal protective equipment (PPE) [6, 7]. This emphasizes the need for effective vaccines for frontline HCWs [8].

Most of the currently available data on primary series and booster vaccine effectiveness (VE) come from cohorts that used mRNA vaccines as the primary series [9, 10]. However, viral vector or inactivated virus vaccines have been the primary vaccines in many countries. In Brazil, we found a lower primary series VE with 2 doses of Oxford-AstraZeneca (ChAdOx1) or CoronaVac compared with the VE reported in the literature with 2 doses of mRNA vaccines [11]. Therefore, our institution started administering mRNA vaccine boosters (Pfizer/BioNTech) in October 2021 for HCWs who had received either ChAdOx1 or CoronaVac as their primary series (2 doses).

We assessed the VE of an mRNA vaccine booster following 2 doses of ChAdOx1 or CoronaVac against laboratory-confirmed COVID-19 among HCWs in Brazil.

METHODS

Population and Setting

We conducted a retrospective cohort study of all adult HCWs (≥18 years) working at the Hospital Israelita Albert Einstein (HIAE) between 1 January and 30 December 2021.

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The HIAE is a Brazilian nonprofit healthcare, educational, and research organization, headquartered in São Paulo, managing diverse services from primary to tertiary care in the public and private healthcare sectors. It operates 40 healthcare units, mainly in the state of São Paulo. In 2020, HIAE had 700 000 emergency department visits, 900 000 outpatient visits, and 70 000 hospital discharges. Since the beginning of the COVID-19 pandemic, HCWs with COVID-19 symptoms had access to free-of-charge SARS-CoV-2 reverse transcription–polymerase chain reaction (RT-PCR) testing conducted by the institution's laboratory.

We included HCWs who completed at least 2 doses of either ChAdOx1 or CoronaVac vaccines and compared VE in those who received a booster dose of mRNA vaccine with those who only received 2 non-mRNA doses. Individuals who tested positive for COVID-19 within 14 days of the second vaccine dose, and those vaccinated before the study period, were excluded from the study. We also excluded HCWs who no longer worked at HIAE, received just 1 dose of any COVID-19 vaccine, received other combinations of COVID-19 vaccines (eg, Janssen vaccine + Pfizer/BioNTech vaccine), or received the Pfizer COVID-19 vaccine as the first or second dose, because the sample size was too small (~17 HCWs) to obtain an estimate of VE (Supplementary Appendix 1).

Real-Time RT-PCR Methodologies for SARS-CoV-2 Detection

Diagnostic confirmation for COVID-19 was performed using RT-PCR on specimens obtained via nasopharyngeal swab, according to the protocol instituted at HIAE. The following RT-PCR kits were utilized: XGEN MASTER COVID-19 (Mobius, Pinhais, Paraná, Brazil), Cobas SARS-CoV-2 Test (Roche Molecular Systems, Branchburg, NJ, USA), Xpert Xpress SARS-CoV-2 (Cepheid, Sunnyvale, CA, USA), and Abbott RealTime SARS-CoV-2 (Abbott Molecular, Inc, Des Plaines, IL, USA).

Next-Generation Sequencing of the Viral Full-Length Genome

We extracted total nucleic acid from naso-oropharyngeal (NOP) swab samples with the QIAamp Viral RNA Mini kit (QIAGEN, Hilden, Germany). After purification and concentration, DNAse I treatment, and depletion of human ribosomal RNA, samples were submitted to random amplification [12]. Preparation of sequencing libraries for the Illumina platform was carried out with DNA Prep (Illumina, San Diego, CA, USA) using the random 2-step PCR amplification product as input. Libraries were quantified with the Qubit instrument (ThermoFisher Scientific, Waltham, MA, USA) and loaded on the NextSeq 550 equipment (Illumina) for sequencing with MID 300 paired-end reads (Illumina).

