Rapid Evidence Review

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

Version 6, 29th June 2020

National Centre for Pharmacoeconomics
NCPE Ireland

Medicines Management Programme

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Key changes (highlighted in yellow) between Version 5 (9th June 2020) and Version 6 (29th June 2020): Press-release from MHRA announcing that the COPCOV (hydroxychloroquine prevention trial) can resume; The trial of chloroquine as a prophylactic agent not proceeding by the CROWN clinical trial collaboration; Press release announcing top-line results from the HCQ4COV19 clinical trial; One systematic review of registered trials of hydroxychloroquine and one case report published which examined the adverse effects of hydroxychloroquine as prophylaxis in HCWs. Two additional trials have been registered which will examine the use of other therapeutic options for prophylaxis against COVID-19.

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 32.2% of all cases confirmed to date [12].

One RCT has reported from the U.S. and Canada [19], which examined the use of hydroxychloroquine as post-exposure prophylaxis. This study enrolled 821 asymptomatic adults who described having a household or occupational exposure to someone with confirmed COVID-19. The authors found that the incidence of new illness compatible with the virus did not significantly differ between the hydroxychloroquine and placebo groups. The study was subject to a number of methodological limitations.

A cross sectional study has reported from India [21] examining specifically the safety profile of hydroxychloroquine among COVID-19 negative and asymptomatic healthcare workers. While the authors concluded that the incidence of side effects was higher compared to other studies which involved patients with SLE and RA, on long term maintenance therapy, the study itself is subject to limitations and no definitive conclusions can be drawn.

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. There is 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. An experimental trial from China has just reported on the

preventative effect of rhIFN-α nasal drops against COVID-19 in HCWs [18], where the authors suggest that rhIFN-α nasal drops may have a role in preventing infection, however this study also is limited by its design (open label, non-randomised, no control group, potential confounding factors, no confirmatory tests of infection were carried out).

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.

One systematic review has been published [23] of registered trials published of HCQ prophylaxis for HCWs in the first quarter of 2020. Essentially, the review summarises the trial design and a qualitative analysis of the HCQ drug regimen, where the most frequent prophylactic regimen (6/31 (19%)) was an HCQ loading dose of 800 mg on day 1, followed by HCQ 400 mg for four additional days.

One case series has been published [24] which reported on four cases of palmoplantar itching among health care workers who were on prophylactic doses of HCQ and their management with cetirizine and methylprednisolone.

One study has been completed to date examining the use of HCQ in post exposure prophylaxis. There are 35 clinical trials (n=34 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 30 clinical trials commenced or registered (with ClinicalTrials.gov, the Chinese clinical trial register (www.chictr.org.cn) or the European Clinical Trials register) to commence which will examine the use of other products as prophylaxis for HCWs or close contacts.

Press-releases

The UK's medicines regulator, the Medicines and Healthcare products Regulatory Agency (MHRA), announced on 26 June that it would again permit recruitment to the COPCOV COVID-19 prevention clinical trial [29]. The COPCOV study is a double-blind, randomised, placebo-controlled global trial that aims to enrol 40,000 healthcare workers and other at-risk staff to determine definitively if chloroquine and hydroxychloroquine can prevent COVID-19. The MHRA decision came 5 weeks after it had instructed UK clinical trialists using hydroxychloroquine for treatment *and* prevention of COVID-19, to suspend recruitment of further participants into their trials [25]. This announcement was made following consideration of three of the largest international trials of anti-virals for the treatment of COVID-19, the WHO SOLIDARITY, the UK RECOVERY trial and the US ORCHID trial, all of which stopped enrolling patients to the hydroxychloroquine arm of their studies, following interim results which showed no clinical benefit [30].

The top-line results from the HCQ4COV19 clinical trial (Spain) were released on 9 June 2020. HCQ4COV19 was a Spanish study that randomised more than 2300 people exposed to COVID-19 to either HCQ or the usual care [26]. Although not yet published, the top-line results show no significant difference between the number of people in each group who developed COVID-19, which was reported in Science journal online [27]. Full trial results have been submitted for publication.

