Effectiveness of inactivated COVID-19 vaccines against SARS-CoV-2 infections among healthcare personnel in Pakistan: a test-negative case-control study

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STRENGTHS AND LIMITATIONS OF THIS STUDY

Our study was conducted among a well-defined group of healthcare personnel (HCP) with robust and consistent testing parameters that did not change during the study period.

Our study uses a test-negative design which mitigates the risk of bias associated with healthcare access and seeking behaviour.

Due to the limited sample size in our study, we were unable to match more than one variable.

Our study does not evaluate inactivated vaccines' effectiveness against severe COVID-19 or hospitalisation as most HCP at our institution did not get severe disease.

INTRODUCTION

The COVID-19 pandemic impacted global health, and as of 9 December 2022, more than 657 million COVID-19 cases and 6 million deaths have been reported to WHO.1 Mass vaccination remains a cornerstone of public health interventions to counter the COVID-19 pandemic. Several vaccines have proven efficacious in phase III trials and received emergency approval for mass vaccination campaigns.2–4 As healthcare personnel (HCP) are at a higher risk of contracting the disease and can become a source of infection to vulnerable patients,5 6 both the Centers for Disease Control and Prevention (CDC) and WHO have recommended that national vaccine strategies prioritise vaccination of HCP.7 8

In Pakistan, the government-driven vaccination campaign commenced in February 2021. Vaccines with more than 50% efficacy in clinical trials were approved for mass vaccination by the health regulatory authorities, and HCP were prioritised for vaccination.9 In the first phase, conventional inactivated vaccines BBIBP-CorV and CoronaVac were administered. Over the next...
few months, replication-deficient adenovector vaccines, including single-dose Ad5-nCoV (CanSino Bio) and the two-dose ChAdOx1 nCoV-19 (Oxford-AstraZeneca), became available and were administered to HCP and the public.10

While CoronaVac and BBIBP-CorV were efficacious in clinical trials,11 12 most were conducted before SARS-CoV-2 variants of concern (VOCs) appeared. It, therefore, became crucial to assess the effectiveness of these vaccines in real-world settings during the emergence of VOCs. This information can provide critical insights to help with policy decisions, including the need to give boosters or additional vaccination. We report the effectiveness of BBIBP-CorV and CoronaVac vaccines against reverse transcription PCR (RT-PCR)-confirmed SARS-CoV-2 infections among HCP. 4 months into the vaccination drive at a large private healthcare system in Pakistan, with an existing robust employee surveillance system. Our study was conducted in the setting of the third and fourth waves of COVID-19 in Pakistan between April and September 2021 during which Alpha, Beta, Gamma and Delta variants were prevalent.13 14

**Study population**

**Inclusion criteria**
- HCP working at AKU and who got an RT-PCR test for SARS-CoV-2 at AKU Hospital Clinical Laboratories between 1 April and 30 September 2021.
- HCP who were unvaccinated or vaccinated with one or two doses of BBIBP-CorV or CoronaVac.

**Exclusion criteria**
- HCP with missing vaccination data.
- HCP who received other vaccines (Ad5-nCoV, AZD1222 (ChAdOx1), mRNA-1273, Janssen (Johnson & Johnson), Gam-COVID-Vac, BNT162b2).
- HCP who were enrolled in COVID-19 vaccine trials.

**Study setting**

AKU, a not-for-profit organisation, runs a large healthcare system within Pakistan. Its main campus in Karachi is a 750-bed tertiary care hospital, a medical college and a nursing school. Additionally, 4 secondary care hospitals in 2 cities, 19 integrated medical centres and 290 laboratory collection centres in 120 cities across Pakistan are part of the AKU healthcare system. The University employs 13,960 staff, of which 80% are involved in direct healthcare.15

Since the beginning of the pandemic, multiple policies were put in place to facilitate HCP getting tested. Free assessments, testing and treatment were offered through the Office of Employee Health in the Department of Family Medicine. In addition, time away from work due to quarantine and isolation was not counted from HCP’s annual leaves. For each employee who tested positive, detailed contact tracing was performed. With these employee-friendly policies, HCP have used the Office of Employee Health; to date, 30,000 tests have been conducted.

