



Infection prevention and control risk factors for SARS-CoV-2 infection in health workers: a global, multi-centre, case–control study

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SUMMARY

Background: Health workers were at higher risk for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection during the coronavirus disease 2019 (COVID-19) pandemic due to occupational risk factors. This study aimed to characterize these risk factors as part of the World Health Organization (WHO) Unity Studies initiative.

Methods: This global, multi-centre, nested, case–control study was conducted in 121 healthcare facilities in 21 countries. Cases were health workers who tested positive for SARS-CoV-2 infection with documented occupational exposure to COVID-19 patients in the 14 days pre-enrolment. Controls were enrolled from the same facilities with similar exposure but negative serology. Case and control status was confirmed with serological testing at baseline and after 3–4 weeks. Demographic and infection risk factor data were collected using structured questionnaires.

Findings: Between June 2020 and December 2021, data were obtained for 1213 cases and 1844 controls. Risk of SARS-CoV-2 infection was associated with non-adherence to personal protective equipment (PPE) guidelines [adjusted odds ratio (aOR) 1.67, 95% confidence

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Adherence



interval (CI) 1.32–2.12] and not performing hand hygiene consistently after patient contact (aOR 2.52, 95% CI 1.72–3.68). Direct close contact with COVID-19 patients was also associated with increased risk of SARS-CoV-2 infection, particularly during prolonged contact (>15 min). Items associated with lower risk of SARS-CoV-2 infection were use of a respirator during aerosol-generating procedures; and use of gloves, and a gown or coverall during contact with contaminated materials/surfaces. No difference was observed between health workers using respirators vs surgical masks for routine care.

Conclusion: Appropriate implementation of infection prevention and control measures and use of PPE remain a priority to protect health workers from SARS-CoV-2 infection.

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Introduction

Health workers were identified as being at high risk of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, particularly during the first waves of the coronavirus disease 2019 (COVID-19) pandemic [1]. Between March and May 2020, health workers accounted for 10% of COVID-19 cases reported to the World Health Organization (WHO) surveillance system, which represented a risk of infection approximately three-fold higher compared with the general population [hazard ratio 3.40, 95% confidence interval (CI) 3.37–3.43]. A living literature review reported that up to 43.3% of health workers worldwide were infected with SARS-CoV-2 [2], and 115,500 health workers were estimated to have died from COVID-19 between January 2020 and May 2021 [1]. Infectious health workers can also be a source of nosocomial COVID-19 transmission, and outbreaks among vulnerable patients and other colleagues [3,4]. Resulting absenteeism may place undue stress on health systems due to high workload, thus impeding optimal care delivery [5].

Even before the advent of vaccines, there were indications of declining numbers of cases of SARS-CoV-2 infection among health workers as the pandemic progressed. By September 2020, health workers accounted for 2.5% of all COVID-19 cases, suggesting that the progressive implementation of infection prevention and control (IPC) measures, including training for health workers and the appropriate use of personal protective equipment (PPE), were effective for their protection [6–8].

Understanding SARS-CoV-2 infection among health workers and associated risk factors, including best protective measures, was one of the key areas for urgent research highlighted within the WHO R&D Blueprint since the beginning of the pandemic [9,10] to inform IPC policies at healthcare facility and national levels. Previous studies found that SARS-CoV-2 exposure without appropriate PPE increased the risk of infection during invasive procedures, especially direct contact with patients or their bodily fluids, or during aerosol-generating procedures [2]. In addition, availability and correct use of PPE, hand hygiene and training in IPC were associated with decreased risk of infection among health workers, especially in lower-income settings [2]. However, these studies tended to be conducted in single centres with heterogeneous methodologies [11]. Given the limited number of case–control studies and the discrepancies in methodologies and study findings, this multi-centre, multi-country, case–control study with rigorous methodology was conducted to explore these risk factors at length.

As part of WHO Unity Studies [12] and in accordance with the WHO R&D Blueprint agenda [9], the WHO IPC Hub conducted a

case–control study to identify SARS-CoV-2 infection exposure and IPC risk factors among health workers involved in the COVID-19 response [13]. This study aimed to describe the sociodemographic characteristics of health workers infected with SARS-CoV-2, to quantify the relative importance of exposure risks for health workers, and to identify both facility- and individual-level risk factors, including effective IPC measures against SARS-CoV-2 transmission.

Methods

Study design and participants

This global, multi-centre, case–control study involved health workers involved in the care of COVID-19 patients. The main study protocol was developed by the WHO IPC Hub in collaboration with the WHO Collaborating Centre for Infectious Disease Epidemiology and Control at the University of Hong Kong, and disseminated widely through the WHO website, regional offices and related networks. The protocol was approved by the WHO Ethics Board in June 2020 (Reference No. ERC.0003356). Healthcare facilities were selected according to their capacity to recruit and conduct appropriate participant follow-up, perform molecular testing for SARS-CoV-2 infection, and collect complete high-quality data.

A health worker was defined as any person who provided care for a COVID-19 patient, including those not involved in direct care, but in contact with patients' body fluids, potentially contaminated items or environmental surfaces. Enrolled health workers included allied and auxiliary health workers (physicians, nurses and assistants, cleaning and laundry personnel, radiology technicians, clerks, phlebotomists, therapists, nutritionists, social workers, laboratory personnel, patient transporters and catering staff). Exposure to COVID-19 patients was defined as contact with a suspected/probable/confirmed COVID-19 patient or indirect contact with fomites linked to a suspected/probable/confirmed COVID-19 patient in the 14 days prior to the health worker's SARS-CoV-2 infection confirmation test (cases) or recruitment to the study (controls).

