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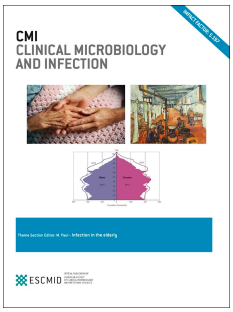

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PII: S1198-743X(21)00040-9

DOI: https://doi.org/10.1016/j.cmi.2021.01.013

Reference: CMI 2399

To appear in: *Clinical Microbiology and Infection*

Received Date: 6 November 2020

Revised Date: 30 December 2020

Accepted Date: 9 January 2021

Please cite this article as: Smit M, Marinosci A, Agoritsas T, Ford N, Calmy A, Prophylaxis for COVID-19: a systematic review, *Clinical Microbiology and Infection*, https://doi.org/10.1016/j.cmi.2021.01.013.

Prophylaxis for COVID-19: a systematic review

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Keywords: COVID-19, SARS-CoV-2, prophylaxis, systematic review

Abstract

Background While the landscape of vaccine and treatment candidates against the novel coronavirus (COVID-19) has been reviewed systematically, prophylactic candidates remain unexplored.

Objectives Map pre- and post- exposure prophylactic (PrEP and PEP) candidate for COVID-19

Data sources PubMed/Medline, Embase, International Committee of Medical Journal Editors and International Clinical Trials Registry Platform clinical trial registries and MedRxiv.

Study eligibility criteria and Participants All studies in humans or animals and randomized clinical trials (RCTs) in humans reporting primary data on prophylactic candidates against COVID-19, excluding studies focused on key populations.

Interventions PrEP and PEP candidate for COVID-19.

Methods Systematic review (SR) and qualitative synthesis of COVID-19 PrEP and PEP studies and RCTs complemented by search of MedRxiv and PubMed and Embase for studies reporting RCTs outcomes since SR search completion.

Results We identified 13 studies (out of 2,119 database records) and 117 RCTs (out of 5565 RCTs in the registries) meeting inclusion criteria. Non-RCT studies reported on cross-sectional studies using hydroxychloroquine (HCQ) in humans (*n=2)* or reported on animal studies (*n=7)* most of which used *antibodies.* All five completed RCTs focused on the use of HCQ as either PrEP or PEP and these and the cross-sectional studies reported no prophylactic effect. The majority of ongoing RCTs evaluated HCQ or other existing candidates including non-SARS-CoV-2 vaccines, anti(retro)virals, or use of vitamins and supplements.

Conclusions The key message from completed studies and RCTs seems to be that HCQ does not work, there is little evidence regarding other compounds with all RCTs using candidates other than HCQ still ongoing. It remains to be seen if the portfolio of existing molecules being evaluated in RCTs will identify successful prophylaxis against COVID-19 or if there is a need for the development of new candidates.

Introduction

The world is facing the biggest global public health emergency of this generation as a result of the novel coronavirus pandemic. The severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) is the causative agent for coronavirus disease 19 (COVID-19), characterised by rapid human-to-human transmission and important pathogenicity [1]. At the time of writing this article, the world has passed a new worrying milestone of one million confirmed COVID-19 deaths [2].

Beyond the human suffering, the COVID-19 pandemic has caused unprecedented pressures on healthcare systems and supply chains [3,4], with the ensuing lock-downs resulting in growing frailties for national economies[5,6]. Containing the COVID-19 pandemic will necessitate a multi-pronged strategies including effective vaccination, prophylaxis and treatment, in addition to existing protective measures such as social distancing, masking and hand hygiene [7–9]. This pandemic has resulted in an unparalleled galvanization of the medical and scientific community to identify pharmacological candidates for its prevention and treatment. While the landscape of vaccine [10,11] and treatment [12,13] candidates has been reviewed systematically, evidence synthesis of prophylactic candidates remains unexplored.