Outcome Measures and Statistical Analyses

Laboratory-confirmed COVID-19 was considered the primary outcome for calculating VE. RT-PCR testing for the diagnosis of COVID-19 was performed only on symptomatic HCWs. Hospitalization related to COVID-19 infection, length of stay, intensive care unit (ICU) admission, mechanical ventilation, and death were considered secondary outcomes. Vaccination status and SARS-CoV-2 RT-PCR results of all study participants were obtained from institutional electronic records. We excluded those with a positive COVID-19 infection diagnosed before 15 January 2021 (date of first vaccine availability plus 14 days). For those vaccinated, the initial follow-up date was 14 days after the second vaccine dose. The last date was defined as the date COVID-19 infection was diagnosed, or up to 14 January 2022 for the censored cases without a positive diagnosis of COVID-19 infection (this date was determined as 14 days after administration of the booster dose, 30 December 2021).

Qualitative variables were characterized using absolute and relative frequencies in general and by interest groups. For comparisons, we used chi-square or Fisher's exact tests. Quantitative variables were described by medians, interquartile range (IQR; first and third quartiles), and minimum and maximum values due to the asymmetry observed in the variables [13], and comparisons were performed via nonparametric Mann-Whitney tests. Vaccine effectiveness was defined as 1 − incidence rate ratio (IRR) [14], with IRR determined by adjusting Poisson models with laboratory-confirmed COVID-19 as the outcome and vaccination as the main explanatory variable. The models assumed logarithmic link function, logarithmic of time of exposure as an offset to account for different follow-up times between groups, and unadjusted and adjusted estimations, with models adjusted for sex, age, and HCW job type (direct patient contact vs no direct patient contact). Cumulative incidence curves of COVID-19 infection for the vaccinated groups (CoronaVac primary series + Pfizer/BionTech booster; ChAdOx1 primary series + Pfizer/BionTech booster; and 2-dose primary series: CoronaVac, ChAdOx1 vaccines) were estimated using the Kaplan-Meier method [15] and the cumulative incidence was estimated at 90 days with unadjusted models. All analyses were performed with R software for statistical computing (graphics version 4.1.0; R Core Team) [16]. All reported tests were 2-sided and P values $<.05$ were considered significant. The study was approved by the HIAE Ethics Committee (CAAE 47110421.7.0000.0071) and the need for informed consent was waived.

RESULTS

During the study period, a total of 18 359 individuals were screened for eligibility and 11 427 HCWs met inclusion criteria (Supplementary Appendix 1). Most were female (71.4%) and the median age was 36 years. Of those included, 1157 (10.1%) received 2 doses of CoronaVac vaccine, 4472 (39.1%) received

Table 1. Baseline Characteristics of Study Participants: Hospital Israelita Albert Einstein, São Paulo, Brazil, 1 January 2021 to 30 December 2021

