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Review of Therapeutic Guidelines and Hydroxychloroquine Recommendations for COVID-19 in the Pediatric Population

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Abstract

Rationale: Hydroxychloroquine (HCQ) is a medicine approved by the FDA and european states' regulatory bodies for the pediatric population in rheumatoid and dermatologic indications, as well as for the treatment of acute attacks and prophylaxis of malaria. During the current COVID-19 pandemic, this medicine was recommended by many scientific societies and organizations for the treatment of children infected with SARS-CoV-2. However, there were no studies conducted in this population that could demonstrate its efficacy and safety for this indication, and there are potential serious adverse effects in children exposed to HCQ.

Objectives: To describe guidance on indications, dosing, and monitoring of HCQ treatment for COVID-19 in children in clinical practice guidelines and protocols.

Methods: We performed a systematic review of clinical practice guidelines including guidance on the treatment of COVID-19 in children. We searched in Medline and performed manual searches of grey literature and guideline-focused repositories, including online sites of national and international clinical and public health bodies and scientific societies worldwide.

Results: 56 guidelines were included in this review. A cumulative analysis was made considering the date of publication of guidelines and its updates. Throughout time, the amount of guidelines that recommended the use of HCQ in the treatment of children infected with SARS-CoV-2 decreased progressively, constituting 60,0% of total guidelines published until the end of May (n=25), 43,8% of guidelines published until the end of July (n=48), 32,7% of guidelines published until the end of September (n= 55), and 30,4% of guidelines published until the end of November (n=56).

Conclusions: Therapeutic recommendations for COVID-19 have been fluctuating over time. Scientific societies worldwide rushed in recommending the use of HCQ, based on low-quality evidence.

Keywords: COVID-19; SARSCoV-2; Pediatrics; Guidelines; Hydroxychloroquine.

Resumo

Introdução: A hidroxicloroquina (HCQ) é um medicamento aprovado pela FDA e pelos organismos reguladores de vários países europeus para indicações reumatológicas, dermatológicas, e para o tratamento e profilaxia de malária em crianças. Durante a pandemia de COVID-19, a HCQ foi recomendada por sociedades científicas para o tratamento de crianças infetadas com SARS-CoV-2. Contudo, não foram conduzidos estudos nesta população que demonstrassem a sua eficácia e segurança para esta indicação, e existem potenciais efeitos adversos graves em crianças expostas à HCQ.

Objetivo: Descrever as orientações provenientes de normas de orientação clínica (NOCS) relativas aos critérios, dosagem e monitorização do tratamento de COVID-19 com HCQ na população pediátrica.

Métodos: Foi realizada uma revisão sistemática de NOCS que incluíssem orientações sobre o tratamento da infeção por SARS-CoV-2 em crianças. Foi consultada a Medline e foram realizadas pesquisas manuais em repositórios focados em NOCS, incluindo *sites* de órgãos de saúde pública e clínicos nacionais e internacionais e de sociedades científicas de todo o mundo.

Resultados: Foram incluídos nesta revisão 56 documentos orientadores. Uma análise cumulativa foi feita tendo em consideração a data de publicação dos documentos e as suas atualizações. Ao longo do tempo, o número de NOCS que recomendavam o uso de HCQ no tratamento de crianças infetadas com SARS-CoV-2 diminuiu, constituindo 60,0% do total de normas publicadas até o final de maio (n=25), 43,8% das normas publicadas até o final de julho (n=48), 32,7% das normas publicadas até o final de setembro (n=55) e 30,4% das normas publicadas até o final de novembro (n=56).

Conclusão: As recomendações terapêuticas para o tratamento da COVID-19 têm flutuado ao longo do tempo. As sociedades científicas a nível mundial anteciparam-se na recomendação do uso de HCQ, com base em evidência pouco sólida.

Palavras-chave: COVID-19; SARS-CoV-2; Pediatria; Normas; Hidroxicloroquina.

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Introduction

Rationale

Hydroxychloroquine (HCQ) was developed to treat malaria and was first approved in 1955 by the Federal Drug Administration (FDA, 1955). Later it was found to have immunomodulatory properties. In the pediatric population, it is approved for rheumatoid and dermatologic indications (juvenile idiopathic arthritis – in association with other treatments; systemic lupus erythematosus; discoid lupus erythematosus) and for the treatment of acute attacks and prophylaxis of malaria caused by *Plasmodium vivax*, *P. falciparum*, *P. ovale,* and *P. malariae*. In Europe, it was approved individually by each states' regulatory bodies. In Portugal, the approved on-label indications of HCQ are similar and include rheumatoid and dermatologic indications (juvenile idiopathic arthritis; systemic lupus erythematosus; discoid lupus erythematosus; dermatologic disturbances enhanced by sun light exposure) and the treatment of acute attacks of malaria caused by *Plasmodium vivax*, *P. ovale, P. malariae* and susceptible strains of *P. falciparum*, as well as eradication of the latter (Infarmed, 2018).

Early in the current COVID-19 pandemic, HCQ showed promise as a treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected patients. In vitro studies showed both chloroquine and HCQ increase the endosomal pH, inhibiting fusion of SARS-CoV-2 and the host cell membranes (Wang et al., 2020). Also, studies showed both drugs might block the transport of SARS-CoV-2 from early endosomes to endolysosomes, possibly preventing the release of the viral genome (J. Liu et al., 2020). Both chloroquine and HCQ also have immunomodulatory effects, and it was hypothesized that these were other potential mechanisms of action for the treatment of COVID-19. However, despite having demonstrated antiviral activity in some *in vitro* systems, HCQ did not reduce upper or lower respiratory tract viral loads or demonstrate clinical efficacy in a rhesus macaque model (Maisonnasse et al., 2020).

Chloroquine and HCQ, with or without azithromycin, was studied in multiple clinical trials for the treatment of COVID-19 in adults. The clinical trial performed by Gautret et

al. was the first to show benefit on surrogate outcomes in the use of HCQ in adult patients, but it has some potential biases, as it was an open-label and non-randomized clinical trial (Gautret et al., 2020).

Despite the lack of evidence, throughout time this medicine has been recommended by many scientific societies, and national and international organizations for the treatment of children infected with SARS-CoV-2, extrapolating data from adults' trials.

Regarding the pediatric population, there were no studies conducted that demonstrated the efficacy and safety of HCQ for this indication. Data on pharmacokinetics is limited, and there are potentially serious adverse effects in children exposed to HCQ (Juurlink, 2020). Therefore, it is important to determine the risk/benefit of the use of this medicine in a population whose infection by SARS-CoV-2 seems to be less serious and less frequent, as is the case for the pediatric population (Bialek et al., 2020).

Later, multiple subsequent randomised clinical trials (RCTs) conducted in adults failed to demonstrate benefits with HCQ administration, such as the Solidarity Trial (WHO, 2020), the ORCHID Study (Self et al., 2020), the RECOVERY Trial (Horby et al., 2020), a Brazilian Trial (Cavalcanti et al., 2020), among others.

We hereby conduct a review of guidelines on the use of HCQ in children for the treatment of SARS-CoV2 infection, considering the evolution of recommendations through time, as additional evidence was collected on HCQ efficacy and safety in COVID-19 patients.

Objectives

To identify and describe guidance on indications, dosing, and monitoring of HCQ and chloroquine treatment for COVID-19 in children in local, national, and international clinical practice guidelines and protocols during the COVID-19 pandemic.

Methods

A protocol following the PRISMA-P checklist was elaborated before starting the study. A systematic review of clinical practice guidelines and related documents was conducted.

Eligibility criteria

Clinical practice guidelines and guidance documents with recommendations for the treatment of COVID-19 and/or SARS-CoV-2 infection in children (less than 18 years old) that were produced by national or international clinical, public health and regulatory bodies, and scientific societies, as well as local and institutional guidelines, were eligible for inclusion. We also included guidelines that we consulted and that were later superseded, registering the date of publication before its update and the date of the update, and taking this in consideration in the analysis of the evolution of recommendations throughout time during the pandemic. The following documents were excluded: clinical trials, systematic reviews not part of clinical practice guidelines, and review articles by a single author and that were not clearly a consensus-based group document.

Search strategy

Citation and abstract screening of the electronic medical literature database Medline through PubMed interface was conducted on the 8th of September 2020, including all results until this date. This screening was conducted by a reviewer and checked by a second reviewer. The search keywords can be found on appendix A.

Manual search of grey literature and guideline-focused repositories (Google Scholar, National Guidelines Clearinghouse, BMJ Best Practice, TripDatabase, National Institute for Health and Care Excellence, Scottish Intercollegiate Guidelines Network, World Health Organization) was conducted on the 6th of July of 2020, including all results until this date. This screening was conducted by a reviewer and checked by another reviewer. Search keywords for each of these repositories can also be found on appendix A.

Moreover, we conducted a manual search for guidelines on online *sites* of national pediatric, pulmonology, infectology, and public health bodies and scientific societies of all countries worldwide, as well as international scientific bodies and societies. This search was done in a comprehensive way between the months of May and November 2020 in three different periods. Screening was conducted by each country, and it was performed by one reviewer and checked by another reviewer. Disagreements were resolved after a discussion between reviewers.

We used Mendeley for citations management.

Data extraction

Data extraction was performed by one reviewer and checked by another reviewer, into standard templates on excel spreadsheets.

The extraction of data from guidelines from the manual search was conducted between May and November 2020. We checked for updates in every guideline in two moments (September and November), and registered which guidelines had been updated or superseded in each of these moments. This allowed us to divide documents in four different groups: published before May; published between May and the end of July; published between August and the end of September; and published between October and the end of November.

The extraction of data from guidelines from Medline and repositories was conducted in September 2020, and these guidelines were also distributed in the four groups mentioned above.