Inclusion criteria for cases were: exposure to a COVID-19 patient in a healthcare setting; and confirmed SARS-CoV-2 infection according to the WHO definition [14]. Confirmed SARS-CoV-2 infection according to the WHO definition required either a positive nucleic acid amplification test, regardless of clinical/epidemiological criteria; or meeting clinical criteria and/or epidemiological criteria with a positive professional-use or self-test SARS-CoV-2 antigen rapid diagnostic test [14]. Controls – who were not classified as suspected/probable/confirmed COVID-19 cases and who had two negative,

consecutive SARS-CoV-2 serological tests (at recruitment and 3–4 weeks later) – were identified from the same facility. Local versions of the study protocol ensured that the same case definitions were applied in a universal manner. Serological testing was performed using the Wantai SARS-CoV-2 reverse transcriptase polymerase chain reaction kit. Controls were recruited in parallel with cases, based on incidence density sampling to reflect the overall pool of health workers who shared similar occupational exposure risk factors for SARS-CoV-2 infection. A recruitment target was set for at least two to four controls for every case enrolled at the same facility. Local ethics committee approvals and data sharing agreements with WHO were required to be in place prior to study initiation. Written informed consent was obtained from all participants.

Data collection

The core study team at the WHO IPC Hub developed a range of resources to support implementation of the protocol; conducted online training; and maintained frequent contact with the principal investigators and their local study teams to confirm that IPC recommendations were consistent with those from WHO, and to achieve high-level consistency of study methods and data collection across sites. Participants were invited to complete a detailed questionnaire at enrolment and at follow-up 3–4 weeks later, translated into local languages (Arabic, Georgian, Italian, Russian, Serbian and Ukrainian). Blinding of the participants' status as a case or control was recommended to reduce interviewer bias. Serological samples were collected from participants at the same time points. The exclusion criterion was receipt of any SARS-CoV-2 vaccine >14 days prior to completing the first questionnaire. Only sites that enrolled both cases and controls were included in the main analysis.

Data entry was mainly performed on Go.Data and stored on a central WHO server. Sites using other data collection tools extracted and assembled their data according to a standardized format, and merged data with the main database. All data were anonymized prior to sharing with WHO. Data variables obtained from the questionnaires included: demographic factors (age, sex, country of residence and educational level); personal risk factors (occupation, hygiene practices, and various types of exposure to SARS-CoV-2 infection), including high-risk procedures (aerosol-generating procedures [15], prolonged contact for >15 min, and contact with contaminated surfaces/materials) and those where PPE was worn; institutional risk factors (IPC policies and training in place, and available PPE resources); and COVID-19 symptoms and clinical outcomes (SARS-CoV-2 infection, symptoms, mortality, hospitalization, and serological responses) (see [Supplementary appendix](#), pp. 21–39). Aerosol-generating procedures referred to interventions that enable aerosols to be transmitted from one person to another (e.g. tracheal intubation and extubation, open airway suctioning, sputum induction, bronchoscopy, and non-invasive ventilation).

The main exposures of interest were occupational risk factors arising from personal hygiene and IPC practices, and the availability of IPC resources to health workers at the facility level. The main confounders were factors associated with both health workers' occupational exposure to SARS-CoV-2 and the outcome of contracting SARS-CoV-2 infection, notably community exposure. This was accounted for by including the

health workers' response on social contacts and use of public transport in the questionnaire.

Sample size calculation

The sample size was estimated for each study site, as the proportion of health workers with different exposures was expected to vary widely between facilities. Sample size calculation was based on a type I error of 5%, power of 80%, a minimum case-to-control ratio of 2, and a correlation coefficient of 0.2 for exposure between matched cases and controls (see [Supplementary appendix](#), pp. 66–69) [16,17]. The maximum calculated sample size per site was 735. This study also used a range of crude data and odds ratios (ORs) reported by previous case–control studies focusing on key potential risk factors for SARS-CoV-2 infection [18–20] including nursing as an occupational role [18], performing aerosol-generating procedures [19], and not wearing a N95 respirator during close contact with a COVID-19 patient [20]. As the number of sites participating in the study was expected to exceed 50, the overall number of participants was likely to exceed the required sample size to detect differences between matched cases and controls with 80% power.

Statistical analysis

Descriptive statistics include frequency tables for categorical data, means (with standard deviations) and medians (with interquartile ranges), depending on data distribution.

Univariable and multi-variable regression models were used to identify risk factors for SARS-CoV-2 infection in health workers. Variables in the regression models were selected through consensus between the study authors and cross-tabulation tables. Variables indicative of similar characteristics (e.g. if the participant attended in-person IPC training and the duration of the sessions) were tested for collinearity with Cramer's V measure. Highly collinear variables were removed from the model or merged, as appropriate. Model fit was checked with Akaike and Bayesian Information Criterion. Conditional logistic regression was used to estimate ORs adjusted for confounding variables [21]. As cases and controls were matched based on the healthcare facility at enrolment, 'healthcare facility' was used as grouping strata in the conditional regression model. All tests of significance were performed at 5%.

Three multi-variable logistic regression models were used in the analyses, and fitted to examine general occupational risk factors; high-risk, procedure-specific risk factors; and items of PPE. Independent variables included sociodemographic factors, such as age, gender and occupational role. In the models used to determine associations between use of PPE and SARS-CoV-2 infection, individual IPC practices and IPC training were included as confounding variables. Due to low occurrence of missing data for participants who were included in the main analysis (maximum ~10% for key variables, see [Supplementary appendix](#), pp. 17–20), complete data analysis was conducted without employing any imputation techniques.