	Total (N = 11 427)	Two Doses of CoronaVac (n = 1157)	Two Doses of CoronaVac + 1 Dose of Pfizer/ BioNTech (n = 4472)	Two vs 3 Doses, CoronaVac Group, *P*	Two Doses of ChAdOx1 (n = 1871)	Two Doses of ChAdOx1 + 1 Dose of Pfizer/BioNTech (n = 3927)	Two vs 3 Doses, ChAdOx1 Group, *P*
Sex, n (%)				.223[C]			.048[C]
Female	8150 (71.4)	830 (71.7)	3284 (73.5)		1270 (67.9)	2766 (70.4)	
Male	3272 (28.6)	327 (28.3)	1183 (26.5)		601 (32.1)	1161 (29.6)	
Missing	5	0	5		0	0	
Age, y				<.001[M]			<.001[M]
Median [IQR]	36 [29; 42]	34 [28; 40]	37 [31; 43]		33 [26; 40]	37 [30; 43]	
Minimum–maximum	18–83	18–69	19–82		18–75	18–83	
Missing	4	2	1		0	1	
Job type, n (%)				<.001[C]			<.001[C]
No direct patient contact	5823 (51.0)	389 (33.6)	1019 (22.8)		1357 (72.5)	3058 (77.9)	
Direct patient contact	5604 (49.0)	768 (66.4)	3453 (77.2)		514 (27.5)	869 (22.1)	
Any comorbidity, n (%)[a]	2416 (26.6)	177 (21.2)	879 (25.7)	.008[C]	344 (24.7)	1016 (29.4)	.001[C]
Hypertension, n (%)[a]	752 (8.3)	51 (6.1)	270 (7.9)	.082[C]	94 (6.8)	337 (9.8)	.001[C]
Diabetes mellitus, n (%)[a]	221 (2.4)	16 (1.9)	76 (2.2)	.591[C]	31 (2.2)	98 (2.8)	.232[C]
Obesity, n (%)[a]	877 (9.6)	67 (8.0)	302 (8.8)	.468[C]	123 (8.8)	385 (11.2)	.017[C]
Dyslipidemia, n (%)[a]	521 (5.7)	24 (2.9)	212 (6.2)	<.001[C]	65 (4.7)	220 (6.4)	.023[C]
Asthma, n (%)[a]	388 (4.3)	36 (4.3)	129 (3.8)	.462[C]	47 (3.4)	176 (5.1)	.010[C]
Bronchitis, emphysema, or COPD, n (%)[a]	177 (1.9)	15 (1.8)	37 (1.1)	.091[C]	44 (3.2)	81 (2.3)	.106[C]
Arthritis, n (%)[a]	100 (1.1)	4 (0.5)	34 (1.0)	.157[C]	18 (1.3)	44 (1.3)	.958[C]
Stroke, n (%)[a]	26 (0.3)	5 (0.6)	6 (0.2)	.030[C]	2 (0.1)	13 (0.4)	.187[C]
Chronic kidney disease, n (%)[a]	12 (0.1)	1 (0.1)	1 (0.0)	.279[C]	3 (0.2)	7 (0.2)	.929[C]
Cancer, n (%)[a]	216 (2.4)	13 (1.6)	91 (2.7)	.065[C]	21 (1.5)	91 (2.6)	.018[C]
Follow-up between second and third COVID-19 vaccine doses, d							
Median [IQR]	…	…	233 [228; 245]		…	191 [185; 201]	
Minimum–maximum	…	…	39–317		…	46–250	
Follow-up period, d[b]							
Median [IQR]	73 [51; 93]	213 [119; 312]	79 [66; 87]	<.001[M]	228 [137; 239]	50 [38; 57]	<.001[M]
Minimum–maximum	1–323	1–323	1–136		1–274	1–102	
COVID-19 infection (by PCR), n (%)	630 (5.5)	364 (31.5)	42 (0.9)	<.001[C]	184 (9.8)	40 (1.0)	<.001[C]
Number of hospitalizations, n (%)				.001[F]			.500[F]
0	11 385 (99.6)	1145 (99.0)	4461 (99.8)		1864 (99.6)	3915 (99.7)	
1	39 (0.3)	11 (1.0)	11 (0.2)		7 (0.4)	10 (0.3)	
2	3 (0.03)	1 (0.09)	0 (0.00)		0 (0.00)	2 (0.05)	
Length of hospital stay, d				.104[M]			.432[M]
Median [IQR]	5 [3; 9]	6 [4; 10]	3 [3; 6]		6 [4; 30]	5 [2; 16]	
Minimum–maximum	1–40	2–14	1–8		3–40	2–32	
Mechanical ventilation, n (%)	4/42 (9.5)	0/12 (0.0)	1/11 (9.1)	.478[F]	1/7 (14.3)	2/12 (16.7)	>.99 [F]
ICU, n (%)	11/42 (26.2)	4/12 (33.3)	1/11 (9.1)	.317[F]	2/7 (28.6)	4/12 (33.3)	>.99 [F]

Abbreviations: C, chi-square test; ChAdOx1 vaccine, Oxford-AstraZeneca vaccine; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; F, Fisher's exact test; ICU, intensive care unit; IQR, interquartile range; M, Mann-Whitney test; PCR, polymerase chain reaction.

