Pre exposure Hydroxychloroquine use is associated with reduced COVID19 risk in healthcare workers

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Abstract

Background: While several trials are ongoing for treatment of COVID-19, scientific research on chemoprophylaxis is still lacking even though it has potential to delay the pandemic allowing us time to complete research on vaccines.

Methods: We have conducted a cohort study amongst Health Care Workers (HCW) exposed to COVID-19 patients, at a tertiary care center in India where there was an abrupt cluster outbreak within on duty personnel. HCWs who had voluntarily taken hydroxychloroquine (HCQ) prior to exposure were considered one cohort while those who had not were considered to be another. All participants with a verifiable contact history were tested for COVID-19 by rtPCR. The two cohorts were comparable in terms of age, gender, comorbidities and exposure. The primary outcome was incidence rates of rtPCR positive COVID-19 infection amongst HCQ users and non - users.

Results: 106 healthcare workers were examined in this cohort study of whom 54 were HCQ users and rest were not. The comparative analysis of incidence of infection between the two groups demonstrated that voluntary HCQ usage was associated with lesser likelihood of developing SARS-CoV-2 infection, compared to those who were not on it, $X2=14.59$, $p<0.001$. None of the HCQ users noted any serious adverse effects.

Conclusions: This study demonstrated that voluntary HCQ consumption as pre-exposure prophylaxis by HCWs is associated with a statistically significant reduction in risk of SARS-CoV-2. These promising findings therefore highlight the need to examine this association in greater detail among a larger sample using Randomised Controlled Trials (RCT).

Keywords : Covid19, hydroxychloroquine, pre-exposure prophylaxis

Introduction

SARS-CoV-2 is a positive sense RNA virus of the family coronaviridae and the etiological agent responsible for the novel pneumonia (COVID-19) which triggered an outbreak towards the end of 2019 in Wuhan, China. Since then, there has been an unprecedented spread of the disease and COVID-19 was declared a 'global pandemic' by the WHO on March 11, 2020. As of May 24, 2020 it has affected 5.4 million people and caused 344,419 deaths.(1)

In a rapidly evolving situation such as this, we have often had to resort to repurposing old drugs to expedite the process of prevention or treatment of an unfamiliar disease. For treating viral illnesses, often there is a "one bug - one drug" approach which however fails in times of emerging and re-emerging infections. This is especially true during pandemics - when drug discovery races against time. An alternative approach is, to use a broad spectrum antiviral as a pandemic tool.(2) To this effect, even before this recent crisis, at least 108 Broad Spectrum Antivirals (BSA) had already been identified that had shown activity against 78 viruses.(3) These BSAs include 4-aminoquinoline compounds (chloroquine, hydroxychloroquine, amodiaquine) amongst others and have been known to prevent viral entry into host cell.(3),(4) In this study we have chosen to focus on Hydroxychloroquine - particularly it's role, as an antiviral, in prevention of COVID-19.

Hydroxychloroquine (HCQ) is a derivative of Chloroquine (CQ), formulated by introducing a hydroxyl group into CQ and was demonstrated to be much less (~40%) toxic than CQ in animals(5). Both share similar chemical structures and mechanisms of action as a weak base and immunomodulator and have exhibited, in vitro, potent antiviral properties against various viruses.(3)

They are both concentrated in organelles with low pH like the lysosomes and endosomes - hence are also called lysosomotropic agents.(4) CQ increase lysosomal pH and prevent its fusion with autophagosomes in vitro.(6) It can also inhibit endosomal acidification, thus preventing viral entry into host cells. (7) A proposal to use CQ as a candidate drug for influenza virus was al-

ready in place. In fact in Mouse models, CQ and its derivative HCQ had already been used successfully against Avian Influenza [8]. However this success was unfortunately not replicated in Influenza A or B and RCTs[9] failed to demonstrate any preventive role in them.