In this review we aim to address this gap by performing a systematic review of all published studies and clinical trials registries for prophylactic candidates to map out the landscape of existing and future candidates. As this is a fast-moving field, we aim to provide an updated status of the evidence by performing an updated systematic review in the near future.

Methods

Search Strategy and selection criteria

We carried out a systematic review according to PRISMA guidelines [14], to identify studies reporting on prophylactic candidate for COVID-19 and/or SARS-CoV-2. Prophylactic candidates were defined as any drug, biologics-based molecule, dietary supplements or herbal remedies used to prevent infection of disease, regardless of its administration route. This included both pre- and post-exposure prophylaxis (PrEP and PEP) but excluded SARS-CoV-2 vaccines and therapeutic interventions for individuals who are already infected. We excluded

studies focused on populations with specific co-morbidities, including those undergoing specific surgical procedures or with specific co-morbidities (Table 1).

PubMed/Medline, and Embase, were searched from inception to and including 13th December 2020; searches were not restricted by language or quality of study and a broad search strategy was used combining the terms; 'SARS-CoV-2' OR 'COVID-19', AND 'prophylaxis' OR 'prophylactic'.

Table 1. Inclusion and exclusion criteria for identified published studies and RCTs.

Inclusion	Exclusion
• *Population*: humans and animals (for the database search not clinical trial register search), including 'high-risk' older individuals, health care workers and healthy subjects • *Intervention*: drug- or biologic-based prophylaxis (pre OR post-exposure) or those based on dietary supplements or herbal extracts; • *Outcomes*: studies reporting impact on SARS-CoV-2 or COVID-19 incidence or prevalence • *Study*: primary data of prophylactic candidates for COVID-19 or SARS-CoV-2 (RCTs only for MedRxiv and clinical trial registries)	• *Population*: *in vitro* studies; studies focused on key population (e.g. those with specific co-morbidities) • *Intervention*: reporting on other prevention approaches (such as social distancing, masks or SARS-CoV-2 vaccines); theoretical candidates or reporting on populations on long-term medication for other conditions and their impact on COVID-19 • *Outcomes*: safety profiles, pharmacological outcomes or studies reporting on outcomes related to other prevention approaches or treatment; • *Study:* studies focusing on previous coronavirus strains, e.g. SARS-CoV; MERS, opinion or narrative pieces, case reports, trial protocols

In order to provide a complete picture of the current prophylactic landscape, we also searched the clinical trials registries (both the International Committee of Medical Journal Editors (ICMJE) and International Clinical Trials Registry Platform (ICTRP)) (Supplement Table S1) for any randomized clinical trials (RCTs) of prophylaxis against COVID-19 and/or SARS-CoV-2, focusing on RCTs evaluating the impact of prophylactic candidates on SARS-CoV-2 or COVID-19 incidence /new cases in humans as a primary endpoint [15,16]. We included all RCTs, irrespective of status, but excluded RCTs with other primary endpoints such as safety (Table 1).

The ICMJE and ICTRP search was conducted up to 13th December 2020 using the same terms as the database search and limiting to interventional studies where possible. Furthermore, MedRxiv was searched from inception to 30th December 2020 for any studies reporting the outcomes of prophylaxis RCTs, using the search terms "COVID-19" AND "prophylaxis" AND "Trial". Finally, an additional search of PubMed/Medline and Embase was performed to identify peer-reviewed papers reporting on clinical trial outcomes since search completion (13th December 2020) using the search terms; 'SARS-CoV-2' OR 'COVID-19', AND 'prophylaxis' OR 'prophylactic' AND 'clinical trial', limited to title and abstract and published between 1st December 2020 to 30th December 2020.