One reviewer assessed whether guidelines supported or rejected specific recommendations, made other specific recommendations, such as using HCQ only in the context of clinical trials, and highlighted equivocal evidence such as when HCQ was not specifically mentioned or when the authors did not commit to a specific recommendation. Based on this, we categorized guidance documents in five different groups in each of the four periods of time:

- Use of HCQ not recommended.

- Use of HCQ recommended.
- Use of HCQ recommended only in the context of RCT.
- HCQ not specifically mentioned.
- Authors do not commit to a specific recommendation regarding HCQ.

This was checked by a second reviewer. Disagreements were resolved after a discussion between reviewers.

We collected information on: country(ies) of origin, institution, type of document, date of publication, source, criteria for HCQ use, setting for treatment, HCQ formulation, dosing, duration of treatment, expected adverse events, monitoring, contraindications/precautions and references/citations supporting the recommendations. If chloroquine was reported, we also extracted similar data.

Data analysis

We conducted a cumulative analysis of guidelines published throughout time, considering the four groups in time mentioned above (published before May; published between May and the end of July; published between August and the end of September; and published between October and the end of November) and characterizing in each of these groups the recommendations on HCQ in each of the 5 categories established.

Adverse events reported were registered according to MedDRA – SOC (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), 2018).

We used Google Translate to retrieve information from guidelines written in languages that were not dominated by neither team member.

Results

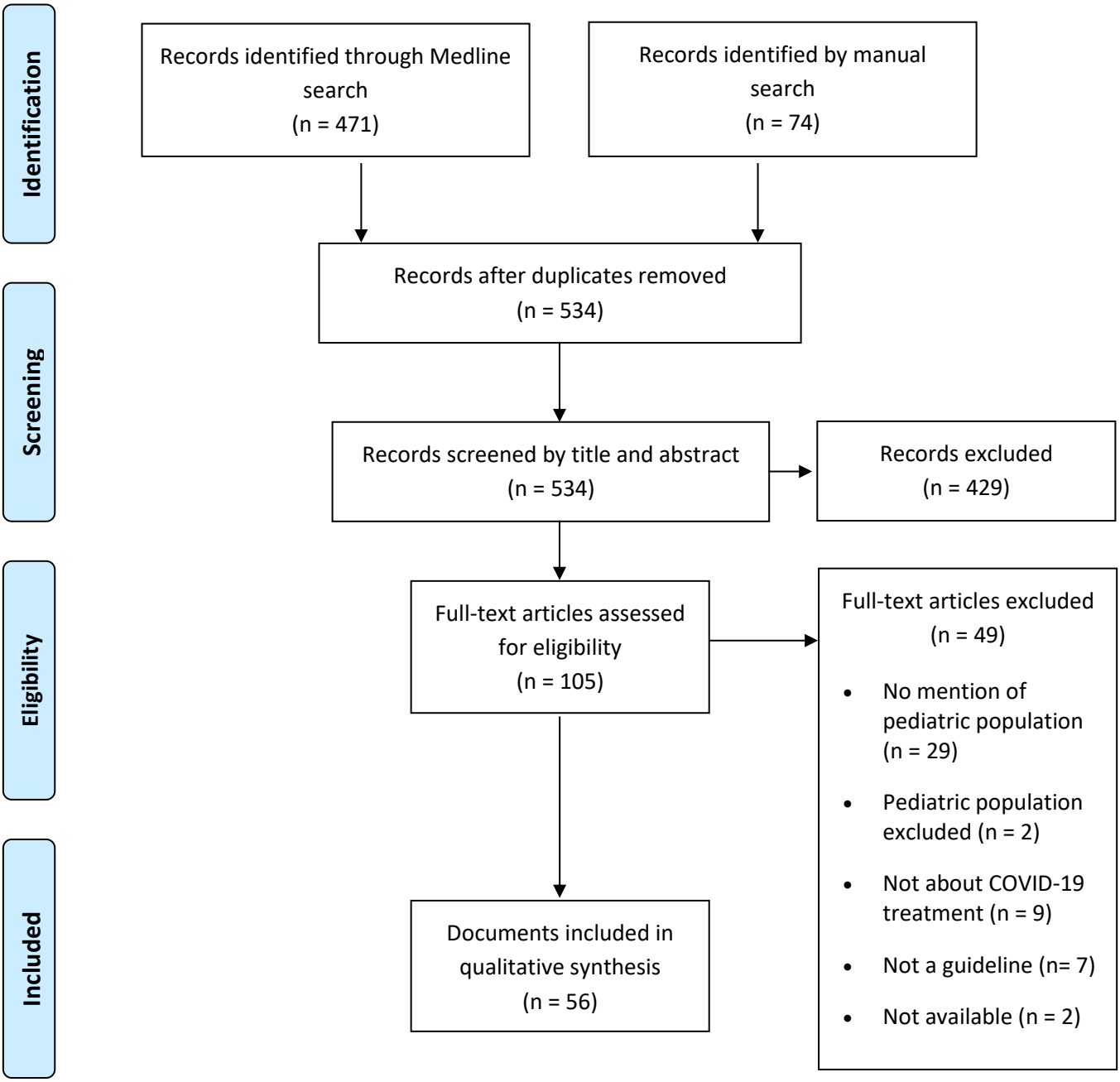

Figure 1. Flowchart of studies

A total of 56 documents were included in this review. Documents identified were published between February and November 2020. Of these, 45 were identified through comprehensive search of scientific societies from countries worldwide, as well as repositories and other sources of grey literature. Eighteen (18) were from European countries (Agoritsas et al., 2020; Bilimse Danışma Kurulu T.C. SAĞLIK BAKANLIĞI, 2020; Buyse et al., 2020; Direção-Geral de Saúde (DGS), 2020; Feldt et al., 2020; Flick et al., 2020; German Society of Pediatrics and Adolescent Medicine (Deutsche Gesellschaft für Kinder- und Jugendmedizin - DGKJ), 2020; Haut Conseil de Santé Publique, 2020; Health Ministry of Russian Federation, 2020; Hellenic Society of Pediatric Infections, 2020; Ministry of Health of the Republic of Belarus, 2020; National Public Health Organization, 2020; Petri et al., 2020; Rey et al., 2020; Sławatyniec et al., 2020; Sociedade Portuguesa de Pediatria, 2020; Stichting werkgroep antibioticabeleid (SWAB), 2020; Whittaker et al., 2020); 6 from Asian countries

Figure 2. Distribution of documents by continent of origin

(EMR Division Directorate General of Health Services Ministry of Health and Family Welfare, 2020; Health Ministry of Russian Federation, 2020; Medical Programme & Ministry of Health Malaysia, 2020; Ministry of Health Services Regulations and Coordination Government of Pakistan, 2020; National Health Commission & State Administration of Traditional Chinese Medicine, 2020; Working Group on Medical Treatment and Prevention of Healthcare-Associated Infection Department of Medical Services Ministry of Public Health, 2020); 6 from African countries (Ghana Ministry of Health, 2020; Libyan National Center for Disease Control

(NCDC), 2020; Ministry of Health and National Public Health Institute of Liberia (NPHIL), 2020; République de Djibouti Ministère de la Santé, 2020; Rossouw et al., 2020; Rwanda Biomedical Centre, 2020); 3 from Oceanian countries (ASID-ANZPID, 2020; National COVID-19 Clinical Evidence Task Force, 2020; PNG Paediatric Society, 2020); and 12 from American countries (Alger et al., 2020; Bhimraj et al., 2020; Camacho et al., 2020; Canadian Critical Care Society and Association of Medical Microbiology and Infectious Disease (AMMI), 2020; Centres for Disease Control and Prevention (CDC), 2020; Chiotos et al., 2020; Ministerio de Salud de Bolivia, 2020; Ministerio de Salud de Republica Dominicana, 2020; National Institute of Health (NIH), 2020; Philippine Pediatric Society & Pediatric Infectious Disease Society of the Philippines, 2020; Rodríguez et al., 2020; Yale New Haven Children's Hospital, 2020). The other 11 guidelines were identified through Medline database search: 1 from an European country (Calvo et al., 2020); 5 from American countries (Carlotti et al., 2020; Diamond et al., 2020; Hennon et al., 2020; Kache et al., 2020; Shekar et al., 2020); and 5 from Asian countries (Chawla et al., 2020; Chen et al., 2020; E. Liu et al., 2020; Miao et al., 2020; Shen et al., 2020).

All the 11 documents identified through Medline search were dated static documents. From the 43 documents identified by the manual comprehensive search of scientific societies' websites, 6 had no mention of the date of publication, 28 were dated static documents, and 9 were web pages that were continuously updated (at least monthly).

From the 9 website-based guidelines, 4 were first consulted in the May to July period. In this first consultation, 1 recommended against the use of HCQ, although there was information about previous recommendations for the drug (Stichting werkgroep antibioticabeleid (SWAB), 2020); 1 did not mention HCQ (Centres for Disease Control and Prevention (CDC), 2020); and 2 recommended the use of HCQ (Whittaker et al., 2020; Yale New Haven Children's Hospital, 2020). Updates of these two guidelines were consulted in September, and HCQ was no longer recommended in either of them. Four of the other 5 website-based guidelines were first consulted in the August to September period (Agoritsas et al., 2020; Bhimraj et al., 2020; Canadian Critical Care Society and Association of Medical Microbiology and Infectious Disease (AMMI), 2020; National COVID-19 Clinical Evidence Task Force, 2020), and the last website-based guideline was consulted in the October to November period (National Institute of Health (NIH), 2020), in which moments

four recommended against the use of HCQ and 1 recommended the use of HCQ only in the context of RCT (Canadian Critical Care Society and Association of Medical Microbiology and Infectious Disease (AMMI), 2020); Two of them mentioned a previous recommendation for the use of the drug (Agoritsas et al., 2020; Bhimraj et al., 2020).

From the 41 static documents, 2 were published in February, 9 were published in March, 12 were published in April, 8 were published in May, 3 were published in June, 4 were published in July, 3 were published in August. One of the documents published in May and first consulted in the May to July period recommended against the use of HCQ in children, but had the mention that this drug was recommended for this indication in previous versions of the document (Health Ministry of Russian Federation, 2020). One of the documents published in April was updated in October, no longer recommending HCQ in the new version (Direção-Geral de Saúde (DGS), 2020). One other document first published in March recommended the use of HCQ but the recommendation was withdrawn in an August update of the document (Rey et al., 2020). One document first consulted in July recommended the use of HCQ in the context of RCT, but was later updated in October, when the recommendation was withdrawn and the authors did not commit with a specific recommendation, only mentioning several entities that recommended against the use of HCQ (Petri et al., 2020). All other static documents remained accessible in November 2020, without any update or information on withdrawal.

The 6 non-dated static documents were first consulted in the May to July period. None of them was updated or superseded. Two of these documents recommended the use of HCQ (Hellenic Society of Pediatric Infections, 2020; Working Group on Medical Treatment and Prevention of Healthcare-Associated Infection Department of Medical Services Ministry of Public Health, 2020), while the other 4 guidance documents had no mention of the drug (McGuire et al., 2020; Ministerio de Salud de Bolivia, 2020; Ministry of Health Services Regulations and Coordination Government of Pakistan, 2020; Rwanda Biomedical Centre, 2020).

Regarding all documents, 25 of the 56 documents included in this review had been published until the end of April 2020. From these, 15 guidance documents recommended the use of HCQ in children infected with SARS-CoV-2 (60,0%; n=25). From the remaining 10 guidance documents, 2 recommended against the use of HCQ (8,0%; n=25), 1 recommended its use only in the context of clinical trials (4,0%; n=25), 5 did not mention HCQ (20,0%; n=25), and 2 did not commit with a specific recommendation regarding the use of this drug (8,0%; n=25).

Regarding the second period of analysis, where we included all cumulative data and updates until the end of July, 48 of the 56 documents included in this review had been published. In this group we included the webpage-based guidelines (except the SWAB guideline, that had reference to have been online before May, which had already been included in the first group; and two of the four webpages we first consulted in August to November – we included the Agoritsas et al. and the National COVID-19 Clinical Evidence Task Force guidelines in this period, because recommendations previous to August were mentioned). We also included from this period on all the undated documents, considering we first consulted them in May. From these, 21 guidance documents recommended the use of HCQ in children infected with SARS-CoV-2 (43,8%; n=48). From the remaining guidance documents, 5 recommended against the use of HCQ (10,4%; n=48), 5 recommended its use only in the context of clinical trials (10,4%; n=48), 12 did not mention HCQ (25,0%; n=48), and 5 did not commit with a specific recommendation regarding the use of this drug (10,4%; n=48).

Regarding the third period of analysis where we considered all cumulative data and updates until the end of September, 55 of the 56 documents included in this review had been published. Eighteen (18) guidance documents recommended the use of HCQ in children infected with SARS-CoV-2 (32,7%; n=55), only one being a newly published guideline in this period (Miao et al., 2020). At this time, 13 guidance documents recommended against the use of HCQ (23,6%; n=55), 5 of which resulted from updates on guidelines that made this recommendation in the second period (Agoritsas et al., 2020; Bhimraj et al., 2020; Rey et al., 2020; Whittaker et al., 2020; Yale New Haven Children's Hospital, 2020), and 1 of which consisted in a webpage-based guideline consulted for

the first time in August/September, as there was no information regarding previous recommendations (National COVID-19 Clinical Evidence Task Force, 2020). One additional webpage-based guideline first consulted in this period recommended the use of HCQ only in the context of clinical trials (Canadian Critical Care Society and Association of Medical Microbiology and Infectious Disease (AMMI), 2020), completing a total of 6 documents (10,9%; n=55), and one other did not mention HCQ (Centres for Disease Control and Prevention (CDC), 2020), completing a total of 13 documents (23,6%; n=55). Relatively to the previous period, the same 5 did not commit with a specific recommendation regarding the use of this drug (9,1%; n=55).

In the last period of analysis, conducted in the end of November, one guideline was added (National Institute of Health (NIH), 2020), completing the 56 documents included in this review. From these, 17 guidance documents recommended the use of HCQ in children infected with SARS-CoV-2 (30,4%; n=56). In the last moment of analysis, 15 guidance documents recommended against the use of HCQ (26,8%; n=56), 1 of which resulted from an October update of a guideline (Direção-Geral de Saúde (DGS), 2020). Regarding the other categories of recommendations, 5 recommended the use of HCQ only in the context of clinical trials (9,3%; n=56), and one document that previously recommended the use of HCQ in RCT was updated. In this new version, the authors whithdraw this recommendation, and mentioned many scientific societies that no longer recommended HCQ, although they did not commit with a specific recommendation (Petri et al., 2020), making a total of 6 documents that did not commit with a specific recommendation regarding the use of this drug (10,7%; n=56). The same 13 documents did not mention HCQ (23,2%; n=56). This information is summarized in table 1.

In total, and considering superseded and updated versions, we identified a total of 25 documents that recommended the use of HCQ until November 2020 (of which we only had access to 21, because 4 had already been retrieved when we discovered them); 15 documents that recommended against the use of HCQ; 6 documents recommending the use of HCQ only in the context of RCT; 12 documents that did not mention HCQ; and 6 documents that did not commit with a recommendation on the use of HCQ.

	Total number of documents according to form	Recommended HCQ until the end of April	Maintained or initiated the recommendation in May to July	Maintained or initiated the recommendation in August to September	Maintained or initiated the recommendation in October to November
No date (first consulted in May)	6 (2 recommended HCQ)	-	2	2	2
Continuously updated web pages	9	1	3	0	0
Dated static documents	41	14	16	16	15
Total of documents that recommended HCQ in each period		15 (n=25) 60,0%	21 (n=48) 43,8%	18 (n=55) 32,7%	17 (n=56) 30,4%

Table 1. Update of documents' recommendations on HCQ in the 3 moments of search

Of remark, in 10 out of the 21 guidelines that recommended HCQ use (Alger et al., 2020; Buyse et al., 2020; Ghana Ministry of Health, 2020; Hellenic Society of Pediatric Infections, 2020; Miao et al., 2020a; Ministerio de Salud de Republica Dominicana, 2020; Ministry of Health and National Public Health Institute of Liberia (NPHIL), 2020; Rey et al., 2020; Rodríguez et al., 2020), and 1 out of 5 that recommended its use in RCT (Petri et al., 2020), chloroquine was also recommended. Only in one of these chloroquine was recommended in preference to HCQ (Whittaker et al., 2020). One guideline that did not mention HCQ, recommended chloroquine but only for the adult population (National Health Commission & State Administration of Traditional Chinese Medicine, 2020).

Considering the 50 dated guidelines and its respective updates, most guidelines that recommended the use of HCQ were published between March and June, as it is clear in figure 3. There was a progressive decline on the recommendation of HCQ use in children infected with SARS-CoV-2 over time. From September on, no new guidelines recommended HCQ use in children with COVID-19.

From the 56 guidance documents, in 9 of them, although children were mentioned in the document, it was not clear in any of the versions whether the recommendation made regarding HCQ specifically included the pediatric population (Agoritsas et al., 2020; Flick et al., 2020; Ministerio de Salud de Bolivia, 2020; National COVID-19 Clinical Evidence Task Force, 2020; National Health Commission & State Administration of Traditional Chinese Medicine, 2020; Petri et al., 2020; République de Djibouti Ministère de la Santé, 2020; Smith et al., 2020; Stichting werkgroep antibioticabeleid (SWAB), 2020).

Regarding the guidance documents nature, as they were identified by their authors, 43 were identified as guidelines, 6 were identified as recommendations, 1 was identified as clinical advice, 5 as clinical pathways and 1 as an expert consensus.

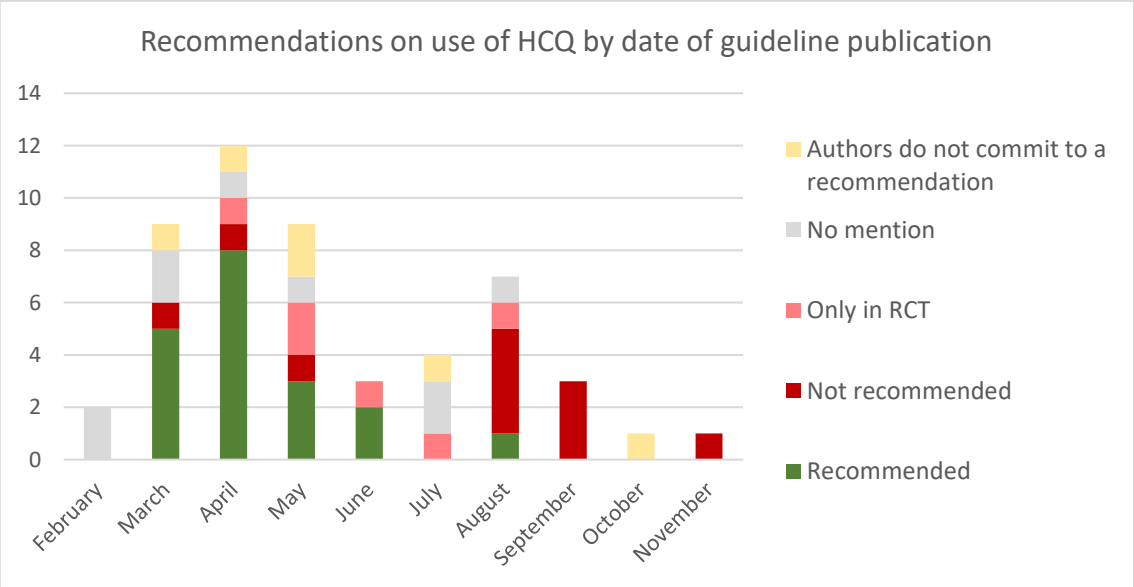

Figure 3. Recommendations on the use of HCQ by date of guideline publication

Criteria and settings for the use of HCQ

Considering the 21 guidance documents that recommended the use of HCQ in any point in time to which we had access, 5 recommended the use of HCQ only in ICU

settings, 8 recommended its use in hospitalized patients and 8 guidelines did not specify the setting where treatment with HCQ might take place. Criteria to recommend HCQ treatment varied greatly, with:

- 1 guideline recommending it in asymptomatic children (Ghana Ministry of Health, 2020);
- 1 guideline recommending it in children with mild clinical findings and a normal chest radiograph (Working Group on Medical Treatment and Prevention of Healthcare-Associated Infection Department of Medical Services Ministry of Public Health, 2020);
- 1 guideline recommending it in children with mild clinical findings but with evidence of pneumonia on chest radiograph and need for O2 supplement (Rodríguez et al., 2020);
- 7 guidelines recommending it in moderate cases and/or children with co-morbidities (Bilimse Danışma Kurulu T.C. SAĞLIK BAKANLIĞI, 2020; Camacho et al., 2020; Direção-Geral de Saúde (DGS), 2020; Hellenic Society of Pediatric Infections, 2020; Miao et al., 2020c; Rey et al., 2020; Sociedade Portuguesa de Pediatria, 2020);
- 9 guidelines recommending it only in severe cases (Alger et al., 2020; Buyse et al., 2020; Chiotos et al., 2020; EMR Division Directorate General of Health Services Ministry of Health and Family Welfare, 2020; German Society of Pediatrics and Adolescent Medicine (Deutsche Gesellschaft für Kinder- und Jugendmedizin - DGKJ), 2020; Medical Programme & Ministry of Health Malaysia, 2020; Ministerio de Salud de Republica Dominicana, 2020; République de Djibouti Ministère de la Santé, 2020; Whittaker et al., 2020);
- 2 guidelines did not clearly specify criteria for the use of HCQ in children with SARS-CoV-2 infection (Ministry of Health of the Republic of Belarus, 2020; Yale New Haven Children's Hospital, 2020).

Six out of the 9 guidelines that recommended the use of HCQ in severe cases indicated severity criteria, and these criteria were relatively uniform between documents. The criteria consisted in:

- Need for Intensive Care Unit (ICU) admission
- Need for respiratory support
- Presence of Acute Respiratory Distress Syndrome (ARDS)
- Presence of septic shock
- Presence of altered mental status
- Presence of multi-organ failure

Doses and duration of treatment

From the 21 guidance documents that recommended HCQ, 2 did not advise regarding posology. One of the documents that did not commit to a specific recommendation on the use of HCQ – Greece National Public Health Organization –also suggested a dosing regimen.

Country	Institution/ Journal	Recommended posology for HCQ	Duration
Belgium	Sciensano (Buyse et al., 2020)	Day 1: 6,5 mg/kg/time (max 400mg) twice daily Day 2-5: 3,25 mg/kg/time (max 200 mg) twice daily	5 days
Bolivia	Ministerio de Salud (Camacho et al., 2020)	400 mg tablets each 12h *per os* in the first day, followed by 200 mg tablets each 12h *per os.*	5 to 10 days
Byelorussia	Ministry of Health (Ministry of Health of the Republic of Belarus, 2020)	Day 1: 6,5 mg/kg per 12h (max 400 mg every 12h) Days 2-5: 3,25 mg/kg per 12h (max 200 mg every 12h). Subject to portability, consider the possibility of reducing the maintenance dose up to once a day (for example, 6,5 mg/kg every 24 hours instead of 3,25 mg/kg every 12 hours).	5 days
China	European Journal of Clinical Microbiology & Infectious Diseases (Miao et al., 2020)	3–5 mg/kg/day (max dose: 400 mg) Hydroxychloroquine sulfate IV, twice daily	5 days
Djibouti	Ministère de la Santé (République de Djibouti Ministère de la Santé, 2020)	Chloroquine 500mg 1 tablet twice daily	10 days
Dominican Republic	Sociedad Dominicana de Infectologia (Rodríguez et al., 2020)	First day: 400 mg every 12h After that: 200 mg every 12h	4 days
Ghana	Republic of Ghana - Ministry of Health (Ghana Ministry of Health, 2020)	3 mg/kg 8 hourly (max: 200 mg/dose)	10 days

Greece	National Public Health Organization (National Public Health Organization, 2020)	Hydroxychloroquine sulfate (Plaquenil formulation): There is no data on dosing for COVID infection in children. The typical dose for malaria is 1st dose: 13 mg hydroxychloroquine sulfate per kg BW (maximum dose 800 mg) 6 hours later: 6,5 mg per kg BW (maximum dose 400 mg) The dose 24 hours after the first: 6,5 mg per kg BW (maximum dose 400 mg) The dose 48 hours after the first: 6,5 mg per kg BW (maximum dose 400 mg)	Not specified
Greece	Hellenic Society of Pediatric Infections (Hellenic Society of Pediatric Infections, 2020)	First dose: 13 mg/kg (maximum: 800 mg) *per os* 6 hours after: 6,5 mg/kg (maximum: 400 mg) *per os* After that: 6,5 mg/kg (maximum 400 mg) *per os* daily Alternative regimen: 7 mg/kg/day *per os* in one or two daily doses (max 400 mg/day) for 5 days (Johns Hopkins)	3 days
Honduras	Sociedad Hondureña de Enfermedades Infecciosas (Alger et al., 2020)	<6 years: 6.5 mg/kg/day each 12h. >6 years: 10 mg/kg/day each 12h. >40 kg: 400 mg/day each 12h.	at least 7 days
India	Ministry of Health & Family Welfare (EMR Division Directorate General of Health Services Ministry of Health and Family Welfare, 2020)	400mg twice daily – for 1 day followed by 200mg twice daily for 4 days	5 days
Malaysia	Malaysian Paediatric Association (MPA) (Medical Programme & Ministry of Health Malaysia, 2020)	First day: 6,5mg/kg/dose (max: 400mg) PO 12-hourly After that: 3,25mg/kg/dose (max: 200mg) PO 12-hourly	5 days
Portugal	DGS (Direção-Geral de Saúde (DGS), 2020)	First day: 6,5mg/kg/dose 12/12h (max 400mg per dose) Maintenance dose: 6,5mg/kg/day 12/12h (max 400mg per day)	At least 5 days, 7 days for severe cases (max 10 days). Consider discontinuing if fever ceases.
Portugal	Sociedade Portuguesa de Pediatria (Sociedade Portuguesa de Pediatria, 2020)	First day: 6,5 mg/kg/dose (max: 400 mg/dose), 12/12h; After that: 3,25 mg/kg/dose (max: 200 mg/dose), 12/12h	5 days (max 10 days)
Spain	AEPED (Rey et al., 2020)	<6 years: 6,5 mg/kg/day each 12h (max 400 mg/día) >6 years: 10 mg/kg/day each 12h (max 400 mg/día).	5 to 14 days (after 5 days use half of the dose)
Thailand	Ministry of Public	Day 1: 10 mg/kg/dose (equivalent to chloroquine	Not specified

	Health (Working Group on Medical Treatment and Prevention of Healthcare-Associated Infection Department of Medical Services Ministry of Public Health, 2020)	base 7,5 mg/kg/dose) twice daily) Subsequent days: 6.5 mg/kg/dose (equivalent to chloroquine base 5 mg/kg/dose) twice daily	
Turkey	Türkiye cumhuriyeti sağlık bakanlığı (Bilimse Danışma Kurulu T.C. SAĞLIK BAKANLIĞI, 2020)	First day: 6,5 mg/kg/dose twice a day on the first day (max: 400 mg/dose); After that: 2,5-3,25 mg/kg/dose twice a day per day (max: 200 mg/dose)	5 days
United Kingdom	Royal College of Pediatrics and Child Health (Whittaker et al., 2020)	6,5 mg/kg 12 hourly on day 1 (maximum initial dose = 400 mg), followed by 3,25 mg/kg 12 hourly on days 2 - 5 (maximum dose = 200 mg)	5 days
United States of America	Yale New Haven Children's Hospital (Yale New Haven Children's Hospital, 2020)	First day: 6,5mg/kg/dose every 12h x 1 day (max 400mg/dose) After that: 3,25-3,5mg/kg/dose every 12h x 4 days* (max 200mg/dose) - Use ideal body weight for dosing to reduce side effects	*4 days (max 10 days)
United States of America	Journal of the Pediatric Infectious Diseases Society (Chiotos et al., 2020)	Infants, children, and adolescents: 13 mg/kg (maximum: 800 mg) PO followed by 6,5 mg/kg (maximum: 400 mg) PO at 6, 24, and 48 hours after initial dose (duration could be extended for up to 5 days on a case-by-case basis) or 6,5 mg/kg/dose (maximum: 400 mg/dose) PO BID on day 1, followed by 3,25 mg/kg/dose (maximum: 200 mg/dose) PO BID for up to 5 days Neonates: Dosing not established; consider use on a case-by-case basis	5 days

Table 2. Doses and duration of treatment proposed in guidelines that recommended the use of HCQ.

Most documents (71,4% - 15 guidelines) recommended the use of a loading dose on the first day of treatment, followed by half the dose on following days. There was heterogeneity in dosing recommendations. Eight guidelines suggested to start with 6,5 mg/kg/dose twice daily (Buyse et al., 2020; Chiotos et al., 2020; Direção-Geral de Saúde (DGS), 2020; Medical Programme & Ministry of Health Malaysia, 2020; Ministry of Health of the Republic of Belarus, 2020; Sociedade Portuguesa de Pediatria, 2020; Whittaker et al., 2020; Yale New Haven Children's Hospital, 2020), while 3 suggested to start with a first dose of 13 mg/kg (Hellenic Society of Pediatric Infections, 2020; National Public Health Organization,

2020; Yale New Haven Children's Hospital, 2020). One guideline suggested starting day 1 with 10 mg/kg/dose twice daily (Working Group on Medical Treatment and Prevention of Healthcare-Associated Infection Department of Medical Services Ministry of Public Health, 2020). Three guidelines recommended starting with fixed 400 mg twice daily regardless of age or weight (Camacho et al., 2020; EMR Division Directorate General of Health Services Ministry of Health and Family Welfare, 2020; Rodríguez et al., 2020). The other 5 guidelines recommended a fixed schema, without a loading dose (Alger et al., 2020; Ghana Ministry of Health, 2020; Miao et al., 2020c; République de Djibouti Ministère de la Santé, 2020; Rey et al., 2020).

Comparing these results, guidelines that recommended the highest loading dose recommended a 3.3 times higher dose compared to guidelines that recommended the lowest dose (20 mg/kg/day vs 6 mg/kg/day in the first 24h). Regarding maintenance dose, we found a 2.2 times higher dosing between the highest and lowest dose recommended (13 mg/kg/day vs 6 mg/kg/day). Concerning cumulative dose, the difference is of 3.6 times (90 mg/kg vs 25 mg/kg).

Recommended duration of treatment varied between 3 and 10 days. Recommended formulation was only reported in 2 guidelines. Doses and duration of treatment recommended by each guideline can be found in table 2.

Reporting of adverse events and monitoring recommendations

Possible adverse events of the use of HCQ were reported by 13 out of the 21 guidance documents that recommended HCQ use; 2 out of 5 that recommended using HCQ only in RCT settings; and 1 out of 15 that advised against the use of HCQ.

Following MedDRA – SOC (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), 2018) guidelines that reported adverse effects reported them in the following SOC:

- SOC Cardiac disorders: 15 guidelines (QTc prolongation) (Alger et al., 2020; Bilimse Danışma Kurulu T.C. SAĞLIK BAKANLIĞI, 2020; Camacho et al., 2020; Chiotos et al., 2020; EMR Division Directorate General of Health Services Ministry of Health and Family Welfare, 2020; Ghana Ministry of Health, 2020; Haut Conseil de Santé Publique,

2020; Hellenic Society of Pediatric Infections, 2020; Miao et al., 2020; Ministry of Health and National Public Health Institute of Liberia (NPHIL), 2020; Ministry of Health of the Republic of Belarus, 2020; National Public Health Organization, 2020; Petri et al., 2020; Rey et al., 2020; Sociedade Portuguesa de Pediatria, 2020; Yale New Haven Children's Hospital, 2020)

- SOC Blood and lymphatic system disorders: 8 guidelines (Hemolytic anemia in G6PD-deficiency) (Camacho et al., 2020; Chiotos et al., 2020; Ghana Ministry of Health, 2020; Hellenic Society of Pediatric Infections, 2020; Medical Programme & Ministry of Health Malaysia, 2020; Sociedade Portuguesa de Pediatria, 2020; Working Group on Medical Treatment and Prevention of Healthcare-Associated Infection Department of Medical Services Ministry of Public Health, 2020; Yale New Haven Children's Hospital, 2020)
- SOC Endocrine disorders: 7 guidelines (Hypoglycemia) (Alger et al., 2020; Buyse et al., 2020; Ghana Ministry of Health, 2020; Medical Programme & Ministry of Health Malaysia, 2020; Rey et al., 2020; Sociedade Portuguesa de Pediatria, 2020; Yale New Haven Children's Hospital, 2020)
- SOC Gastrointestinal disorders: 5 guidelines (Nausea, vomiting, hepatotoxicity) (Camacho et al., 2020; Medical Programme & Ministry of Health Malaysia, 2020; Sociedade Portuguesa de Pediatria, 2020; Working Group on Medical Treatment and Prevention of Healthcare-Associated Infection Department of Medical Services Ministry of Public Health, 2020; Yale New Haven Children's Hospital, 2020)
- SOC Eye disorders: 5 guidelines (Retinopathy) (Camacho et al., 2020; Hellenic Society of Pediatric Infections, 2020; Medical Programme & Ministry of Health Malaysia, 2020; Rey et al., 2020; Yale New Haven Children's Hospital, 2020)
- SOC Skin and subcutaneous tissue disorders: 3 guidelines (Rash) (Camacho et al., 2020; Medical Programme & Ministry of Health Malaysia, 2020; Working Group on Medical Treatment and Prevention of Healthcare-Associated Infection Department of Medical Services Ministry of Public Health, 2020)
- SOC Nervous system disorders: 2 guidelines (Irritability) (Camacho et al., 2020; Hellenic Society of Pediatric Infections, 2020)

Regarding monitoring, most documents focused on ECG monitoring of the QT interval: 8 out of 21 that recommended the use of HCQ (Bilimse Danışma Kurulu T.C. SAĞLIK BAKANLIĞI, 2020; Buyse et al., 2020; Camacho et al., 2020; EMR Division Directorate General of Health Services Ministry of Health and Family Welfare, 2020; Medical Programme & Ministry of Health Malaysia, 2020; Rey et al., 2020; Sociedade Portuguesa de Pediatria, 2020; Yale New Haven Children's Hospital, 2020); and 1 out of 5 that recommended using HCQ only in RCT settings (Haut Conseil de Santé Publique, 2020). Two documents recommended monitoring of glucose levels (Buyse et al., 2020; Rey et al., 2020), and 4 other documents recommended monitoring of hemolysis daily with a complete blood count in patients with G6PD deficiency (Medical Programme & Ministry of Health Malaysia, 2020; Sociedade Portuguesa de Pediatria, 2020; Yale New Haven Children's Hospital, 2020) and every 3 days in patients without G6PD deficiency (Miao et al., 2020c). Two documents recommended screening of G6PD deficiency before initiating treatment with HCQ (Ghana Ministry of Health, 2020; Working Group on Medical Treatment and Prevention of Healthcare-Associated Infection Department of Medical Services Ministry of Public Health, 2020); one guideline recommended liver function monitoring every 3 days (Medical Programme & Ministry of Health Malaysia, 2020).

Precautions and Counterindications

Five (5) guidance documents reported counterindications, all of them stating a QTc > 500 msec as a counterindication for the use of HCQ (Alger et al., 2020; Buyse et al., 2020; Medical Programme & Ministry of Health Malaysia, 2020; Sociedade Portuguesa de Pediatria, 2020; Yale New Haven Children's Hospital, 2020). One of them also stated antecedents of arrythmia as a counterindication (Sociedade Portuguesa de Pediatria, 2020). One of these guidelines stated as counterindications myasthenia gravis, porphyria, retinal pathology and epilepsy, and as a precaution to take in consideration eventual drug interactions (Buyse et al., 2020). A second document stated as counterindication epilepsy and myelosuppression (Alger et al., 2020). A third document stated as counterindications retinopathy of any degree or etiology and stated as a precaution the use in children aged less than 6 months (Sociedade Portuguesa de Pediatria, 2020), a precaution also stated in the fourth guidance document (Yale New Haven Children's Hospital, 2020).

Cited evidence by guidance documents

Out of the 25 guidance documents that recommended HCQ use, 8 did not specifically cite any evidence to support their recommendations (EMR Division Directorate General of Health Services Ministry of Health and Family Welfare, 2020; German Society of Pediatrics and Adolescent Medicine (Deutsche Gesellschaft für Kinder- und Jugendmedizin - DGKJ), 2020; Ghana Ministry of Health, 2020; Medical Programme & Ministry of Health Malaysia, 2020; Ministry of Health of the Republic of Belarus, 2020; Working Group on Medical Treatment and Prevention of Healthcare-Associated Infection Department of Medical Services Ministry of Public Health, 2020). Five (5) documents were updated, no longer recommending HCQ when they were consulted for this purpose, and it was not possible to retrieve previous bibliography to support the recommendation (Agoritsas et al., 2020; Direção-Geral de Saúde (DGS), 2020; Health Ministry of Russian Federation, 2020; Working Group on Medical Treatment and Prevention of Healthcare-Associated Infection Department of Medical Services Ministry of Public Health, 2020; Yale New Haven Children's Hospital, 2020). Only 12 guidelines cited evidence, of which 7 presented in-text reference relative to the reported recommendation and 5 only had the references in the end of the document, not having in-text reference of the bibliography (Buyse et al., 2020; Camacho et al., 2020; Ministerio de Salud de Republica Dominicana, 2020; République de Djibouti Ministère de la Santé, 2020; Rodríguez et al., 2020) – detailed on appendix B.

Out of the 15 guidance documents that recommended against the use of HCQ in children for the treatment of COVID-19 (including the updated versions of documents that previously recommended its use), 12 guidelines cited evidence justifying this position, with in-text citations – detailed on appendix B. Two documents did not have in-text citations of the bibliography presented in the end (Rey et al., 2020; Yale New Haven Children's Hospital, 2020). One document did not cite evidence to support the recommendation on HCQ (Direção-Geral de Saúde (DGS), 2020).

Out of the 6 guidance documents that recommended HCQ use in children for the treatment of COVID-19 only in the context of clinical trials, 5 guidelines cited evidence – detailed on appendix B, and 1 did not present any bibliography (ASID-ANZPID, 2020).

Documents that recommended HCQ cited more often *in vitro* studies (17%) than the ones that did not recommend HCQ (13%). Most guidelines cited evidence produced during the pandemic and in the context of the pandemic. Documents that recommended HCQ cited evidence related to the pediatric population more often than documents that did not recommend HCQ. A summary of this information can be found in table 3.

	Study type				Context			Population		
	In vitro	Animal model	Human		COVID-19 related	Non COVID-19 related		Adult	Pediatric	Not specified
Guidelines that recommend HCQ	8	1	38		56	4		22	26	8
%	17%	2%	81%		93%	7%		39%	46%	14%
Guidelines that do not recommend HCQ	12	2	82		83	14		71	15	1
%	13%	2%	85%		86%	14%		82%	17%	1%
Guidelines that recommend HCQ only in RCT	0	0	1		10	0		9	1	0
%	0%	0%	100%		100%	0%		90%	10%	0%

Table 3. Categorization of cited evidence by identified clinical practice guidelines.

On further sub-group analysis, detailed in table 4, when we look to cited evidence of guidelines divided by each continent of origin, we can see that the characteristics of cited evidence did not change significantly based on this factor. The only meaningful difference we found was in the Asian countries guidelines' that recommended HCQ use, where the percentage of *in vitro* studies cited to support this recommendation was significantly higher compared to guidelines with origin in other continents.

Guidelines that recommend HCQ use

	In vitro	Animal model	Human	Total	COVID-19 related	Non COVID-19 related	Total	Adult	Pediatric	Not specified	Total
Europe	1	0	25	26	32	1	33	6	24	4	34
	3,8%	0,0%	96,2%		97,0%	3,0%		17,6%	70,6%	11,8%	
Asia	3	0	0	3	5	1	6	1	1	2	4
	100,0%	0,0%	0,0%		83,3%	16,7%		25,0%	25,0%	50,0%	
S. America	0	0	0	0	2	1	3	2	1	2	5
	--	--	--		66,7%	33,3%		40,0%	20,0%	40,0%	
N. America	3	1	8	12	10	1	11	8	0	0	8
	25,0%	8,3%	66,67%		90,91%	9,1%		100,00%	0,0%	0,0%	
Africa	1	0	5	6	7	0	7	5	0	0	5
	16,7%	0,0%	83,33%		100,00%	0,0%		100,00%	0,0%	0,0%	

Guidelines that recommended HCQ use only on the context of RCT

	In vitro	Animal model	Human	Total	COVID-19 related	Non COVID-19 related	Total	Adult	Pediatric	Not specified	Total
Europe	0	0	5	5	5	0	5	5	0	0	5
	0,0%	0,0%	100,0%		100,0%	0,0%		100,0%	0,0%	0,0%	
Asia	0	0	3	3	3	0	3	2	1	0	3
	0,0%	0,0%	100,0%		100,0%	0,0%		66,7%	33,3%	0,0%	
N. America	0	0	1	1	1	0	1	1	0	0	1
	0,0%	0,0%	100,0%		100,0%	0,0%		100,0%	0,0%	0,0%	

Guidelines that recommended against the use of HCQ

	In vitro	Animal model	Human	Total	COVID-19 related	Non COVID-19 related	Total	Adult	Pediatric	Not specified	Total
Europe	1	0	25	26	25	1	26	18	11	0	29
	3,8%	0,0%	96,2%		96,2%	3,8%		62,1%	37,9%	0,0%	
Asia	1	0	7	8	8	0	8	7	0	0	7
	12,5%	0,0%	87,5%		100,0%	0,0%		100,0%	0,0%	0,0%	
N. America	10	2	27	39	30	9	39	24	3	1	28
	25,6%	5,1%	69,2%		76,9%	23,1%		85,7%	10,7%	3,6%	
Oceania	0	0	22	22	19	4	23	21	1	0	22
	0,0%	0,0%	100,0%		82,6%	17,4%		95,5%	4,5%	0,0%	
Africa	0	0	1	1	1	0	1	1	0	0	1
	0,0%	0,0%	100,0%		100,0%	0,0%		100,0%	0,0%	0,0%	

Table 4. Sub-group analysis of cited evidence based on continent of origin of guidelines.

Discussion

In 56 guidance documents addressing the treatment of COVID-19 in children we found significant discrepancies between recommendations on the use of HCQ provided by different scientific societies worldwide. This included recommendations for or against the use of HCQ, and different recommendations regarding posology, formulation and monitoring of children on HCQ therapy. Early in the pandemic we found more guidance documents supporting the use of HCQ (60,0% of guidelines published until May vs 30,4% of guidelines published until November 2020). However, we still identified active documents that recommended the use of HCQ in children infected with SARS-CoV-2 in November 2020, when results of several RCT enrolling adults had showed that HCQ is probably not effective against SARS-CoV-2 infection.

It is interesting to notice that, in guidelines published between February and July, we identified a higher number of documents that recommended the use of HCQ in children for the treatment of COVID-19. Evidence cited to support these recommendations was almost universally based on *in vitro* studies and the open label non-randomized clinical trial conducted by Gautret et al. (Gautret et al., 2020). Although this was a clinical trial, its design had frailties. The lack of randomization and the lack of a covariate adjusted analysis limits the conclusions that should be drawn from this study. Moreover, the choice of presence/absence of the virus at 6 days post-inclusion as the primary outcome was selected to report and probably was not the best, as it is not clear how this outcome relates to other outcomes that are of importance to patients, like 28-day mortality (Dahly et al., 2020).

From July on, we noticed an increasing number of guidelines that recommended against the use of HCQ, both in children and adults, mainly based on the results of RCTs such as RECOVERY (Horby et al., 2020), Solidarity (WHO, 2020) and the trial by Cavalcanti et al. (Cavalcanti et al., 2020). Several other studies and clinical trials have been conducted and show that there is no evidence of efficacy of the use of HCQ neither early in the disease course (Skipper et al., 2020), (Mitjà et al., 2020) nor in seriously ill (Mahévas et al., 2020) and hospitalized patients (Ulrich et al., 2020).

This shows that there was a certain rush in the recommendation of HCQ by multiple scientific societies worldwide in an initial phase, when evidence supporting this recommendation was not solid. We can further verify this considering approximately 12,5% of the guidance documents we gathered cited at least one preprinted article as evidence to support their recommendations (7 in a total of 56 documents, from which only 32 of the documents that made specific recommendations regarding HCQ cited evidence to support their recommendations).

This rush in recommending possibly effective therapeutics is understandable considering the rapid onset of this worldwide pandemic, and the lack of therapeutic tools towards it, pressuring health care providers to try experimental therapies with limited evidence, particularly repurposed drugs that showed promise at pre-clinical level and were readily available to use. Regulatory bodies and scientific societies were also pressured to support these decisions, given the public health threat. However, it also led to the recommendation and use of a drug in many patients that, as shown later, probably had no benefit fighting SARS-CoV-2. Moreover, safety issues were well known, such as the potential for QTc prolongation and precipitation of arrhythmias (Juurlink, 2020). This situation is more questionable when we consider the pediatric population, because, although there are reports of children with COVID-19 requiring intensive care unit level of care, large epidemiologic studies (Bialek et al., 2020; Dong et al., 2020) suggest that acute disease manifestations are substantially less severe in children than in adults (Ludvigsson, 2020). This makes the risk-benefit ratio for the use of HCQ in this population even higher. Considering this, we believe it is important to carefully evaluate the risk-benefit ratio of every recommendation made, even in a time of pandemics, as well as the quality and appropriateness of evidence supporting it.

Diversely, even in a time of pandemics, we identified problems in many of these guidelines, that are common when we talk about a special population like this. Several guidelines (9 out of 56 – 16%) mention children along the text (mostly the differences in the clinical presentation relative to adults) but fail to specify if the therapeutic recommendations made on subsequent chapters also apply to children. Most of the guidelines that were excluded did not mention the pediatric population. This is a

problem because most of these guidelines do not explicitly express the target population, leaving clinicians confused about whether the recommendations could be applicable to special populations. It is key to specify the target population in every guideline, and particularly important to notice whether recommendations can be extended to the pediatric population or not, mentioning the evidence supporting these statements.

The lack of specificity in some of the guidelines regarding their target population is one of the limitations we find in our study. We can have excluded guidelines that could have been intended by their authors to include children, but failed to report it. On the other hand, we could have included guidelines in which, although the pediatric population was mentioned, HCQ recommendations did not apply to children.

Another limitation to our study is the fact that 6 guidelines were written in foreign languages that were not mastered by the authors of this study. Google Translate was used to extract the main data requested, but details might have been lost in translation. However, a recent study form Jackson et al. showed that Google Translate is a viable tool for translating articles published in other languages into English for the purpose of abstracting data for systematic reviews (Jackson et al., 2019), with agreement approaching 90% for 9 languages, which were the languages of 4 of our 6 studies in these conditions.

We can also point the fact that we did not assess guidelines' quality with AGREE II as a possible limitation, although we made this decision because of high heterogeneity on the structure of clinical guidance documents found, considering many of them were not classical guidelines. Also, this assessment would be much more limited by language, considering Google Translate is useful and reliable to extract the main data requested, but, as exposed above, details that could be important in quality assessment could be lost in translation.

One final limitation we identified in our study is the fact that some guidelines are continuously being updated – which is great for clinicians but makes it harder to set a point in time when we analyze them. On the one hand, from the 25 guidelines that

recommended HCQ, 6 were superseded or updated, no longer recommending the use of HCQ for the treatment of COVID-19 in November 2020. On the other hand, from the 15 guidelines found that recommend against the use of HCQ in children, 3 recommended the use of HCQ before subsequent updates. In effect, this was one of the biggest challenges of this study, that we tried to overcome by understanding the evolution of recommendations in pair with the evolution of evidence throughout time. This becomes clear when we look at the number of guidelines that recommended HCQ for the treatment of children infected with SARS-CoV-2 back in April vs in November 2020. This is an extraordinary example of a rapid fluctuation of recommendations with the rapid production of evidence that has never been witnessed before, as we are witnessing now with the COVID-19 pandemics.

Conclusion

Since the beginning of the pandemic of COVID-19, many guidelines have been published regarding the treatment of this disease, including in the pediatric population – at a much faster rate than usual. The recommendations within guidelines have also been highly fluctuating, with frequent updates as evidence builds up. There were many guidelines recommending the use of HCQ in the first months after the pandemic started, based on low-quality evidence. Many of these guidelines have, since then, been updated or superseded, and most recent guidelines recommend against the use of HCQ in SARS-CoV-2 infection in children, based on the results of various subsequently published RCT that failed to demonstrate benefits with HCQ administration for this indication.

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Appendix A

Search strategy for Medline

COVID-19/

SARS-CoV-2/

"COVID-19".ti.ab

"SARS-CoV-2".ti.ab

1 or 2 or 3 or 4

Child*

Guideline/ or practice guideline/

Guidelines as topic/ or practice guidelines as topic/

(guideline* or algorithm* or standard*).ti.ab.

"best practice".ti.ab.

"clinical pathway".ti.ab.

7 or 8 or 9 or 10 or 11

5 and 6 and 12

Grey literature search terms

Google Scholar – 'COVID-19 guidelines' or 'SARS-CoV-2 guidelines'

National Guidelines Clearinghouse – 'COVID-19' or 'SARS-CoV-2'

BMJ Best Practice – 'COVID-19' or 'SARS-CoV-2'

Scottish Intercollegiate Guidelines Network – 'COVID-19' or 'SARS-CoV-2'

National Institute for Clinical Excellence - 'COVID-19' or 'SARS-CoV-2'

TripDatabase - 'COVID-19' or 'SARS-CoV-2'

World Health Organization - 'COVID-19' or 'SARS-CoV-2'

Appendix B

[Numbers of the citation order in original documents were kept in this tables for easier orientation on the analyses of guidelines.]

B1. Evidence cited by guidelines that recommend HCQ use in children for the treatment of COVID-19

Country	Institution / Journal	Bibliography
Honduras	Sociedad Hondureña de Enfermedades Infecciosas (no in-text reference)	Dong Y et al. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China. Pediatrics 2020 Mar 16; [e-pub]. (https://doi.org/10.1542/peds.2020-0702).
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B3. Evidence cited by guidelines that recommend HCQ use in children for the treatment of COVID-19 only in the context of RCT

Country	Institution / Journal	Bibliography
Canada	Government of Canada	P. Horby and M. Mafham, "Effect of Hydroxychloroquine in Hospitalized Patients with COVID-19: Preliminary results from a multi-centre, randomized, controlled trial.," medRxiv, 2020.
China	Annals of Translational Medicine	43. Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe COVID-19. N Engl J Med 2020. [Crossref] [PubMed]
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United Kingdom	BMJ Best Practice	2. World Health Organization. Clinical management of COVID-19: interim guidance. 2020 [internet publication].

Appendix C

All guidance documents included in the review, access dates and updates' dates, target population, and the recommendations on HCQ use at each moment.

DOI (documents retrieved from Medline search)	Country of origin	Author institution / Published Journal	Date of Publication / Updates	Accessed at	Target population	Recommendation on HCQ
	USA	Yale New Haven Children's Hospital	Webpage, first consulted in May 2020	https://www.lucidchart.com/documents/embeddedchart/7a86fcb7-d313-4313-bd66-f069517fbda6	Pediatric, any age	HCQ recommended
			From Sep-20 on			HCQ not recommended
10.1542/hpeds.2020-0170	USA	American Academy of Pediatrics	26-Aug-20	https://hosppeds.aappublications.org/content/early/2020/08/25/hpeds.2020-0170/tab-article-info	Pediatric, any age	HCQ not recommended
	Dominican Republic	Ministerio de Salud Pública	01-Mar-20	https://repositorio.msp.gob.do/bitstream/handle/123456789/1725/ProtocologiagnosticoytratamientoCOVID-19%29.pdf?sequence=1&isAllowed=y	Pediatric and Adult	HCQ recommended
	China	National Health Commission & State Administration of Traditional Chinese Medicine	03-Mar-20	https://www.chinadaily.com.cn/pdf/2020/1.Clinical.Protocols.for.the.Diagnosis.and.Treatment.of.COVID-19.V7.pdf	Not clearly expressed	No mention of HCQ
10.6061/clinics/2020/e1894	Brasil	Clinics Sao Paulo	13-Apr-20	https://pubmed.ncbi.nlm.nih.gov/32321116/	Pediatric, any age	Authors do not commit with a recommendation regarding HCQ
10.1007/s12519-020-00343-7	China	World Journal of Pediatrics	07-Feb-20	https://link.springer.com/article/10.1007/s12519-020-00343-7?utm_source=getftr&utm_medium=getftr&utm_campaign=getftr_pilot	Pediatric, any age	No mention of HCQ
	Bolivia	Ministerio de Salud	No mention on date of publication, first consulted in May 2020	https://www.minsalud.gob.bo/component/jdownloads/?task=download.send&id=501&catid=30&m=0&Itemid=646	Pediatric and Adult	No mention of HCQ
	Bolivia	Ministerio de Salud	01-May-20	https://www.minsalud.gob.bo/component/jdownloads/?task=download.send&id=423&catid=30&m=0&Itemid=646	Not clearly expressed	HCQ recommended

	Pakistan	Pakistan Paediatric Association (PPA)	No mention on date of publication, first consulted in May 2020	https://static.wixstatic.com/media/13d97c_da7c9b47290548daa5e9bbe63b7f5a19~mv2.jpg	Pediatric, any age	No mention of HCQ
	UK	Royal College of Pediatrics and Child Health	Webpage, first consulted in May 2020	https://www.rcpch.ac.uk/resources/covid-19-clinical-management-children-admitted-hospital-suspected-covid-19	Pediatric, any age	HCQ recommended
			From September 2020 on			HCQ not recommended
	Switzerland	Swiss Society for Infectious Diseases	In-text mention of previous recommendation for the use of HCQ	Retrieval not possible	Not clearly expressed	HCQ recommended
			Webpage, first consulted in September 2020	https://ssi.guidelines.ch/guideline/3352		HCQ not recommended
	Lybia	Ministry of Health	01-Mar-20	http://seha.ly/en/wp-content/uploads/2020/03/1584158976633293.pdf	Pediatric and Adult	No mention of HCQ
	Djibouti	République de Djibouti - Ministère de la Santé	18-Mar-20	https://sante.gouv.dj/storage/publications/April2020/cMcQEVZc9fS4wLjvUSqA.pdf	Not clearly expressed	HCQ recommended
	Spain	Asociación Española de Pediatría	21-Mar-20	https://www.aeped.es/noticias/recomendaciones-aep-tratamiento-especifico-en-casos-covid19-en-pacientes-pediatricos-com	Pediatric, any age	HCQ recommended
			From Aug-20 on			HCQ not recommended
	Belgium	Sciensano	31-Mar-20	https://gbs-vbs.org/fileadmin/user_upload/Unions/PED/Belg_Recomm_COVID_ped_31mar_NL.pdf	Pediatric, any age	HCQ recommended
	Honduras	Sociedad Hondureña de Enfermedades Infecciosas	01-Apr-20	http://www.desastres.hn/COVID-19/covid19guiasprovisionalesresumidasyextendidas/Infectologia_COVID19_VersionExtendida_01042020.pdf		HCQ recommended
	Poland	Polskie Towarzystwo Pediatryczne	03-Apr-20	https://ptp.edu.pl/covid-19	Pediatric, any age	No mention of HCQ
	Bielorrusia	Ministry of Health	06-Apr-20	http://minzdrav.gov.by/upload/dadvfiles/letter/%D0%98%D0%BD%D1%81%D1%82%D1%80%D1%83%D0%BA%D1%86%D0%B8%D1%8F%20%D0%B4%D0%B5%D1%82%D0%B8.pdf	Pediatric, any age	HCQ recommended
	Portugal	Sociedade Portuguesa de Pediatria	22-Apr-20	https://drive.google.com/file/d/1zv_aM0HgNk4BrfsM1G-7msVi-5gbv3Ff/view?usp=sharing	Pediatric, any age	HCQ recommended

	Portugal	Direção Geral da Saúde (DGS)	23-Mar-20	https://www.dgs.pt/directrizes-da-dgs/normas-e-circulares-normativas/norma-n-0042020-de-23032020-pdf.aspx	Pediatric and Adult	HCQ recommended
			From Oct-20 on	https://covid19.min-saude.pt/wp-content/uploads/2020/10/Norma_004_2020_act_14_10_2020.pdf		HCQ not recommended
	Austria	Österreichische Gesellschaft für Pneumologie (ÖGP)	27-Apr-20	https://www.ogp.at/wp_ogp/wp-content/uploads/%C3%96GP-Statement-zu-COVID_20200427_IC.pdf	Not clearly expressed	HCQ recommended only in the context of RCT
	Ghana	Republic of Ghana - Ministry of Health	30-Apr-20	https://www.moh.gov.gh/wp-content/uploads/2016/02/COVID-19-STG-JUNE-2020-1.pdf	Pediatric and Adult	HCQ recommended
	Greece	National Public Health Organization	14-May-20	https://eody.gov.gr/wp-content/uploads/2020/03/covid-19-odigies-therapeias.pdf	Not clearly expressed	Authors do not commit with a recommendation regarding HCQ
	Liberia	Ministry of Health and National Public Health Institute of Liberia (NPHIL)	01-Jun-20	https://moh.gov.lr/wp-content/uploads/Interim_Guidance_for_care_of_Pts_with_Covid_19_in_Liberia.pdf	Pediatric and Adult	HCQ not recommended
	Turkey	Türkiye cumhuriyeti sağlık bakanlığı	03-Jun-20	https://covid19bilgi.saglik.gov.tr/depo/rehberler/covid-19-rehberi/COVID-19_REHBERI_COCUK_HASTA_YONETIMI_VE_TEDAVI.pdf	Pediatric, any age	HCQ recommended
	Greece	Hellenic Society of Pediatric Infections	No mention on date of publication, first consulted in May	https://e-child.gr/news/%ce%bf%ce%b4%ce%b7%ce%b3%ce%af%ce%b5%cf%82-%cf%84%ce%b7%cf%82-%ce%b5%ce%bb%ce%bb%ce%b7%ce%bd%ce%b9%ce%ba%ce%ae%cf%82-%ce%b5%cf%84%ce%b1%ce%b9%cf%81%ce%b5%ce%af%ce%b1%cf%82-%cf%80%ce%b1%ce%b9%ce%b4/	Pediatric, any age	HCQ recommended
	India	Government of India - Ministry of Health & Family Welfare -	31-Mar-20	https://www.mohfw.gov.in/pdf/RevisedNationalClinicalManagementGuidelineforCOVID1931032020.pdf	Pediatric, over 12 years old	HCQ recommended

		Directorate General of Health Services				
10.1007/s13312-020-1852-4	India	Indian Pediatrics	01-Apr-20	https://link.springer.com/article/10.1007/s13312-020-1852-4	Neonatal	HCQ not recommended
	UK	Journal of the Pediatric Infectious Diseases Society	15-Apr-20	https://pubmed.ncbi.nlm.nih.gov/32318706/	Pediatric, any age	HCQ recommended
	Papua New Guinea	PNG Paediatric Society	01-May-20	https://pngpaediatricsociety.org/wp-content/uploads/2020/05/COVID-19-Paediatric-Guidelines-for-Health-Care-Workers-May-1-2020.pdf	Not clearly expressed	Authors do not commit with a recommendation regarding HCQ
	Australia	Australian Society of Infectious Diseases - Australia and New Zealand Peadiatric Disease Group	15-May-20	https://www.asid.net.au/documents/item/1909	Pediatric, any age	HCQ recommended only in the context of RCT
10.21037/atm-20-3754	China	Annals of Translational Medicine	22-May-20	https://www.mendeley.com/catalogue/2221cfd5-6d24-369d-8553-96c4d8d49a13/?utm_source=desktop&utm_medium=1.19.4&utm_campaign=open_catalog&userDocumentId=%7Bbc7f4e2a-749f-4840-9389-fa03b00cabb7%7D	Pediatric, any age	HCQ recommended only in the context of RCT
10.1016/j.ppedcard.2020.101232	USA	Progress in Pediatric Cardiology - Elsevier	23-May-20	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7244417/	Pediatric, any age	No mention of HCQ
	Malaysia	Malaysian Paediatric Association (MPA)	25-May-20	https://mpaeds.my/clinical-management-of-coronavirus-disease-2019-covid-19-in-paediatrics/	Pediatric, any age	HCQ recommended
10.1097/MAT.0000000000001193	USA	ASAIO Journal	01-Jul-20	https://journals.lww.com/asaiojournal/Fulltext/2020/07000/Extracorporeal_Life_Support_Organization.1.aspx	Pediatric and Adult	Authors do not commit with a recommendation regarding HCQ
10.1038/s41390-020-1053-9	USA	Peadiatric Research	07-Jul-20	https://www.mendeley.com/catalogue/47ba5a58-0457-3419-bd91-34e3dc4fe9e0/?utm_source=desktop&utm_medium=1.19.4&utm_campaign=open_catal	Pediatric, any age	No mention of HCQ

				og&userDocumentId=%7B5936f46a-3ade-478a-b32d-365fbf1d2e25%7D		
	Philippines	Philippine Pediatric Society	20-Aug-20	https://pps.org.ph/wp-content/uploads/2020/08/INTERIM-GUIDELINES-ON-THE-SCREENING-ASSESSMENT-AND-CLINICAL-MANAGEMENT-OF-PEDIATRIC-PATIENTS-WITH-SUSPECTED-OR-CONFIRMED-CORONAVIR.pdf	Pediatric, any age	HCQ not recommended
	Australia	National COVID-19 Clinical Evidence Task Force	Webpage, first consulted in 03-Sep-20	https://app.magicapp.org/#/guideline/L4Q5An		HCQ not recommended
	Rwanda	Ministry of Health and Rwand Biomedical Center	No mention on date of publication, first consulted in May 2020	https://moh.gov.rw/fileadmin/Publications/Guidelines___Protocols/Covid%20-19%20Clinical%20Management%20Guideline.pdf	Pediatric and Adult	No mention of HCQ
	South Africa	Pediatric Society	No mention on date of publication, first consulted in May 2020	https://docs.mymembership.co.za/docmanager/52adf6ce-ffe5-11d4-9fb9-0090279a6a88/00150940.pdf	Pediatric, any age	No mention of HCQ
	Thailand	Ministry of Public Health	No mention on date of publication, first consulted in May 2020	https://ddc.moph.go.th/viralpneumonia/eng/file/guidelines/g_CPG.pdf	Pediatric and Adult	HCQ recommended
	USA	NIH	Webpage, first consulted in 03-Nov-20	https://www.covid19treatmentguidelines.nih.gov/special-populations/children/	Pediatric, any age	HCQ not recommended
	USA	Infectious Diseases Society of America	In-text mention of previous recommendation for the use of HCQ	https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/	Pediatric and Adult	HCQ recommended
			Webpage, first consulted in 20-Aug-20 on			HCQ not recommended
	USA	CDC	Webpage, first consulted in 19-Aug-20	https://www.cdc.gov/coronavirus/2019-ncov/hcp/pediatric-hcp.html	Pediatric, any age	No mention of HCQ
	Canada	Government of Canada	Webpage, first consulted in 17-Aug-20	https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/clinical-management-covid-19.html	Pediatric and Adult	HCQ recommended only in the context of RCT

	Dominican Republic	Sociedad Dominicana de Infectologia	02-Apr-20	http://sdird.org/pdf/DIRECTRICES_MANEJO_FARMACOLOGICO_PACIENTES_CRITICOS.pdf	Pediatric and Adult	HCQ recommended
10.1007/s12519-020-00345-5	China	World Journal of Pediatrics	05-Feb-20	https://link.springer.com/article/10.1007/s12519-020-00345-5	Pediatric, any age	No mention of HCQ
	Germany	STAKOB Geschäftsstelle am Robert Koch-Institut	01-Mar-20	https://pneumologie.de/fileadmin/user_upload/Stellungnahme-Covid-19_Therapie_Diagnose-2.pdf	Pediatric and Adult	Authors do not commit with a recommendation regarding HCQ
10.1016/j.anpedi.2020.02.001	Spain	Anales de pediatria	12-Mar-20	https://pubmed.ncbi.nlm.nih.gov/32173188/	Pediatric, any age	HCQ not recommended
	Germany	German Society of Pediatrics and Adolescent Medicine (DGKJ)	09-Apr-20	https://www.dgkj.de/unsere-arbeit/wissenschaft/stellungnahmen/ansicht/covid19-medikamentoese-therapie-bei-kindern?cHash=86d839b6088edfd9d65dc2fe54a4e637	Pediatric, any age	HCQ recommended
	Russia	Союзе педиатров России	In-text mention of previous recommendation for the use of HCQ	Retrieval not possible	Pediatric, any age	HCQ recommended
			27-May-20	http://www.pediatr-russia.ru/COVID-19/detail.php?ELEMENT_CODE=koronavirusnaya-infektsiya-u-detey		HCQ not recommended
	France	Haut Conseil de la santé publique	17-Jun-20	https://splf.fr/wp-content/uploads/2020/06/HCSP-Coronavirus-SARS-CoV-2-recommandations-therapeutiques-17-06-20.pdf	Not clearly expressed	HCQ recommended only in the context of RCT
10.1007/s10096-020-03973-x	China	European Journal of Clinical Microbiology & Infectious Diseases	06-Aug-20	https://link.springer.com/article/10.1007/s10096-020-03973-x	Pediatric, any age	HCQ recommended
	Neetherlands	Stichting werkgroep antibioticabeleid	In-text mention of previous recommendation for the use of HCQ	Retrieval not possible	Not clearly expressed	HCQ recommended
			Webpage, first consulted in May 2020	https://swab.nl/nl/covid-19		HCQ not recommended
	United Kingdom (Scotland)	Scottish Intercollegiate	10-Jul-20	https://www.gov.scot/publications/coronavirus-covid-19-clinical-advice/	Not clearly expressed	

		Guidelines Network (SIGN). Scottish Governmen t.				
	United Kingdom	BMJ Best Medical Practice	First consulted: Jul-20	https://drive.google.com/file/d/159BoyqdFjrVbu2v5tOQlJgp0oFaiJJ4q/view?usp=sharing	Not clearly expressed	HCQ recommended only in the context of RCT
			Update consulted: Oct-20	https://bestpractice.bmj.com/topics/en-gb/3000201/pdf/3000201/Coronavirus%20disease%202019%20%28COVID-19%29.pdf		Authors do not commit with a recommendation regarding HCQ