[a]Information available for 9093 participants: 833 with 2 doses of CoronaVac vaccine, 1391 with 2 doses of ChAdOx1 vaccine, 3419 with 2 doses of CoronaVac vaccine + Pfizer/BioNTech vaccine, and 3450 with 2 doses of ChAdOx1 vaccine + Pfizer/BioNTech vaccine.

[b]Follow-up was initiated 14 days after second dose for those vaccinated.

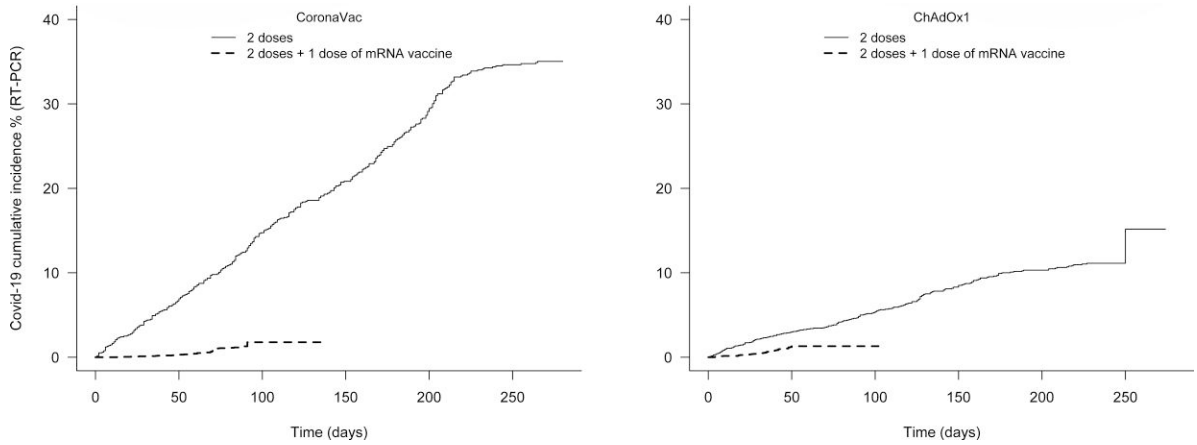

Figure 1. Cumulative incidence of COVID-19 infection (by RT-PCR) among HCWs vaccinated with 2 doses of CoronaVac (left) or Oxford-AstraZeneca (ChAdOx1) (right), with and without a third (booster) dose with mRNA (Pfizer/BioNTech) vaccine. Abbreviations: COVID-19, coronavirus disease 2019; HCW, healthcare worker; RT-PCR, reverse transcription–polymerase chain reaction.

2 doses of CoronaVac vaccine plus mRNA (Pfizer/BioNTech) booster, 1871 (16.4%) received 2 doses of ChAdOx1 vaccine, and 3927 (34.4%) received 2 doses of ChAdOx1 vaccine plus mRNA (Pfizer/BioNTech) booster.

Compared with the group who received 2 doses of CoronaVac vaccine, the group who received a Pfizer/BioNTech booster following CoronaVac vaccine was significantly older, had a greater proportion of HCWs with patient contact, and a greater proportion of comorbidities (Table 1). Compared with the group who received 2 doses of ChAdOx1 vaccine, the group who received a Pfizer/BioNTech booster following a ChAdOx1 primary series was significantly older, had a greater proportion of women, a smaller proportion of HCWs with patient contact, and a greater proportion of comorbidities.

