SEROPREVALENCE OF COVID-19 AMONG HEALTH WORKERS IN THE KATHMANDU VALLEY, NEPAL: A LONGITUDINAL COHORT STUDY

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ABSTRACT

Coronavirus Disease 2019 (COVID-19) burden, often underestimated by case-based incidence reports, can be accurately estimated by measuring the population that has developed antibodies following an infection. Here, we report the prevalence of COVID-19 antibodies among health workers in Kathmandu, Nepal. This seroepidemiology of COVID-19 was a longitudinal survey of hospital-based health workers working in 20 hospitals in the Kathmandu Valley. A total of 800 participants were chosen in December 2020 by a two-stage cluster-stratified random sampling method and administered a questionnaire eliciting COVID-19 related history. A blood sample was also obtained from the participants and tested for COVID-19 IgG antibodies using a Chemiluminescence Immunoassay (CLIA). We then used a probabilistic multilevel regression model with post-stratification to correct for test accuracy, the effect of hospital-based clustering, and to ensure representativeness. The final analytic sample included 800 participants; 522 (65.2%) of them were female, 372 (46%) were between ages 18-29, 287 (36%) were nurses. Of the total 800, 321 (40.1%) individuals tested positive for COVID-19 antibodies. Adjusted for test accuracy and health-worker population, the seroprevalence was 38.2% (95% Credible Interval (CrI) 29.26%–47.82%). Posterior predictive hospital-wise seroprevalence ranged between 38.1% (95% CrI 30.7.0%–44.1%) and 40.5% (95% CrI 34.7%–47.0%). Our study suggested that about two in five health workers in the Kathmandu Valley were seropositive against SARS-CoV-2 by December 2020; a substantial proportion of them did not have a documented infection.

KEYWORDS

COVID-19, seroprevalence, health workers, Nepal

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INTRODUCTION

Population-based seroprevalence studies have been useful in quantifying the cumulative incidence of the coronavirus disease 2019 (COVID-19) epidemic. Nepal (population 30 million) reported its first infection of SARS-CoV-2 on January 24, 2020–the same week several countries including France, Vietnam, United States, and India reported their first infection. Since then, more than 700,000 people have been diagnosed with COVID-19 in Nepal, among which more than 10,000 have died as of September 2021.[1]

Nepal's first wave of COVID-19 infections peaked in November 2020. Although seroprevalence studies suggest that the cumulative burden of SARS-CoV-2 infection is often several-folds greater than the reported case burden[2–4], the second wave that began in March 2021 indicates that a significant percentage of the population was still susceptible to infection after the first wave.

Seroprevalence studies are helpful in estimating the true extent of viral spread because they detect seroconversion (i.e. presence of antibodies) after an infection, even among those without clinical or laboratory evidence of active disease. Based on our current understanding, in almost all infected individuals, antibodies against SARS-CoV2 appear within 3 weeks of onset of symptom.[5] Seroprevalence studies among at-risk populations like health workers may be a leading indicator of infection burden in the community. In this report, we present results of a longitudinal-cohort seroprevalence (sero-conversion) study among hospital-based health workers in Kathmandu Valley after the "first wave" of COVID-19.

MATERIALS AND METHODS

Study design and population: In this study, participants were chosen by means of a two-stage cluster-stratified random sampling method. In the first stage, we formed a sampling frame of all hospitals in the Kathmandu Valley with more than 100 staff-members (63 out of 74 hospitals, with about 25700 staff members), following which we selected 20 hospitals based on the Probability Proportionate to Size (PPS) method.[6] In the second stage, we selected 40 staff members from each of the 20 hospitals based on simple random sampling (SRS) when possible, resulting in a sample size of 800 health workers. This sample size was expected to estimate the seroprevalence with a margin of error of less than 5%. PPS with SRS ensures that each health worker in the selected hospitals has the same probability of being sampled in the study.[6]

Hospital staff (clinical as well as administrative) above 18 years of age were eligible to participate. Staff names were obtained from hospital human resources departments and randomly ordered using a spread-sheet. Hospital staff were then telephoned in that random order until 40 participants could be recruited for the study. Six hospitals were unable to provide phone numbers for staff members. At those hospitals, a convenience sample of 40 staff members was randomly sampled from among those present at the hospital on the day of sampling.

