

Risk Factors for Healthcare Personnel Infection With Endemic Coronaviruses (HKU1, OC43, NL63, 229E): Results from the Respiratory Protection Effectiveness Clinical Trial (ResPECT)

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Background. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) presents a large risk to healthcare personnel (HCP). Quantifying the risk of coronavirus infection associated with workplace activities is an urgent need.

Methods. We assessed the association of worker characteristics, occupational roles and behaviors, and participation in procedures with the risk of endemic coronavirus infection among HCP who participated in the Respiratory Protection Effectiveness Clinical Trial (ResPECT), a cluster randomized trial to assess personal protective equipment to prevent respiratory infections and illness conducted from 2011 to 2016.

Results. Among 4689 HCP seasons, we detected coronavirus infection in 387 (8%). HCP who participated in an aerosol-generating procedure (AGP) at least once during the viral respiratory season were 105% (95% confidence interval, 21%–240%) more likely to be diagnosed with a laboratory-confirmed coronavirus infection. Younger individuals, those who saw pediatric patients, and those with household members <5 years of age were at increased risk of coronavirus infection.

Conclusions. Our analysis suggests that the risk of HCP becoming infected with an endemic coronavirus increases approximately 2-fold with exposures to AGPs. Our findings may be relevant to the coronavirus disease 2019 (COVID-19) pandemic; however, SARS-CoV-2, the virus that causes COVID-19, may differ from endemic coronaviruses in important ways.

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Keywords. Coronavirus; HKU1, OC43, NL63, 229E; aerosol generating procedure; risk factors.

Interruption of transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to healthcare personnel (HCP) is a major clinical and public health challenge in the current coronavirus disease 2019 (COVID-19) pandemic. Uncertainty exists about the relative risk posed to HCP who participate in aerosol-generating procedures (AGPs) and about which demographic factors and behaviors influence the risk of

healthcare-associated infection. Data collected in studies on endemic coronaviruses that circulate widely in humans (strains HKU1, OC43, NL63, 229E, and HKU1) might help inform urgent questions on SARS-CoV-2 risks. Here, we report the results of a post hoc subanalysis from a cluster randomized trial.

METHODS

The Respiratory Protection Effectiveness Clinical Trial (ResPECT) was conducted at 137 outpatient sites at 7 US health systems between 2011 and 2016. Participating outpatient clinics and emergency departments were cluster-randomized for HCP to wear either N95 respirators or medical masks when positioned within 6 feet of patients with signs or symptoms of respiratory illness; however,

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when participating in AGPs, individual participants were instructed to follow study site health system policies reflecting Centers for Disease Control and Prevention (CDC) guidance, regardless of intervention group. Participants reported symptoms weekly and underwent anterior nasal and pharyngeal swabbing when ill with signs or symptoms of respiratory illness and twice at randomly selected times when asymptomatic during each respiratory virus season for 4 consecutive years. Participants self-reported adherence to personal protective equipment (PPE) weekly, which was measured as “always,” “sometimes,” “never,” and “did not recall.” Data presented are aggregated and includes all participants irrespective of type of infection acquired. Length of individual participation-time was quantified as HCP-seasons, since some HCP contributed multiple seasons of observation.

Multiplex reverse-transcription polymerase chain reaction [1] was used to detect coronavirus nucleic acid. Adherence to assigned PPE and participation in AGPs (defined by protocol as intubation, respiratory/airway suctioning, nebulizer treatment, and/or nasopharyngeal aspiration) were self-reported. Full details of the trial have been previously published [2, 3]. The primary trial was not designed or powered to specifically look at coronavirus infection as an outcome on its own, and thus our results in respect to the association of coronavirus outcomes with N95 or medical mask use should be viewed with caution. Primary and secondary outcomes were designed to look at influenza and aggregate outcomes of respiratory viruses across a number of viral etiologies (including the 4 endemic human coronaviruses). For this post hoc subanalysis, we used the per-protocol subset (those completing at least 8 weeks of follow-up) to estimate the odds of laboratory-confirmed coronavirus infection (includes symptomatic and asymptomatic infections) among participant intervention groups, using logistic regression adjusting for our cluster design. We used these same analyses to identify risk factors for coronavirus infections. Within the PP subset, a very small proportion of HCP-seasons had any missing covariate data (<1%), and those HCP-seasons for which a covariate was missing were dropped from the analysis. Adjustment for covariates was performed using a list of covariates that were prespecified in the parent trial including participant age, household members under the age of 5, and whether participants saw adult, pediatric, or both patient populations. When comparing odds of endemic coronavirus infection between participants randomized to N95 respirator vs medical mask clusters, we repeated the analysis conducted in the parent trial [2] but on laboratory-confirmed endemic coronavirus rather than aggregate respiratory virus outcomes.