After removal of duplicates, two reviewers (MS and AM) screened abstracts and RCTs independently according to pre-specified inclusion and exclusion criteria (Table 1). Where two studies reported on the same study, the most recent one reporting on the impact of the prophylaxis was chosen. Where the same RCT was found in two or more registries or an RCT was also found in a published article, it was only reported once. Conflicts were resolved by the two reviewers on a case-by-case basis, with conflicts resolved with a third reviewer (AC) where needed. Reference lists of included full-text articles were screened to identify additional studies. The screening and selection process are presented in Figure 1.

Data extraction and synthesis

All data was extracted in Microsoft Excel by MS and AM, in a data extraction form which was piloted on five studies and five clinical trials. All data extraction was quality checked by the other co-author for quality assurance. Data extracted from full-text articles included first author, publication year, country of study, study type, prophylaxis type, molecule name or combination and class, host, study outcome. For RCTs data extraction included trial title, country of sponsor, prophylaxis type, name of molecule or combination and class, target population, sample size and status.

A qualitative data synthesis was performed outlining the landscape of prophylactic candidates, geographical distribution of studies, stage of development and trial status. Risk of bias was assessed by a single reviewer (MS) for all published (peer-reviewed and pre-print) studies using

the Version 2 of the Cochrane risk-of-bias tool for RCTs (RoB 2) and the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool [17,18].

Results

The database search identified 2,119 records. After removing duplicates, we screening 867 citations and assessed 67 full-text reports (Figure 1). Of these, 13 met the inclusion and exclusion criteria and were included in the qualitative synthesis. The majority of the studies excluded at the full-text assessment were studies that did not focus on prophylactic candidate, including *in vitro* studies or studies focused on functional or safety outcomes (*n=20)* or because they reported on trial protocols (*n=12)*. In addition, the search of MedRxiv identified one study reporting on the results of prophylactic RCTs. No additional studies were identified through the hand-picked search of the database. All studies reporting on RCT results (four from database search; one from MedRxiv) were from RCTs identified in the clinical trial registries and so are only counted once.

The search of the clinical registry identified 556 clinical trials. After removing duplicates and full screening, 117 RCTs were identified that met the inclusion criteria and which were included in the qualitative synthesis.

The geographical distribution of the included studies and clinical trials was limited in scope (Supplement Figure S1). The majority of the studies and RCTs (*n=45)* were conducted in the United States of America (USA), Spain (*n=13)*, and Canada (*n=8)*, with the African continent having the fewest studies and RCTs.

Figure 1. Systematic search flow diagram and search terms.

Overview of published studies

A total of five RCTs were identified, including 1 in pre-print. All the remaining studies reported on cross-sectional studies in humans (*n=2)* or on animal studies (*n=7).* This section will focus on reporting on non-RCT studies, with the studies reporting on clinical trial results are reported separately below together with RCTs identified through the clinical trial registries. The majority

of the non-RCTs studies reported on PrEP (*8/9)* with one focused on PEP. Five studies focused on hydroxychloroquine (HCQ), the remainder focused on antibodies (*n=4)* and one study looked at both HCQ and the antiviral favipiravir.

Of the two human studies reporting on HCQ, one found no COVID-19 cases in the intervention arm and 3 cases in the control arm but did not perform statistical analyses on the results [19] and the other found no observed effect [20], although risk of bias was moderate to high (Supplement).

Amongst the seven animal studies, four looked at the use of antibodies [21–24]. All found an effect although they did not report comparable outcomes. Jones et al [21] reported reduced viral replication, Li et al and Tortorici et al reported high prophylactic efficacy [22,24], while rogers et al reported a 50% reduction in disease as measured by weight loss [25].The three remaining animal studies looked at the effect of HCQ alone [25,26] or compared to favipiravir [25]. All three demonstrated no observed effect of HCQ but Kaptein et al did show that favipiravir significantly reduced infectious titre [25]. Again, risk of bias amongst studies evaluating candidates other than HCQ has a moderate to high risk of bias (Supplement 1). Table 2 details the full-texts studies.