CROWN CORONA [28] was a double-blind, randomised, placebo-controlled adaptive designed trial, in which healthcare workers were due to be randomly assigned to receive one of three different doses of chloroquine for a period of three months. The trial steering committee came to a recent decision not to proceed with chloroquine (personal communication), due to the emerging evidence from post-exposure prophylaxis trials which shows that there is very little, if any benefit of hydroxychloroquine [19].

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, melatonin, recombinant human interferon alpha 1b spray, Peginterferon Lambda-1a, mefloquine, vitamin D, MMR vaccine, VPM1002 and a dendritic cell vaccine, emtricitabine/tenofovir alafenamide, GLS-1200, bromhexine, dietary supplementation in an oropharygeal spray), quercetin, lactoferrin, ivermectin. 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).

Boulaware et al NEJM

The first randomised, double blind, placebo controlled trial to test hydroxychloroquine as post-exposure prophylaxis has reported [19]. This study, like many investigating treatments for COVID-19, was a pragmatic design and was undertaken in both Canada and the US. Participants were recruited through social media and almost all data were reported by the participants. This study enrolled 821 asymptomatic adults who described having a household or occupational exposure to someone with confirmed COVID-19 at a distance of less than six feet for more than 10 minutes without any or some protective face gear (mask and eye shield). The primary outcome was the incidence of either laboratory-confirmed Covid-19 or illness compatible with Covid-19 within 14 days.

Healthcare workers were initially recruited due to the presumption that that health care workers would have access to COVID-19 testing if symptomatic; however, access to testing was limited throughout the trial period. Recruitment was initially within 3 days of exposure however eligibility changed 6 days after the trial initiated to patients with a positive polymerase chain reaction (PCR) and the exposure window was changed to four days.

Within the first four days after exposure, the participants were randomly assigned to receive (by mail) either placebo (n=407) or hydroxychloroquine (n=414) (800 mg once, followed by 600 mg in six to eight hours, then 600 mg daily for four additional days). HCW's accounted for 66.4% of participants and 27% had reported chronic health conditions. The median age was 40 years (IQR 33 to 50). 87.6% of the participants had high risk exposures. The results showed that new COVID-19 (either PCR confirmed or symptomatically compatible) developed in 107 of 821 participants (13.0%) during the 14 days of follow up and did not differ significantly between the two groups. It should be noted that COVID-19 was confirmed by PCR assay in less than 3% of the participants. The incidence of a new illness compatible with COVID-19 did not differ significantly between participants receiving hydroxychloroquine (49 of 414 [11.8%]) and those receiving placebo (58 of 407 [14.3%]).

Although participant-reported side effects were significantly more common in those receiving hydroxychloroquine (40.1%) than in those receiving placebo (16.8%), no serious adverse reactions were reported.

This trial has many limitations, acknowledged by the investigators. The trial methods did not allow consistent proof of exposure to SARS-CoV-2 or consistent laboratory confirmation that the symptom complex reported represented a SARS-CoV-2 infection. The specificity of participant-reported COVID-19 symptoms is low, so it is hard to be certain how many participants in the trial actually had COVID-19. Adherence to the interventions could not be monitored, and participants reported less-than-perfect adherence, more notably in the group receiving hydroxychloroquine. In addition, those enrolled in the trial were younger (median age, 40 years) and had fewer coexisting conditions than persons in whom severe COVID-19 is most likely to develop, so enrollment of higher-risk participants might have yielded a different result. In addition the blinding in the trial was poor; 46.5% of the participants in the hydroxychloroquine group guessed corrected that they were on hydroxychloroquine, 35.7% in the control group guessed correctly.

The trial design also raises questions about the expected prevention benefits of hydroxychloroquine. Studies of postexposure prophylaxis are intended to provide an intervention in the shortest possible time to prevent infection. In a small-animal model of SARS-CoV-2 infection [20], prevention of infection or more severe disease was observed only when the experimental antiviral agent was given before or shortly after exposure. In the current trial, the long delay between perceived exposure to SARS- CoV-2 and the initiation of hydroxychloroquine (≥3 days in most participants) suggests that what was being assessed was prevention of symptoms or progression of COVID-19, rather than prevention of SARS-CoV-2 infection.