HCP were tested if they: (1) had symptoms consistent with COVID-19; (2) had a high-risk exposure, as defined by the US CDC criteria,16 to a person infected with COVID-19 either in the community or at the workplace; or (3) were part of an outbreak investigation in a specific part of the University. Additional details regarding the assessment and testing protocols used for the testing of HCP can be located in our previously published article.17 All testing was performed by SARS-CoV-2 PCR on a nasal specimen using the Cobas 6800 Roche assay.18 The samples were collected at the HCP’s workplace, and all testing was done at the AKU Hospital Clinical Laboratories, accredited by the College of American Pathologists, USA.15

The Office of Employee Health maintained a password-protected database for COVID-19-related data that is separate from HCP’s medical records. Once vaccination began, HCP also provided the dates of vaccine administration and the type of vaccine. Vaccine information was confirmed by verifying with the national database using the short-message-service (SMS-based) system developed by the government of Pakistan.10 Vaccinations were available without any priority policy to all AKU HCP, regardless of age, comorbidities, area of work or previous SARS-CoV-2 infections.

**Definitions**

*Healthcare personnel:* all employees working within the healthcare system with the potential of direct and indirect exposures to patients or infectious material were considered HCP.19

*Case:* HCP who had a positive SARS-CoV-2 RT-PCR test during the study period and had an absence of a positive test result in the preceding 90-day period.

*Control:* HCP with a negative SARS-CoV-2 RT-PCR test result during the study period and the absence of a positive test result in the preceding 90-day period and the subsequent 14-day period.
Vaccination status: using the WHO definition, we defined vaccination status at the time of testing as:
- Unvaccinated: if no dose of any vaccine was received.
- Single dose received: if only the first dose of BBIBP-CorV or CoronaVac vaccine was received. This group was further divided into two subgroups: (a) 0–15 days since receiving the first dose; (b) ≥14 days since receiving the first dose of a two-dose vaccine.
- Two doses received: if both doses of BBIBP-CorV or CoronaVac vaccine were received. This group was also further divided into two: (a) 0–13 days since receiving the final dose; (b) ≥14 days since receiving the final dose.

SARS-CoV-2 infection: all HCP who tested positive for SARS-CoV-2 by RT-PCR, regardless of the presence or absence of symptoms.

Symptomatic SARS-CoV-2: all HCP who tested positive for SARS-CoV-2 by RT-PCR and had one or more COVID-19-related symptoms in 0–10 days before the RT-PCR test for SARS-CoV-2.

Work area: HCP not working in direct clinical care (eg, laboratory personnel, housekeeping staff, food providers and administrative staff) were classified as ‘non-clinical’; those providing direct clinical care in areas not designated for patients with COVID were classified as ‘clinical non-COVID’; whereas HCP working in designated areas for COVID suspect or COVID-confirmed patients were categorised as ‘clinical COVID’.

Statistical analysis
Data on demographics, results of the SARS-CoV-2 RT-PCR test, vaccination status and dates, reason for testing, work area and history of infection (positive RT-PCR test) were retrieved from the Office of Employee Health database for statistical analysis. Vaccination status was allocated based on predefined definitions stated above.

As the study was during the surge, with per cent positivity changing weekly, we matched cases and controls by the date of the RT-PCR test (±7 days) to reduce bias. Each case was matched to a minimum of two controls and a maximum of six controls.

We compared demographics, reason for testing, work area, history of RT-PCR-confirmed SARS-CoV-2 infection and vaccination status between cases and controls using $\chi^2$ test for categorical variables and t-test for normally distributed continuous-level data. Using unvaccinated individuals as a reference, we used conditional logistic regression to estimate the odds of having RT-PCR-confirmed SARS-CoV-2 infections in HCP vaccinated with a single dose and both doses of the two-dose inactivated vaccines. We calculated unadjusted and adjusted ORs, accounting for covariates that included age, sex (using females as a reference), work area (using non-clinical as a reference) and history of RT-PCR-confirmed SARS-CoV-2 infection (using those without a history of RT-PCR-confirmed SARS-CoV-2 infection as a reference). Vaccine effectiveness was calculated as per cent VE using (1-OR)*100. Additionally, we performed a subgroup analysis to assess the effectiveness of vaccines against symptomatic SARS-CoV-2 infection.

Based on Hitchings et al study, we plotted the weekly positivity rate and cumulative vaccine coverage from

Figure 1 Process for the selection of healthcare personnel (HCP). *Other vaccines: Ad5-nCoV (n=342), AZD1222 (ChAdOx1) (n=60), mRNA-1273 (n=20), Janssen (n=1), Gam-COVID-Vac (n=18), BNT162b2 (n=11). RT-PCR, reverse transcription PCR.
January 2021 to September 2021 to understand the impact of vaccines on SARS-CoV-2 infections in the healthcare system.

Patient and public involvement
Patients and the public were not involved in the conduct of this study.

RESULTS

Between 1 April and 30 September 2021, a total of 4599 HCP were tested for SARS-CoV-2 via RT-PCR. Figure 1 shows the process for the selection of HCP in the study. After exclusion, 4074 HCP remained, of whom 1037 tested positive and were classified as cases, and 3037 tested negative and were classified as controls. Of these, 3095 (959 cases and 2136 controls) were tested for symptoms. Cases were matched to controls by the date of the RT-PCR test (±7 days). Each case was matched to two to six controls. No HCP had to be excluded due to non-matching.

Table 1 shows the characteristics of all cases and controls. Compared with controls, cases were older (35.3±9.7 vs 33.1±8.6; p<0.001). 73.9% of cases and 74.8%
of controls were administered the BBIBP-CorV vaccine. 61.4% of cases and 60.3% of controls had received the second dose at least 14 days before the test. Among HCP who had received both doses of vaccine before the RT-PCR test, there was no significant difference in mean duration between the second dose and test between cases and controls (94.8±41.6 vs 91.7±45.1 days; p=0.123).

Online supplemental table S1 describes the characteristics of symptomatic cases and controls (3095/4074; 76.0%). There was no significant difference in the mean interval between the onset of symptoms and the RT-PCR test between cases and controls (2.1±2.0 vs 1.9±2.3 days; p=0.017).

Table 2 shows the odds of contracting SARS-CoV-2 infection by the time since vaccination. After adjusting for age, sex, work area and history of SARS-CoV-2 infection, we found that a single dose of the two-dose vaccines was ineffective within the first 13 days (VE 32%, 95% CI −25, 62; p=0.210) or even after 13 days had elapsed (VE 17%, 95% CI −10, 39; p=0.261). This shows that one dose is not enough to prevent SARS-CoV-2 infections. While the vaccines were effective during the period <14 days after the second dose (VE 43%, 95% CI −5, 69; p=0.068), the results were not significant. The vaccines were most effective ≥14 days after the second dose against a SARS-CoV-2 infection (VE 30%, 95% CI 7, 48; p=0.015).

Table 3 shows the odds of contracting symptomatic SARS-CoV-2 infection by the time since vaccination. After adjusting for age, sex, work area and history of RT-PCR-confirmed SARS-CoV-2 infection, we found that the first dose was ineffective against a symptomatic SARS-CoV-2 infection. The vaccines were most effective ≥14 days after the second dose against a symptomatic SARS-CoV-2 infection (VE 33%, 95% CI 6, 52; p=0.022).

Figure 2 displays the weekly RT-PCR tests conducted and the cumulative coverage of the first and second doses of inactivated vaccines among HCP at our institution. We see that despite 75% coverage with two doses of inactivated vaccines, we observed an increase in positivity rates that correlated with the Delta variant surge in Pakistan.13 This also shows the modest effectiveness of inactivated vaccines against VOCs.

**DISCUSSION**

Our study among HCP found that BBIBP-CorV and CoronaVac were not as effective as seen in the efficacy trials11 12 in preventing SARS-CoV-2 infections, even 14 days after
the second dose of the two-dose vaccines. Vaccines did not provide significant protection against infection after the first dose and within the first 2 weeks of the second dose. During our study period, the predominant variants in Pakistan switched from Alpha, Beta and Gamma variants in April to June to the highly transmissible Delta variant in July 2021.\(^{13,14}\) The Delta variant constituted up to 97% of the total genomes sequenced from July to September 2021.\(^{13,22}\)

Existing evidence on the effectiveness of inactivated vaccines against infections is inconsistent. Our results agree with a test-negative case–control study conducted in Brazil among healthcare workers during the Gamma variant epidemic, which reported modest effectiveness of two doses of CoronaVac, with adjusted effectiveness of 37.1% against symptomatic COVID-19 infections and 37.9% against all COVID-19 infections.\(^{21}\) Similarly, another study from Brazil reported a 47% effectiveness of CoronaVac against symptomatic infections in elderly during widespread transmission of the Gamma variant.\(^{23}\)

During the Delta variant surge in China, moderate effectiveness against COVID-19 infections was estimated for inactivated vaccines.\(^{24,25}\) In contrast, the effectiveness estimated in our study is lower than that of CoronaVac reported among healthcare workers in Turkey (65%).\(^{26}\)

Several possibilities exist for the lower than expected effectiveness of inactivated vaccines in our study. Neutralising antibody levels correlate with protection against COVID-19 infections,\(^{27,28}\) and inactivated vaccines produce inferior antibody responses compared with mRNA vaccines.\(^{9,29-31}\) Moreover, the weakened neutralisation potency of inactivated vaccines against the dominant VOCs circulating during our study period, especially the vaccine-resistant Delta variant, may have contributed to the limited effectiveness.\(^{31,32}\)

