

Rapid Evidence Review

Clinical evidence on the use of
pharmacological prophylactic therapy in
healthcare workers or contacts of cases of
COVID-19

Version 3, 1st May 2020



**National Centre for
Pharmacoeconomics**
NCE Ireland



Prepared by the COVID -19 Evidence Review Group *with clinical contribution provided by Prof. Ellen O’Sullivan, Consultant Anaesthetist, St. James Hospital.*

Key changes (highlighted in yellow) between version 2 (20th April 2020) and version 3 (1st May 2020): fourteen additional clinical trials registered which will examine the use of hydroxychloroquine (HCQ) as pharmacological prophylaxis for HCWs. Ten additional clinical trials registered which will examine the use of other products as prophylaxis for HCWs. The results from one single arm interventional trial from Korea reporting on the use of HCQ as PEP in a long term care facility.

The COVID-19 Evidence Review Group for Medicines was established to support the HSE in managing the significant amount of information on treatments for COVID-19. This COVID-19 Evidence Review Group is comprised of evidence synthesis practitioners from across the National Centre for Pharmacoeconomics (NCPE), Medicines Management Programme (MMP) and the National Medicines Information Centre (NMIC). The group respond to queries raised via the Office of the CCO, National Clinical Programmes and the Department of Health and respond in a timely way with the evidence review supporting the query.

Summary

Infection among healthcare workers (HCWs) places an extra burden on healthcare environments at a crucial time due to staff absence and spread to family members. Healthcare workers who are front facing/ have regular patient contact, have been identified as a priority case for testing in Ireland and the infection rate among HCWs is approximately 28% of all cases confirmed to date [12]. One study from China describes prophylaxis using umifenovir however this was a case control study and several biases were noted including the retrospective design, the potential selection bias because the collection of data was through telephone calls and the awareness of the population to treatment options available [5]. It should also be noted that umifenovir, an anti-viral (fusion inhibitor) used mainly in Russia and China for treatment of influenza, is not licensed or currently available for use in Ireland. Also, one single arm interventional trial examining the use of hydroxychloroquine (HCQ) as PEP in patients and care workers in a long term care facility in Korea has been published [15] however this study also has several limitations (single arm, no control group, lack of detail provided on potential confounding factors), and the authors could not conclude that PEP is effective for prevention of COVID-19 in close contacts.

Two systematic reviews have been published, the first of which examined the role of chloroquine (CQ) and HCQ in preventing the spread of COVID-19 [13]. The review concluded that there was no evidence which supported the use of these products as prophylactic treatments for COVID-19. The second systematic review published examined the use of HCQ and has not been peer reviewed [14]. The authors also highlight that due to the toxicity profile, chances of overdoses and poisoning can pose serious health threats if HCQ is used widely and therefore reason against the use HCQ as prophylaxis both in the general population as well as HCWs.

No studies have been completed to date with treatments including HCQ or lopinavir and ritonavir. There are 29 clinical trials (n=28 interventional and n=1 observational) either commenced or registered to commence, examining the use of HCQ for prophylaxis in HCWs or close contacts. One study is registered in Ireland (CROWN-CORONATION). There are 20

clinical trials (n=17 interventional and n=3 observational) commenced or registered (with clinicaltrials.gov or the Chinese clinical trial register (www.chictr.org.cn)) to commence which will examine the use of other products as prophylaxis for HCWs or close contacts.

Conclusion

There is currently no robust evidence to support the use of prophylactic therapy in healthcare workers or those in contact with cases of COVID-19.

A number of trials are ongoing examining the use of the following compounds, as prophylactic therapies in COVID-19 (hydroxychloroquine, chloroquine, lopinavir/ritonavir, inhaled nitric oxide gas, BCG vaccination, emtricitabine/tenofovir, vitamins in combination with hydroxychloroquine, lactobacillus coryniformis, levamisole and isoprinosine, nitazoxanide, measles vaccine and melatonin recombinant human interferon alpha 1b spray and Peginterferon Lambda-1a). The completion of trials may better inform whether this strategy is beneficial as a means of transmission risk reduction in this high-risk group.

Caution: Much of the evidence emerging on the clinical efficacy of treatments for COVID-19 is reported in unpublished scientific manuscripts or “preprints”. These are preliminary reports which have not been subjected to peer-review – the conventional model for judging the quality of research. In the interests of speed and open access, the international scientific community has recognised the advantage of preprints, particularly in settings where there is an urgent need for evidence. However, without peer-review, there is also a greater potential for dissemination of low-quality research. The ERG critical appraisal of the available research includes an assessment of the quality of study reports and their limitations.

Rapid Evidence Review

Background

The current COVID-19 pandemic, caused by SARS-CoV-2, represents a significant risk people at high risk of infection—particularly close contacts and HCWs. Early evidence from China reports high estimates for the secondary attack rates of SARS-CoV-2 in households (~15%) and among close contacts (~10%), suggesting potential strategies to protect those at high risk are warranted [1]. Infection among HCWs places an extra burden on healthcare environments at a crucial time due to staff absence and spread to family members. Additionally, there is a significant risk to non-infected patients already hospitalised, and Wang et al reported in one centre that 41% of their patients had suspected nosocomial transmission [2]. Critical care, for example, represents a high-risk environment for nosocomial transmission of SARS-CoV-2 with procedures such as non-invasive ventilation, intubation and suction causing a bioaerosol that may represent more of a potential inoculum than by community transmission [3]. Steps to reduce transmission within the healthcare delivery environment could minimise the overall impact on the healthcare system.

Pre-exposure prophylaxis and postexposure prophylaxis (PEP) with antimicrobial drugs can be effective in preventing illness before potential exposure or after documented exposure to a variety of microbial pathogens, and in reducing the risk of secondary spread of infection. For example, PEP with rifampicin is given to people exposed to index cases of invasive meningococcal infection, and oseltamivir has been recommended by WHO for people at high risk of infection before or after exposure to pandemic influenza [4]. Antiviral drugs administered shortly after symptom onset can reduce infectiousness to others by reducing viral shedding in the respiratory secretions of patients and targeted prophylactic treatment of contacts could reduce their risk of becoming infected [4].

This review examines the available evidence on the use of prophylactic pharmacological therapy in HCWs and close contacts of cases of COVID-19.

Evidence

A targeted search strategy was adopted for this review (Appendix 1). No completed randomised controlled clinical trials were identified which investigated the role of prophylactic therapy in healthcare workers or close contacts of cases with COVID-19.

Two systematic reviews of the literature have been published; the first of which examined the role of CQ and HCQ in preventing the spread of COVID-19 [13]. No evidence was found which supported the use of these products as prophylactic treatments for COVID-19. The authors search strategy included any articles published up to 30th March 2020. The authors concluded that in the absence of robust in vivo and clinical evidence, it seems premature to recommend CQ and HCQ for the prophylaxis of COVID-19, and the second of which, (which included a search strategy up to April 15th 2020) reasons against the use HCQ as prophylaxis both in the general population as well as HCWs. The authors also highlight that due to the toxicity profile, chances of overdoses and poisoning can pose serious health threats if HCQ is used widely [14]. *It should be noted that this article has not been peer-reviewed.* Ongoing well designed clinical trials are expected to provide explicit answer in near future.

One completed case control study has been conducted in China which examined the use of PEP with umifenovir (Arbidol®) in reducing transmission of SARS-CoV-2, among healthcare workers and families who members with COVID-19 [5]. Umifenovir is an anti-viral (fusion inhibitor) used mainly in Russia and China for treatment of influenza.

The authors proposed that umifenovir could reduce infection risk in family and hospital settings, however this is a preliminary report and subject to several biases including the retrospective design of the case-control study, the potential selection bias because the collection of data was through telephone calls and the awareness of the population to treatment options available.

One single arm interventional trial examining the use of HCQ as PEP in patients and care workers in a long term care facility in Korea has been published [15]. The study was a single arm trial in which 193 patient and 29 care workers were offered PEP with HCQ due to their exposure to the index case and a second case. HCQ was administrated orally at a dose of

400mg daily until the completion of 14 days of quarantine. While the study showed that all patients and careworkers who received PEP did not develop COVID-19, the study has several limitations (single arm, no control group, lack of adequate description of potential confounding factors), the authors could not conclude that PEP is effective for prevention of COVID-19 in close contacts.

Clinical Trials

A number of products are currently under investigation in clinical trials for pre-exposure or PEP of SARS-CoV-2 infection. Hydroxychloroquine, an antimalarial agent with anti-inflammatory and immunomodulatory activities, has gained significant interest as a potential therapeutic option for use in the prophylactic setting. There are currently 29 clinical trials registered internationally, which are investigating the use of HCQ alone or in combination with other products for the prevention of COVID-19 in HCWs (Appendix 2). The majority of these studies are double-blind and randomised controlled in nature which is recognised as the gold standard for ascertaining efficacy and safety data on a specific treatment. Dosing and duration of HCQ for prophylactic use differs between the trials and ranges from 200mg once daily to 600mg twice a day. Currently, based on these studies, the Indian Council of Medical Research [10] has recommended the use of HCQ for prophylaxis of:

- All HCWs who are involved in the care of suspected or confirmed cases of COVID-19: 400 mg twice a day on day 1, followed by 400 mg once weekly for next 7 weeks.
- Asymptomatic household contacts of laboratory confirmed cases may be prescribed 400 mg twice a day on day 1, followed by 400mg once weekly for the next 3 weeks. A rationale was not provided for dose or duration.

A rationale was not provided for dose or duration.

Pourdowlat et al have also made a recommendation on the use of HCQ for prophylactic use in healthcare workers; 200mg HCQ per day, except for those with any contraindication as

per the SmPC to HCQ (hypersensitivity to the active substance, 4-aminoquinoline compounds or to any of its excipients, myasthenia gravis, pre-existing maculopathy of the eye, retinitis pigmentosa, those below 6 years of age (200mg tablets not adapted for weight <31 kg), and also in patients with cardiac comorbidities where QTc prolongation is known to result [17].

For post-exposure cases, a loading dose of 600-800 mg on the first day followed by 200mg daily is recommended [11].

Several other therapeutic options for prophylactic therapy have commenced or are registered to commence in clinical trials (n=20), which examine the use of CQ, inhaled nitric oxide gas, vitamins in combination with HCQ, BCG vaccination, *Lactobacillus coryniformis*, levamisole and isoprinosine, nitazoxanide, measles vaccine, melatonin, recombinant human interferon alpha 1b spray and Peginterferon Lambda-1a (Appendix 2).

Also reported in the literature is a proposal to use povidone iodine nasal spray specifically for HCWs. Povidone-iodine (iodine with the water-soluble polymer polyvinylpyrrolidone, PVP-I) has higher virucidal activity than other commonly used antiseptic agents including chlorhexidine and benzalkonium chloride [6]. It has been shown to be active *in vitro* against the coronaviruses that have caused epidemics in the last two decades, namely SARS-CoV causing the severe acute respiratory syndrome (SARS) epidemic of 2002–3 and MERS-CoV the agent responsible for causing the Middle East respiratory syndrome (MERS) epidemic of 2012–13 [7, 8]. Kirk-Bayley et al propose that a protocolised nasal inhalation and oropharyngeal wash of PVP-I should be used in the current COVID-19 pandemic to limit the spread of SARS-CoV-2 from patients to healthcare workers (and vice versa) and thus reduce the incidence of COVID-19 [9]. It should be noted however, that this proposal has not been peer reviewed. Povidone-Iodine Intranasal Prophylaxis is now being investigated as part of a clinical trial [16].

Registry

The Healthcare Worker Exposure Response and Outcomes (HERO) Registry Study, COVID-19 has been set up in the United States and aims to provide a resource for collecting

information on HCWs currently working in the United States. The overall goal of the Registry is to develop the infrastructure necessary to create and engage a community of HCWs who may be eligible for participation in future research studies, including those of COVID-19 prophylaxis and treatment.

The main objectives of the study are, 1) create a virtual community of adult HCWs in the United States, 2) identify HCWs interested in engaging in upcoming research studies, including those related to COVID-19, and 3) create a dataset of health related measurements, risk factors, and outcomes for future analysis. The population of interest is adult healthcare workers in the United States (Appendix 2, Table 3).

Clinical opinion

Clinical opinion advises that use for this indication should be in the context of clinical trial only given the unknowns in relation to benefit.

ERG Conclusion on Clinical Studies

There is currently no robust evidence to support the use of prophylactic therapy in healthcare workers or those in contact with cases of COVID-19 outside of clinical trials. Evidence from controlled clinical trials are required to determine whether pharmacological prophylaxis will be of benefit in reduction of viral loads and the subsequent consequences of COVID-19.

Appendix 1

A targeted literature review was conducted to inform the Rapid Evidence Review based on a search strategy developed by the Information Specialist at the National Centre for Pharmacoeconomics. A typical hierarchy of evidence was considered in the search, from highest to lowest:

- Systematic Literature Reviews and meta-analyses
- Randomized Controlled Trials
- Observational studies
- Published expert opinion

TABLE 1: Sources of evidence searched to inform the literature review.

Source	Search
PubMed - Advanced Search for coronavirus and nosocomial infection and healthcare professionals.	(((((coronavirus [MeSH]) OR ("coronavirus infections"[MeSH Terms]) OR (coronavirus [All Fields]) OR ("covid 2019") OR ("SARS2") OR ("SARS-CoV-2") OR ("SARS-CoV-19") OR ("severe acute respiratory syndrome coronavirus 2" [supplementary concept]) OR (coronavirus infection) OR ("severe acute respiratory" pneumonia outbreak) OR ("novel cov") OR (2019ncov) OR (sars cov2) OR (cov2) OR (ncov) OR (covid-19) OR (covid19) OR (coronaviridae) OR ("corona virus")))) AND ((nosocomial infection OR cross infection OR Hospital acquired infection or Healthcare associated infection))) AND ((nurse or nursing or nurses or healthcare professional or healthcare worker)) AND prophylaxis
Google Scholar	“2019-nCoV” AND prophylaxis for healthcare workers
LitCovid	Pharmacological prophylaxis for healthcare workers
MedRxiv/ BioRxiv	Pharmacological prophylaxis for healthcare workers
ChinaXiv	“COVID-19” AND “pharmacological prophylaxis for healthcare workers”.
EU Clinical Trials Register	Prepopulated with COVID-19 clinical trials and “prophylaxis for healthcare workers”.
ClinicalTrials.gov	COVID-19 (synonyms 2019-nCoV, SARS-CoV-2, 2019 novel coronavirus, severe acute respiratory syndrome coronavirus 2) AND prophylaxis in healthcare workers
Cochrane COVID-19 study register	Prepopulated with COVID-19 clinical trials. “prophylaxis”.
Chictr.org.cn	COVID-19 AND prophylaxis

Appendix 2

Table 1: Summary of ongoing clinical trials of hydroxychloroquine for chemoprophylaxis in healthcare workers.

NCT Number	Title	Interventions	Study Type	Start Date	Completion Date	Locations
NCT04331834	Pre-Exposure Prophylaxis With Hydroxychloroquine for High-Risk Healthcare Workers During the COVID-19 Pandemic	Drug: Hydroxychloroquine Drug: Placebos	Interventional	April 3, 2020	October 30, 2020	ISGlobal, Barcelona, Spain
NCT04364815	The University of the Philippines Hydroxychloroquine PEP Against COVID-19 Trial	Drug: Hydroxychloroquine plus standard preventive measures Drug: Placebo plus standard preventive measures	Interventional	Apr-20	May-21	
NCT04352946	Health Care Worker pROphylaxis Against COVID-19: The HERO Trial	Drug: Hydroxychloroquine Pre-Exposure Prophylaxis Drug: Placebo oral tablet	Interventional	April 24, 2020	August 24, 2020	United States
NCT04363450	Hydroxychloroquine as Prophylaxis for COVID-19 in Healthcare Workers (HCQPreP)	Drug: Hydroxychloroquine Drug: Placebo	Interventional	April 27, 2020	August 3, 2020	United States
NCT04370015	Hydroxychloroquine Chemoprophylaxis for COVID-19 Infection in High-risk Healthcare	Drug: Hydroxychloroquine Drug: Placebo oral tablet	Interventional	Apr-20	Oct-20	

	Workers: Randomised Control Trial					
NCT04333225	Hydroxychloroquine in the Prevention of COVID-19 Infection in Healthcare Workers	Drug: Hydroxychloroquine	Interventional	April 3, 2020	July 30, 2020	Baylor University Medical Center, Dallas, Texas, United States
NCT04336748	HCQ for Primary Prophylaxis Against COVID19 in Health-care Workers	Drug: Hydroxychloroquine	Interventional	Apr-20	Aug-20	
NCT04340349	Low-dose Hydroxychloroquine and Bromhexine: a Novel Regimen for COVID-19 Prophylaxis in Healthcare Professionals	Drug: Hydroxychloroquine Sulfate Drug: Bromhexine 8 MG	Interventional	April 10, 2020	July 10, 2020	National Institute of Rehabilitation, Mexico City, Cdmx, Mexico
NCT04354597	Hydroxychloroquine and Azithromycin as Prophylaxis for Healthcare Workers Dealing With COVID19 Patients	Drug: HCQ & AZ	Interventional	April 15, 2020	October 15, 2020	King Hussein Cancer Center, Amman, Jordan
NCT04349228	Assessment of the Efficacy and Safety of (HCQ) as a Prophylaxis for COVID19 for Health Professionals	Drug: Hydroxychloroquine (HCQ) Drug: Placebo oral tablet	Interventional	April 15, 2020	July 15, 2020	Tunisia
NCT04359537	Efficacy of Various Doses of Hydroxychloroquine in Pre-Exposure Prophylaxis for COVID 19	Drug: Hydroxychloroquine Sulfate 200 MG Other: Placebo	Interventional	April 25, 2020	September 25, 2020	

NCT04345653	Hydroxychloroquine as Chemoprevention for COVID-19 for High Risk Healthcare Workers	Drug: Hydroxychloroquine Sulfate (HCQ)	Interventional	April 14, 2020	April 8, 2022	United States
NCT04334928	Randomized Clinical Trial for the Prevention of SARS-CoV-2 Infection (COVID-19) in Healthcare Personnel	Drug: Emtricitabine/tenofovir disoproxil Drug: Hydroxychloroquine Drug: Placebo: Emtricitabine/tenofovir disoproxil Placebo Drug: Placebo: Hydroxychloroquine	Interventional	April 15, 2020	July 31, 2020	Spain
NCT04328285	Chemoprophylaxis of SARS-CoV-2 Infection (COVID-19) in Exposed Healthcare Workers	Drug: Hydroxychloroquine Drug: Placebo of Hydroxychloroquine Drug: Lopinavir and ritonavir Drug: Placebo of LPV/r Tablets	Interventional	April 14, 2020	November 30, 2020	France
NCT04354870	COVID-19 PrEP HCW HCQ Study	Drug: Hydroxychloroquine (HCQ)	Interventional	April 3, 2020	September 1, 2020	United States
NCT04347889	Preventing COVID-19 in Healthcare Workers With HCQ: A RCT	Drug: Hydroxychloroquine Other: Vitamin C	Interventional	April 20, 2020	December 30, 2020	

NCT04341441	Will Hydroxychloroquine Impede or Prevent COVID-19	Drug: Hydroxychloroquine - Daily Dosing Drug: Hydroxychloroquine - Weekly Dosing Other: Placebo oral tablet Diagnostic Test: Monitoring Visit - Baseline Diagnostic Test: Monitoring Visit - Week 4 Diagnostic Test: Monitoring Visit - Week 8 Other: Weekly Assessment	Interventional	April 7, 2020	April 30, 2021	Henry Ford Hospital, United States
NCT04318015	Hydroxychloroquine Chemoprophylaxis in Healthcare Personnel in Contact With COVID-19 Patients (PHYDRA Trial)	Drug: Hydroxychloroquine Drug: Placebo oral tablet	Interventional	April 14, 2020	March 31, 2021	Mexico

NCT04329923	The PATCH Trial (Prevention And Treatment of COVID-19 With Hydroxychloroquine)	Drug: Hydroxychloroquine Sulfate 400 mg twice a day Drug: Hydroxychloroquine Sulfate 600 mg twice a day Drug: Hydroxychloroquine Sulfate 600 mg once a day Drug: Placebo oral tablet	Interventional	April 9, 2020	December 1, 2021	United States
NCT04353037	PATCH 2&3:Prevention & Treatment of COVID-19 (Severe Acute Respiratory Syndrome Coronavirus 2) With Hydroxychloroquine	Drug: Group A HCQ Drug: Group B Control	Interventional	April 7, 2020	June 15, 2021	United States
NCT04303507	Chloroquine/ Hydroxychloroquine Prevention of Coronavirus Disease (COVID-19) in the Healthcare Setting	Drug: Chloroquine or Hydroxychloroquine Drug: Placebo	Interventional	Apr-20	Apr-21	
NCT04326725	Proflaxis Using Hydroxychloroquine Plus Vitamins-Zinc During COVID-19 Pandemia	Drug: Plaquenil 200Mg Tablet	Observational	March 20, 2020	September 1, 2020	Turkey
NCT04346329	Immune Monitoring of Prophylactic Effect of Hydroxychloroquine in Healthcare Providers Highly Exposed to COVID-19	Drug: Hydroxychloroquine Drug: Placebo oral tablet	Interventional	April 20, 2020	October 1, 2020	Colombia

NCT04329611	ALBERTA HOPE COVID-19 for the Prevention of Severe COVID19 Disease	Drug: Hydroxychloroquine	Interventional	April 13, 2020	September 30, 2020	University of Calgary Canada
NCT04334148	Healthcare Worker Exposure Response and Outcomes of Hydroxychloroquine	Drug: Hydroxychloroquine Drug: Placebo oral tablet	Interventional	Apr-20	Jul-20	
NCT04333732	CROWN CORONATION: Chloroquine Repurposing to healthWorkers for Novel CORONAVirus mitigation	Drug: Low-dose chloroquine/hydroxychloroquine Drug: Mid dose chloroquine or hydroxychloroquine Drug: High does chloroquine or hydroxychloroquine Drug: Placebo	Interventional	Apr-20	Feb-21	United States Australia Canada Ireland South Africa United Kingdom Zambia
NCT04342156	Safety And Efficacy Of Hydroxychloroquine For At Risk Population (SHARP) Against COVID-19	Drug: Hydroxychloroquine Sulfate 200 milligram (mg) Tab	Interventional	Apr-20	Oct-20	
NCT04352933	PROLIFIC Chemoprophylaxis Trial (COVID-19)	Drug: Hydroxychloroquine - Daily dosing Drug: Hydroxychloroquine - Weekly Dosing Other: Matched Placebo Hydroxychloroquine	Interventional	Apr-20	Apr-21	

NCT04364022	Efficacy of Pragmatic Same-day COVID-19 Ring Prophylaxis for Adult Individuals Exposed to SARS-CoV-2 in Switzerland	Drug: Hydroxychloroquine Sulfate 200 MG [Plaquenil] Drug: Lopinavir/ritonavir	Interventional	Apr-20	Oct-20	Switzerland
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Table 2: Summary of ongoing clinical trials for chemoprophylaxis (*for other products*).

NCT Number	Title	Interventions	Study Type	Start Date	Completion Date	Locations
NCT04366180	Evaluation of the Probiotic Lactobacillus Coryniformis K8 on COVID-19 Prevention in Healthcare Workers	Dietary Supplement: Probiotic Dietary Supplement: Control	Interventional	April 24, 2020	Oct-20	Spain
NCT04364802	COVID-19: Povidone-Iodine Intranasal Prophylaxis in Front-line Healthcare Personnel and Inpatients	Drug: Povidone-Iodine Nasal Spray and Gargle	Interventional	May-20	May-21	United States
NCT04362124	Performance Evaluation of BCG Vaccination in Healthcare Personnel to Reduce the Severity of SARS-COV-2 Infection	Biological: vaccine BCG Other: Placebo	Interventional	Apr-20	Nov-21	Colombia

NCT04360122	Levamisole and Isoprinosine in Immune-prophylaxis of Egyptian Healthcare Workers Facing COVID-19	Drug: Levamisole Drug: Isoprinosine Drug: Levamisole and Isoprinosine	Interventional	April 20, 2020	December 1, 2020	Egypt
NCT04359680	Trial to Evaluate the Efficacy and Safety of Nitazoxanide (NTZ) for Pre- or Post Exposure Prophylaxis of COVID-19 and Other Viral Respiratory Illnesses (VRI) in Healthcare Workers	Drug: Nitazoxanide Drug: Placebo	Interventional	April 30, 2020	August 31, 2020	
NCT04357028	Measles Vaccine in HCW	Drug: Measles-Mumps-Rubella Vaccine Drug: Placebos	Interventional	May 1, 2020	November 1, 2020	Egypt
NCT04353128	Efficacy of Melatonin in the Prophylaxis of Coronavirus Disease 2019 (COVID-19) Among Healthcare Workers.	Drug: Melatonin 2mg Drug: Placebo oral tablet	Interventional	Apr-20	Jul-21	
NCT04350931	Application of BCG Vaccine for Immune-prophylaxis Among Egyptian Healthcare Workers During the Pandemic of COVID-19	Biological: intradermal injection of BCG Vaccine Other: placebo	Interventional	April 20, 2020	December 1, 2020	Egypt
NCT04349371	Saved From COVID-19	Drug: Chloroquine Drug: Placebo oral tablet	Interventional	Apr-20	Apr-21	United States
NCT04348370	BCG Vaccine for Health Care Workers as Defense Against COVID 19	Biological: BCG Vaccine Biological: Placebo Vaccine	Interventional	April 20, 2020	Nov-21	United States
NCT04342806	Healthcare Worker Exposure Response and Outcomes (HERO) Registry Study, COVID-19		Observational	April 10, 2020	December 31, 2020	United States

NCT04337918	Nitric Oxide Releasing Solutions to Prevent and Treat Mild/Moderate COVID-19 Infection	Drug: NORS (Nitric Oxide Releasing Solution)	Interventional	April 27, 2020	September 30, 2020	
NCT04334876	Rapid SARS-CoV-2 IgG Antibody Testing in High Risk Healthcare Workers	Diagnostic Test: SARS-CoV-2 IgG Antibody Testing Kit	Observational	April 1, 2020	January 1, 2021	
NCT04328441	Reducing Health Care Workers Absenteeism in Covid-19 Pandemic Through BCG Vaccine	Drug: BCG Vaccine Drug: Placebo	Interventional	March 25, 2020	December 25, 2020	Netherlands
NCT04327206	BCG Vaccination to Protect Healthcare Workers Against COVID-19	Drug: BCG Vaccine	Interventional	March 30, 2020	March 30, 2022	Australia
NCT04312243	NO Prevention of COVID-19 for Healthcare Providers	Drug: Inhaled nitric oxide gas	Interventional	April 2, 2020	March 20, 2022	
NCT04290780	COVID-19 - Multicenter Study on Nosocomial Transmission of SARS-CoV-2 Virus	Other: nosocomial infection/hospital acquired infection	Observational	March 9, 2020	October 30, 2020	France
NCT04343248	Trial to Evaluate the Efficacy and Safety of Nitazoxanide (NTZ) for Post-Exposure Prophylaxis of COVID-19 and Other Viral Respiratory Illnesses in Elderly Residents of Long-Term Care Facilities (LTCF)	Drug: Nitazoxanide Drug: Placebo	Interventional	April 30, 2020	August 31, 2020	

ChiCTR2000030013	A study on the efficacy and safety of recombinant human interferon alpha 1b spray in preventing novel coronavirus (COVID-19) infection in highly exposed medical staffs.	Drug: human IFN alpha 1b spray	Interventional	Feb 20, 2020		Beijing
NCT04344600	Peginterferon Lambda-1a for the Prevention and Treatment of SARS-CoV-2 Infection	Drug: Peginterferon lambda alfa-1a subcutaneous injection Other: Saline	Interventional	Apr-20	Jun-21	United States

Table 3: HERO registry of healthcare workers in the United States.

Title	Status	Study Type	Start date	Completion date	Location
Healthcare Worker Exposure Response and Outcomes (HERO) Registry Study, COVID-19	Health Care Worker (HCW) COVID-19	Observational	April 10, 2020	December 31, 2099	Duke Clinical Research Institute, Durham, North Carolina, United States

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