Sampling was done between December 3 to 25, 2020. Study enumerators spent 1-2 days at each study site where they administered a questionnaire to the 40 pre-selected participants after obtaining a written informed consent from each of them. The questionnaire consisted of information on demographics, symptoms, testing, contacts and travel history. Enumerators also obtained a 4 ml blood sample from each participant. Blood samples were then transported to the Biochemistry Labs at Tribhuvan University Teaching Hospital (TUTH), and tested for antibodies against SARS-CoV-2. Ethical approval for all the study sites was granted by the Nepal Health Research Council's Ethical Review Board (ERB) (approval reference number: 609).

Antibody test and validation: A chemiluminescence immunoassay (CLIA) based antibody (IgG) test manufactured by Ortho Clinical Diagnostics (Vitros CoV2G) was used to assess for the presence of antibodies against SARS-CoV-2 among the study individuals.(7) The test detects IgG antibodies against S1 spike protein of SARS-CoV-2. Details on the validation method for the antibody test are given in the supplementary appendix (section A).

Statistical analysis: The statistical analysis was done to adjust for test inaccuracy in calculating the population based seroprevalence, to account for the effects of hospital based clustering, and to make the study findings representative of the study population. To do the first, we modeled the serology test result as a Bernoulli process.(8) We then used Bayes' rule to account for the test inaccuracy by populating it with measures of test sensitivity and specificity. (9) To account for clustering at the hospital, we extended this model to a hierarchical Bayesian logistic regression model with partial pooling. To ensure representativeness of the study, we further extended this model into a

multilevel (or hierarchical) regression model with post-stratification (MRP) by including age, gender, and occupation as predictors. We then weighted estimates of seroprevalence by the proportionate weight of these predictors to calculate the final seroprevalence among health workers in Kathmandu Valley. The statistical framework for our analysis is represented as below:[2,10-14]

$x_i \sim \text{Bernoulli}(p_i*\text{sens} + (1 - p_i)*(1 - \text{spec}))$

$p_i = \text{logit}^{-1}(\text{alpha} + \alpha_h*\text{sigma} + (\text{Age\_Grp}_i + \text{Gender}_i + \text{Occupation}_i)*\beta)$

$p \sim \text{Normal}(0.2, 1)$

$\text{alpha} \sim \text{Normal}(0, 1)$

$\alpha_h \sim \text{Normal}(0, 1)$

$\text{sens} \sim \text{Beta}(71, 9)$

$\text{spec} \sim \text{Beta}(440, 2)$

$x^+ \sim \text{Binomial}(n^+, \text{sens})$

$x^- \sim \text{Binomial}(n^-, \text{spec})$

$p(y_{pred} \mid y) \sim \int_0^1 \int_0^1 p(y_{pred} \mid \text{theta})*p(\text{theta} \mid y)d(\text{theta})$

Relative Risk (RR) for group g:

$(RR_g) = p_g/p = \text{logit}^{-1}(\text{alpha} + \beta_0 + \beta_g + \alpha_h*\text{sigma}) / \text{logit}^{-1}(\text{alpha} + \beta_0 + \alpha_h*\text{sigma})$

Here, x_i is the result of the sero-survey for the i^{th} individuals, p_i is the true underlying probability of a positive test for the i^{th} individual, sens is the test sensitivity, spec is the test specificity, alpha is the fixed intercept term, sigma is the standard deviation for the hospital random effect and, α_h is the extent of deviation of the random effect in terms of sigma. β is a vector of the coefficients of the predictor variables (age group, gender and occupation). Theta represents the fitted parameters, y_{pred} is the new predicted data. Based on previous findings, we assumed a weakly informative normally distributed prior for the overall seroprevalence with a mean of 0.2 and a standard deviation of 1. We created 40 strata (4 age categories x 2 gender categories x 5 occupation categories), and calculated seroprevalence for each of these 40 strata, which we then multiplied by their respective population weights to obtain the final seroprevalence.

We implemented this probabilistic model in the Stan programming language and interfaced it in R (version 4.0.3), via the Rstan package.[15,16] Stan samples the posterior parameter space using Hamiltonian Monte Carlo (HMC) No U-Turn Sampler (NUTS). We ran 4 chains with 5000 iterations per chain and discarded the first 1000, resulting in 16,000 sampling iterations. To assess the model convergence, we used the R hat statistic, the number of effective samples, the energy parameter and visual measures. Visual model diagnostics are given in the supplementary appendix (section B).

Overall and hospital-wise seroprevalence among health workers is reported as the mean and the 95% Credible Interval (CI) of the conditional probability of seropositivity given the data. Effect sizes are reported in terms of odds or relative risks. While calculating relative risk, the largest groups (age group 18–29 years, female gender, and nurses) were considered the respective reference groups.

RESULTS

821 participants from 20 clusters (hospitals) participated in the survey. For each of the 20 clusters, we included the first 40 participants based on their order in the randomized sampling list, resulting in 800 records in our analytic sample. Of these 800 individuals, 522 (65.2%) were female, 372 (46%) were between ages 18-29, and 7 (0.9%) were 60 or above. 287 (36%) of the participants were nurses, 172 (22%) were administrative staff, 147 (18%) were doctors, 56 (7%) were laboratory and pharmacy staff while 137 (17%) were other staff with clinical or bedside roles. 529 (66%) were married, 485 (61%) had a bachelor's degree or higher while 6% had no formal education (Table 1). In comparison, based on records at the health ministry, 63% of health workers in the Kathmandu valley are females, 42% are between ages 18-29, 3% are above age 60, 30% are nurses, 36% are administrative staff and 20% are doctors.

Table 2 presents the frequency of common COVID-19 symptoms since January 2020 among seropositive and seronegative individuals. Only about 70% of seropositive individuals in our study had one or more of the specific symptoms. Even when cough (with odds of seropositivity less than 1), was included among the symptoms, only 75% of the seropositive individuals had at least one symptom. Though, 597 of the 800 participants had at least one PCR test. One hundred eighty one participants (i.e. 23%) had a positive PCR test in the past. Odds of sero-conversion among health workers who had a positive PCR test in the past were 3.02, while they were 0.34 among individuals who had a negative PCR. Among health workers who did not have a PCR test in the past, the odds of sero-conversion were 0.60 (corresponding to a probability of 37%).

Table 1: Demographic characteristics of SEVID-KaV participants based on SARS-CoV-2 antibody status

Characteristic	Overall (N = 800)[1]	Antibody Status		P- value[2]
		Negative (N = 479)[1]	Positive (N = 321)[1]	
Age Group				0.2
18-29	372	214 (58%)	158 (42%)	
30-49	355	213 (60%)	142 (40%)	
50-59	66	47 (71%)	19 (29%)	
>= 60	7	5 (71%)	2 (29%)	
Gender				0.3
Female	522	305 (58%)	217 (42%)	
Male	278	174 (63%)	104 (37%)	
Occupation				0.8
Nurse	288	167 (58%)	121 (42%)	
Doctor	147	90 (61%)	57 (39%)	
Other bedside/ patient-care role (e.g. patient transport)	137	79 (58%)	58 (42%)	
Laboratory/ Pharmacy	56	34 (61%)	22 (39%)	
Administration (including security)	172	109 (63%)	63 (37%)	
Marital Status				0.2
Married	529	319 (60%)	210 (40%)	
Unmarried	266	155 (58%)	111 (42%)	
Divorced /Separated/ Widowed	5	5 (100%)	0 (0%)	
Education				0.074
Illiterate	25	9 (36%)	16 (64%)	
Literate but no formal education	23	11 (48%)	12 (52%)	
Primary education (Grade 5 or below)	26	14 (54%)	12 (46%)	
Secondary education (Grade 6 to 12)	241	145 (60%)	96 (40%)	
Bachelor degree or higher	485	300 (62%)	185 (38%)	
Income				
Up to Rs 20,000	131	74 (56%)	57 (44%)	
Rs 20,001-50,000	271	156 (58%)	115 (42%)	
Rs 50,001-100,000	164	103 (63%)	61 (37%)	
More than 100,000	136	86 (63%)	50 (37%)	
Don't know/ can't say	98	60 (61%)	38 (39%)	

[1]n (%) [2]Fisher's exact test; Pearson's Chi-squared test

Percentages are in terms of the row total. One participant had missing occupation data and was coded as a Nurse (the largest group). 1 US$ =~ 117 Rs.

Table 2: COVID-19 related symptoms in SEVID-KaV study participants

Symptom	Overall (N = 800)[1]	Antibody Status: Negative (N = 479)[1]	Antibody Status: Positive(N = 321)[1]	Odds	p-value[2]
Fever	172	43 (25%)	129 (75%)	3	<0.001
Shortness of Breath	94	28 (30%)	66 (70%)	2.36	<0.001
Cough	277	140 (51%)	137 (49%)	0.98	<0.001
Sputum Production	77	42 (55%)	35 (45%)	0.83	0.3
Loss of Smell	141	25 (18%)	116 (82%)	4.64	<0.001
Headache	372	192 (52%)	180 (48%)	0.94	<0.001
Myalgia	257	104 (40%)	153 (60%)	1.47	<0.001
Diarrhea	79	33 (42%)	46 (58%)	1.39	<0.001
Rash	25	9 (36%)	16 (64%)	1.78	0.013
Joint Pain	115	49 (43%)	66 (57%)	1.35	<0.001

[1]n (%) [2]Pearson's Chi-squared test

Percentages are in terms of the row total. Columns add up to more than the column total because many individuals reported more than one symptom. Any report of symptoms since January 2020, when the pandemic started, is recorded as a positive. Odds indicate the odds of having a positive antibody status given a symptom.

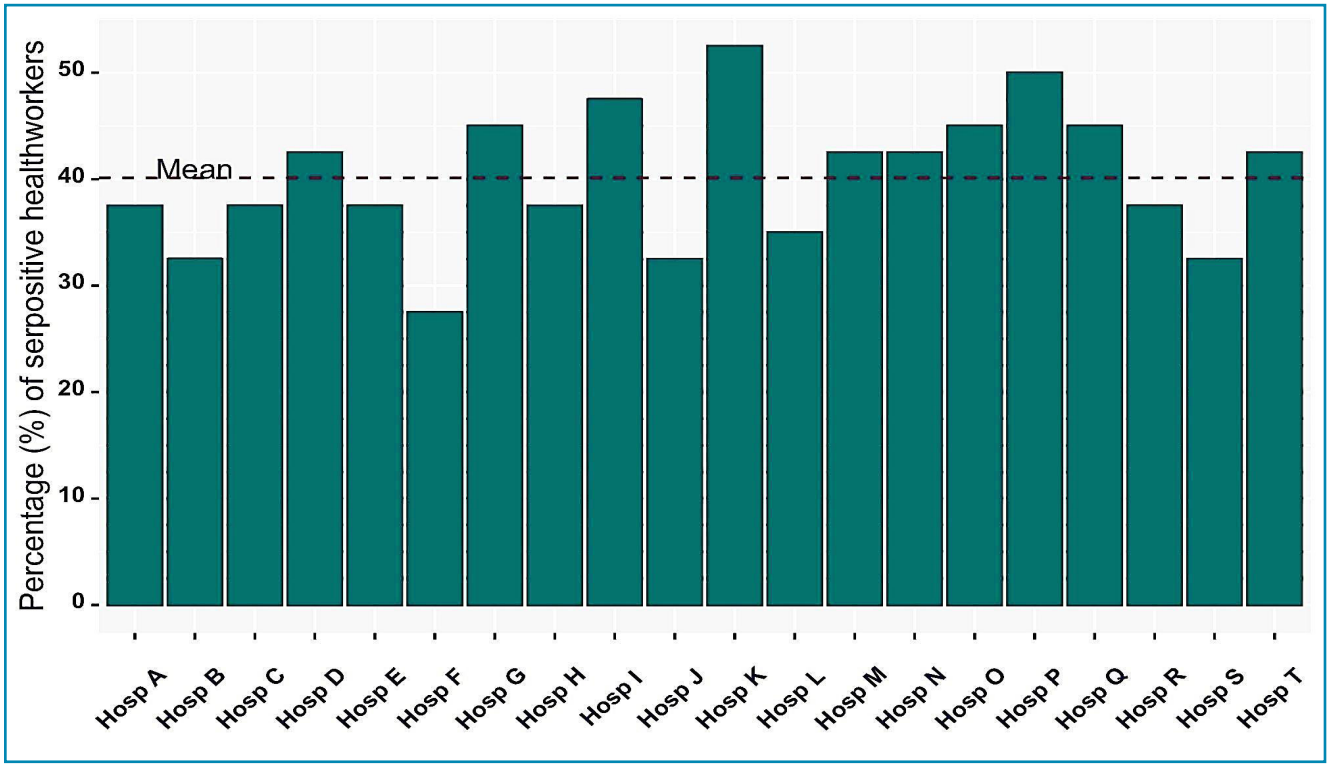

Fig. 1: Unadjusted seroprevalence of COVID-19 among health workers in the Kathmandu Valley (Dotted line represents the mean unadjusted overall seroprevalence. Cyan bars represent unadjusted seroprevalence for individual hospitals).

Table 3: Relative risk of COVID-19 seropositivity based on age, gender and health worker occupation

	Mean Sero-prevalence %	Relative Risk (95% Credible Interval)
Age Group		
18-29#	41.7	1
30-49	40.5	0.97 (0.81-1.2)
50-59	30.7	0.74 (0.48-1)
60<=	36.6	0.88 (0.31-1.6)
Gender		
Female#	42.0	1
Male	39.0	0.94 (0.75-1.1)
Occupation		
Nurse#	41.7	1
Administration	39.0	0.94 (0.72-1.2)
Bedside support	44.3	1.1 (0.83-1.3)
Doctor	40.8	0.98 (0.74-1.3)
Laboratory/ Pharmacy Personnel	41.8	0.99 (0.69-1.3)

#Reference group. Administration includes personnel that do not have a direct patient care responsibility including security personnel. Beside support refers to nurses aides and patient transporters.

Of the 800 health workers included in our study, 321 tested positive for COVID-19 antibodies. A pooled (non-hierarchical) model of the overall seroprevalence without adjusting for test accuracy (sensitivity and specificity) resulted in an unadjusted seroprevalence of 40.2% (95% CrI 36.8–43.6%). A model with no pooling between hospitals, unadjusted for test accuracy resulted in hospital-wise seroprevalence that ranged between 28.6% (95% CrI 16.17%–43.08%) and 52.1% (95% CrI 37.4%–67.0%) (Fig. 1). Adjusted for test accuracy, the seroprevalence estimate from the unpooled model ranged between 33.6% (95% CrI 18.5%–51.5%) to 62.2% (95% CrI 44.0%–80.7%).

Hospital-wise seroprevalence calculated from the fitted parameters generated from the final multilevel model with post-stratification was between 38.1% (95% CrI 30.7%–44.1%) and 40.5% (95% CrI 34.7%–47.0%) (Fig 2). Overall seroprevalence based on the final multilevel model with post-stratification, adjusted for test sensitivity and specificity was 38.99% (95% CrI 29.08%–43.91%). When weighted based on the age group, gender and occupation of health workers in the Kathmandu Valley, the seroprevalence was 38.17% (95% CrI 29.26%–47.82%). Relative risk of seropositivity was the greatest among 18–29 year olds, females and bedside care providers; however, none of these differences achieved statistical significance at the 95% credible interval (Table 3).

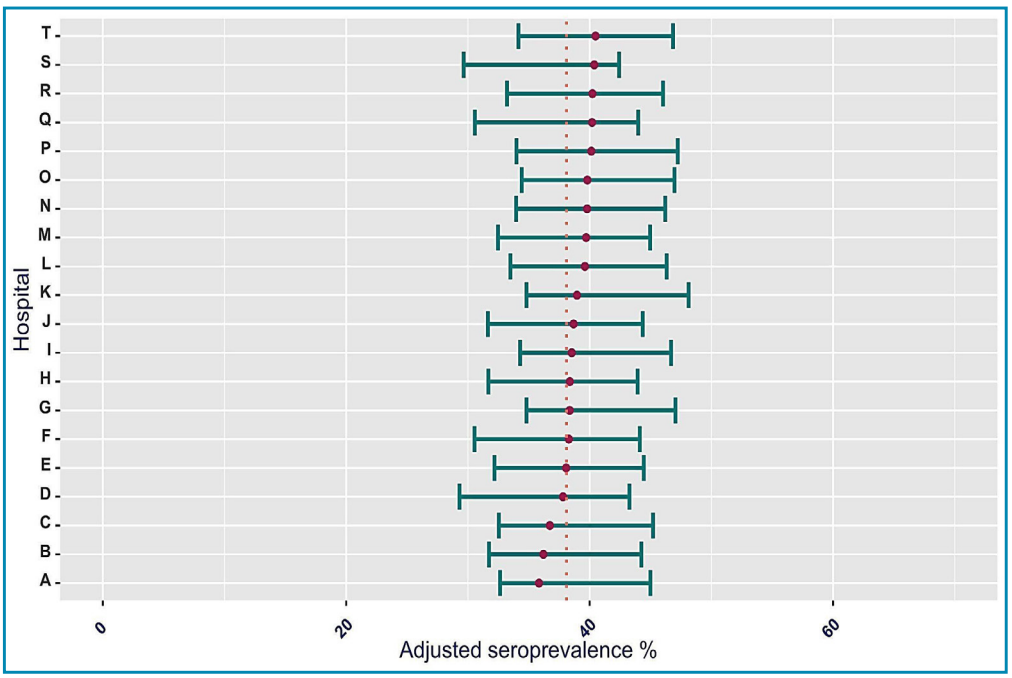

Fig. 2: Adjusted hospital-wise seroprevalence of COVID-19 among health workers in the Kathmandu Valley

Note: Red dots represent the mean seroprevalence for each hospital. Cyan error bars represent the 95% central predictive interval of the seroprevalence for each hospital. The dotted line represents the overall adjusted seroprevalence.

DISCUSSION

Our analysis of the prevalence of antibodies against SARS-CoV-2 among hospital-based health workers in the Kathmandu Valley, Nepal revealed a substantial exposure to the infection by the winter of 2020. By mid-December 2020, about 40% of the health workers had already developed antibodies against SARS-CoV-2, well before vaccination against COVID-19 had begun in Nepal. This means that these health workers had already been exposed to SARS-CoV-2 by the end of November, 2020 and subsequently developed antibodies against it. In addition, our findings showed that seroprevalence is marginally higher (trending toward statistical significance) among health workers who have a direct patient care role (nursing and bedside clinical support roles). COVID-19 seroprevalence also appears to be inversely correlated–albeit weakly-with socioeconomic indicators (educational attainment and financial status). Although a large proportion of seropositive health workers experienced at least one symptom that was consistent with COVID-19, the most specific symptoms were a loss of sense of taste or smell, fever and shortness of breath. As expected, a positive PCR test in the past increased the odds of seropositivity substantially.

Because of the nature of their work, health care workers were thought to have a potentially higher risk of exposure to SARS-CoV-2. There are reasons for such expectations. Early in the epidemic, several countries, including Nepal, faced a shortage of personal protective equipment. This might have led to greater workplace exposure to SARS-CoV-2 among health workers. In addition, early in the epidemic there was also an inadequate understanding of the risk and mode of transmission (for e.g. transmission from asymptomatic individuals and airborne transmission or higher risk of transmission in unventilated closed spaces), this could have resulted in high risk of infection among health and other frontline workers.