Studies conducted during the Delta variant epidemic have demonstrated only modest effectiveness of two doses of BBIBP-CorV and CoronaVac against infections.\(^ {24,33}\)

We did not have serological information for our study cohort. However, by February 2021, immunoglobulin G (IgG) seropositivity to spike protein was 53% in healthy blood donors in Karachi.\(^ {34}\) Additionally, a study conducted primarily among the healthcare cohort at AKU found that among individuals vaccinated with BBIBP-CorV, IgG responses to spike protein were enhanced by a history of COVID-19.\(^ {35}\)

Our data indicate that HCP who tested negative (controls) had a higher proportion of individuals with a history of RT-PCR-confirmed COVID-19 infection than HCP who tested positive (cases). Furthermore, among HCP with a prior confirmed COVID-19 infection, those who tested negative (controls) had a shorter interval between their previous infection and current testing compared with HCP who tested positive (cases). These findings are consistent with previous studies indicating that a prior COVID-19 infection may provide protection against infections and symptomatic disease caused by various SARS-CoV-2 variants, including the Delta variant.\(^ {36}\) Despite waning over time, SARS-CoV-2 infections can provide protection against subsequent infection for up to 40 weeks.\(^ {36}\)

The mean interval between the second dose of vaccine and COVID-19 infection was more than 90 days in our study. Studies have demonstrated a decline in neutralising antibody titres 3 months after vaccinations with the two-dose BBIBP-CorV and CoronaVac.\(^ {31,37-39}\) It is possible that there was a significant waning of neutralising antibody responses after vaccination in our study population. Considering that inactivated vaccines were the most
widely used vaccines in low and middle-income countries (LMICs), this finding supports the provision of homologous or heterologous booster doses among recipients of these vaccines. In particular, individuals who received a primary series of inactivated vaccines may benefit more from heterologous boosters as they have been found to be much more effective against symptomatic disease and severe COVID-19 infection compared with homologous boosters.\cite{40}

Our study has some limitations. Our sample size did not allow us to match more than one variable. However, we did adjust for age, sex, work area and previous COVID-19 infection in the logistic model. Additionally, most HCP in our setting did not develop severe disease or require hospitalisation during the study period. Therefore, we cannot comment on vaccines’ effectiveness against severe disease in our study population. However, a recent study conducted in our hospital did find full vaccination with BBIBP-CorV to be protective against severe COVID-19, regardless of the variant.\cite{41} It is, however, essential to note that in healthcare settings, infected HCP can risk spreading the infection to vulnerable patients. Thus, it is vital to examine the impact of vaccines from the perspective of the infected person and its impact on the system at large. Unfortunately, as this was a retrospective review of employee health records, we do not have serological testing data available for HCP at the time of their COVID-19 diagnosis. Also, we do not have information about the viral load of PCR tests conducted. Additionally, we could not directly ascertain effectiveness against the circulating VOCs as samples from HCP in our study population did not undergo genomic sequencing. Finally, as our study was conducted on HCP which were a highly exposed group of individuals through the pandemic, the results may not be generalisable to the population outside of healthcare settings.

Despite these limitations, our study has clear strengths. Our findings are from a large, well-defined group of HCP with consistent testing parameters that did not change during the study period. We used RT-PCR which is sensitive to detecting SARS-CoV-2 infections.\cite{18} Moreover, the vaccine status was highly accurate as it was validated through the national vaccine registry. Using a test-negative design, we mitigated the risk of bias/confounding associated with healthcare access and seeking behaviour. Finally, our study was conducted among HCP whose well-being is imperative to continue to offer uninterrupted quality care to patients in a pandemic.

Our study was conducted in an LMIC with a high population density and limited resources. Thus, examining the effectiveness of vaccines in these settings is essential to prevent public health crises. Pakistan and other developing economies with weak healthcare systems need effective vaccines to meet the unprecedented challenge of dealing with the morbidity and mortality associated with COVID-19. Our study adds new estimates to the effectiveness of these vaccines in HCP. It may guide future policies in Pakistan and other LMICs that mainly administered inactivated vaccines in their mass vaccination campaigns. By finding complete vaccination with CoronaVac and BBIBP-CorV vaccines to be only modestly effective against COVID-19 infections, our study strengthens the case for boosters or additional vaccination among recipients of these vaccines. Additionally, with new variants being identified regularly, it is crucial to prioritise conducting studies at different times and in various settings to continuously examine the effectiveness of these vaccines and boosters against the prevailing variants in real-world settings.

CONCLUSIONS

Absence of strong effectiveness of inactivated vaccines against COVID-19 infections among HCP, especially during the spread of VOCs in our setting, is concerning and builds a case for boosters and/or additional vaccination. There is a need for further studies to continuously assess effectiveness in the setting of emerging variants to guide policies regarding boosters to ensure adequate protectiveness. Since the time of this study, inactivated vaccine and mRNA vaccine boosters have been introduced in Pakistan.\cite{42} Heterologous boosters in the setting of a primary series of inactivated vaccines have been found to be effective in decreasing mortality and severe infection.\cite{40} Further studies examining the effectiveness of boosters against infections in our setting would help inform public policy especially for HCP.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Ethical Review Committee (ERC: 2021-5629-18170), Aga Khan University.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. As this is employee-related data, we do not have permission to make it publicly accessible. However, data are available from the corresponding author upon reasonable request after approval from the University’s ethics review committee.

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Table S1
Characteristics of symptomatic cases and controls (N= 3095)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Cases (n= 959)</th>
<th>Controls (n= 2136)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean ± SD)</td>
<td>35.0 ± 9.5</td>
<td>32.5 ± 8.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age groups, n (%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>19-29 years</td>
<td>339 (35.4)</td>
<td>973 (45.6)</td>
<td></td>
</tr>
<tr>
<td>30-39 years</td>
<td>357 (37.2)</td>
<td>790 (37.0)</td>
<td></td>
</tr>
<tr>
<td>40-49 years</td>
<td>166 (17.3)</td>
<td>258 (12.1)</td>
<td></td>
</tr>
<tr>
<td>50-59 years</td>
<td>85 (8.9)</td>
<td>99 (4.6)</td>
<td></td>
</tr>
<tr>
<td>60 years and over</td>
<td>12 (1.2)</td>
<td>16 (0.8)</td>
<td></td>
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<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>469 (48.9)</td>
<td>1115 (52.2)</td>
<td>0.09</td>
</tr>
<tr>
<td>Male</td>
<td>490 (51.1)</td>
<td>1021 (47.8)</td>
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</tr>
<tr>
<td>Work area, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-clinical</td>
<td>273 (28.5)</td>
<td>535 (25.1)</td>
<td></td>
</tr>
<tr>
<td>Clinical non-COVID</td>
<td>54 (5.6)</td>
<td>227 (10.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Clinical COVID</td>
<td>632 (65.9)</td>
<td>1374 (64.3)</td>
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</tr>
<tr>
<td>Vaccination status, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unvaccinated</td>
<td>93 (9.7)</td>
<td>190 (8.9)</td>
<td></td>
</tr>
<tr>
<td>Single dose, 0-13 days</td>
<td>17 (1.8)</td>
<td>42 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Single dose, ≥ 14 days</td>
<td>249 (26.0)</td>
<td>581 (27.2)</td>
<td>0.565</td>
</tr>
<tr>
<td>Two doses, 0-13 days</td>
<td>16 (1.7)</td>
<td>52 (2.4)</td>
<td></td>
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<tr>
<td>Two doses, ≥ 14 days</td>
<td>584 (60.9)</td>
<td>1271 (59.5)</td>
<td></td>
</tr>
<tr>
<td>Vaccine name, n (%)</td>
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<tr>
<td>Unvaccinated</td>
<td>93 (9.7)</td>
<td>190 (8.9)</td>
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<tr>
<td>BBIBP-CorV</td>
<td>709 (73.9)</td>
<td>1610 (75.4)</td>
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<tr>
<td>CoronaVac</td>
<td>157 (16.4)</td>
<td>336 (15.7)</td>
<td>0.663</td>
</tr>
<tr>
<td>Interval between first dose and</td>
<td>113.8 ± 49.7</td>
<td>115.5 ± 55.0</td>
<td>0.446</td>
</tr>
<tr>
<td>RT-PCR test in HCPs with only a</td>
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<tr>
<td>single dose of vaccine (days,</td>
<td>mean (SD))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interval between second dose</td>
<td>95.0 ± 41.5</td>
<td>91.4 ± 45.1</td>
<td>0.094</td>
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<tr>
<td>and RT-PCR test in HCPs with</td>
<td></td>
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<tr>
<td>two doses of vaccine, (days,</td>
<td>mean (SD))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interval between symptom onset</td>
<td>2.1 ± 2.0</td>
<td>1.9 ± 2.3</td>
<td>0.017</td>
</tr>
<tr>
<td>and RT-PCR test, days (mean ±</td>
<td></td>
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<tr>
<td>SD)</td>
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SD: standard deviation; RT-PCR: reverse transcription polymerase chain reaction; HCP: health care personnel; IQR: interquartile range