During the study period, 630 HCWs (5.5%) were diagnosed with COVID-19. Overall, COVID-19 cases occurred in 31.5% of HCWs who received 2 doses of the CoronaVac vaccine and 0.9% who received a booster ($P < .001$). COVID-19 cases also occurred in 9.8% who received 2 doses of the ChAdOx1 vaccine and 1.0% who received a booster ($P < .001$). The cumulative incidence curves were significantly lower among those with a booster dose compared with those with 2 doses only (Figure 1). In addition, 1% of HCWs who received 2 doses of CoronaVac had at least 1 hospitalization compared with 0.2% of HCWs who received a booster dose following CoronaVac vaccine ($P < .001$). On the other hand, no difference was observed in hospitalizations between those with 2 doses of the ChAdOx1 vaccine and those with a booster dose following ChAdOx1 vaccine ($P = .50$). There was no statistically significant difference between those with 2 doses (either ChAdOx1 or CoronaVac) and a booster dose in length of stay, ICU stays, or mechanical ventilation use (Table 1). Only 1 HCW who was vaccinated with 2 doses of the ChAdOx1 vaccine died during the study period, before the booster dose was released. This HCW was immunocompromised due to systemic lupus erythematosus treatment.

The estimated VE was 91.6% (95% confidence interval [CI]: 88.6–94.0%) for the group who received 2 doses of CoronaVac vaccine + Pfizer/BioNTech booster (compared with 2 doses of CoronaVac vaccine) and 58.6% (95% CI: 42.4–71.0%) for the group who received 2 doses of ChAdOx1 vaccine + Pfizer/BioNTech booster (compared with 2 doses of ChAdOx1 vaccine). After controlling for age, sex, and professional category, the estimated VE was 92.0% (95% CI: 89.1–94.3%) and 60.5% (95% CI: 44.9–72.4%), respectively (Table 2).

Whole-Genome Sequencing Analysis

During the study period, 246 SARS-CoV-2 samples from 246 HCWs were screened for mutations. One (0.4%) case was the Alpha variant, 54 (22%) were P1 strain (Gamma SARS-CoV-2 variant), and 191 (77.6%) were Delta. In July and August 2021, 66% of cases were Gamma and 34% were Delta. Almost all cases (97%) were Delta in September and October and were 100% in November and December (Table 3).

DISCUSSION

This retrospective study revealed that HCWs with 2 doses of either CoronaVac or ChAdOx1 vaccine followed by mRNA booster had better protection than those with only 2 doses, even after adjusting for important variables such as the time to event from the last dose (ie, exposure duration) and infection with the Delta variant. This study suggests that those who received either the CoronaVac or ChAdOx1 vaccine for the first 2 doses should receive an mRNA booster, if available.

Table 2. Estimated Incidence Rate Ratios of COVID-19 by RT-PCR and Vaccine Effectiveness Among Healthcare Workers After COVID-19 Vaccine Second and Third Doses: Hospital Israelita Albert Einstein, São Paulo, Brazil, 1 January 2021 to 30 December 2021

	Two Doses of CoronaVac (n = 5629)			Two Doses of ChAdOx1 (n = 5798)		
	IRR (95% CI)	*P*	VE (95% CI)	IRR (95% CI)	*P*	VE (95% CI)
COVID-19 infection						
COVID-19 vaccines						
Second dose	1.0 (Ref)			1.0 (Ref)		
Third dose (Pfizer/BioNTech)	.084 (.060; .114)	<.001	91.6% (88.6%; 94.0%)	.414 (.290; .576)	<.001	58.6% (42.4%; 71.0%)
COVID-19 infection adjusted for covariates						
COVID-19 vaccines						
Second dose	1.0 (Ref)			1.0 (Ref)		
Third dose (Pfizer/BioNTech)	.080 (.057; .109)	<.001	92.0% (89.1%; 94.3%)	.395 (.276; .551)	<.001	60.5% (44.9%; 72.4%)
Sex (male)	.787 (.624; .983)	.039		.856 (.636; 1.139)	.295	
Age (y)	1.016 (1.004; 1.027)	.006		1.010 (.997; 1.023)	.131	
HCW job type	1.178 (.937; 1.495)	.170		.818 (.592; 1.111)	.210	

Poisson models with COVID-19 infection as outcome and log (exposure time) as offset.
Abbreviations: ChAdOx1, Oxford-AstraZeneca COVID-19 vaccine; CI, confidence interval; COVID-19, coronavirus disease 2019; HCW, healthcare worker; IRR, incidence rate ratio; Ref, reference; RT-PCR, real-time polymerase chain reaction; VE, vaccine effectiveness.