Although the infection burden among health workers as shown by our study was substantial, it is not clear the extent to which this burden is different from the disease burden at the level of the community. Several studies have shown that seroprevalence among health workers often tracks seroprevalence in the community.[17-21] On the contrary to earlier expectations, at least a few studies have shown that in hospitals where adequate infection control practices are in place, health workers have a low risk of contracting the infection in the workplace.[20,23] Therefore, it is unclear whether the seroprevalence seen in our study, although substantial, was the consequence of risk of exposure at the workplace or the high community burden of the infection in Kathmandu Valley. Across densely populated urban communities of South Asia, there appears to have been a significant spread of COVID-19 within the first year of the pandemic. An as yet unpublished estimate indicates that at least 17% of the overall population in and around Kathmandu Valley may have already been infected by September 2020.[23] In pockets of urban India, where COVID-19 related epidemic dynamics are similar in many ways to Kathmandu Valley, this proportion was found to be even higher.[22–24]

The 38% seroprevalence among the valley's 25,000 or so health workers indicates that about 10,000 had contracted the infection by the end of November 2020. However, official reports indicate that until then, only about 2500 of them had been diagnosed.[27] This is even while health workers have comparatively better access to testing–many facilities in Kathmandu routinely test their staff on a periodic basis. In fact, about 80% of the health workers in our sample had already had at least one PCR test as part of routine surveillance. The four fold gap between cases and infections is partly explained by the fact many individuals who contracted the infection appear to have developed no symptoms at all, or experienced mild symptoms for which they did not seek testing. In the general population, the gap between cases and infections could be even higher as they have poorer access to testing services, or may not seek care in the first place.

Our study has several strengths. First, the study was designed to be representative of all the hospital based health workers in the Kathmandu Valley. As our comparison with the overall health worker population of Kathmandu shows, our sampled population appears to well represent Kathmandu's health workers based on their age group, gender and occupational group. In addition, our study post-stratified and weighted seroprevalence based on these demographic variables to make the findings representative of the study population. The fact that post-stratification resulted in less than a percentage difference between the un-weighted and weighted seroprevalence means that our study sample was remarkably representative of the overall health worker population. Our methodology allowed for an easy correction of test accuracy. The study sampled more than 3% of the study population. The comparatively large sample size, combined with the hierarchical statistical framework allowed for

more accurate estimates of seroprevalence. The longitudinal cohort design of this study means that it will allow us to study not only the temporal variation of seroprevalence but also to study antibody decay in the future.

A major limitation of this study is our measure of test accuracy. Our unadjusted measure for sensitivity was 82% while it was 90% based on the manufacturer's data alone. It is possible that some of the PCR test results that we used to identify positive controls were falsely positive, especially among individuals who did not have a clinical diagnosis of COVID-19. To account for this limitation, we derived strongly informative Bayesian priors from the manufacturer's data and allowed them to influence our final calculation of test accuracy. Because of this, our measure of the test accuracy in the final model—with an 89% sensitivity and greater than 99% specificity closely matches manufacturer's data (supplementary appendix). The added benefit of our validation data may be that it may reflect upon local testing conditions. Surveys like these might be biased because individuals who agree to participate in such surveys may have a greater tendency to seek care, or may be at a higher risk. In our survey, 40% of those invited agreed to participate and an overwhelming majority of those who declined cited scheduling conflict as the reason for not participating. In addition, unadjusted seroprevalence among those who had not had a PCR test in the past (correlating to health care seeking behaviour and risk), was 37%, meaning that our survey sample was fairly well balanced.

A significant proportion of health workers in Kathmandu Valley appeared to have been infected with COVID-19 by the end of 2020. Although it is not entirely clear to what extent health workers were infected at the workplace, these seroprevalence figures still warrant a reassessment of infection control practices at Kathmandu's hospitals. Future waves of this study will be useful in assessing the progress of the epidemic over time, and now that a sizable proportion of health workers has been vaccinated, future studies could also generate insight on the real world evidence of vaccine efficacy.

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