In the case of Coronaviruses, for SARS CoV1 , CQ and its derivatives were found to show strong antiviral properties in vitro. Apart from interfering with lysosomal and endosomal activities, it also inhibits terminal glycosylation of ACE2 receptor [10] which is involved in viral entry. [11],[12] Impaired terminal glycosylation of ACE2 may reduce the binding efficiency between ACE2 on host cells and the SARS-CoV spike protein.[13]Moreover, Both CQ and HCQ blocked the transport of SARS-CoV-2 from early endosomes to early lysosomes,[14] which appears to be a requirement to release the viral genome as in the case of SARS-CoV[15]

Similar to SARS CoV1, COVID-19 also utilizes the surface receptor ACE2[16] for cellular entry. In vitro data have also demonstrated that CQ as well as its derivative HCQ are potent inhibitors of SARS CoV 2.[14]In spite of it's in vitro success in inhibiting SARS-CoV-2, much like in the case of SARS-CoV-1 clinical trials have failed to show any benefit of HCQ as a therapy for SARS CoV2 infection[17].

However, data on its Prophylactic role is still incomplete. Noting the in vitro data and theoretical benefits of HCQ usage, ICMR had proposed its prophylactic use for Health Care Workers in India. [18]

This cohort explores the usage of HCQ in a tertiary health care center in India amongst healthcare workers and investigates its prophylactic potential in prevention of COVID-19 infection.

Methods

Study design and patient selection

This is a cohort study based on an online survey of 106 health care personnel, who worked at Medical College, Kolkata, a tertiary care teaching hospital in India, dealing with COVID-19 patients, in the first two weeks of May, 2020. In the given period, a cluster outbreak of cases

amongst HCWs in this hospital had occurred - with about 28 HCW testing positive over a period of two weeks.

Since late March, Indian Council of Medical Research (ICMR) [18], which is the apex body of medical research in India, has proposed consumption of HCQ for prophylaxis against COVID-19. In accordance with that guideline, some of the HCWs were voluntarily on Pre-exposure HCQ prophylaxis whereas few others were not. After the outbreak was identified, all those who fulfilled the contact criteria were quarantined and tested for COVID-19 between Day 7-14 th of suspected exposure as per Ministry of Health and Family Welfare (MoHFW), Government of India, guidelines[19]. The end results of these tests were recorded and COVID-19 positive health care workers were sent for isolation and treatment to appropriate facilities after proper contact tracing.

We conducted an online survey amongst exposed health care workers after their test reports were available. To be included in the survey the participant needed to be a Health Care Worker, currently working at the tertiary care centre and on duty at the same centre during the last 1 month preceding the survey, and was tested for COVID-19 by rtPCR in the same hospital. (Figure 1)

Two cohorts of HCWs were identified: Cohort 1, which included all the health care workers who were contacts of COVID-19 positive cases & were tested for SARS-CoV-2 Infection in the hospital during the one month period, and history of intake of at least the loading dose of hydroxychloroquine prophylaxis as per ICMR guidelines[18].

Cohort 2, all the health care workers who were contacts of COVID-19 positive cases and were tested for SARS-CoV-2 Infection in the hospital during the same one month period, and had either no history of hydroxychloroquine prophylaxis or had history of inadequate intake of HCQ as per ICMR guidelines[18].

The exclusion criteria were refusal to give consent for the study, not being a contact of COVID-19 positive case as per definition given by the National Centre of Disease Control, India (NCDC)[19].

The outcome of Interest was to see whether voluntary HCQ prophylaxis was related to positivity rates by rtPCR in Health Care Workers.

Testing for SARS-CoV-2 infection

Detection of SARS-CoV-2 in clinical specimens were done by RT-PCR using TaqPath COVID-19 Combo Kit (Applied Biosystems).The real time assay uses the TaqMan fluorogenic probe based chemistry that uses the 5´ nuclease activity of Taq DNA polymerase and enables the detection of a specific PCR product as it accumulates during PCR cycles. COVID-19 Real Time PCR Assay Multiplex-Multiplexed assays that contain three primer/probe sets specific to different SARS-CoV-2 genomic regions and primers/probes for phage MS2 (Internal process control for nucleic acid extraction)[20]. Samples with a result of SARS-CoV-2 Inconclusive were tested again and all were found to be negative and thus, were treated as negative (Table 1).

Sample size

According to available publications, a total of 2,082[21] out of the 2.53 million healthcare workers[22] were found to be affected by COVID 19 across India. Taking this data into consideration, we anticipated that the prevalence rate will be 0.08% amongst the health care workers. Using a test of proportion, a two sided alpha of 0.05 and power 99.7% we estimated that the effective sample size was 82 participants. After the internet based online survey, and necessary exclusion and inclusion as per criteria, a sample size of 106 participants was considered.