Table 3. Participants With SARS-CoV-2 Variants of Concern (n = 246) Detected by Whole-Genome Sequencing: Hospital Israelita Albert Einstein, São Paulo, Brazil, 1 January 2021 to 30 December 2021

	WGS Bimonthly (2021)						Total
SARS-CoV-2 VOC Lineage	January–February	March–April	May–June	July–August	September–October	November–December	
Alpha	…	1 (7.7)	…	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Delta	…	0 (0.0)	…	19 (33.9)	145 (96.7)	27 (100.0)	191 (77.6)
Gamma	…	12 (92.3)	…	37 (66.1)	5 (3.3)	0 (0.0)	54 (22.0)
Total	0	13 (100.0)	0	56 (100.0)	150 (100.0)	27 (100.0)	246 (100.0)

Data are presented as n (%).
Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VOC, variant of concern; WGS, whole-genome sequencing.

Multiple papers have reported the benefits of a third COVID-19 vaccine dose [8–10, 17]. Rates of COVID-19 infection cases were lowest among fully vaccinated individuals (2 doses with booster dose), compared with those unvaccinated or fully vaccinated individuals without a booster dose [10]. The Food and Drug Administration (FDA) authorized the mix-and-match strategy in October 2021 and the Centers for Disease Control and Prevention endorsed the approach in federal guidelines, allowing vaccinated individuals to choose their booster shot [18]. While there have been limited studies evaluating VE due to heterologous COVID-19 booster vaccinations, available results have shown that receiving a booster dose of a different vaccine had an acceptable safety profile and was as protective as receiving another dose of the same vaccine as the initial series [17]. In some studies, heterologous vaccine boosting was associated with even lower COVID-19 infection rates than homologous boosting [19, 20]. ChAdOx1 and CoronaVac vaccines were the first 2 COVID-19 vaccines authorized by the Brazilian Health Surveillance Agency [21]. Therefore, most of the HCWs in our facility completed the initial 2 doses with either of those vaccines [22]. This present study demonstrated that there was significantly more protection after a booster with the Pfizer/BioNTech vaccine during the Delta variant dominant period in Brazil, independent of prior COVID-19 vaccine (CoronaVac or ChAdOx1 vaccine).

Our prior study revealed that VE for 2 doses of ChAdOx1 vaccine was 88% and 51% for 2 doses of CoronaVac [11, 23]. Similarly, a Chilean study reported that VE after 2 doses of CoronaVac was 65.9% for the prevention of COVID-19 infection compared with the unvaccinated group [23]. In the present study, VE for mRNA booster was significantly different between CoronaVac or ChAdOx1 as a primary series (92% and 60.5%, respectively); however, this does not indicate that the ChAdOx1/booster combination is inferior to the CoronaVac/booster, since these estimates were based on the comparison of the respective 2 doses without a booster. The cumulative incidences were comparable between CoronaVac/booster and ChAdOx1/booster (Figure 1). Cerqueira-Silva et al [24] recently showed that the VE of the Pfizer/BioNTech vaccine booster following 2 doses of CoronaVac vaccine was 92.7% when compared with 2 doses of CoronaVac vaccine in Brazil. Although this study did not focus on HCWs, VE was very similar to our findings among HCWs. On the other hand, Andrews

et al [19] found that the VE of the Pfizer/BioNTech booster following 2 doses of ChAdOx1 vaccine was 86% when compared with 2 doses of ChAdOx1 vaccine in England. This number was much higher than the estimated VE in our study, at 60.5%. The reason for the substantial difference between these 2 studies is not clear given that both studies were done when the Delta variant was dominant both in Brazil and England [19, 24]. We hypothesize that the study population of HCWs only might have contributed to the lower VE in our study. To our knowledge, this is the first study evaluating the effectiveness of heterologous prime-booster COVID-19 vaccines using both CoronaVac vaccine and ChAdOx1 vaccine in the same population.

During the first half of the study period, the dominant variant in circulation was P.1 (Gamma variant) and the Delta variant was dominant in the second half. Our study demonstrated that the third dose of Pfizer/BioNTech vaccine following either CoronaVac or ChAdOx1 vaccine provides significant protection even with these variants. More studies are needed on new SARS-CoV-2 variants of concern with multiple spike protein mutations, which appear to be more infectious or cause more disease than other circulating SARS-CoV-2 variants [25]. Some deletions in the spike protein mutations can alter the shape of the spike and may help it evade some antibodies [26]. There is no COVID-19 vaccine that is 100% effective against SARS-CoV-2 infection, as demonstrated by breakthrough infections reported in HCWs after COVID-19 vaccination [27, 28]. The emergence of the Omicron (B.1.1.529) variant was announced by the World Health Organization on 26 November 2021 [29]. During our study period, we did not detect the Omicron variant in our HCW samples. We intend to evaluate the same HCWs for a longer period of time to investigate how VE of the booster dose with Pfizer/BioNTech vaccine changes along with the emergence of the Omicron variant in Brazil.

Our study had several limitations. First, this was an observational study, which is subject to multiple biases [30]. However, this is the most common study design in the infection-prevention literature [30]. We did not perform a test-negative-design case-control study because this study was retrospectively conducted using data from symptom-based testing. There is a possibility that HCWs had asymptomatic SARS-CoV-2 infection and did not undergo testing, leading to misclassification of the outcome [19, 24]. Second, we did not directly compare VE between those with 2 doses of CoronaVac followed by mRNA vaccine and those with 2 doses of ChAdOx1 followed by mRNA vaccine. However, Figure 1 demonstrates that cumulative incidence rates were comparable between the 2 groups. Third, we could not perform further analyses by immunocompromised status due to the limited number of cases. Fourth, non-neutralizing viral antigen-binding antibody levels were not available in our HCW cohort study. However, the US FDA does not recommend antibody testing for SARS-CoV-2 to determine immunity or protection from COVID-19, especially among those who are vaccinated [31]. Fifth, past medical history was available for 9093 (79.6%) HCWs only and this was not included in the main multivariable analysis. After adjusting for the presence of comorbidities, estimated VE was similar to the main multivariable analysis: 92.5% (95% CI: 89.5–94.8%) for the 2 doses of CoronaVac vaccine + Pfizer/BioNTech booster (compared with 2 doses of CoronaVac vaccine) and 67.5% (95% CI: 53.6–77.9%) for the 2 doses of ChAdOx1 vaccine + Pfizer/BioNTech booster (compared with 2 doses of ChAdOx1 vaccine), respectively (Supplementary Appendix 2). Since our study focused only on short-term VE for the third dose against COVID-19 infection among HCWs, we could not fully evaluate VE for other outcomes such as COVID-19 hospitalization, COVID-19 reinfection, or COVID-19 death. Also, we were not able to adjust for waning immunity and varying incidence of immune escape variants in this population. Last, we were not able to predict the duration of protection against COVID-19 infection following booster vaccination (third dose) and whether another booster (fourth dose) will be necessary.

Conclusions

We found that viral vector and inactivated virus COVID-19 vaccines can significantly prevent COVID-19 infection among HCWs when boosted with a third dose of Pfizer/BioNTech mRNA vaccine. This heterologous vaccine strategy was also effective among HCWs even after the emergence of new SARS-CoV-2 variants (Gamma and Delta). More studies are needed to evaluate VE for other heterologous prime-booster COVID-19 vaccines, COVID-19 breakthrough infection, and genomic surveillance for a better understanding of VE against newer SARS-CoV-2 variants, such as Omicron.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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