It was not possible to perform a stratified analysis according to facility-level characteristics in order to quantify relationships between system-level IPC capacities (e.g. having an IPC programme or a dedicated and trained focal point, hand hygiene audits) and risk of SARS-CoV-2 infection, as most

facilities answered 'yes' to most questions in the questionnaire (see [Supplementary appendix](#), pp. 37–39). Serological titre values were collected, but were not analysed as they were reported inconsistently.

Sensitivity analyses were performed to account for uncertainties and potential biases in the data to ensure robustness of the key findings. The same statistical models described above were applied to a broader group of participants who were excluded from the main analysis (i.e. cases with either missing data on SARS-CoV-2 confirmation test results, vaccination dates, or interviewed >14 days after testing positive for COVID-19; and controls with missing or inconclusive data in either one or both COVID-19 serological tests 3–4 weeks apart, or missing

data on vaccination dates). The complete analysis plan is provided in the [Supplementary appendix](#) (pp. 56–65). All analyses were performed in the R environment [22]. Analysis codes are available on GitHub, and are publicly available at <https://github.com/WorldHealthOrganization/covid-hcworkspacecontrol>. The STROBE checklist is available in the [Supplementary appendix](#).

Results

Overall, 5501 (1757 cases, 3744 controls) health workers from 121 healthcare facilities in 21 countries were enrolled in the study between 1st June 2020 and 31st December 2021

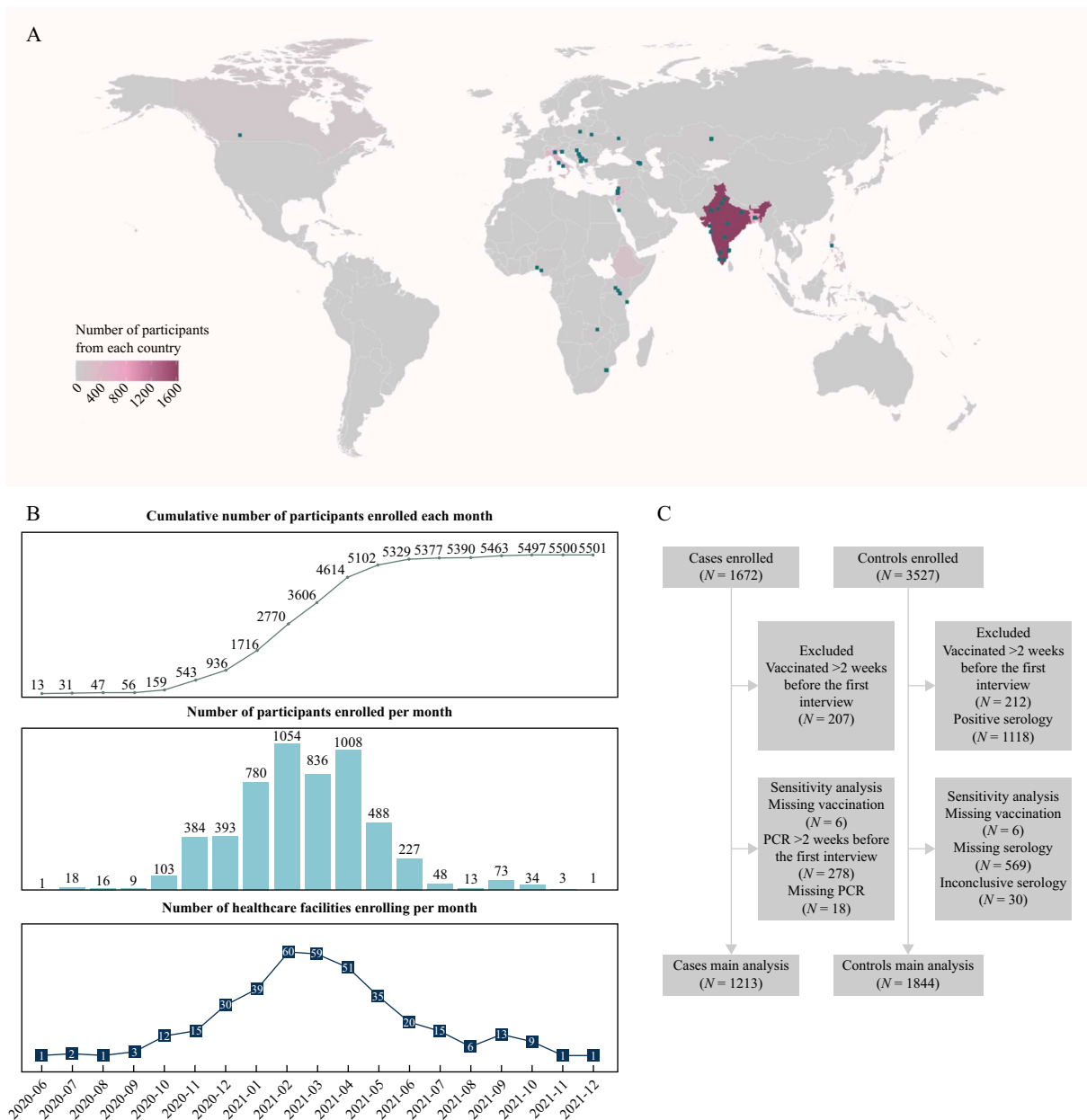


Figure 1. Characteristics of study participants enrolled. (A) Countries (pink) and healthcare facilities (green) where participants were enrolled. Numbers of enrolled participants are represented in shades of pink. (B) Number of participant enrolments over time. (C) Study participants enrolled and reasons for exclusion from the main analysis. Participants excluded from the main analysis could have had more than one reason for exclusion. PCR, polymerase chain reaction.