Table 2. Summary of peer-reviewed non-RCT studies on prophylactic candidates against COVID-19 and/or SARS-CoV-2.

Study				P(r)EP details						
First Author (Reference)	**Publication Year**	**Country**	**Study Type**	**P(r)EP Type**	**Name of molecule/ combination**	**Type of molecule**	**Host**	**Host details**	**Sample size**	**Study Conclusion**
Human Studies										
Revollo [20]	2020	Spain	Cross-sectional	PrEP	HCQ	Antimalarial	Human	HCQ	69 intervention arm; 418 control arm	No observed effect
Simova [19]	2020	Bulgaria	Cross-sectional	PEP	HCQ	Antimalarial	Human	HCW	156 intervention arm; 48 control arm	No COVID-19 in intervention; 3 cases in control arm
Animal Studies										
Jones [21]	2020	USA	Animal study	PrEP	Neutralising Antibody	Antibody	Animal	Macaques	Not specified	Reduced viral replication
Kaptein [25]	2020	Belgium	Animal study	PrEP	HCQ; favipiravir	Antimalarial; antiviral	Animal	Syrian hamster	Not specified	HCQ showed no observed effect; high doses of favipiravir significantly reduced infectious titre
Li [22]	2020	USA	Animal Study	PrEP	Monoclonal Antibodies	Antibody	Animal	Mice and hamster	Not specified	High efficacy
Maisonnasse [31]	2020	France	Animal study	PrEP	HCQ	Antimalarial	Animal	Macaques	13	No observed effect
Rogers[23]	2020	USA	Animal study	PrEP	Neutralising Antibodies	Antibody	Animal	Syrian hamster	Not specified	50% reduction in disease (as measured by weight loss)
Rosenke [26]	2020	USA and UK	Animal study	PrEP	HCQ	Antimalarial	Animal	Hamster; rhesus macaque	30 hamsters; 10 macaques	No observed effect
Tortorici [24]	2020	USA	Animal study	PrEP	Antibodies	Antibody	Animal	Syrian hamster	Not specified	Notable protective efficacy

Abbreviation: COVID-19, coronavirus disease 19; HCQ, hydroxychloroquine; HCW, health care workers; HR, hazard ratio; IgG1, immunoglobulin G1; PEP, post-exposure prophylaxis; PrEP, pre-exposure prophylaxis; UK, United Kingdom; USA, United States of America; VH-Fc, heavy variable domain fragment crystallization region.

Overview of planned or ongoing RCTs

The search of the databases and MedRxiv identified five published studies reporting on results of RCTs. The search of clinical trial registries identified 117 RCTs that met the inclusion criteria. Of those,85 focused on PrEP, 29 on PEP and three on both PrEP and PEP (Supplement Table S2). The RCTs mainly targeted health care workers alone (*n=72)* or in combination with close contacts, patients, first responders or nursing residents (*n=11),* with 15 RCTs targeting close contacts of index cases alone. Nine studies focused on at risk populations such as geriatric patients, nursing home residents, front line workers and two studies focused on military staff. Only seven clinical trials were completed, with 57 either recruiting or ongoing, 38 not yet recruiting and five either suspended of prematurely ended.

With regards to the molecules being tested, the majority focused on antimalarials including HCQ and chloroquine (*n=63*) either alone (*n=57)* or together with antivirals (*n=3), antibiotics (n=2)* or antiseptic and anthelmintic (*n=1).* Eighteen RCTs investigate the use of non-SARS-CoV-2 vaccines, especially BCG vaccine (*n=12*). Ten RCTs are evaluating the impact of antivirals or antiretrovirals. Seven RCTs are investigating the use of vitamin D or supplements such as lactoferrin, probiotics and quercetin on COVID-19 and seven others investigate the impact of anthelmintic or antiprotozoal. RCTs focused on HCQ mainly tested HCQ alone against either placebo or surveillance.