ResPECT was approved by the human subjects research board at the National Institute for Occupational Safety and Health (protocol number 10-NPPTL-O5XP) and the institutional review boards (IRBs) at the 7 participating health

systems, and approved or exempted by IRBs at the analysis and sample storage sites.

RESULTS

We observed 4689 HCP-seasons in the per-protocol subset, following 2614 unique participants (mean age, 43 years; 2193 women [84%]). Among the 4689 HCP-seasons, 387 (8%) developed symptomatic or asymptomatic coronavirus infections (Table 1). In univariate analysis, younger participant age, having a household member <5 years of age, caring for pediatric patients, and performing AGPs were associated with increased odds of coronavirus infection. Increasing age significantly decreased the odds of acquiring laboratory-confirmed coronavirus infection, with odds of infection declining by 20% (95% confidence interval [CI], 12%–27%) for every 10-year increase in age. The presence of each household member <5 years of age increased the odds of coronavirus infection by 23% (95% CI, 7%–42%). HCPs who saw pediatric patients had a 57% (95% CI, 22%–101%) increased odds of coronavirus infection compared to those who saw only adult patients. Those who participated in an AGP at least once during the viral respiratory season were 105% (95% CI, 21%–240%) more likely to be diagnosed with a laboratory-confirmed coronavirus infection. HCPs with higher proportions of daily exposures to others with respiratory illness in their workplace were also at increased odds of coronavirus (6% increase in odds for each 10% increase in proportion of workdays with exposure to respiratory illness [95% CI, 1%–23%]). Sex, race, categorical occupation risk level (defined as low, medium, or high), and self-reported adherence to hand hygiene were not associated with the odds of coronavirus infection.

In multivariate analysis using all covariates that were statistically significant in univariate analyses, and 1 covariate that was not significant but that was deemed relevant, we found that only performance of an AGP (80% increase in odds [95% CI, 4%–210%]) remained statistically significant.

The adjusted odds ratio [OR] associated with acquisition of endemic coronavirus in the N95 respirator group was 0.71 (95% CI, .49–1.03). Qualitatively similar results were found in unadjusted analysis of the association of N95 respirator use on endemic coronavirus infection outcome (OR, 0.74 [95% CI, .52–1.06]). Adherence was reported on daily surveys. “Always” was reported 14 566 (65.2%) times in the N95 respirator group and 15 186 (65.1%) times in the medical mask group; “sometimes,” 5407 (24.2%) times in the N95 respirator group and 5853 (25.1%) times in the medical mask group; “never,” 2272 (10.2%) times in the N95 respirator group and 2207 (9.5%) times in the medical mask group; and “did not recall,” 85 (0.4%) times in the N95 respirator group and 69 (0.3%) times in the medical mask group.

Table 1. Odds Ratios of Laboratory-confirmed Endemic Coronavirus Infection Among Healthcare Personnel in the Respiratory Protection Effectiveness Clinical Trial (ResPECT) Per-Protocol Subset (All Years Included in Analysis)

Characteristic	With CoV (n = 387 HCP Seasons)	Without CoV (n = 4302 HCP Seasons)	Univariate OR (95% CI)	Multivariate OR (95% CI)
Age (per 10-y increase), mean	40.1	42.9	0.80 (.73–.88)	0.78 (.58–1.03)
No. of household members <5 y of age, mean	0.44	0.32	1.23 (1.07–1.42)	1.32 (.93–1.83)
Patients seen:				
Adults only	189 (49%)	2428 (56%)	Ref	Ref
Adults and children	86 (22%)	960 (22%)	1.15 (.88–1.50)	0.86 (.39–1.81)
Children only	112 (29%)	914 (21%)	1.57 (1.22–2.01)	1.06 (.49–2.18)
Sex				
Female	337 (87%)	3666 (85%)	Ref	...
Male	50 (13%)	636 (15%)	0.87 (.63–1.17)	...
Proportion of workdays with exposure ^a to patients or coworkers with respiratory illness (per 10% increase), mean	14.3%	11.7%	1.06 (1.01–1.23)	1.05 (.95–1.09)
PPE				
Medical masks	215 (56%)	2231 (52%)	Ref	...
N95 respirator	172 (44%)	2071 (48%)	0.74 (.52–1.06)	...
Categorical occupation risk level ^b (per 10% increase) ^c				
Low	96 (25%)	1220 (28%)	Ref	Ref
Medium	39 (10%)	518 (12%)	1.34 (.57–3.12)	1.21 (.90–1.40)
High	252 (65%)	2563 (60%)	1.20 (.50–2.86)	1.39 (.75–2.67)
Unreported	0 (0%)	1 (0%)
Performed an AGP ^d during season of observation				
No	314 (81%)	3741 (87%)	Ref	Ref
Yes	73 (19%)	535 (12%)	2.05 (1.21–3.4)	1.80 (1.04–3.1)
Performed intubation				
No	375 (97%)	4167 (96.9%)	Ref	...
Yes	12 (3%)	109 (2.5%)	1.16 (.59–2.07)	...
NA	0 (0%)	26 (0.6%)
Performed air suctioning				
No	353 (91%)	4060 (94.4%)	Ref	...
Yes	34 (9%)	216 (5.0%)	1.77 (1.19–2.57)	...
NA	0 (0%)	26 (0.6%)
Performed nebulizer treatment				
No	324 (84%)	3865 (89.8%)	Ref	...
Yes	63 (16%)	411 (9.6%)	1.81 (1.34–2.42)	...
NA	0 (0%)	26 (0.6%)
Performed nasopharyngeal aspiration				
No	360 (93%)	4126 (95.9%)	Ref	...
Yes	27 (7%)	150 (3.5%)	2.01 (1.27–3.04)	...
NA	0 (0%)	26 (0.6%)

Data are presented as no. (%) unless otherwise indicated. Bold indicates estimates significantly different from 1.

Abbreviations: AGP, aerosol-generating procedure; CI, confidence interval; CoV, coronavirus; HCP, healthcare personnel; NA, not available; OR, odds ratio; PPE, personal protective equipment; Ref, reference group.

^aExposure to individuals with respiratory illnesses was defined as self-reported proximity within 6 feet of a person with respiratory illness.

^bEach HCP role in the study was given a score by investigators on this project based on perceived risk of respiratory infection exposure.

^cThough this covariate did not reach statistical significance in univariate analysis, we a priori deemed this an important covariate to adjust for due to the different types of roles and risks that participants faced and included it in the multivariate model. Model estimates did not vary greatly (<2%) with its inclusion or not.

^dProcedures that constituted AGP (intubation, air suctioning, nebulizer treatment, nasopharyngeal aspiration) were treated separately in univariate models but not included in assessed multivariate models.

DISCUSSION

Our analysis suggests that with these endemic coronaviruses, the risk of HCP becoming infected with a coronavirus respiratory tract infection in high-exposure outpatient settings increases approximately 2-fold with exposures to AGPs. This finding remained significant, even when controlling for other

variables on multivariate analysis. Other investigators have found that AGPs increase the risk of HCP acquiring viral respiratory tract infections. In a systematic review, Tran and colleagues examined the risk posed by AGPs to HCP from 5 case-control and 5 cohort studies emerging from the severe acute respiratory syndrome experience [4]. Tracheal intubation

increased the risk 6.6-fold, noninvasive ventilation increased the risk 3.1-fold, and manual ventilation before intubation increased the risk of acquiring respiratory infections 2.8-fold. In the Tran et al analysis, procedures typically performed in outpatient settings (where ResPECT was conducted), such as endotracheal aspiration, suction of body fluids, nebulizer treatment, oxygen administration, manipulation of oxygen masks, insertion of nasogastric tube, and collection of sputum, were not associated with an increased risk of HCP infection. A recent article describing risk factors for developing COVID-19 among HCPs demonstrates an association with administering nebulizer treatments [5]. Given minimal previous data, our finding of increased risk of HCP infection after an AGP is particularly relevant. Our data suggest that these less invasive procedures increase risk to HCP and support the need for respiratory protection when they are performed. These data on the risk of AGPs increasing the risk of endemic coronavirus infections support the current CDC and World Health Organization guidelines for the use of N95 respirators with AGPs [6, 7].

The risk of acquiring respiratory infection among highly exposed HCP is important in the settings of both endemic and epidemic respiratory viruses. Personal protective equipment is essential to protect HCPs from the SARS-CoV-2 virus. Although the difference between N95 respirators and medical masks in providing protection to HCP against endemic coronavirus infections did not achieve statistical significance, our adjusted estimate of N95 effectiveness in this pragmatic trial (OR, 0.71 [95% CI, .49–1.03]) had a broad CI and nearly did not include 1. Thus, these data do not dismiss the possibility that N95 could be more effective than medical masks at protecting HCP against endemic coronaviruses. These data are consistent with the findings of the larger clinical trial, which included an aggregate infection outcome including infections due to 17 respiratory pathogens as a secondary endpoint. However, importantly, during the COVID-19 pandemic when risks are perceived to be higher, adherence to mask use may be higher than during our study, which was conducted during viral respiratory season in the absence of a pandemic. Our study only addresses endemic coronaviruses with the interventions as implemented in our HCP. Additional studies designed specifically to assess the effectiveness of N95 vs medical masks in preventing coronavirus infections as a primary outcome could help address this uncertainty. Given the uncertainty about mode(s) of transmission of SARS-CoV-2, potential differences between endemic coronaviruses and SARS-CoV-2, and the pragmatic nature of our trial and this post hoc assessment, our results should be interpreted with caution. Since pragmatic clinical trials may underestimate efficacy differences between intervention groups [8], these results highlight the need for additional focused research [9].

Among the important limitations of this analysis, the parent trial was not powered or designed to test the effectiveness of these interventions for endemic coronavirus infections alone, which may have led to our finding of no statistically significant difference between our interventions. This is a post hoc and unplanned analysis. The study was intentionally conducted as a pragmatic effectiveness trial and incomplete participant adherence to assigned protective devices could have led to some unprotected exposures, increasing the probability of finding no difference between interventions. Further, AGP participation was self-reported daily, which may have been less accurate than observer-reported behaviors. Many participants were nonadherent with existing healthcare policies about appropriate use of protection, which may have contributed to increased risk of endemic coronavirus infection. Participants reported wearing N95 respirators 19%, 25%, 40%, and 39% of the time for our AGPs of intubation, air suctioning, nebulizer treatment, and nasopharyngeal aspiration, respectively. Participants reported wearing medical masks 51%, 68%, 56%, and 45% of the time, respectively, for these AGPs. Given that HCP did not wear their assigned intervention during AGPs but followed the guidance of their health facility, our study does not address the relative effectiveness of N95 vs medical masks for AGPs. HCP in this study may have been infected by endemic coronaviruses through exposures outside of their workplace. Despite these limitations, we found an association between participation in AGPs and coronavirus infection. Regarding relevance to the SARS-CoV-2 virus, clinical manifestations, epidemiology, and pathogenesis of SARS-CoV-2 may differ from endemic coronaviruses, limiting the generalizability of our findings.

In summary, among HCP working in outpatient settings, participating in AGPs increased the risk of acquiring endemic coronavirus infection. While endemic coronaviruses are different than the novel coronavirus, the findings from this study suggest that infection prevention measures across the spectrum of administrative and engineering controls and PPE are important steps to minimize of the chances of occupationally acquired infections when participating in AGPs. Additional research about HCP risk of acquiring SARS-CoV-2 is needed.

Notes

Author contributions. L. J. R. and T. M. P. conceived, designed, coordinated, and supervised the study and drafted the manuscript. D. A. C., M. B., A. C. N., C. G., M. R., C. S. P., and M. S. S. designed, coordinated, and supervised the study and drafted the manuscript. D. A. C. designed the study, conceived and designed the epidemiologic and statistical analyses, and drafted the manuscript. G. G. and C. G. designed the study, conceived and designed laboratory analyses, and drafted the manuscript. N. R. designed, coordinated, and supervised the study, conceived and designed the epidemiologic and statistical analyses, and drafted the manuscript. A. B. and A. K. organized the datasets, conducted the statistical analyses, and drafted the manuscript. All authors read and approved the final manuscript.

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