(Figure 1A). Most participants were enrolled between October 2020 and June 2021, prior to receipt of any SARS-CoV-2 vaccines (Figure 1B) as this was part of the exclusion criteria. Ninety-five study sites enrolled both cases and controls, and contributed 5199 study participants. Of these, 3057 (59%) were included in the main analysis (Figure 1C). The main reason for the exclusion of participants enrolled as cases was due to receipt of vaccine >14 days prior to completion of the first questionnaire (207/1672; 12%). The main reasons for the exclusion of participants enrolled as controls were positive serology (1118/3527; 32%) and receipt of vaccine >14 days prior to completion of the first questionnaire (212/3527; 6%). In 62% (1805/3057) of initial interviews, the interviewers were blinded to case/control status. Most participants were female (1970/3057; 64%), nurses (1565/3057; 51.2%), had a university education (2295/3057; 75%), and were enrolled from lower- and upper-middle-income countries (2459/3057; 80%) (Table I).

Eighty-eight percent (84/95) of healthcare facilities were tertiary care hospitals, with 48% (46/95) having <500 beds. All facilities reported high IPC capacity, with 99% (94/95) having a dedicated area for the triage and care of COVID-19 patients; and adequate availability of high-quality PPE and alcohol-based hand rub, water, sanitation and hygiene services and materials, IPC guidelines, and training. Most facilities reported having dedicated staff for COVID-19 patients (88%; 84/95), while 75% (71/95) and 73% (69/95) of facilities performed hand hygiene and IPC audits, respectively. However, only 5% (5/95) and 2% (2/95) of facilities reported having an IPC programme and/or an IPC focal point, respectively. One-half of facilities

screened staff based on active monitoring (25%; 24/95) or self-reporting (44%; 42/95) of symptoms.

General exposure risk factors for SARS-CoV-2 infection

Most participants provided care to both COVID-19 patients and non-COVID-19 patients during the 14 days prior to completing the first questionnaire (1990/3057; 65%), while the rest cared exclusively for COVID-19 patients. Fifty-four percent (1649/3057) of participants had direct close contact (within 1 m) with COVID-19 patients. A further 40% (1197/3057) and 44% (1357/3057) had contact with either materials or surfaces, respectively, in the environment of COVID-19 patients. Among participants who had direct contact with COVID-19 patients, 63% (1033/1649) had prolonged contact for >15 min and 37% (602/1649) performed aerosol-generating procedures. Regarding potential community exposure to SARS-CoV-2, 27% (822/3057) reported exposure outside of work. Fifty-five percent (1685/3057) of participants used public transport, and 77% (2336/3057) had social contact outside of work (e.g. markets, shops).

In a multi-variable logistic regression analysis of exposure risk factors, risk of infection was associated with male gender [adjusted OR (aOR) 1.24, 95% CI 1.03–1.50] and not adhering to PPE guidelines (aOR 1.67, 95% CI 1.32–2.12) (Table II). Direct close contact exposure to COVID-19 patients was associated with increased risk of infection (aOR 1.43, 95% CI 1.11–1.83), but self-reported poor adherence to hand hygiene, availability of PPE, and IPC training were not found to be associated with SARS-CoV-2 infection. The results of univariable regression

Table I
Demographic characteristics of study participants

	Cases (N=1213)	Controls (N=1844)	All (N=3057)
Sex			
Female	750 (61.8%)	1220 (66.2%)	1970 (64.4%)
Male	463 (38.2%)	624 (33.8%)	1087 (35.6%)
Age (years)			
Mean (standard deviation)	36.8 (13.0)	36.6 (11.4)	36.7 (12.1)
Median [IQR]	34.0 [18.0, 256]	34.0 [0, 73.0]	34.0 [0, 256]
Education			
Primary/secondary	316 (26.1%)	446 (24.2%)	762 (24.9%)
Tertiary/university	897 (73.9%)	1398 (75.8%)	2295 (75.1%)
Occupational role			
Medical doctor	343 (28.3%)	475 (25.8%)	818 (26.8%)
Nurse and allied health worker	602 (49.6%)	963 (52.2%)	1565 (51.2%)
Other non-patient auxiliaries	268 (22.1%)	406 (22.0%)	674 (22.0%)
WHO region			
Africa	314 (25.9%)	504 (27.3%)	818 (26.8%)
Americas	6 (0.5%)	18 (1.0%)	24 (0.8%)
Eastern Mediterranean	132 (10.9%)	261 (14.2%)	393 (12.9%)
Europe	340 (28.0%)	549 (29.8%)	889 (29.1%)
South-East Asia	409 (33.7%)	461 (25.0%)	870 (28.5%)
Western Pacific	12 (1.0%)	51 (2.8%)	63 (2.1%)
World Bank income level			
Low	80 (6.6%)	121 (6.6%)	201 (6.6%)
Lower-middle	696 (57.4%)	906 (49.1%)	1602 (52.4%)
Upper-middle	303 (25.0%)	554 (30.0%)	857 (28.0%)
High	134 (11.0%)	263 (14.3%)	397 (13.0%)

WHO, World Health Organization.

Table II

General exposure risk factors associated with severe acute respiratory syndrome coronavirus-2 infection among health workers: results of univariable and multi-variable logistic regression analysis

Characteristics ^a	Univariable			Multi-variable		
	OR	95% CI	P-value	aOR	95% CI	P-value
Sex						
Female	1.0	-	-	1.0	-	-
Male	1.29	1.08–1.53	0.004	1.24	1.03–1.50	0.026
Age	1.00	0.99–1.01	0.760	1.00	0.99–1.01	0.532
Education						
Tertiary/university	1.0	-	-	1.0	-	-
Primary/secondary	1.01	0.82–1.26	0.909	1.15	0.90–1.47	0.272
Occupational role						
Medical doctor	1.0	-	-	1.0	-	-
Nurse and allied health worker	0.78	0.63–0.96	0.020	0.87	0.68–1.11	0.268
Other non-patient auxiliaries	0.82	0.63–1.06	0.133	0.93	0.68–1.27	0.650
Exposed to COVID-19 patients within 1 m						
No	1.0	-	-	1.0	-	-
Yes	1.40	1.13–1.74	0.002	1.43	1.11–1.83	0.006
Unknown	1.14	0.83–1.55	0.416	1.13	0.82–1.57	0.460
Exposed to contaminated surfaces or materials soiled with body fluid						
No	1.0	-	-	1.0	-	-
Yes	1.20	0.98–1.45	0.071	0.91	0.73–1.14	0.420
Awareness of WHO's 'Five Moments for Hand Hygiene'						
Aware	1.0	-	-	1.0	-	-
Not aware	0.98	0.79–1.22	0.8882	0.88	0.70–1.13	0.318
Practice hand hygiene moments						
Always	1.0	-	-	1.0	-	-
Not always	1.30	1.08–1.58	0.006	1.16	0.92–1.46	0.209
Alcohol-based hand rub available at point of care						
Yes	1.0	-	-	1.0	-	-
No/not sure	0.87	0.61–1.24	0.436	0.70	0.48–1.04	0.079
Adherence to required personal protective equipment for COVID-19 patients						
Always	1.0	-	-	1.0	-	-
Not always	1.65	1.34–2.02	<0.001	1.67	1.32–2.12	<0.001
Personal protective equipment available						
Yes	1.0	-	-	1.0	-	-
No/not sure	1.02	0.77–1.34	0.905	0.96	0.71–1.30	0.792
Following IPC standard precautions when in contact with patients						
Always	1.0	-	-	1.0	-	-
Not always	1.34	1.11–1.62	0.002	1.21	0.95–1.54	0.119
Received in-person IPC training						
In-person	1.0	-	-	1.0	-	-
Only remotely/theoretical	0.83	0.67–1.04	0.102	0.83	0.66–1.04	0.106
Unsure what IPC standard precautions entail	0.61	0.46–0.81	0.001	0.56	0.41–0.76	<0.001

OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio; WHO, World Health Organization; COVID-19, coronavirus disease 2019; IPC, infection prevention and control.

^a Confounders included in the multi-variable regression but not presented in the table include: used public transport during 14 days prior to completing the first questionnaire; and had social contact outside of work during 14 days prior to completing the first questionnaire.

analysis can be found in the supplementary appendix (Table 3.3, pp. 74–75).

Specific risk factors during high-risk exposures or procedures using multi-variable logistic regression [i.e. direct close contact (within 1 m) of COVID-19 patients, and exposure to materials and surfaces in the direct patient environment] were examined. Direct close contact with COVID-19 patients was reported by 1614 participants (603 cases, 1011 controls) (Figure 2A). During these encounters, prolonged patient exposure (>15 min) was associated with increased risk of

infection (aOR 1.36, 95% CI 1.01–1.83), but the reported number of close contacts with COVID-19 patients was not associated with increased risk of infection (aOR 0.77, 95% CI 0.58–1.01). Not performing hand hygiene consistently after direct close contact was strongly associated with increased risk of infection (aOR 2.52, 95% CI 1.72–3.68).

Exposure to COVID-19 patient materials was reported by 1131 (407 cases, 724 controls) participants (Figure 2B). Being exposed to COVID-19 patient material more than 10 times was significantly associated with lower risk of infection (aOR 0.67,

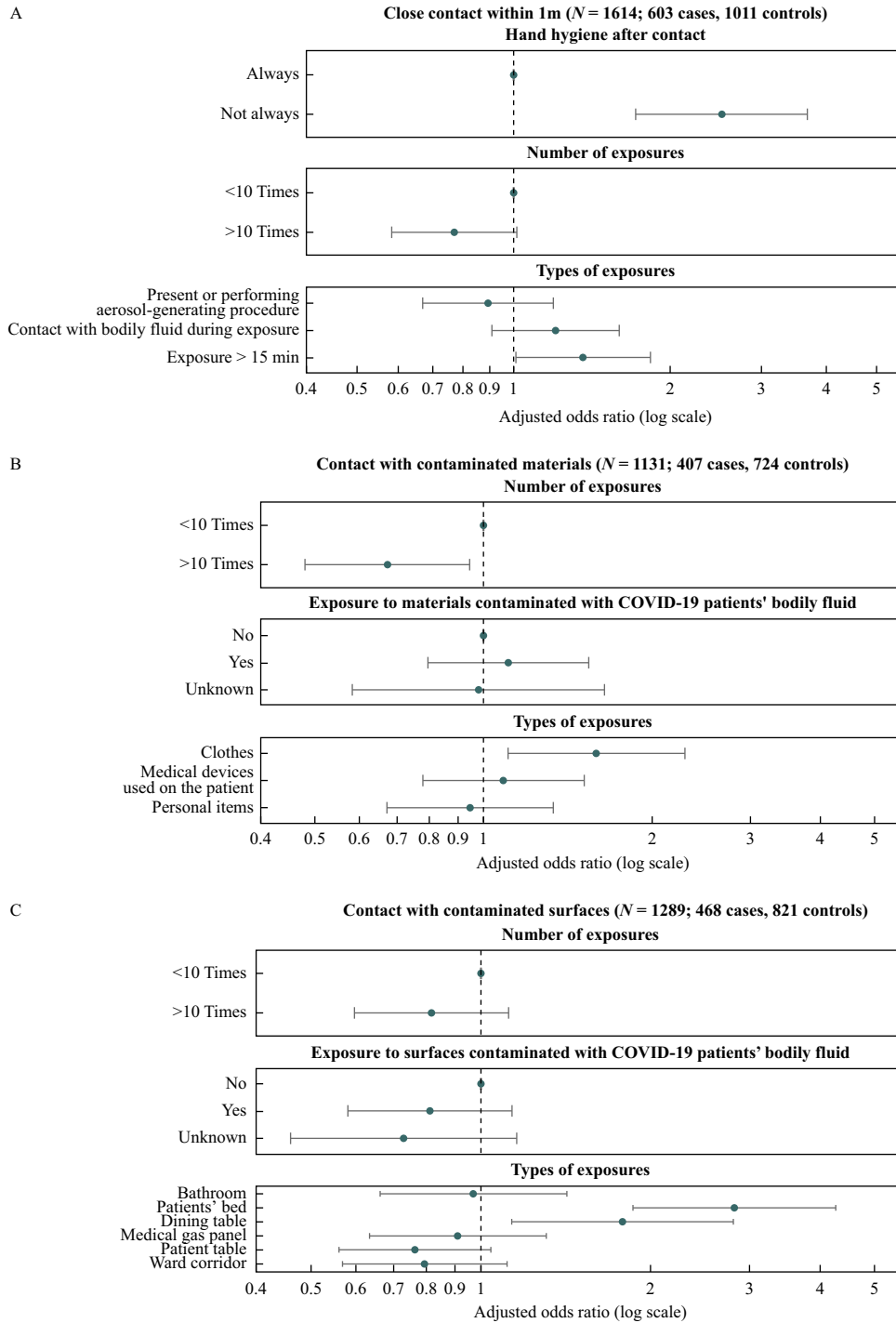


Figure 2. Risk factors associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection among health workers during high-risk procedures from multi-variable logistic regression results. (A) After direct close contact (within 1 m) with coronavirus disease 2019 (COVID-19) patients. (B) After exposure to COVID-19 patient materials (e.g. clothing). (C) After exposure to surfaces (e.g. bed, dining table) around COVID-19 patients. Confounders included in the multi-variable regression but not presented in the plot include: used public transport during 14 days prior to completing the first questionnaire; had social contact outside of work during 14 days prior to completing the first questionnaire; adherence to personal protective equipment guidelines; exposure to SARS-CoV-2 infection outside of work; and received in-person infection prevention and control training. X-axis represents the adjusted odds ratio (log scale). Horizontal bars represent 95% confidence intervals. Green points represent the adjusted odds ratio estimates. Odds ratio values from both univariable and multi-variable analyses are included in supplementary appendix (Tables 3.3–3.5).

95% CI 0.48–0.94). The type of material associated with the highest risk of infection was patient clothing (aOR 1.59, 95% CI 1.11–2.29). Exposure to surfaces close to COVID-19 patients was reported by 1289 (468 cases, 821 controls) participants (Figure 2C). Types of surfaces associated with the highest risk of infection were the patient's bed (aOR 2.86, 95% CI 1.86–4.27) and dining table (aOR 1.78, 95% CI 1.13–2.80). Exposure frequency was not associated with risk of infection. The results of univariable regression analysis are shown in the supplementary appendix (Table 3.4, pp. 76–77).

Items of PPE associated with SARS-CoV-2 infection

Most participants wore at least one item of PPE during high-risk activities. Specifically, PPE was worn during aerosol-generating procedures, prolonged close contact, and contact with materials or surfaces contaminated with potentially infectious bodily fluids by 94% (518/554), 96% (462/483) and 95% (441/463) of participants, respectively. Use of a respirator was associated with a four-fold reduction in the risk of infection (aOR 0.24, 95% CI 0.11–0.51) during aerosol-generating procedures compared with use of a surgical mask, but not during prolonged close contact or contact with contaminated materials and surfaces (Figure 3, left panel). In contrast, wearing gloves and a gown or coverall was associated with an

approximate two-fold reduction in the risk of infection (aOR 0.48, 95% CI 0.23–0.99; aOR 0.49, 95% CI 0.25–0.98, respectively) during contact with contaminated materials and surfaces (Figure 3, right panel). The results of univariable regression analysis are shown in the supplementary appendix (Table 3.5, pp. 77–78).

COVID-19 symptoms and outcomes

Three-quarters of cases reported at least one COVID-19-associated symptom. The most common symptoms reported by >50% of cases were fatigue, cough, fever, muscle ache and headache (supplementary appendix, Figure 3.1, p. 79). Two percent (57/3057) of cases were hospitalized and two participants died during follow-up.

Discussion

To the authors' knowledge, this is the largest multi-country, multi-centre, nested case–control study conducted across different resource settings to investigate both individual- and system-level factors associated with SARS-CoV-2 infection among health workers. Notably, specific items of PPE associated with risk of SARS-CoV-2 infection in this population were identified. Use of a respirator was associated with a four-fold

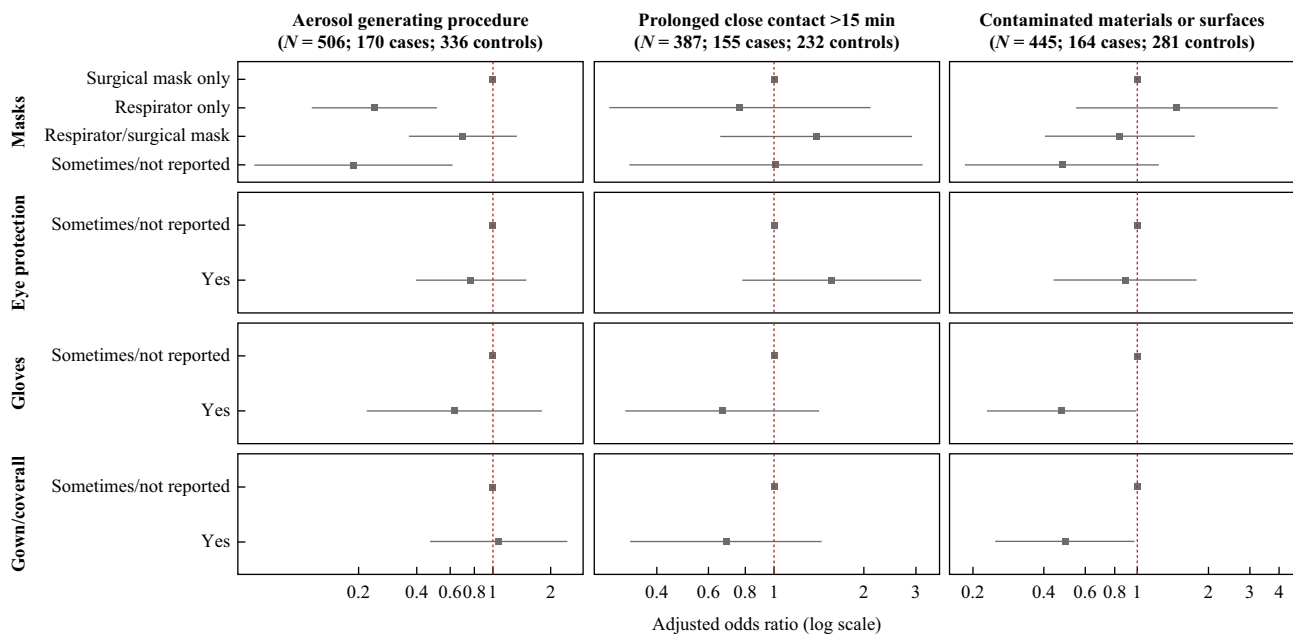


Figure 3. Personal protective equipment items and risk of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection during high-risk procedures. Three vertical panels refer to, from left to right, aerosol-generating procedures, prolonged close contact >15 min (excluding aerosol-generating procedures), and contact with contaminated materials or surfaces. Number of participants who had these high-risk exposures and had matched cases/controls from the same healthcare facility are indicated in brackets. Horizontal panels refer to the different types of mask, including respirators and surgical masks; eye protection, including goggles and face shields; gloves; and gowns or coveralls. Grey squares indicate odds ratios for wearing each item of personal protective equipment and risk of SARS-CoV-2 infection during each high-risk exposure. The accompanying horizontal grey bars indicate 95% confidence intervals for each odds ratio. The categorical variable, respirator/surgical mask, was given a value of 1 when participants chose both respirator and surgical mask options for the question on which items of personal protective equipment were worn during the respective procedures. The vertical red dashed line highlights an odds ratio of 1. Confounders included in the above multi-variable regression analyses, but not presented in the graph, include adherence to personal protective equipment guidelines, hand hygiene adherence, and received in-person infection prevention and control training.

reduction in risk of infection compared with use of a surgical mask during aerosol-generating procedures, but not during prolonged close contact or contact with contaminated materials and surfaces. Wearing gloves and a gown or coverall was associated with an approximate two-fold reduction in risk of infection during contact with contaminated materials and surfaces, after adjusting for adherence to hand hygiene during these exposures. The protective effect of wearing a gown during contact with contaminated materials/surfaces has been reported in other studies [23]. Similar to the living literature review by Chou *et al.* [2], this study found that non-adherence to appropriate PPE guidance increased the risk of infection, but the age or occupational role of the health worker did not.

Similar to other case–control studies [23], direct close exposure to COVID-19 patients was associated with increased risk of infection, even after adjusting for exposure in the community or to colleagues infected with SARS-CoV-2. The risk was higher for health workers with prolonged contact with COVID-19 patients (>15 min), suggesting that the amount of time spent caring for a patient carries more risk of infection than the number of patients visited [8,24]. In addition, recurrent exposure to COVID-19 patient material (more than 10 times) was associated with lower risk of infection. This may indicate that staff who were exposed frequently were more careful or experienced with IPC procedures. At the healthcare facility level, most participating centres reported an infrastructure such as triage, dedicated staff and areas for COVID-19 patients, sufficient and appropriate PPE, alcohol-based hand rub, water, sanitation and hygiene services, and provision of IPC guidelines and recent training to health workers. However, only 5% reported having an IPC programme, and 2% reported an IPC focal point within the facility, which mirrors findings from the 2019 WHO global survey on IPC core component implementation at the facility level, especially in low- and middle-income settings [25].

These findings highlight the crucial role played by appropriate adherence to use of PPE and hand hygiene in preventing SARS-CoV-2 infection among health workers. Most participants reported providing care to both COVID-19 and non-COVID-19 patients during the 14 days prior to completing their first questionnaire, indicating that most centres did not have adequate human resources for either type of patient. Moreover, a high proportion of health workers identified as controls (32.5%) had positive serological tests within 4 weeks of enrolment. These asymptomatic health workers may represent a silent reservoir of SARS-CoV-2 infection driving nosocomial outbreaks, as pointed out by findings in wastewater analysis during nosocomial outbreaks [19]. Hence, improving IPC measures and training remain critical to protect health workers and patients, and prevent nosocomial transmission in healthcare facilities.

A major strength of this study is the large number of health workers recruited from health facilities worldwide before the widespread use of vaccines. The large sample size and high power allowed detailed examination of specific IPC risk factors and items of PPE, and an assessment of their association with risk of infection compared with similar smaller studies. For example, smaller studies using the same protocol implemented in a major tertiary care hospital in Trieste, Italy and in Mumbai, India did not detect meaningful associations between the variables with risk of SARS-CoV-2 infection [26,27]. However, it should be emphasized that both studies also reported a high level of IPC capacity for preventing nosocomial SARS-CoV-2

transmission. The large dataset of the present study also improved the generalizability of findings to different settings, bridging evidence gaps in low- to middle-income countries. Another strength is the fact that steps were put in place to ensure data quality and consistency across sites. Implementation resources and training and coordination opportunities were offered by the WHO IPC Hub team and some WHO country offices. Classification of cases and controls was ensured by mandating two sets of serological tests (at recruitment and 3–4 weeks later) using standardized testing kits provided by WHO to all participating sites. The main cohort analysis was strictly limited to participants who satisfied the pre-specified enrolment criteria.

Other crucial health factors related to COVID-19 affect health workers, including stress, burnout and mental disorders. Moreover, these factors are multi-dimensional and touch upon the social role of health workers and their well-being (e.g. stigmatization and relationship with family members), their working conditions (e.g. strikes; temporary contracts; lack of insurance; and psychological support, violence and harassment) and the availability and distribution of health workers [1].

This study has some limitations. First, case–control studies by design are subject to recall, response, selection and interviewer bias. This study attempted to overcome these biases by limiting the recall time to 14 days, ensuring that exposures between both cases and controls were similar during control selection, and blinding interviewers to participants' case/control status. Second, while there were few missing data within questionnaires completed by the participants, there were missing serological data which prevented the inclusion of all participants in the final analysis. Of the 5199 participants recruited initially, only slightly more than one-half (53.0%) were included in the final analysis. Most excluded participants were controls (55.0% vs 30.4% of cases), mainly due to missing (16.3%) and/or positive serology (32.5%). This led to large and potentially spurious CIs for some variables, such as 'sometimes/not reported' (Figure 3) to have worn any type of mask during high-risk procedures. However, the robustness of the conclusions was assessed with a sensitivity analysis, which produced similar results (Supplementary appendix, pp. 80–87). It was also not feasible to ensure the quality of the PPE used at each participating site, and that the PPE was worn correctly as reported in the questionnaires, although all participating sites had access to the necessary information to ascertain the quality and appropriate use of PPE. Lastly, while the questionnaire was kept short to maximize participation and minimize missing data, some questions may lack granularity. For example, the subspeciality of the medical staff, and the number of aerosol-generating procedures to which each participant was exposed were not ascertained.

Several challenges were encountered when implementing this study. Despite publishing and disseminating the study protocol rapidly in May 2020, logistical issues (i.e. contractual agreements, ethical approvals, and procurement and delivery of serological kits) did not allow commencement of recruitment at most sites until October 2020. This could have resulted in a diminished observed impact of certain measures, such as IPC training. Additionally, the rapid SARS-CoV-2 vaccination campaigns rightly prioritized health workers, but decreased the number who were eligible for enrolment, especially after June 2021 (Figure 1). Stigmatization of COVID-19 also caused a high proportion of cases to decline follow-up and repeated

serological testing, which resulted in either refusal to participate or loss to follow-up.

In conclusion, this study contributes to fill a critical research gap by providing evidence about high-risk exposures for SARS-CoV-2 infection among health workers, and on most appropriate IPC measures. The findings carry important implications for IPC policies globally, particularly to maintain readiness for any COVID-19 surges and to better prepare for the next pandemic. The association of non-adherence to appropriate PPE measures and risk of infection highlights the strong need for continuing to provide IPC training, and for strengthening adherence to IPC measures in healthcare facilities [25]. All countries should ensure sustainability of efforts made during the COVID-19 pandemic, and have in place the core components for effective IPC programmes according to WHO evidence-based recommendations and endorsed by a recent resolution of the World Health Assembly [28]. Further progress is needed urgently to avoid the tragic suffering and loss of health workers and patients due to the avoidable nosocomial spread of pathogens.

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Author contributions

BA and AC conceived the study and drafted the study protocol and implementation resources. AS, BC and YM contributed to finalization of the protocol. AS coordinated the study implementation, together with the study's principal investigators, WHO regional and country office focal points in the various countries, and individual participating sites. MY developed the data collection tool and training tools for data collection and input, and led online training in sites; she also conceived the statistical analysis plan, assessed the quality of the collected data, and performed the statistical analysis. BA, AC, AS, BC, GG and YM contributed to the statistical analysis plan and verified the analysis. MY and AC drafted the first version of the manuscript, and BA and AS contributed to its writing. All authors contributed to data interpretation and manuscript review. All authors had access to all the data. BA takes final responsibility for the decision to submit for publication. The views expressed in this publication are those of the authors and not necessarily those of the funding bodies.

Conflict of interest statement

None declared.

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Data sharing statement

All analysis codes are available at <https://github.com/WorldHealthOrganization/covid-hwcacasecontrol>.

Disclaimer

The opinions expressed in this article are those of the authors and do not reflect the official position of WHO. WHO takes no responsibility for the information provided or the views expressed in this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhin.2024.04.031>.

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