Amongst the five studies reporting on the results of completed RCTs, all focused on HCQ [27–30,32]. Two studies focused on PrEP [30,33] and three on PEP [28,29,32]. None of the studies established a prophylactic effect of HCQ against COVID-19 (Table 3).

Table 3. Summary of RCT results of prophylactic candidates against COVID-19 and/or SARS-CoV-2.

First Author (Reference)	P(r)EP Type	Intervention	Control	Target Population	Intention to Treat	Sample size	Study Conclusions
Abella [27]	PrEP	HCQ (600 mg daily, 8 weeks)	Placebo	HCW	HCQ: 4 of 64 [6.3%] vs Control: 4 of 61 [6.6%]; P > .99	Total: 132 HCQ: 66; Control: 66	No observed effect
Barnabas [28]	PEP	HCQ (400 mg daily; 3 days and 200 mg daily; 11 days)	Ascorbic acid (500 mg daily; 250 mg daily)	Contacts	Hazard ratio=1.1; 95% CI 0.73-1.66, p>0.20	Total: 671 HCQ: 337; Control: 334	No observed effect
Boulware [29]	PEP	HCQ (800 mg once; 600 mg in 6-8 hours, 600 mh for 4 days)	Placebo	Household contacts; HCW	HCQ : 49 of 414 [11.8%] vs Control : 58 of 407 [14.3%] ; P=0.35	Total: 821 HCQ: 414; Control: 407	No observed effect
Mitja [32]*	PEP	HCQ (800 mg once; 400 mg daily for 6 days)	No intervention	Contacts	Risk Ratio=0.89; 95% CI 0.54-1.46	Total; 2,314 HCQ: 1,116; Control: 1,198	No Observed effect
Rajasingham [30]	PrEP	HCQ (400 mg twice in 6-8 hours; 400 mg once weekly for 12 weeks or 400 mg twice weekly for 12 weeks)	Placebo	HCW	Once weekly : HR=0.72 (95%CI 0.44 to 1.16; P=0.18) Twice weekly : HR=0.74 (95%CI 0.46 to 1.19; P=0.22)	Total: 1,483 HCQ once weekly: 494; HCQ twice weekly: 495; Control: 494	No observed effect

*studies identified through MedRxiv

**studies identified post database search

Abbreviation: CI, confidence intervals; COVID-19, coronavirus disease 19; HCQ, hydroxychloroquine; HCW, health care workers; p, p-value; PEP, post-exposure prophylaxis; PrEP, pre-exposure prophylaxis; UK, United Kingdom; USA, United States of America; VH-Fc, heavy variable domain fragment crystallization region.

Discussion

A range of prophylactic candidates against COVID-19 are being evaluated in RCTs across the world. While the key message from completed studies and RCTs seems to be that HCQ does not work, there is little evidence regarding other compounds with all RCTs using candidates other than HCQ still ongoing. It remains to be seen if the portfolio of candidates being evaluated in RCTs will identify successful prophylaxis against COVID-19 or if there is a need for the development of new candidates.

The large number of studies and ongoing RCTs into prophylactic candidates for COVID-19 highlights the global efforts to rapidly identify effective strategies to mitigate the pandemic. Despite these efforts, around half of the registered RCTs are either not yet recruiting or suspended, and only a handful have been completed, none of them demonstrating an impact. This highlights two important points. First, despite the high level of commitment the conduct of RCTs faces a number of constraints and challenges [34,35]. Second, that the only preventative measures the world currently possessed are social distancing, wearing of masks and hand hygiene [7], until effective prophylactic and vaccine candidates can be identified.