Data collection

An internet-based cohort study was designed where participants volunteered to provide data either on an online form or over the telephone. The online survey form was circulated via online messenger services amongst health care workers who were encouraged to recirculate the same amongst their colleagues. After satisfying the inclusion criteria, a total of 106 participants were considered.

The survey included data on demographic profile like age, sex, presence of comorbidities (defined as Hypertension, Diabetes, Coronary Artery Disease, Chronic Kidney Disease & COPD),

[23],[24],[25]and use of hydroxychloroquine prophylaxis as per ICMR guidelines[19]. Data on type of exposure, nature of contact, use of PPE was also collected in the survey.

Statistical analysis

Data was analysed by means of R Software and Stata 12 for Windows. Statistical analysis was performed by using test of means of two populations viz Felch two independent samples T-test,Categorical Data Analysis in the form of contingency tables, partial contingency tables, Chi-squared tests of independence Chi-squared test of homogeneity, large sample tests of proportion viz one sample test of proportion and two sample test for proportions.

Controlling for possible confounders was done by stratification.

A P value of less than 0.05 was considered statistically significant.

Result

The two cohort groups of those taking hydroxychloroquine and those not taking hydroxychloroquine were comparable in terms of age, gender, degree of exposure and type of exposure and comorbidities. (Table 2). The mean number of COVID-19 cases with whom the workers had come in contact was also found to be the same in the two groups by a Welch two sample t-test which was found to be 3. The comparative analysis of incidence of Infection between the two groups demonstrated that the rate of positive incidence of SARS-CoV-2 on HCQ pre-exposure prophylaxis was significantly less than non-HCQ cohort, $X2=14.59$, $p<0.001$. This result suggests participants who voluntarily took HCQ were observed to be less likely to develop Covid-19.

Adverse effects, mostly mild, were noted in 29.8% of those on HCQ Prophylaxis (Chart 1), thus corroborating previous treatment trials [26]. Among those taking hydroxychloroquine prophylaxis, GI upset was found to be the most common adverse effect by paired proportion tests.

Discussion

The COVID-19 pandemic has put healthcare systems across the world in crisis with significant social and economic burden on countries. A number of clinical trials[27] are underway to test the efficacy of several repurposed drugs including chloroquine (CQ), hydroxychloroquine (HCQ), ivermectin, remdesivir, ritonavir/lopinavir for treatment of COVID-19. None have so far shown exceptional results. [28],[29],[30]. Of these, although HCQ has gathered particular worldwide attention based on in vitro results that demonstrate efficacy against SARS-CoV-2, there is now mounting evidence that HCQ does not offer any significant additional clinical benefit for the treatment of hospitalised COVID-19 patients, and may even be harmful [31] when used in conjunction with antibiotics such as azithromycin.

Although unprecedented progress has been made amidst this pandemic towards development of vaccines, including three candidate vaccines already in clinical trials, most estimates place the timeline for the launch of a safe and effective vaccine at least more than a year away. This highlights the need for possible alternative vaccines for preventing COVID-19. Chemoprophylaxis has been demonstrated to be a successful modality in preventive medicine in a number of other infectious diseases including malaria, HIV and influenza. A mathematical model[32] exploring effectiveness of prophylaxis vs treatment in an Influenza pandemic predicted that targeted prophylaxis could delay the onset of a pandemic by 6-18 months during which effective vaccines against the disease could be developed. However, despite chemoprophylaxis being a promising modality, research on this subject in the context of COVID-19 is currently a missing link.
The first in vitro data on prophylaxis against COVID-19 by HCQ or CQ was put forward by Yao et al[33] In this study, HCQ was found to be more potent than CQ in achieving EC50. Several other in vitro studies [14],[34] found a preventive role for CQ/ HCQ. As discussed in the introduction of this article, COVID-19 initiates viral entry through a surface ACE2 receptor, initial viral replication is followed by systemic inflammation. CQ/ HCQ can prevent viral entry has been demonstrated by Wang et al [34] through their time-of-addition studies.

Based on these encouraging preclinical trials and supported further by preliminary internal observational studies [35], ICMR, which is the key government body handling India's COVID response, recommended the use of HCQ by high risk individuals such as HCW for prevention of COVID-19. Given the well-established safety profile in rheumatology practice with HCQ being safe even during pregnancy, ICMR's recommendation is justified, taking into consideration the substantial risks faced by healthcare workers.

The current cohort study therefore aimed to investigate if hydroxychloroquine could be effective as a pre-exposure prophylaxis for COVID-19 among high risk individuals such as healthcare workers. This results from this study, has demonstrated that voluntary consumption of HCQ as prophylaxis among high risk individuals was associated with a significantly reduced risk of testing positive for COVID19 as compared to individuals who did not volunteer to take HCQ $X2=14.59$, $p<0.001$. To minimize confounding factors, both the cohorts were balanced in terms of age, gender, comorbidities, type and degree of exposure. Incidentally, one COVID-19 positive participant who was a long-term user of HCQ for Rheumatoid Arthritis, reported discontinuing the drug 1 month prior to exposure. It was also observed that among HCQ takers exposed to a symptomatic contact, only 9.38% were positive whereas among non HCQ takers exposed to a symptomatic contact, 54.55% tested to be positive. Similarly, it was seen that proportions of those testing to be positive were less in HCQ takers among those having a face to face contact, direct contact and environmental contact. Those who used recommended [36] personal protective equipment (PPE), even among them, HCQ takers had a lesser proportion of positive cases (7.69%) than those not taking HCQ prophylaxis(34.78%). These observations need to be further analyzed by future studies. (Table 3).The current study also validated the known safety profile for HCQ with no serious adverse events reported by the participants. This promising data represents the first clinical evidence on the potential role of a chemoprophylactic agent.

This study is however limited by - small sample size, non randomised and observational nature meaning that it is not possible to exclude unmeasured confounding factors. Therefore, despite a very strong statistical association, a cause-effect relationship can not be inferred. This data also

applies only to the young , healthy individuals with no or limited relevant underlying health conditions, reflecting the demographics of health care workers . Although these limitations warrant a conservative interpretation of our findings, the statistical significance needs to be explored further. Thus, we recommend further validation through large scale RCT to interrogate the significant association between voluntary HCQ consumption and reduced clinical risk of contracting COVID-19 that emerged from this study.

Conclusion

In this cohort study involving healthcare workers who had been exposed to SARS-CoV-2, voluntary pre-exposure Hydroxychloroquine use was associated with a statistically significant lowered risk of testing positive for SARS-CoV-2. No serious adverse effects were found among those taking HCQ Prophylaxis.

Limitations

Non random sampling was done based on a voluntary response online survey and thus sampling bias and recall bias might be present in the data set. All confounding factors could not be measured. Among those not taking HCQ a higher number of positives might be because of their risk taking behaviour that prevents them from taking prophylaxis and protective measures as well. On the contrary it might be so that there is a false sense of protection among HCQ takers that predisposes them to more risk-taking behavior. Blinding was not done at any level. The adverse effects which require special assessment like bradycardia and prolonged QT interval could not be recorded. Adverse effect data was based solely on patient history.

Other information

Funding

This was a non-sponsored study with no funding.

Ethical consideration

The research protocol was approved by the institutional ethics committee and all participants gave written informed consent.

Data was redacted and anonymized data was stored in password protected computer.

Disclosure Conflict of interests

The authors had no conflict of interests in this study and have nothing to disclose, as per ICMJE disclosure forms.

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Tables, charts and figures

Table 1: Result interpretation for patient samples[20]

OR-F1ab	N gene	S gene	MS2	Status	Result	Action
NEG	NEG	NEG	NEG	Invalid	NA	Repeat test. If the repeat result remains invalid, consider collecting a new specimen.
NEG	NEG	NEG	POS	Valid	SARS-CoV-2 Not Detected	Report results to healthcare providers. Consider testing for other viruses.
Only one SARS-CoV-2 target = POS			POS or NEG	Valid	SARS-CoV-2 Inconclusive	Repeat test. If the repeat result remains inconclusive, additional confirmation testing should be conducted if clinically indicated.
Two or more SARS-CoV-2 targets			POS or NEG	Valid	Positive SARS- CoV-2	Report results to healthcare providers and appropriate public health authorities.

Table 2: Baseline characteristics of participants in the two cohort groups

Parameters	*Cohort 1 (HCQ takers)*	*Cohort 2 (Non HCQ)*	*p value**
	N=54	*N=52*	
Age (mean ± SD)	26.46 ± 3.93	27.71 ± 7.24	0.13
Gender			
Male	28 (51.85%)	24 (46.15%)	0.22
Female	26 (48.15%)	28 (53.85%)	
Degree of Exposure			
Face to face contact	51 (94.44%)	41 (78.85%)	0.85
Direct contact	29 (53.70%)	22 (42.31%)	0.70
Environmental contact	23 (42.59%)	19 (36.54%)	0.28
Type of Exposure			
Asymptomatic contact	22 (40.74%)	19 (36.54%)	0.48
Symptomatic contact	32 (59.26%)	33 (63.46%)	
Comorbidities	2 (3.70%)	2 (3.85%)	0.92

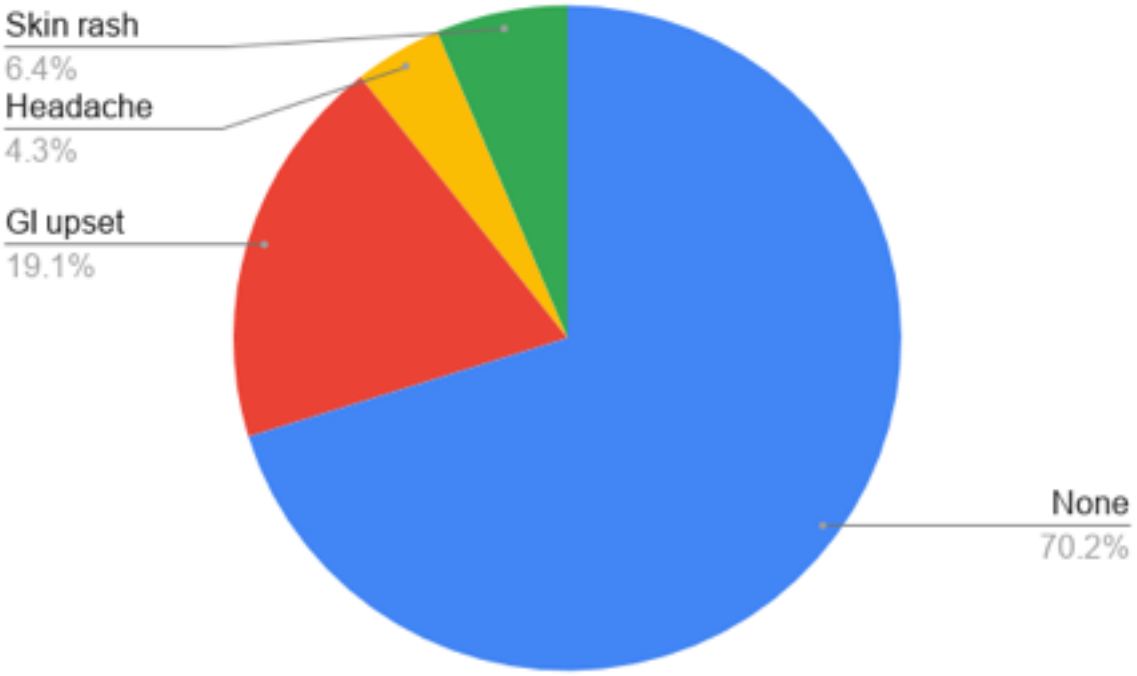
*Continuous data was compared using t-test and categorical data was compared using Chi-squared test for homogeneity.

Table 3: Two way frequency tables showing distribution of COVID-19 test results in the two cohort groups after restricting observations for different parameters

Parameters		*COVID-19 +*	*COVID-19 -*	*TOTAL*
Symptomatic contacts	HCQ +	3 (9.38%)	29 (90.63%)	32 (100%)
	HCQ-	18 (54.55%)	15 (45.45%)	33 (100%)
Face to face contact+	HCQ +	4 (7.84%)	47 (92.16%)	51 (100%)
	HCQ-	16 (39.02%)	25 (60.98%)	41 (100%)
Direct contact+	HCQ +	3(10.34%)	26(89.66%)	29(100%)
	HCQ-	11(50.00%)	11(50.00%)	22(100%)
Environment contact+	HCQ +	0(0.00%)	23(100%)	23(100%)
	HCQ-	8(42.11%)	11(57.89%)	19(100%)
Recommended PPE use*	HCQ +	3(7.69%)	36(92.31%)	39(100%)
	HCQ-	8(34.78%)	15(65.22%)	23(100%)

*Recommended as per guidelines on rational use of personal protective equipment (PPE) in a hospital setting by the Ministry of Health and Family Welfare, Government of India[37].

Chart 1: Pie chart showing the adverse effects among those taking HCQ Prophylaxis



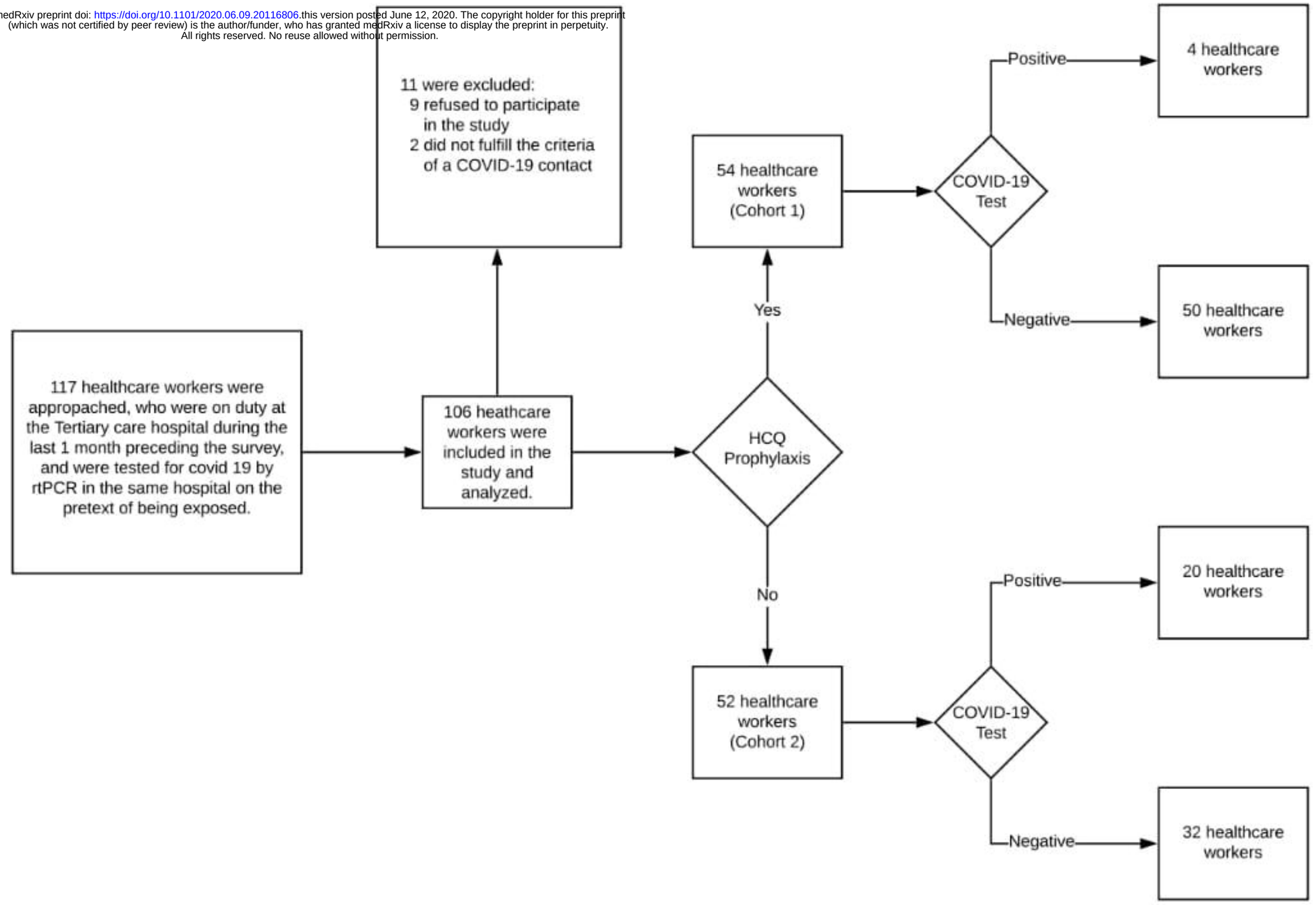


Figure 1: Participant flow chart showing the study cohort.