Nagaraja et al (J. Public Health)

Nagaraja et al [22] reported the results of a cross sectional study specifically examining the safety profile of hydroxychloroquine in an asymptomatic population. A questionnaire was circulated among large doctors and nursing social network forums across India. Out of 174 responses, 8 were excluded, leaving 166 responses for analyses. The side-effect profile

analysis highlighted that 63 (37.9%) of participating healthcare professionals experienced at least one adverse drug reaction following use of the drug. The results analysed from the multivariate binomial logistic regression analysis revealed that younger age (<40 years) (OR: 2.44, 95% CI: 1.18–5.05) was an independent risk factor for the development of side-effects. First dose of hydroxychloroquine, was found to be associated with higher incidence of adverse events (OR: 2.38, 95% CI: 1.17–4.84): association of female sex (OR: 1.34, 95% CI: 0.66–2.71), substance use (OR: 1.19, 95% CI: 0.57–2.45), direct contact with patient (OR: 1.28, 95% CI: 0.65–2.66) with higher incidence of side- effects. Association of pre-existing diseases with side-effect profile could not be concluded due to smaller sample size and heterogeneity in study population. While the authors concluded that the incidence of side effects was relatively higher compared to other studies which involved patients with SLE and RA, on long term maintenance therapy, the study itself it subject to limitations involving the self-reporting nature of the participants involved, as well as a lack of information on the many potentially confounding factors in the study, for example a limited number of independent variables are listed which were subject to the regression analysis.

A case report has been published from France [22], which described the clinical work-up of a patient who was admitted to hospital due to fever, dyspnoea and polypnoea and had been receiving HCQ prophylactically for sarcoidosis for a year. However it's relevance to the current review is limited – it does not address whether HCQ taken prophylactically had any benefit or otherwise against COVID-19, instead it addresses the merits of therapeutic drug monitoring to aid diagnoses in the clinical setting. It is also unclear if the patient in the report developed confirmed COVID-19. It is therefore not included as part of this review.

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 longterm care facility in Korea has been published [15]. The study included 193 patient and 29 care workers who 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.

One experimental (prospective, open-label) trial reported on the protective effect of rhIFN-α nasal drops against COVID-19 in HCWs at a hospital in China [18]. 2944 medical staff members were recruited and allocated into low-risk group or high-risk groups according to whether they were directly exposed to COVID-19 patients. Participants in the low-risk group received rhIFN-α nasal drops (2-3 drops/nostril/time, 4 times/day) for 28 days with first-level protection (e.g. work clothes, masks, hand hygiene); those in the high-risk group received identical rhIFN-α nasal drops combined with thymosin-α1 (1.6 mg, hypodermic

injection, once a week) along with secondary-level (e.g. work clothes, masks, goggles/screens, gloves, shoe covers) or third-level protection (a comprehensive protective mask and double gloves in addition to the secondary-level protection). The primary outcome was new-onset COVID-19 pneumonia over 28 days. The secondary outcome was new-onset fever or respiratory symptoms but with negative pulmonary images. Results indicated that in both the low and high risk exposure groups, there were no new cases of COVID-19 pneumonia diagnosed and or no new onset cases with fever/respiratory symptoms. However, the study is subject to several limitations: the study is not randomized or controlled (the authors do allude to a group from another hospital serving as a control for this trial but no further information is provided), the study is also limited by other design features, such as not properly accounting for possible confounding factors. The authors reported COVID-19 related pneumonia as the primary outcome measure with no details of how this was assessed or confirmed, but also report that the main reason for using this outcome was that no COVID-19 diagnostic kits had been approved at the beginning of the study. Hence, it cannot be truly confirmed that there were no cases of COVID-19 in the study group.

One systematic review has been published [23] of registered prospective trials of HCQ prophylaxis for HCWs in the first quarter of 2020. The aim of this review was to give an overall picture of global use of HCQ as COVID-19 prophylaxis. The review contained all interventional studies registered in ClinicalTrials.gov on the 27th of April under the disease "COVID" and "hydroxychloroquine prophylaxis". No other filter was used. Studies using HCQ as treatment, studies that did not record details about HCQ regimen, as well as those using HCQ in combination with other drugs, were not included. All interventional clinical trials that studied the use of HCQ for COVID-19 prophylaxis were included in the qualitative analysis. Forty- one (*n* = 41) studies were identified through ClinicalTrials.gov on the 27th of April. After screening for eligibility record details of the selected studies, 31 studies were included in the qualitative analysis. Ten studies were not included: reasons for exclusion included the absence of details about HCQ regimen (*n* = 1), the use of HCQ as indication other than prophylaxis (*n* = 3), and the combination of HCQ to other drugs or vitamins (*n* = 6). The qualitative analysis focused on HCQ drug regimens of the 31 included studies as recorded in ClinicalTrials.gov from the 17th of March to the 24th of April.

Among the included studies, all but three were randomized and parallel and most of them (74%, 23/31) were double-blinded to quadruple-blinded studies. On the 27th of April, 55% (17/31) of them were recruiting. Estimated enrolment in HCQ arm was from 45 to 20,000 participants, with a median of 380 participants and a total of 45,728 persons receiving HCQ.

The review provided useful information regarding the HCQ regimen. Sixty one percent (61%, 19/31) of the included studies used an HCQ loading dose, followed by daily (14/19) or weekly (5/19) doses. The range of the loading doses was from 400 to 1400 mg on day 1. The most common daily doses were 400 mg (12/31 (39%)) and 200 mg (9/31 (29%)); a 600 mg daily dose was less common and was recorded for only 13% (4/31) of the studies. The remaining six studies used weekly doses of 400 mg. The duration of prophylaxis was highly variable, ranging from 5 to 180 days (median = 40 days) for a daily regimen, and 3 to 24 weeks for weekly regimen (median = 12 weeks). The most frequent prophylactic regimen (6/31 (19%)) was an HCQ loading dose of 800 mg on day 1, followed by HCQ 400 mg for four additional days. Among the studies (*n* = 5) that did not use a loading dose but a 400 mg daily dose, duration of prophylaxis was highly diverse from 4 to 180 days (median = 60). For the studies (*n* = 2) that reported a 200 mg daily dose, one study used a loading dose of 800 mg on day 1 and 2, followed by 90 days of 200 mg HCQ, and the other one used a loading dose of 400 mg from day 1 to 3, followed by 14 days of 200 mg HCQ.

The review's inclusion criteria were more restrictive (e.g. examining only the ClinicalTrials.gov database, identifying only interventional trials, and those looking at HCQ only, between March 17th and April 27th) therefore the number of trials identified differs from the current review (Appendix 2, Table 1). However it does demonstrate the great interest among the scientific community in answering this research question.

One case series has been published which reported on the cutaneous side effects of HCQ in HCWs in a COVID-19 referral hospital [24]. As previously reported in this review (Version 1, April 7th), the Indian Council of Medical Research (ICMR) had recommended the empirical use of HCQ for prophylaxis amongst HCWs in a dose of 400 mg twice a day on day 1 followed by 400 mg weekly for the next 7 weeks [10]. This prophylactic regimen of ICMR was followed by HCWs at risk of exposure with a general advisory to avoid in cases of, known QT interval prolongation, porphyria, psoriasis, and pregnancy. Of the six cases, four

HCWs were confirmed (by adverse drug reaction probability Naranjo scale) to have cutaneous side effects in the form of urticaria, maculopapular rash, and palmoplantar itching considered to be triggered by HCQ (Naranjo scale 4-5 (Probable)). While all four HCWs were administered oral antihistamines (cetirizine 10 mg OD and doxepin 20 mg HS), oral methyl-prednisolone (16mg) was added for 1week in the case who presented with maculopapular rash & severe pruritus which was not relieved on antihistamines. In two cases who had palmoplantar pruritus, the symptom persisted even after 14 days use of antihistamines.

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, gained significant interest as a potential therapeutic option for use in the prophylactic setting. The emerging and published evidence however demonstrates that hydroxychloroquine is not beneficial in the treatment of COVID [30]. There are currently 35 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. Emerging evidence from the post-exposure prophylaxis setting is showing that there is very little, if any, benefit with hydroxychloroquine [19]. In light of this, the trial steering committee of the CROWN CORONA trial, a double-blind, randomised, placebo-controlled adaptive designed trial, in which healthcare workers were due to be randomly assigned to receive one of three different doses of chloroquine for a period of three months, have decided not to proceed with chloroquine (personal communication)[28]. This is due to the emerging evidence from post-exposure prophylaxis trials which shows that there is very little, if any benefit of hydroxychloroquine.

The top-line results from the HCQ4COV19 clinical trial (Spain) which were released on 9 June 2020 showed no significant difference between the number of people in each group who developed COVID-19, which was reported in Science journal online [26] [27]. HCQ4COV19

was a Spanish study that randomised more than 2300 people exposed to COVID-19 to either HCQ or the usual care [26]. Full trial results have been submitted for publication.

The UK's medicines regulator, the Medicines and Healthcare products Regulatory Agency (MHRA), announced on 26 June that it would again permit recruitment to the COPCOV COVID-19 prevention clinical trial [29]. The COPCOV study is a double-blind, randomised, placebo-controlled global trial that aims to enrol 40,000 healthcare workers and other at-risk staff to determine definitively if chloroquine and hydroxychloroquine can prevent COVID-19. The MHRA decision came 5 weeks after it had instructed UK clinical trialists using hydroxychloroquine for treatment *and* prevention of COVID-19, to suspend recruitment of further participants into their trials [25]. This announcement was made following consideration of three of the largest international trials of anti-virals for the treatment of COVID-19, the WHO SOLIDARITY, the UK RECOVERY trial and the US ORCHID trial, all of which stopped enrolling patients to the hydroxychloroquine arm of their studies, following interim results which showed no clinical benefit [30].

Again, these changes to the clinical trials demonstrate how fluid the situation is in relation to the intervention under assessment, but also the medium through which the results are reported.

Several other therapeutic options for prophylactic therapy have commenced or are registered to commence in clinical trials (n=30), 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, Peginterferon Lambda-1a, mefloquine, vitamin D, MMR vaccine, VPM1002 and a dendritic cell vaccine, emtricitabine/tenofovir alafenamide, GLS-1200, bromhexine, dietary supplementation in an oropharygeal spray, quercetin, lactoferrin, ivermectin (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].

Guidelines

PEP or PREP is not recommended by any of the consensus Guidelines published. The only recommendations have been by the Indian Council of Medical Research. 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.

Pourdowlat et al, in a letter, 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]. The authors also recommended post-exposure cases, a loading dose of 600-800mg on the first day followed by 200mg daily [11]. The letter was published in the Advanced Journal of Emergency Medicine however very little supporting data was provided.

Registries

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.

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 one RCT did not demonstrate a benefit of hydroxychloroquine in preventing COVID-19 infection. However this study had some significant biases and methodological shortcomings. Further 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 lierature 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, 2021	
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 Workers: Randomised Control Trial	Drug: Hydroxychloroquine|Drug: Placebo oral tablet	Interventional	Apr-20	October 2020	

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	August 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	April 2021	
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	July 2020	
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	February 2021	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	October 2020	
NCT04352933	PROLIFIC ChemoprophylaxisTrial (COVID-19)	Drug: Hydroxychloroquine - Daily dosing|Drug: Hydroxychloroquine - Weekly Dosing|Other: Matched Placebo Hydroxychloroquine	Interventional	Apr-20	April 2021	

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	October 2020	Switzerland
NCT04371523	Hydroxychloroquine to Prevent COVID-19 Disease Amongst Healthcare Workers	Drug: Apo-Hydroxychloroquine|Drug: Matched Placebo	Interventional	May 1, 2020	August 30, 2020	Canada
NCT04414241	Hydroxychloroquine to Prevent SARS-CoV-2 Infection	Drug: Hydroxychloroquine	Interventional	Jun-20	October 2020	Peru
NCT04408456	Efficacy of Hydroxychloroquine (HCQ) as Post Exposure Prophylaxis (PEP) for Prevention of COVID-19	Drug: HCQ|Other: Standard therapy	Interventional	March 1, 2020	June 30, 2020	India
NCT04384458	COVID-19 Prophylaxis With Hydroxychloroquine Associated With Zinc For High-Risk Healthcare Workers	Drug: Hydroxychloroquine	Interventional	Jun-20	October 2020	Brazil

NCT04374942	Does Hydroxychloroquine Before & During Patient Exposure Protect Healthcare Workers From Coronavirus?	Drug: Hydroxychloroquine|Drug: Placebo oral tablet	Interventional	April 30, 2020	January 30, 2022	University Health Network, Toronto, Ontario, Canada
NCT04372017	Hydroxychloroquine as Post-Exposure Prophylaxis Against COVID-19 Infection	Drug: Hydroxychloroquine|Dietary Supplement: Vitamin D	Interventional	May 14, 2020	June 4, 2021	Sanford Health, Sioux Falls, South Dakota, United States

*Note: A number of these studies are not yet recruiting despite the recruitment start date having passed.

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	October 2020	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 2021	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	July 2021	
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	April 2021	United States
NCT04348370	BCG Vaccine for Health Care Workers as Defense Against COVID 19	Biological: BCG Vaccine|Biological: Placebo Vaccine	Interventional	April 20, 2020	November 21	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	
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	

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	June 2021	United States
EUDRACT 2020-001194-69	Pilot study to evaluate the efficacy and safety of mefloquine as prophylaxis in people exposed to the disease caused by the new SARS-CoV-2 coronavirus	Drug: mefloquine Other: placebo	Interventional			
NCT04386850	Oral 25-hydroxyvitamin D3 and COVID-19	Drug: Oral 25-Hydroxyvitamin D3	Interventional	April 14, 2020	March 15, 2021	Iran
NCT04386252	Phase Ib-II Trial of Dendritic Cell Vaccine to Prevent COVID-19 in	Biological: AV-COVID-19	Interventional	Sept 2020	April 2021	

	Frontline Healthcare Workers and First Responders					
NCT04357028	Measles Vaccine in HCW	Drug: Measles-Mumps-Rubella Vaccine|Drug: Placebos	Interventional	May 1, 2020	November 1, 2020	Egypt
NCT04387409	A Phase III, Double-blind, Randomized, Placebo-controlled Multicentre Clinical Trial to Assess the Efficacy and Safety of VPM1002 in Reducing Healthcare Professionals' Absenteeism in the SARS-CoV-2 Pandemic by Modulating the Immune System	Biological: VPM1002|Biological: Placebo	Interventional	May 18, 2020	June 30, 2021	
NCT04408183	GLS-1200Topical Nasal Spray to Prevent SARS-CoV-2 Infection (COVID-19) in Health Care Personnel	Drug: GLS-1200|Drug: Placebo	Interventional	June 1, 2020	November 20	University of Pennsylvania, United States
NCT04405999	Prevention of Infection and Incidence of COVID-19 in Medical Personnel Assisting Patients With New Coronavirus Disease	Drug: Bromhexine Hydrochloride	Interventional	May 14, 2020	September 30, 2020	Russia
NCT04405271	TAF/FTC for Pre-exposure Prophylaxis of COVID-19 in Healthcare Workers (CoviPrep Study)	Drug: Emtricitabine/Tenofovir Alafenamide 200 MG-25 MG Oral Tablet|Drug: Placebo	Interventional	June 15, 2020	November 15, 2020	Argentina

NCT04420260	Primary Prevention of Infection by COVID-19 in Health Providers	Dietary Supplement: Group A: oropharygeal spray and immunostimulant|Dietary Supplement: Group B: Placebo oropharyngeal spray + Active principle immunostimulant|Dietary Supplement: Group C:Active principle oropharyngeal spray + Placebo taken PO|Dietary Supplement: Group D:Placebo oropharyngeal spray + Placebo taken PO	Interventional	Jul-20	September 20	
NCT04377789	Effect of Quercetin on Prophylaxis and Treatment of COVID-19	Dietary Supplement: Quercetin Prophylaxis	Interventional	March 20, 2020	July 31, 2020	Turkey
NCT04427865	Efficacy of lactoferrin as a preventive agent for healthcare workers exposed to COVID-19	Drug: prophylactic lactoferrin daily	Interventional	July 2020	September 2020	Egypt
NCT04446104	A Preventive Treatment for Migrant Workers at High-risk of Covid-19	Drug: Hydroxychloroquine Sulfate Tablets|Drug: Ivermectin 3Mg Tab|Drug: Zinc|Drug: Povidone-Iodine|Dietary Supplement: Vitamin C	Interventional	May 13, 2020	Jul-20	Singapore
NCT04422561	Prophylactic Ivermectin in COVID-19 Contacts	Drug: Ivermectin Tablets	Interventional	May 31, 2020	Jul-20	Egypt

*Note: A number of these studies are not yet recruiting despite the recruitment start date having passed.

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