Most ongoing efforts focus on evaluating the use of existing molecules on COVID-19, with few studies and registered RCTs evaluating new molecules. The repurposing of existing drugs is in part driven by observational studies which seemed to suggest that individuals on long-term treatment for example hydroxychloroquine [36], arbidol [37], and thymosin [38] may benefit from protective effect against COVID-19 compared to individuals not on those treatment. Numerous pharmaceuticals and biotechs have joined the race to find vaccines, prophylactic and therapeutic candidates against COVID-19 [39] and this includes a focus on new candidates. Apart from the candidates identified in this review, other molecules cited in the published literature and in the media as possible prophylactic candidates include existing herbal extracts such as Echinacea [40,41], nicotine [42], and new molecules including PAC-MAN (prophylactic antiviral CRISPR in human) for viral inhibition [43] and DARPIN®, multi-target binding neutralizing proteins [44]. The underrepresentation of new molecules in ongoing RCTs is likely in part due to the relative novelty of this virus, and the necessary time lag to develop new molecules prior to testing them in clinical trials.

The world is certainly not unaccustomed to infectious diseases. From the discovery of penicillin at the start of the 20th century [45] and the fight against human immunodeficiency virus (HIV) which started in the 1980s [46,47], the scientific and medical community has demonstrated its ability to galvanise rapidly in order to collate knowledge on transmission, prevention and treatment of infectious diseases. COVID-19 has undisputedly brought the urgency to understand an infectious disease to a new level. However, it has also highlighted the importance of coordinated and aligned efforts, in order to identify effective strategies to fight the pandemic. The large number of prophylactic trials testing the same prophylactic candidate, for example, highlights two points. While the world stood still to halt the spread of the disease, the medical and scientific community has worked under never-before seen pressure, resulting in often fragmented efforts. It has made it hard for communities to coordinate their efforts and join forces. Yet, every trial faces limitations, from selection bias, to sample size issues. Pooling the wealth of clinical trial data that is being produced will allow to construct a clearer of the true effect of these candidates.

Strengths and Limitations

To our knowledge this is one of the first global systematic review to map the landscape of existing and future prophylactic candidates against COVID-19, providing a detailed summary of published studies and both completed and ongoing clinical trials. This review comes at an important time in the pandemic, succeeding the first pandemic wave and preceding a potential second wave.

Yet, this study has a number of limitations. First, it is limited to published data and registered trials and may have missed ongoing, unregistered trials. Given the rapid pace of knowledge generation in relation to this pandemic, data is being published across pre-print platforms which are not peer-reviewed. This review thus provides the best understanding of this large field as per available high-quality data. In fact, since the database search in 17th September, a number of additional studies have emerged, including an additional study reporting that HCQ was not effective as a prophylaxis [27]. Second, given the pace of knowledge generation it provides mainly information on candidates being tested in the prevention of COVID-19, with limited data

available on their clinical and epidemiological effects. Third, the large heterogeneity in existing data on prophylactic impact and the range of candidates being evaluates, means that statistical comparison could not be made to provide an indication of their relative effect.

Conclusions

A range of prophylactic candidates against COVID-19 are currently being evaluated in clinical trials, across a number of countries and settings. Data from completed studies and RCTs seems to suggest that HCQ does not work but the evidence regarding other compounds remains scare, with RCTs using candidates other than HCQ still ongoing. It remains to be seen if the portfolio of existing candidates will identify successful prophylaxis against COVID-19 or if there is a need for the development of new candidates.

Competing interests

The authors have declared that no competing interests exist.

Authors' contributions

MS, AM and AC conceived the paper, formulated the overall aim, scope and lens of the manuscript. MS wrote the protocol and performed the search, and risk of bias. MS and AM carried out the systematic review, extracted the data and wrote the first draft of the manuscript. All authors contributed to the re-drafting and finalisation of the manuscript.

Financial Disclosure

The author(s) received no specific funding for this work.

Additional files

Additional file 1: Supplement 1

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*Database search records excluded with reasons: 32 studies did not explore prophylactic candidates or measure outcome; 11 clinical trial protocol; 9 narrative reviews, opinion pieces or case reports; 1 focused on key populations; 1 could not find full-text
**RCT search records excluded with reasons: