COVID-19 and the Generation of Novel Scientific Knowledge in a Dangerous Time. Part A: Research Questions and Study Designs

Abstract:

Rationale, Aims and Objectives: One of the sectors challenged by the COVID-19 pandemic is medical research. COVID-19 originates from a novel coronavirus (SARS-CoV-2) and the scientific community is faced with the daunting task of creating a novel model for this pandemic or, in other words, creating novel science. This paper aims to explore the intricate relationship between the different challenges that have hindered biomedical research and the generation of scientific knowledge during the COVID-19 pandemic.

Methods: During the early stages of the pandemic, research conducted on hydroxychloroquine (HCQ) was chaotic and sparked several heated debates with respect to the scientific methods used and the quality of knowledge generated. Research on HCQ is used as a case study in this paper. The authors explored biomedical databases, peer-reviewed journals, pre-print servers and media articles to identify relevant literature on HCQ and COVID-19, and examined philosophical perspectives on medical research in the context of this pandemic and previous global health challenges.

Results: This paper demonstrates that a lack of prioritization among research questions and therapeutics was responsible for the duplication of clinical trials and the dispersion of precious resources. Study designs, aimed at minimizing biases and increasing objectivity, were, instead, the subject of fruitless oppositions. These two issues combined resulted in the generation of fleeting and inconsistent evidence that complicated the development of public health guidelines. The reporting of scientific findings highlighted the difficulty of finding a balance between accuracy and speed.

Conclusions: The COVID-19 pandemic presented challenges in terms of (1) finding and prioritizing relevant research questions, (2) choosing study designs that are appropriate for a time of emergency, (3) evaluating evidence for the purpose of making evidence-based decisions and (4) sharing scientific findings with the rest of the scientific community. This paper demonstrates that these challenges have often compounded each other.

Keywords medical research, philosophy of medicine, epistemology, evidence-based medicine

Introduction

On March 11, 2020, what was first described as cases of pneumonia of unknown cause originating from Wuhan was labeled as a pandemic by the WHO. As the COVID-19 pandemic progresses, nations and supranational organizations face a multitude of challenges that impact every facet of society. One of the sectors challenged by the COVID-19 pandemic - and the focus of this paper - is medical research. COVID-19 originates from a novel coronavirus (SARS-CoV-2) and the scientific community has been faced with the daunting task of creating a novel model for the COVID-19 pandemic or, in other words, creating novel science (i.e., knowledge that is unexpected in light of received scientific opinion)[†]. Since January 2020, researchers have attempted to uncover the origin of the virus and its mechanism of replication and have rapidly developed diagnostic tools and a number of vaccine candidates that are still under review.

Building on the experiences of past epidemics - specifically, the 2014-2016 Ebola outbreak - the WHO identified research as an ethical imperative[‡] and an essential part of the response to health emergencies[5,6]. Research is equally essential for generating a knowledge base about the present pandemic, as well as future global health challenges. This newfound consciousness for what is now characterized as 'epidemic preparedness' can be traced back to the 2003 SARS outbreak. The last Ebola epidemic represented a turning point in epidemic preparedness efforts: following this outbreak, the pace at which policymakers and academics developed tools to address the next health emergency increased exponentially[7]. The creation of the term 'Disease X', representing the threat of a pandemic caused by a currently unknown pathogen, as well as the development of initiatives, such as the WHO R&D Blueprint[8] and the

[†] : In *A Coordinated Global Research Roadmap: 2019 Novel Coronavirus* (2020)[1], the WHO repeatedly describes the role of the scientific community as identifying and addressing 'knowledge gaps' (see p.2, 4, 9). However, the issue extends far beyond filling knowledge gaps. The initial model of the COVID-19 pandemic was primarily based on lessons the scientific community learned from the 2003 SARS epidemic and SARS-CoV (the virus causing SARS). Given the approximate 80% similarity between the genomes of the two viruses[2,3] and the similarities in transmission routes, it was widely assumed that conclusions about SARS-CoV could be extrapolated to SARS-CoV-2. However, Wilder-Smith and colleagues[4] call attention to the fact that these viruses are very different, and assumptions about infectious periods, transmission and severity do not always hold. More than filling knowledge gaps, the scientific community needs to create a new scientific model for COVID-19.

[‡] : Section 8 (p. 30-34) of the *WHO Guidance for Managing Ethical Issues in Infectious Disease Outbreaks* (2016)[5] outlines the appropriate role of research during health emergencies. The central argument of this section is that "there is a moral obligation to learn as much as possible as quickly as possible, in order to inform the ongoing public health response, and to allow for proper scientific evaluation of new interventions being tested."[5(p.30)] This WHO document provides guidance on fast-tracking ethics reviews, integrating research and public health responses and selecting appropriate research methods.

Coalition for Epidemic Preparedness Innovations (CEPI), are evidence that there has, indeed, been a shift in consciousness. While the COVID-19 pandemic response has evidently been informed and shaped by these inter-epidemic efforts, generating valuable scientific knowledge during an emergency remains a challenge. In this context, one candidate drug, hydroxychloroquine (HCQ), sparked particular interest among members of the scientific community and will serve as a case study for this paper. HCQ is an antimalarial drug, whose toxicity profile is well-known for approved conditions, such as rheumatoid arthritis and systemic lupus erythematosus. It was thought that HCQ could inhibit the pH-dependent steps of SARS-CoV-2 replication[9]. So far, and especially during the early stages of the pandemic, research conducted on this drug was chaotic and sparked several heated debates with respect to the scientific methods used and the quality of knowledge generated.

In the context of uncertainty and urgency associated with the COVID-19 pandemic, two strategies, which Angus[10] calls 'exploitation' and 'exploration', seem to be in tension with one another[§]. According to Angus, "exploitation refers to acting on current knowledge, habits, or beliefs despite uncertainty. This is the 'just do it' option: give various therapies (e.g., chloroquine) to affected patients based on current knowledge or a hunch. Exploration refers to actions taken to generate new knowledge and reduce uncertainty, e.g., testing therapies in an RCT. This is the "must learn" option. Currently, these approaches are framed as a choice: do something (treat the patient) or learn something (test the drug)."[10(p.1895)] In other words, some prefer to take action quickly despite uncertainty, while others choose to wait for robust evidence before taking any action. The effort to find the right balance between the two underlies most of the challenges that have hindered medical research. Different authors have started to identify some of these challenges, such as patient inclusion in clinical trials[11], data sharing[12], publication ethics[13] and research waste[14]. These articles, which tend to be short columns or editorials, typically focus on very specific issues. However, since these challenges tend to compound each other, it is also enlightening to look at these challenges from a broader perspective and examine their intricate relationships.

In the context of COVID-19 and medical research, the question at hand is the generation of a valuable and actionable body of novel scientific knowledge in a relatively short timeframe. The literature suggests that a set of specific issues often complicate the generation

[§] : Angus[10] locates the source of this tension in the institutional structure of medicine, which is organized in a way that ensures that clinical practice (doing) and clinical research (learning) are separate tasks. Angus contends that there are "huge costs to this division, including delays in knowledge acquisition and dissemination. In normal times, these costs are somewhat suppressed or ignored, but in a crisis such as the COVID-19 pandemic, they come into sharp focus"[10(p.1895)].

of knowledge, regardless of whether research is conducted in a time of emergency or not. These issues are:

1) Inappropriate research questions and study designs. Chalmers and Glasziou[15] argue that "choosing the wrong questions for research"[15(p.86)] and "doing studies that are unnecessary, or poorly designed"[15(p.87)] result in research waste (i.e., scientific knowledge that does not have practical value or is not translated into practice).
2) Data collection and sharing. Data collection and sharing presented a challenge during the H1N5 outbreak in Indonesia, the 2015 Zika outbreak and the 2014-2016 Ebola outbreak, among others¶.

While undoubtedly there are several ways to examine this issue, this paper will take the position that at least four elements are needed to generate valuable scientific knowledge: (1) relevant research questions, (2) adequate and rigorous study designs, and appropriate ways to (3) evaluate, and (4) report newly-acquired knowledge. This first part of a larger study will examine challenges presented by the COVID-19 pandemic in terms of the first two elements. A follow-up paper will turn to the third and fourth elements.

Prioritizing Relevant Research Questions

Ensuring that research questions are relevant to the COVID-19 response is the first step in the generation of valuable knowledge. Without relevant research questions (including the identification of appropriate populations, interventions and outcomes), actionable findings cannot be generated. The difficulty lies in that it is often difficult to identify a clear, testable and relevant hypothesis at the beginning of an outbreak, when information about the pathogen is scarce and fleeting[17]. Prioritizing relevant research questions during a pandemic is crucial and can be justified on ethical and practical considerations.

¶ : The specific examples of the H1N5 outbreak in Indonesia and the 2015 Zika outbreak are described in Section 4, in the second paper. As for Ebola, the author of the National Academy of Medicine (NAM) report[16] identified data sharing as a central issue during the outbreak. Recommendation 2b states that "Data collection should begin as soon as possible, and data should be shared and coordinated in a central database to advance an understanding of the natural history of the disease and of the best practices for standard of care. This information should also be used to inform protocols for clinical trials."[16(p.10)] In the report, the authors argue that the inappropriate prioritization of investigational treatments (i.e., interventions and, to an extent, research questions) and the inappropriate choice of study designs also complicated the generation of a robust body of knowledge[16(section2)].

Ethical and practical justifications

Following the 2014-2016 Ebola outbreak, seven principles guiding research during health emergencies were identified. These principles are outlined in the National Academy of Medicine (NAM) report[16]: 1) scientific and social value, 2) respect for persons, 3) community engagement, 4) concern for participant welfare and interests, 5) favorable risk-benefit balance, 6) justice in the distribution of benefits and burdens, 7) post-trial access[††]. The first principle, which is the one that is most pertinent to this paper, is formulated as follows: "A clinical study's value depends on the quality of the scientific information produced and the relevance of the information to addressing public health or clinical issues"[‡‡] [18(p.477)]. However, the criteria to determine whether a study has more value than another remain unclear. According to the NAM report, the information produced by a trial must justify the risks and the allocation of resources and be of sufficient quality to inform decisions[§§][16]. A trial must also address "an important clinical question that cannot be rapidly answered by other means"[17(p.390)]. However, relying on these criteria to prioritize research questions during a pandemic might be unsatisfactory since the way these criteria are to be operationalized was never explicitly outlined. A research question can be considered irrelevant if there is insufficient evidence warranting the investigation of the hypothesis or if it is already under investigation. In step with Chalmers and Glasziou[15], this paper takes the position that patients and clinicians should be involved in the prioritization process so that their needs and the questions under investigation are better aligned. While this is crucial to facilitate research, how to accomplish this goal in a time of emergency has yet to be theorized, much less put into practice.

From a practical perspective, and even under normal circumstances, choosing an inappropriate research question results in a waste of financial and physical resources[15]. The 2014-2016 Ebola epidemic demonstrated that prioritizing research questions is crucial to

[††††] : These seven principles are outlined on p. 53 to 61 of the NAM report (2017)[16]. They were selected by the report committee using the following documents as a framework: Nuremberg Code (1947), Belmont Report (1979), Convention on Human Rights and Biomedicine (1977), UNESCO Declaration (2005), HHS Common Rule (2009), WMA Declaration of Helsinki (2013), CIOMS Ethical Guidelines (2016).

[‡‡‡‡] : When summarizing the findings of the NAM report[16], Edwards and Kochhar[18] mention that "the knowledge gained must justify the risks to the subjects and the costs associated with the trials"[18(p.478)]. However, how this is to be determined and quantified remains unclear in the article. The importance of the distinction for a theory of evidence between the validity (reliability) of evidence and the relevance (weight) of evidence is argued by Baigrie and Mercuri[19].

[§§§§] : The 'Scientific and Social Value' principle is detailed in Section 2 (p. 54-55) of the NAM report (2017)[16].

avoid overwhelming clinical networks¶¶[16]. The tension between research and care is often associated with a high cost[20], and is especially salient during health emergencies[10]. Healthcare workers have continuously been under pressure because of the growing number of COVID-19 patients, the risks of infections, the lack of equipment, and the pre-existing frailties of health care systems. Until research and care become integrated, every trial runs the risk of being a burden for the healthcare system, even more so if the research question is not directly relevant to the pandemic response. Ideally, during a pandemic, funding should be available for external research teams so as to alleviate the clinical staff's workload[17].

During the 2014-2016 Ebola outbreak, researchers investigated a large number of therapeutics for which the evidence available was very limited. The WHO staff, research funding agencies, and ethics boards were overwhelmed by a large number of proposals. As such, the authors of the NAM Report recommended that "in the event of a rapidly progressing outbreak it is critical to create a mechanism to prioritize investigational agents for study and limit the conduct of the clinical trials to a small number of products, focusing on those with the most promising preclinical or human clinical data, in order to maximize the likelihood that meaningful results will be generated."[16(p.46)] The lesson from these considerations, then, is that pursuit of irrelevant research questions can be explained by an absence of (1) research prioritization and (2) mechanisms to avoid the duplication of research works. In the next section, this paper will examine whether these two issues have been adequately addressed since the last Ebola outbreak.

Absence of Prioritization

Building on experiences from past outbreaks, the 2016 WHO R&D Blueprint[8] recommended developing a research roadmap for each new epidemic, as well as Target Product Profiles for the corresponding pathogens. On March 12, 2020, the WHO published a Research Roadmap for COVID-19[1], which purports to identify knowledge gaps and prioritize urgent questions. The working group concluded that the following nine areas require particular attention†††:

¶¶¶ : Section 2, *Planning Clinical Trials* (p. 45-46) of the NAM report (2017)[16] outlines the authors' recommendations for planning trials and prioritizing candidate therapeutics.

†††††† : These nine areas are outlined on p. 9 of the *WHO Research Roadmap for COVID-19* (Selected Knowledge Gaps section)[1]. The goals of the Research Roadmap are outlined as follows: "To accelerate research that can

1) Virus natural history, transmission and diagnostics,
2) Virus origin and management measures at the human-animal interface,
3) Epidemiological studies,
4) Clinical management,
5) Infection prevention and control,
6) Candidate therapeutics R&D,
7) Candidate vaccines R&D,
8) Ethics considerations for research,
9) Social sciences in the outbreak response.

This broad list covers most, if not all, research directions and does not provide any sort of ranking. Additionally, the WHO has no international jurisdiction and only provided this list as a recommendation. Regardless of whether this prioritization is considered authoritative, there seems to be no proportionality between the WHO's recommendations and research efforts since the onset of the pandemic. Indeed, the diversity of areas prioritized by the WHO has not been reflected in practice: what we have witnessed is a striking emphasis on the development of therapeutics and vaccines with surprisingly little attention given to non-drug interventions, which, interestingly, represent the primary response to COVID-19[14]. It is arguable that efforts should not be exclusively focused on pharmaceutical interventions, especially given the experiences of past epidemics (with the possible exception of smallpox) that have testified that vaccines and therapeutics represent the least promising (and the most time-consuming) options. Research on transmission and mitigation strategies, while not as lucrative, is equally crucial for protecting populations‡‡‡. Until legal bases and incentives are created to encourage a plurality of research objectives, this issue will most likely remain.

To address the NAM's recommendation to limit the number of therapeutics investigated, WHO working groups started, as early as January 24, 2020, to work on therapeutics prioritization[21]. These working groups established a dozen criteria - preclinical efficacy in non-human primates, safety profiles from non-clinical studies, and quality of

contribute to containing the spread of this epidemic and facilitate that those affected receive optimal care; while integrating innovation fully within each thematic research area."[1(p.2)] However, there is no explicit justification behind the decision to select the nine areas listed above as research priorities.

‡‡‡‡‡‡ : The WHO published this list on March 12, 2020, at a time when public health guidelines did not include infection control strategies, such as face coverings or international travel regulations. This can partly explain why research direction 5 did not receive much attention at the time. However, even after the WHO pivoted and recommended infection prevention and source control strategies, the emphasis of research efforts remained on vaccines and therapeutics.

manufacturing as mandatory criteria[22] - and generated a shortlist of around 25 candidate drugs. A few months later, by April, a new list included over 150 therapeutics (or combinations of therapeutics)[23], which appears counter-productive with respect to their first prioritization efforts. Moreover, there is a discrepancy between what has been prioritized - and the evidence behind it - and what is being studied. As of December 20, 2020, 270 of the 2309 trials tested HCQ, whereas only 34 tested Remdesivir[24]. However, the WHO stated in January that "Remdesivir was considered the most promising candidate based on the broad antiviral spectrum, the in-vitro and in-vivo data available […] and the extensive clinical safety database"[21(p.9)].

Duplication of Research Works

Redundancy in research works results in the dispersed allocation of scarce resources (studies are competing for hospital infrastructure, staff, funding, and patient base), which slows down the creation of novel scientific knowledge. This challenge is specific to the COVID-19 pandemic since relatively few trials were conducted during past epidemics (none during the 2003 SARS outbreak[17], 18 during the 2014-2016 Ebola epidemic[16]). Patient enrollment is challenging during a health emergency and, by limiting the number of trials, as suggested in the NAM report, the chances of enrolling enough patients and reaching definite conclusions are maximized[16]. Figure 1 shows that, by the time a trial starts, the number of patients admitted to the ICU has largely decreased (due to the implementation of NPIs), making it difficult to reach a pre-specified sample size[11]. Part of the difficulty is that obtaining ethics approval takes time. During the 2003 SARS outbreak in Toronto, the 18-day delay between the official beginning of the outbreak, and the ethics approval of the first clinical trial (which, ultimately, was not conducted), resulted in a loss of 60% of patients who could have been enrolled[17]. To address this issue, international organizations[5,25], as well as scholars[26,27], developed a system of expedited ethics reviews[§§§]. In the context of COVID-19, the issue is compounded by the difficulties of approving and implementing multi-site protocols, given the differences in national resources and healthcare systems. This has posed numerous challenges to the rapid launching of multi-site trials, such as SOLIDARITY and DISCOVERY (the

[§§§§§§] : In Section 8 of the *WHO Guidance for Managing Ethical Issues in Infectious Disease Outbreaks* (2016)[5], it is recommended that there should be greater collaboration between national research governance systems and local research ethics committees. The authors also suggest that the development of advance reviews of generic protocols can help expedite ethics reviews. Tansey and colleagues[26] developed a framework for expedited reviews that rely on proportionality and procedural flexibility.

French-led arm of SOLIDARITY)[28]. By overwhelming ethics committees and regulatory bodies, the duplication of trials has exacerbated the difficulties associated with red tape that is often excessive.

Mechanisms to limit the number of trials allowed to proceed have not been established since the last Ebola outbreak. While it was reasonable, at the beginning of the pandemic, to expect that HCQ would be tested as a cure, prophylaxis and in combination with other therapeutics, such a high number of studies (270) was not justified. Ideally, trial registration should provide information on what trials are in progress and de-incentivize duplication. However, this rarely happens in practice, especially considering the strong academic and financial incentives that have been in place since the beginning of the outbreak. There is no legal basis for an international body to examine all trial proposals and determine which trials are allowed to proceed. The R&D Blueprint acknowledges this issue, stating that to avoid "unnecessary duplication […] appropriate incentives and other measures" can be implemented[8(p.11)]. However, there is no additional information on what those incentives might be. A few platforms, such as the Trial Innovation Network, SMART IRB or the COVID19 CP, aim to create incentives and facilitators for collaboration at the clinical level. SMART IRB describes itself as: "a platform designed to ease common challenges associated with initiating multi-site research."[29] The other two platforms expedite approval for proposals that create multi-site collaborations[30,¶¶¶ 31]. Unfortunately, their lack of exposure, partnering institutions, and resources explains the persistence of this issue.

While lessons learned from the last Ebola outbreak helped researchers prioritize research questions and identify candidate therapeutics, the duplication of research remains a problem. This issue is compounded by a large number of researchers who exclusively want to work on vaccine and drug development. To address these challenges, the priority is to clearly define what a 'relevant' research question is and to strengthen coordination efforts. While these two steps are crucial in facilitating the generation of valuable scientific knowledge during health emergencies, it will not be sufficient unless behaviors and mindsets also change.

Identifying Appropriate Designs

¶¶¶¶¶ : COVID19 CP does not only act as a trial repository but encourages collaboration between trials. However, it primarily focuses on collaboration between RCTs, as opposed to observational and electronic medical records data[31]. As will be argued in section 3, in the second paper, there has been a tendency to disproportionately rely on RCTs since the beginning of the COVID-19 pandemic. The COVID19 CP's decision to focus on RCTs is yet another example that is indicative of this tendency. During a health emergency, strengthening collaboration for any research enterprise (and not only randomized controlled trials) is crucial.

Since the beginning of the pandemic, researchers seem to have embarked on a quest to find a 'miracle' study design - but disagree on what that design should be. As such, researchers advocate for what they consider to be the best methodological approach while condemning all others. Past health emergencies have also witnessed several disputes regarding how clinical trials ought to be designed, thereby, further delaying their launching††††[16]. The 2009 H1N1 and the 2014-2016 Ebola outbreaks revealed the need for a portfolio of designs that are best suited to a health emergency. This rise in consciousness incentivized scholars to develop new designs meant to address the various challenges engendered by a pandemic. These initiatives resulted in the development of the SOLIDARITY and REMAP-CAP trials, launched on March 18 and April 9, respectively[32,33].

With respect to research conducted on HCQ, the question of study designs sparked lengthy debates across the scientific community, politicians and the public alike. Most parties to this debate acknowledge that the quality of findings generated has been poor[34,35]. Glasziou, Sanders and Hoffman bemoan "a deluge of poor quality research [that] is sabotaging an effective evidence based response"[14(p.1)]. While it is outside of the scope of this paper to conduct a systematic review of all the studies on HCQ and determine its efficacy, it might prove useful to outline some of the characteristics of these studies, such as the number of participants, the type of study design, the publication format and the study's conclusions and limitations. For the purpose of this paper, studies on the efficacy of HCQ as a treatment (not prophylaxis) published between January and July 17, 2020 were selected (35 studies). By July 17, the general consensus was that HCQ would not be an effective treatment for COVID-19[163] (most trials, including the WHO SOLIDARITY trial[36], had removed their HCQ arm and emergency authorizations were revoked[37]). These characteristics are summarized in Appendix A and shed some light on the research conducted since the beginning of the COVID-19 pandemic:

1) Lack of methods transparency: the most striking example is Gao and colleagues' letter of declaration of results[38],

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†††††††† : Section 2 (p. 46-75) of the NAM report (2017)[16] examines the question of choosing appropriate trial designs during a health emergency. During the 2014-2016 Ebola outbreak, stakeholders agreed that "too much time was spent debating trial design, rather than quickly implementing trials and discovering safe and effective products in time to fight the epidemic"[16(p.47)]. Both randomized and non-randomized trials were discussed at the time and in the report. Since ethical and logistical concerns were raised regarding randomization, single-arm studies with historical controls were discussed as an alternative. However, the authors of the NAM report ultimately conclude that: "Randomized controlled trials are the most reliable way to identify the relative benefits and risks of investigational products, and, except when the rare circumstances detailed in Box 2-5 are applicable, every effort should be made to implement them during epidemics."[16(p.75)]

2) Limitations and biases: all 35 studies have been widely criticized and considered methodologically very biased by several commentators[39-44],
3) Inconsistent results: 13 studies show benefits of HCQ[38,45-56], 18 report no significant benefit[57-73] and four report increased risks[74-77],
4) Significant number of retracted studies: three studies on HCQ were retracted[48,76,78] and another was the subject of a statement of concern from Elsevier and is currently under investigation[45],
5) Large amount of non-peer-reviewed articles: only 15 of these studies were peer-reviewed,
6) Lack of adverse event reporting: 17 studies did not formally report adverse events, which is, however, one of the major concerns clinicians have when prescribing HCQ. Indeed, HCQ is known to cause renal, hepatic and cardiovascular adverse effects[9]. COVID-19 patients in the ICU are more likely to have co-morbidities (including renal, hepatic and cardiovascular dysfunctions) and be given high doses of HCQ, thereby increasing the risks of adverse events. Starting in July, studies tended to report adverse events more systematically.

This paper will now analyze the three major strategies that have been suggested since the beginning of the pandemic (traditional designs, Big Data and REMAP-CAP) to determine if a 'miracle' design can, indeed, be found.

Traditional Designs

A vocal constituency of the scientific community advocates for maintaining the standards and methods generally used outside of health emergencies[79]. Simple designs that have been frequently used in the past are thought to help preserve scientific rigor without the prospect of overwhelming the clinical network[80]. While the first few completed clinical trials on HCQ were received from China, the antimalarial drug was placed under the international spotlight due to two French studies that were published in March 2020[45,47]. Despite their methodological limitations (see Appendix A), the advertisement made by Raoult (one of the authors of these French studies) and politicians[81] sparked hope and controversy among the population, with the result that another team of researchers decided to replicate the study by performing a prospective case series of 11 patients. However, this study did not yield conclusive findings[58]. This is a typical example where researchers were obligated to replicate knowledge generated instead of building on it, thereby slowing down research efforts. At the

time, Raoult claimed that a situation of emergency is a license to abandon the scientific method and a call to action (i.e., population-wide distribution of HCQ)‡‡‡‡ [82]. As such, he agitated against RCTs as being unduly time-consuming and contended that including placebos and control groups is unethical[82]. This debate can be traced back to the last Ebola outbreak[84] but seems to have been settled, for the most part, since then§§§§. Regardless, clinicians might rightfully be torn between attempting to cure patients with what is available and continuing unabated with their research. However, while Raoult referenced the Hippocratic Oath to justify giving HCQ to every patient, regardless of the risks[82], it seems reasonable to respond to Raoult that this very same Hippocratic Oath ('first do no harm') mandates against imprudent, population-wide prescriptions of investigational drugs. This brings us to reflect on the prescription of off-label drug use. This practice is widespread¶¶¶¶[85] but 73% of off-label drugs are supported by very poor or no scientific evidence[86]. Prescribing off-label drugs can also undermine research efforts since data cannot be collected on patients who are prescribed the investigational treatment[35,††††† 88]. The 2014-2016 Ebola outbreak incentivized the WHO to

‡‡‡‡‡‡‡‡ : Raoult, in an open letter to a French newspaper, described the scientific method as a "moral dictatorship" and methodologists as "methodology freaks"[82]. He insisted that "we must get rid of mathematicians [whom he earlier described as methodologists], [who are] meteorologists in this area." In his letter, he relied on the parachute paradigm[83] to condemn the conduct of RCTs during health emergencies, arguing that the use of placebos and control groups is not ethical in such situations. Meyer, in a response published in the same newspaper, argued that the parachute paradigm does not hold in the case of HCQ: "this example is not valid: the statistical method is only used when there is obvious uncertainty about the answer, and not when the laws of physics are sufficient to predict the result with a negligible margin of error."[80] [authors' translation].

§§§§§§§§ : Concerns about randomization, control groups and placebos are frequently raised during health emergencies. The NAM report mentions that such a controversy occurred during the 2014-2016 Ebola outbreak: some argued that "communities would not accept a randomized controlled trial because it would 'deny a new experimental treatment to some participants'"[16(p.51)]. Others stated that "trials 'should not include a placebo: exposed and vulnerable people in Ebola-affected and low-resource settings shouldn't be led to think they are either being treated or protected when they're not'"[16(p.65)]. Others, yet, argued that randomization, controls and placebos "would be acceptable to the community if public health leaders were 'to articulate the rationale for conducting scientifically valid trials, to work closely with local health authorities, and to engage community leaders'"[16(p.51)]. In light of these conflicting views, the authors determined that RCTs were ethical and that "[the above] considerations do not warrant the a priori rejection of the use of a placebo but rather should be taken into consideration within the specific context of a trial."[16(p.65)] The 2016 *WHO Guidance for Managing Ethical Issues in Infectious Disease Outbreaks* seems to agree with this conclusion, recommending that: "In clinical trials, the appropriateness of features such as randomization, placebo controls, blinding or masking should be determined on a case-by-case basis, with attention to both the scientific validity of the data and the acceptability of the methodology to the community from which participants will be drawn."[5(p.33)]

¶¶¶¶¶¶¶ : Wittich and colleagues[85] note that prescriptions of off-label drugs represent 21% of all prescriptions in the US and 36.2% of all ICU prescriptions. Despite the fact that this practice is widespread, a study conducted by Cummings showed that two-thirds of patients advocate for the banishment of off-label drug use[87].

†††††††††† : Kalil argues that "in addition to the risk of harming patients without the possibility to even detect the magnitude of harm, the administration of off- label drug use, compassionate drug use, and uncontrolled studies during a pandemic also could discourage patients and clinicians from participating in RCTs, hampering

create MEURI (Monitored Emergency Use of Unregistered Interventions), which stipulates that the distribution of investigational treatments outside of clinical trials is only allowed if the following criteria are met‡‡‡‡‡[5]:

1) Lack of effective treatment,
2) Absence of clinical trials,
3) Availability of efficacy and safety data,
4) Ethical approval,
5) Implementation of risk mitigation strategies,
6) Acquisition of patients' informed consents,
7) Consistent monitoring of patients and sharing of results with the scientific community.

Since criteria 2 and 7 are not met in the context of this pandemic, this paper takes the position, in agreement with Caplan and colleagues[89], that while "there may be a role for MEURI in COVID-19, [the] unconstrained, unevaluated use of therapeutics under the guise of compassionate use or panicked rhetoric about right-to-try must be aggressively discouraged in order for scientists to learn what regimens or vaccines actually work"[89(p.2753)].

Following these two politicized studies, which polarized public and scientific opinion, it became evident for many that only a RCT would provide definite conclusions regarding the efficacy of HCQ. However, the preliminary results of the UK RECOVERY trial (an adaptive factorial trial[90-92]), released on June 5, suggested that a RCT is far from bringing all the answers. The DMC stated that the interim results, based on 4,674 patients, revealed "no beneficial effects of hydroxychloroquine" and that they had decided to "stop enrolling participants to the hydroxychloroquine arm […] with immediate effect"[93]. Nevertheless, researchers were quick to criticize these findings, even though they came from a RCT that, supposedly, ranks high in the evidence hierarchy. The first concern regarding the trial was related to the unusually high dosage of HCQ. Indeed, patients received 2,400mg of HCQ in the first 24h, which is well above the dosage recommended by the FDA on the Emergency Use Authorization (800mg)[94]. While this dosage decision is explained in the protocol on the basis of available data of the IC_{50} for SARS-CoV-2 (how much substance in needed in plasma

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any knowledge that could be gained about the effects of the drug being tested"[88(p.E2)]. When an investigational drug is prescribed under an off-label or compassionate use, adverse events are rarely reported in a systematic manner to the scientific community and knowledge about the efficacy or potential harms of said investigational treatment cannot be generated.

‡‡‡‡‡‡‡‡‡ : These seven principles were summarized and adapted from Section 9 (p. 35-37) of the *WHO Guidance for Managing Ethical Issues in Infectious Disease Outbreaks* (2016)[5].

to inhibit the virus by 50%)[§§§§§92], it remains unclear whether this dosage was warranted and did not pose an unreasonable risk to patients. The population of patients selected was also questioned. Some argued that patients who received HCQ in this trial (mainly severely ill patients) would not benefit from receiving the treatment. This is because COVID-19 is a three-stage disease with an initial viral replication phase, followed by a pulmonary phase and then a 'cytokine storm' causing tissue damage (when patients are in the ICU)[95]. Giving HCQ, an antiviral, would, thus, only be beneficial for patients who were still in the early stages of the disease. This example shows that results from a seemingly well designed, large RCT can be criticized because the trial's hypothesis is not relevant given the available evidence. This consideration reiterates the importance of a relevant question: regardless of the type of study design, if the research question (population and intervention, in the case of RECOVERY) is not appropriate, then research findings will not be generalizable to the intended target population[¶¶¶¶].

Big Data and Electronic Health Records

Angus describes the advantages of using Big Data and Electronic Health Records (EHRs) in clinical research as follows: "The information is relatively inexpensive, generated as a by-product of patient care (overcoming the cost problem), and both specific to individuals (ie, adequately narrow) and, *en masse*, descriptive of the entire delivery system (ie, adequately broad). No individuals are randomized, so the ethical issues appear less complex. The richness and immediacy of these new data could allow tailored treatment decisions in real time, overcoming delays in knowledge translation."[96(p.767)]. Such an approach was used in an observational study published by Mehra and colleagues on May 22, 2020. This study on 96,031 patients concluded that HCQ was associated with a higher risk of mortality and

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§§§§§§§§§§ : This decision is explained as follows in the RECOVERY protocol: "the loading dose in RECOVERY is twice the normal dose for treating malaria. However, this dose has been selected based on the available data of the IC_{50} for SARS-CoV-2. The objective is to reach plasma concentrations that are inhibitory to the virus as soon as safely possible. The plasma concentrations that will result are at the higher end of those encountered during steady state treatment of rheumatoid arthritis. Given the significant mortality in patients hospitalised with COVID-19, this dose is felt to be justified."[92(p.22-23)]

¶¶¶¶¶¶¶¶¶ : In the case of RECOVERY, the research findings may, at best, be generalizable to a population of severely ill patients. However, given the three-stage nature of COVID-19, HCQ should be tested in a population of patients who are still in the early stages of the disease (viral phase). Therefore, the results of RECOVERY are not generalizable to the population that would be the target of a HCQ treatment (i.e., patients who are still in the viral phase).

cardiac arrhythmia[76]. Immediately following this publication, guidelines on the use of HCQ changed dramatically: on May 25, 2020, the WHO suspended all HCQ arms and national trials followed in its path[97]. The French Minister of Health suspended the authorization he had exceptionally issued on the use of HCQ in the clinical setting[98]. The large sample size, which is often - incorrectly - associated with high-quality findings, was used as justification to make these decisions. However, concerns about the study data were quickly raised, first on Twitter[99], and then in an open letter addressed to *The Lancet*, which outlined ten concerns, including discrepancies with government data and inadequate statistical adjustments[100]. Three out of the four authors retracted the study on June 5, 2020[101], which led the WHO and national policymakers to resume clinical trials[97]. In addition to the negative consequences that these contradicting decisions might have had on clinical trials, this study also contributed to making COVID-19 patients following a HCQ treatment even more concerned about their vital prognosis.

Thus, generating data quickly is not helpful if the data collection methods are inappropriate or if the data only supports limited conclusions, which clearly was the case of the data collected by the COVID-19 4CE Consortium††††††[102]. Using patient-level data, if collected adequately and internationally, would yield more generalizable findings than those that are currently available. Nevertheless, advocating for this approach seems to overlook the numerous challenges that remain to be addressed. First, the question of patient privacy and re-identification is often seen as a significant barrier to the sharing of EHRs[104]. Besides, there are currently no incentives to share clinical data since there is no mechanism for academic

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†††††††††††† : The 4CE Consortium is a grouping of 96 international hospitals that gathered and analyzed Electronic Health Records data (using the i2b2 and OMOP platforms) to "inform doctors, epidemiologists and the public about COVID-19 patients with data acquired through the health care process."[103] The report cited here analyzes aggregate data from 27,927 COVID-19 patients. The authors "deliberately aggregated the data to expedite the institutional review board (IRB) process at each institution […]. This thereby constrained [their] analyses to count, rather than patient-level, data."[102(p.13)] The authors acknowledge this limitation as well as the limited amount of diagnosis code data available and issues with data harmonization across sites. They state that "the limits of [their] data collection method, where [the] results are not tied to the patient level and can be associated across populations, highlights the need for caution with any conclusion […]."[102(p.13)]

recognition and data ownership‡‡‡‡‡‡[105-107]. Researchers might prefer to wait until they have conclusions to publish rather than share their raw data.

REMAP-CAP

The third approach, advocated by Angus[10] and others[108,109], is to choose an adaptive design that is "pre-planned, pre-approved and practiced"[110(p.12)] during the inter-epidemic period. Such a design, REMAP-CAP, which stands for Randomized, Embedded (into clinical care), Multifactorial, Adaptive, Platform trial for Community-Acquired Pneumonia (CAP), was developed following the H1N1 outbreak[111]. Following the approval of the core protocol and the pandemic appendix, the trial was launched in 2016 and, as of December 11, 2020, includes 281 sites in 19 countries[11]. Enrollment of COVID-19 patients started soon after the beginning of the pandemic. This design combines elements from a platform trial, upon which multiple research questions can be investigated, and an adaptive trial, which allows for design modifications based on a Bayesian analysis of interim results[112-117]. We are told that this design addresses a "disease or condition, rather than a particular intervention"[117(p.797)], which can be helpful when investigating emerging pathogens, such as SARS-CoV-2. The different adaptations used in REMAP-CAP are§§§§§§[117]:

- Enrichment: population modifications are made if the treatment proves to be more efficient on a subset of the population. According to Angus, this allows for a 'precision medicine' approach and a better estimation of the intervention's effects on individual patients[96],
- Treatment arms: addition or termination of arms based on interim results and simulations,
- Patient allocation: Response-Adaptive Randomization (RAR) allows participants to become more likely to be enrolled in the more promising arm as evidence accumulate.

‡‡‡‡‡‡‡‡‡‡‡ : The lack of academic recognition when sharing clinical data is made explicit in the report by Abramowitz and colleagues (2018)[105]. The authors mention that researchers "are reticent to hand over data for publication without recognition. […] One problem impeding this recognition was that the names of those people who have labored to produce data are not visible to their users."[105(p.65)]. Section V(F) 'Key barriers and facilitators to data sharing' of this document further develop this argument. In the *WHO consultation on Data and Results Sharing During Public Health Emergencies* (2015)[106], sections 1.4 and 1.5 examine the issue of recognition and data ownership. The authors and interviewees suggest that a "cultural" change in "academic reward structures"[106(p.19)] is needed. However, how this should be implemented in practice remains unclear.

§§§§§§§§§§§ : *Adaptive Designs for Clinical Trials of Drugs and Biologics FDA Guidance for Industry* (2019)[117] provides guidance on how adaptive trials ought to be designed and conducted. It is important to note, however, that "there is [currently] no explicit and transparent review process for APTs [adaptive platform trials], and therefore no mechanism for standardized evaluation across different national and international oversight and review bodies."[116(p.801)] Section 5 of this FDA document outlines all the adaptions that can be added to an adaptive platform trial (adaptations to sample size, patient population, treatment arm selection, patient allocation, endpoint selection).

According to Angus, REMAP trials are most adequate to accommodate the complex web of constraints that a pandemic generates[112]. RAR tends to shorten the time required to generate conclusive findings and to decrease the number of participants needed[116,118], which minimizes challenges around patient inclusion. By allowing more participants into the more promising arm, RAR might also be a partial response to clinicians' concerns about randomization[119]. The organization of the protocol (core protocol and appendices for each new arm) also facilitates ethics approval[116]. The many advantages of REMAP trials outlined by Angus can be seen in Table 1[112].

However, these designs also have practical and statistical limitations[¶¶¶¶¶]. An adaptive trial requires a tremendous amount of pre-trial planning and simulations in order to pre-specify the statistical methods and algorithms used to evaluate interim results[116]. Given the uncertainty associated with any pandemic, one can question how much of the trial can actually be planned ahead of time. RAR, while admittedly more intuitive, can also result in a population drift[119]. Participants know that the later they enter the trial, the more chances they have of being allocated to the more promising arm. As such, patients who enroll later are more likely to be healthier since they can afford to wait[†††††††]. Finally, REMAP-CAP, as any multi-site trial, risks having different 'standard of care' practices across sites, due to socio-economic differences. A lack of mechanisms for data harmonization makes it difficult to compare data and generalize results[102]. 'Standard of care' guidelines for COVID-19 patients might also change over time, as new evidence arises[121].

While a REMAP design should not be considered flawless, it seems to adequately address some of the challenges imposed by a pandemic, provided, of course, that it is conducted properly. Given the amount of pre-trial planning required before launching an adaptive trial, it must be designed before the onset of an outbreak, which is why REMAP-CAP has an advantage over other adaptive trials. If the results live up to expectations, REMAP-CAP will show that aiming for a personalized approach to medicine and a learning healthcare system is possible, even during a pandemic[10,122]. However, results and data from the

¶¶¶¶¶¶¶¶¶¶ : Goozner[120] and others[118] note that making modifications based on an interim analysis of the data increases the probability of Type I errors (or false positives).

†††††††††††† : This problem may arise, depending on how the trial is designed and what inclusion criteria are used. Das and Lo carried an analysis of the I-SPY 2 TRIAL (an adaptive platform breast cancer trial) and emphasize that population drift could have been a concern and a limitation in the trial[118(p.170)].

HCQ arm of this trial have yet to be released[‡‡‡‡‡‡‡], making it impossible to assert with certainty that it is the most appropriate design for an emergency.

As demonstrated above, all three approaches have very distinct justifications. Advocates of traditional designs value studies conducted at the bedside that do not overwhelm the clinical staff. Relying on EHRs is often considered as less time and resource-consuming. Finally, advocates of the REMAP trial highlight the ethical and practical benefits of removing less promising treatment arms. RECOVERY and REMAP-CAP (two large, randomized trials) also endorse different values. The rationale behind RECOVERY is to conduct "the simplest [trial] as possible": healthcare systems should not be further overwhelmed by a complex protocol[§§§§§§§123]. REMAP-CAP, on the other hand, and while claiming that the trial is embedded into clinical care, offers a very complex protocol and has yet to show how this integration between research and care works.

During the inter-epidemic period, the question of which design is preferable has been addressed but discussions have resulted in very few definite answers. In the context of the COVID-19 pandemic, members of the scientific community have widely divergent views on what they consider to be the most appropriate design during health emergencies[10]. Given the above considerations, the inescapable conclusion is that the quest for a single, perfect design is futile. Instead, in order to ensure a better alignment between information clinicians and policymakers need and information that is generated by research, two objectives should be pursued: maintaining scientific rigor while embracing a methodological pluralism stipulating that the value of a plurality of designs is its prospect for the acceleration of the generation of scientific knowledge.

Discussion

‡‡‡‡‡‡‡‡‡‡‡‡‡ : Results for the corticosteroid arm of the REMAP-CAP trial were published in *JAMA* on September 2, 2020[124]. This treatment arm was halted after results from other trials were published. Primary results for the HCQ arm should be released in December 2021, and full study results should be published in June 2022[125].

§§§§§§§§§§§§§ : In the video, Peter Horby (RECOVERY trial co-chair) articulates the three main goals of the RECOVERY trial: 1) to generate the best evidence as fast as possible, 2) to protect patients, 3) to protect the healthcare system so that the staff is not overburdened with too much administrative duties[123].

This first paper has demonstrated that the COVID-19 pandemic has presented challenges to the generation of novel scientific knowledge in terms of (1) finding and prioritizing relevant research questions and (2) choosing study designs that are appropriate for a time of emergency. First, a lack of prioritization among research questions and candidate therapeutics, in part at least, has been responsible for the duplication of research works and the dispersion of scarce resources. Because research questions have not always matched the needs of clinicians and policymakers, it is critical that the end-users of research become more actively engaged in the identification of relevant research questions[15]. The duplication of research works, combined with poor-quality research, has greatly contributed to slowing down the creation of novel scientific knowledge. Efforts remain to be made in at least two areas: (1) finding mechanisms to limit the number of candidate therapeutics being investigated and the number of trials allowed to proceed and (2) facilitating collaboration by creating platforms with more exposure and resources. With respect to study designs, this paper has demonstrated that the scientific community embarked on a quest to find the most appropriate design during a time of emergency fraught with danger to the public. Issues raised during previous health emergencies (around patient inclusion, randomization and trial adaptability in light of new findings) has led to the creation of interesting designs, such as the REMAP-CAP trial. However, in the context of the COVID-19 pandemic (and, specifically, research on HCQ), the choice of study designs has been the subject of fruitless oppositions. These oppositions, as well as the overall low methodological quality of studies on HCQ, suggest that methodological rigor and the notion of design complementarity have sometimes been abandoned

COVID-19 and the Generation of Novel Scientific Knowledge in a Dangerous Time. Part B: Evidence-Based Decisions and Data Sharing

Introduction

In the previous paper, it was argued that, in the context of the current COVID-19 pandemic, the scientific community has been faced with numerous challenges with respect to (1) finding and prioritizing relevant research questions and (2) choosing study designs that are appropriate for a time of emergency. This follow-up paper will now examine the challenges presented by the COVID-19 pandemic in terms of (3) evaluating evidence for the purpose of making evidence-based decisions and (4) sharing scientific findings with the rest of the scientific community and the general public.

Making Evidence-Based Decisions

Questions about what kinds of evidence should be used, how evidence is to be evaluated and whether the answers to these questions change during a health emergency have often been discussed. This long-lasting debate among decision-makers, clinicians, researchers, and philosophers of science has been the essence of most discussions around the generation of novel scientific knowledge during the COVID-19 pandemic. Two approaches for making decisions during emergencies are staples in the biomedical literature: the precautionary approach[†] or an evidence-based approach[126]. The precautionary approach is often used to justify the implementation of non-pharmaceutical interventions. However, following the precautionary approach is often seen as harder to justify in the case of pharmaceutical interventions considering the perceived risks associated[128]. Three factors, which this paper will

[†] : The precautionary principle and the precautionary approach are grounded in the belief that decision-makers have a social responsibility to anticipate harm before it occurs ("informed prudence") in order to protect the public from harm, even when the absence of scientific certainty makes it difficult to predict the likelihood of harm occurring, or the level of harm should it occur. The principle itself was formally asserted as Principle number 15 at the Rio Conference in 1992: "[…] the precautionary approach shall be widely applied by the States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty, shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation."[127(p.3)]. Given the legal connotations of the term 'principle,' the Rio Declaration (as quoted above) references a precautionary "approach," which can be read as a relaxing of this term. In this section, we will use the term 'precautionary approach' in recognition of the ongoing debate as to whether the precautionary principle in fact achieved the status of a rule of law.

examine consecutively, might explain why making evidence-based decisions on investigational drugs has been difficult in the context of this pandemic.

The Controversial Nature of Evidence

Thriving to understand the meaning of the term 'evidence' has been the essence of a long-standing debate that has yet to find a definite answer. The growing influence of EBM inspired evaluation frameworks to categorize studies as RCT or non-RCT in a manner that is oblivious to the diversity of designs‡[129]. The idea that RCTs are the 'gold standard' of evidence shapes most of the discussions regarding the efficacy of HCQ and has led to the neglect of relevant pieces of evidence. Most systematic reviews, including that of the WHO, only take into consideration RCTs testing HCQ and automatically discard all other evidence[130]. However, findings from non-RCT studies have sometimes been more robust and generalizable. While RCTs are often considered the ideal design to determine causal inferences and reduce biases, they should not be considered flawless[131,132]. The three limitations that are significant in the context of COVID-19 are:

1) Inability to draw robust causal inferences. Making causal inferences is essential in the context of the COVID-19 pandemic since any proposed intervention must be accompanied by confidence that the intervention will change the outcome. Borgerson notes that "claims about the special ability of RCTs to isolate causes refer to probabilistic causes and downplay the possibility that mechanistic causes could be just as well established, just as epistemically strong, and just as useful in medical practice"[131(p.222)§]. In the context of COVID-19, this is an issue since clinical trials were

‡ : Irving and colleagues outline eight concerns about using grading systems (such as GRADE) to inform public health policies: "(1) lack of information on validity and reliability, (2) poor concurrent validity, (3) may not account for external validity, (4) may not be inherently logical, (5) susceptibility to subjectivity, (6) complex systems with inadequate instructions, (7) may be biased toward randomized controlled trial (RCT) studies, and (8) may not adequately address the variety of non-RCTs."[129(p.244)]. Mercuri and Gafni, in a series of papers, evaluate the appropriateness of the GRADE framework by determining whether aspects of the framework are justified based on theoretical and empirical grounds and conclude that there is an absence of such justification[164-166]. In another paper, Mercuri and Baigrie conclude that "the GRADE framework should strive to ensure that the whole evidence base is considered when determining confidence in the effect estimate"[167].

§ : Borgerson explains the difference between mechanistic and probabilistic causes as follows: "Mechanistic causes are provided by bench research in biochemistry, genetics, physiology, and other basic sciences, and are thought to be especially stable because they hold in all cases (not just selected subpopulations, however carefully or randomly selected). Probabilistic causes establish strength of association between dependent and independent variables in a given population, ideally in repeated studies […]. These causes are often identified through epidemiological research."[131(p.222)]

launched, and decisions were made, without thoroughly understanding the mechanisms of action and transmission of SARS-CoV-2. New information from lab-based, mechanistic studies has sometimes undermined clinical trials[¶].

2) Randomization issues. Randomization is thought to eliminate confounding factors, thereby allowing researchers to isolate the intervention's effects. While randomization certainly has epistemic and scientific values, Worrall has argued persuasively that it only reduces the likelihood that confounding factors will affect the results but does not eliminate it[††][132]. Even if randomization eliminated confounding factors, it would require a larger sample size than those used in the studies on HCQ (see Appendix A for the number of studies that have a sample size of 100 or less). In the context of COVID-19, exclusively focusing our attention on randomization has sometimes been an obstacle to recognizing the quality of findings generated by retrospective cohort studies[‡‡].
3) Lack of external validity. While a RCT is considered, in the evidence hierarchy, as the best design to ensure internal validity, it is not necessarily the best design to generalize results. Black argues that generalization to the whole population is more easily determined from an observational design (since it usually has broad inclusion criteria and preserves the context of care)[133]. In the context of the COVID-19 pandemic, the generalization of research findings has often been a challenge. For example,

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[¶] : For example, learning about the mechanism of action of SARS-CoV-2 (i.e the three-stage nature of COVID-19) has undermined results from the HCQ arm of the RECOVERY trial and, possibly, other clinical trials that tested the efficacy of HCQ as a treatment for severely ill patients. Siddiqi and Mehra describe the three stages of COVID-19 (early infection, pulmonary phase and hyperinflammation phase) and note that the first phase is driven by the virus itself while the last phase is driven by the host response[95]. As such, the authors note that "pharmacotherapy targeted against the virus holds the greatest promise when applied early in the course of the illness, but its usefulness in advanced stages may be doubtful. Similarly, use of anti-inflammatory therapy applied too early may not be necessary and could even provoke viral replication [...]."[95(p.405)] Treating patients with HCQ – a therapy targeted against the virus – is, therefore, not appropriate for severely ill patients (who are in the last, 'hyperinflammation' phase of the disease).

[††††] : In his paper, Worrall examines the claim that RCTs and randomization are more robust than non-RCT designs from an epistemic perspective. He claims that "we are always, quite trivially, at the mercy of the possibility that the two groups are, unbeknown to us, unbalanced in some significant way. And, whatever may be true in the theoretical indefinite long run of endlessly repeated random divisions, for real-world trials, randomization does exactly nothing to alleviate this worry."[132(p.486)]

[‡‡‡‡] : Studies conducted by Geleris and colleagues[60], Rosenberg and colleagues[61] and Arshad and colleagues[56] are all observational, retrospective cohort studies and are generally considered to have produced good-quality evidence, or at least evidence of higher quality than that produced by RCTs conducted early in the pandemic (Chen J. and colleagues[57] and Tang and colleagues[62]).

conclusions obtained by Gautret and colleagues[45] on the efficacy of HCQ could not be reproduced by Molina and colleagues[58]. Thus, their conclusions are not externally valid (either because they are not internally valid, the methods are not reproducible, or the population sampled in the second study was fundamentally different from that of the first study).

Given these limitations, proponents of EBM acknowledge that "there are always exceptions to the general rules"[134(p.165)]. Nevertheless, it is arguable that non-RCT designs and mechanistic studies should not be the exception but, instead, be considered complementary to RCTs[133]. Insights gained from research on HCQ and the theoretical limitations outlined above show that scientific rigor, although crucial, cannot be restricted to the use of RCTs. The scientific community should critically appraise the evidence available on a case-by-case basis, instead of relying on a set of predefined criteria.

Inconsistent and Fleeting Evidence

Upshur reminds us that "all evidence is capable of being overturned or modified in light of new findings"[126(p.109)], which further complicates making evidence-based decisions. Evidence on HCQ has sometimes been uncontested for only a few days before being invalidated by new findings. Moreover, as Russell and colleagues suggest, the generation and evaluation of evidence cannot be completely judgment-free[135]. As such, basing decisions on a single study is problematic though, as we have seen, such decisions have been made frequent during the COVID-19 pandemic[§§]. The threshold of evidence required to take action is ambiguous: there is always a tension between wanting to take immediate action and gathering more evidence[126]. However, the biological, physiological and pharmacological complexity at work does not allow for rushed decisions regarding vaccine and drug approval.

Evaluating Evidence: a Time-Consuming Process

[§§§§] : On the other hand, if independent studies with different designs reach the same conclusion, it is arguable that one is more warranted to believe that conclusion. Indeed, if in-vitro studies and clinical trials both indicate that a treatment is beneficial, then one should be even more confident in using that treatment (mechanistic and probabilistic causes).

Making decisions based on a body of knowledge requires that the evidence be first evaluated. However, conducting systematic reviews takes time (between 6 and 24 months)[136,137]. As such, rapid reviews were developed to evaluate evidence in less than three months and are commonly used during health emergencies[138]. Several methodological modifications are used to fast track the process, such as limiting the scope, the outcomes of interest and the number of databases reviewed, adding more reviewers or defining more restrictive search criteria[138]. Two studies show that very few differences exist between the conclusions reached by both review types[139,140]. Interestingly, however, there is no standard methodology to conduct rapid reviews - which is not an issue as long as the authors are transparent about their methods[141]. In the context of COVID-19, one problem has precisely been the lack of transparency regarding the methods used in rapid and systematic reviews. Ruano and colleagues also claim that out of the 18 peer-reviewed systematic reviews published on COVID-19 up to March 24, 2020, 13 were considered of "critically low" quality by AMSTAR 2[142(p.2)]. This issue is compounded by a tendency to consider RCTs as the only source of evidence, thereby ignoring a valuable part of the knowledge base.

Non-Evidence-Based and Rushed Decisions

Given the limitations regarding the nature of evidence and the complexity of evaluating evidence in a timely manner, some might ask whether basing all decisions solely on evidence is meaningful. National public health leaders have often portrayed their recommendations and injunctions as evidence-based but what is intended by this declaration is not entirely clear. Several organizations have modified their guideline development process[138]. During an emergency, the WHO is no longer bound to support decisions on systematic reviews and can rely exclusively on expert opinion¶¶¶, which, interestingly, ranks at the bottom of the evidence hierarchy. The FDA has also developed ways to fast track the

¶¶¶ : In the WHO Handbook for Guidelines Development, section 1.7.4 describes the changes being made to the guideline development process during an emergency[138]. These modifications include the use of rapid reviews and rapid advice guidelines (ought to be developed in less than three months). The authors emphasize the need for stakeholders to make the guideline development process transparent: "Emergency (rapid response) guidelines – Public health emergencies may necessitate a response from WHO within hours to days. Hence, many of the guideline development processes and methods outlined in this handbook are not applicable. WHO staff will need to quickly identify relevant existing guidelines produced by WHO or other entities or may need to issue recommendations based on expert opinion only […]. It is important that the decision-making process be documented and that the rationale for each recommendation be stated, even if it is based on indirect or very limited evidence or on expert opinion"[138(p.8)].

approval of therapeutics (Fast-track, Breakthrough therapy, Accelerated approval and Priority Review)[143], which have been used, and proved to be efficient, during emergencies. However, the threshold of evidence required to approve a drug under a 'Fast-Track' approach remains unclear, especially given the fleeting and inconsistent nature of evidence.

While it might not be sustainable to maintain the traditional standards of evidence during a pandemic, disproportionately lowering these standards might also be problematic. Several rushed decisions based on a single study were made[144], such as the WHO's decision to halt HCQ treatment arms on May 25, 2020 and resume them on June 3[97]. Other examples of rushed decisions include the FDA's Emergency Use Authorization for HCQ on March 28[94], 2020, which was retracted on June 15[37], and the addition of HCQ to the WHO's list of prioritized drugs (March 13)[145]. Chen J. and colleagues' study on 30 patients was the only completed study on HCQ that could be evaluated by peers before that date[57]. Thus, it can be argued that this decision was primarily influenced by the growing international media coverage on HCQ. Retrospectively, and considering the number of trials that stopped enrollment in their HCQ arms[70,146], these decisions seem to have been rushed. They also resulted in HCQ shortages for patients with conditions other than COVID-19 and more frequent self-medication incidents[89].

Theoretically, the implementation of NPIs might not need to be supported by as much evidence and can be safely implemented following the precautionary approach (given the low risks). Conversely, the approval of pharmaceutical interventions should be supported with much more evidence with respect to the associated perceived risks. However, what has happened since January is precisely the opposite: policymakers have sometimes waited for extensive evidence before implementing NPIs but have made rushed decisions regarding pharmaceutical interventions. This can be explained, in part, because, with respect to NPIs, adherence is more easily obtained if the population believes that the intervention is scientifically supported. On the other hand, the decision to allow the use of HCQ in the clinical setting and the FDA's EUA can be seen as a way to delegate decisions to clinicians' expert judgment. In that case, patients' adherence is facilitated by their trust in their family doctors, whom they see as authority figures.

The fleeting nature of evidence, as well as the complexity of evaluating a body of knowledge in a timely manner, has been an obstacle to the development of guidelines during the COVID-19 pandemic. It has not always been possible to sustain prevailing standards of evidence. While evaluating methodological rigor is essential, other criteria should be taken into account, notably, whether the intervention can be easily and equitably administered,

acceptable to patients and has a favorable cost-benefit profile. This is not something a RCT can always determine[124]. These considerations support the idea that different kinds of studies might be more appropriate depending on whether the prioritized objective is to determine the intervention's effects, produce generalizable results, or draw robust causal inferences[†††]. For evidence to be appropriately used in public health decision-making, both the reliability (which is often assessed using tools such as GRADE) and the relevance of evidence must be evaluated[19]. In the context of this pandemic, evidence that is relevant to the issue at hand may not exclusively originate from RCTs and can just as well be found in observational and mechanistic studies.

Sharing Scientific Findings

The fast reporting of accurate scientific knowledge also proved to be a challenge during the COVID-19 pandemic. The sharing of scientific evidence contributes to the generation of new knowledge by allowing scientists to build on others' work and find new, relevant research questions. Policymakers also need to quickly and easily access these findings to readjust their decisions as new evidence is generated. During a health emergency, the need for rapid reporting of scientific knowledge must not come at the cost of compromising its accuracy. The reporting of inaccurate findings is detrimental both for future research efforts and the public's perception of the pandemic.

Issues regarding the rapid reporting of scientific findings have already been debated during past health emergencies. Concerns first arose in 2007 during the H1N5 outbreak in Indonesia when the country refused to share the virus' genome with the WHO[‡‡‡105]. If shared, the Indonesian government feared that they would not derive any benefit from the development of future vaccines or therapeutics. This crisis incentivized the WHO to develop the Pandemic Influenza Preparedness (PIP) network to ensure that benefits derived from the

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[††††††] : Petticrew and Roberts refer to 'methodological appropriateness' or, in other words, the emphasis on "typologies rather than hierarchies of evidence"[147(p.527)]. They argue that there is a "need to match research questions to specific types of research."[147(p.527)]. Parkhurst & Abeysinghe[148] argue in favor of what they call 'evidence appropriateness', which is an alternative to 'methodological appropriateness'. They argue that "rather than adhering to a single hierarchy of evidence to judge what constitutes "good" evidence for policy, it is more useful to examine evidence through the lens of appropriateness. The form of evidence, the determination of relevant categories and variables, and the weight given to any piece of evidence, must suit the policy needs at hand."[148(p.665)]

[‡‡‡‡‡‡] : Section IV(E) '*Data Sharing During Public Health Emergencies: Histories and Precedents*' of the report by Abramowitz and colleagues[105] describes the events that happened in Indonesia during the H1N1 epidemic.

sharing of genome data would be returned to local populations at a price they can afford[105(p.21)]. The PIP network purports to facilitate the sharing of genome sequences and create a framework whereby the industry has to assist developing countries to have access to genome information[149]. Nevertheless, because the WHO has no international jurisdiction, it remains to be seen whether low and middle-income countries will really have equitable access to the findings of COVID-19 research. The question of transparency in the sharing of research findings was further debated during the Zika outbreak and resulted in the creation of Zika Open, a platform for the open sharing of papers related to the virus[150].

On January 31, 2020, Wellcome, a foundation dedicated to addressing public health challenges, released a statement encouraging researchers, journals and funders to share COVID-19 research findings as rapidly and openly as possible, in an attempt to keep the WHO informed of the latest advancements[151]. This statement outlined five recommendations:

- All peer-reviewed publications on COVID-19 are made open access during the pandemic,
- Research findings are shared with the WHO upon journal submission,
- Research findings are made available on pre-print servers with clear statements regarding the limitations of data,
- Researchers share interim and final research results, together with protocols and standards used to collect the data, as rapidly and widely as possible,
- Authors understand that data shared ahead of submission will not preclude their publication.

Scientific journals have explicitly stated that, in the context of COVID-19, they will expedite all editorial steps. As such, articles have sometimes been published in less than 48h[152]. Following these five principles and compared to past outbreaks, data sharing at the basic science level has been incredible since the beginning of the pandemic. On January 11, the first full genome sequence of SARS-CoV-2 (obtained on January 3) was shared on a discussion forum, virological.org. By February 2, de Oliveira and colleagues had developed a software program to classify genomes of SARS-CoV-2[153]. The development of reagents for diagnostic tests has been relatively fast (January 11), which is important progress compared to past health emergencies (e.g. SARS[153]). The use of pre-prints has also been widely encouraged[§§§154] and has exponentially increased, allowing faster results reporting. While this

§§§§§§ : GloPID-R (Global Research Collaboration for Infectious Disease Preparedness) released a roadmap outlining recommendations for sharing scientific data during public health emergencies[154]. To encourage the use of pre-prints, the authors recommend that we should "align funding policies to ensure that data sets and pre-publications are all included within assessment of researcher outputs (in accordance with the San Francisco Declaration)."[154(p.28-29)] A study by Nabavi Nouri and colleagues suggests that there has been "a dramatic

is crucial for scientists, the growing use of pre-prints has had negative consequences on the public's understanding of the pandemic. Indeed, information derived from papers posted on pre-print servers was reported in the media, often without outlining the study's limitations, and has contributed to the spread of misleading information[155].

The fourth recommendation outlined in the Wellcome statement regarding the sharing of clinical findings has been relatively poorly followed. While interim results of clinical trials have sometimes been shared[70,156], most trials do not release interim results nor protocols. It seems that only the protocols of large, international, highly publicized trials were released (such as REMAP-CAP and RECOVERY, but interestingly not SOLIDARITY). Sharing interim results also comes with its own set of issues: clinicians and researchers involved in the trial might subconsciously change their behavior and alter the outcome as well as patient accrual, adherence and retention¶¶¶[117,157,158]. The reporting of findings at the clinical level is also complicated by the need to accommodate different values and interests. During a health emergency, there is a strong incentive to publish quickly, given the number of knowledge gaps (i.e., the need for novel scientific knowledge) and lives at stake. Generating evidence to inform international and national decisions in a timely manner often comes back as a core ethical requirement during health emergencies[13]. However, and in addition to the 'publish-or-perish' culture in academia, a health emergency provides strong incentives to publish articles that lapse into sensationalism, sometimes at the cost of quality[159]. At the clinical level, there are also numerous potential financial and academic benefits associated with the commercialization or patenting of therapeutics and vaccines. Journals might also have strong incentives to expedite the publication process to be recognized as the first to publish a world-changing paper. Therefore, the need for fast knowledge reporting is, sometimes, in conflict with reporting accurate information. While retraction of scientific papers has always happened, often without sparking public interest, several COVID-related papers, that had been highly publicized in the media, have been retracted. As of December 20, 2020, forty COVID-19 related papers were retracted, five are temporarily retracted, and five are the subject of a statement of concern[160]. Six of these COVID-19 related retracted papers investigated the role of HCQ as a treatment for COVID-19. However, the rapidity with which

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increase in the presence and importance of preprint publications"[155(p.1)]: between the beginning of the pandemic and September 7, 2020, 8,468 pre-prints were published on MedRxiv and BioRiv[155(p.3)].

¶¶¶¶¶ : The FDA guidance document on adaptive trials (2019) warns the reader that "knowledge of accumulating data by trial investigators can adversely affect patient accrual, adherence, retention, or endpoint assessment, compromising the ability of the trial to reliably achieve its objective in a timely manner"[117(p.24)].

errors have been flagged by the scientific community and rectified by editors can be appraised. Compared to a paper published in *The Lancet* on a possible relationship between the MMR vaccine and autism, which was retracted 12 years after its publication, questionable papers related to COVID-19 were retracted within days[152].

The publication of findings during the COVID-19 pandemic highlights the need to follow the five principles outlined by Smith, Upshur and Emanuel[13]: ensuring scientific accuracy, social value (data must be released and (in)validated by the scientific community), protection of research participants, transparency and accountability on the part of journal editors. Contradicting evidence has been reported, almost in real-time, by the media and has affected the public's understanding of the pandemic and trust in science. This has resulted in inappropriate behaviors, such as the panic buying of HCQ, leading to shortages for those who need it[161], and increased risks associated with self-medication[162]. In a time where confusion, uncertainty and fear rule, and where mitigation strategies rely on people's adherence to science-based guidelines, it is particularly important to communicate scientific findings, and their limitations, in a clear and transparent manner.

Discussion

In the context of the COVID-19 pandemic, research conducted on pharmaceutical treatments, and especially HCQ, has generated low-quality and inconclusive findings, which have had negative consequences on patients, the public and other ongoing research efforts. These two papers have attempted to evaluate the factors that have interfered with the generation of novel scientific knowledge and have demonstrated that such challenges are to be found at each step of the research process. First, a lack of prioritization among research questions and therapeutics has, in part at least, been responsible for the duplication of research works and the dispersion of scarce resources. Study designs, aimed at minimizing biases and increasing objectivity, have, instead, been the subject of fruitless oppositions. During the pandemic, it seems that methodological rigor and the notion of design complementarity were somewhat abandoned. These two issues combined have resulted in the generation of fleeting and inconsistent evidence that has been an obstacle to the development of public health guidelines. Finally, the reporting of scientific findings has again highlighted the difficulty of finding a balance between accuracy and speed. Inter-epidemic efforts have shaped and improved the COVID-19 research response, especially in terms of expedited ethics approval and the sharing of basic science research. Interestingly, these achievements constitute the

focus of our efforts since the last health emergencies, which should motivate researchers to address the remainder of challenges that are obstacles to the generation of novel scientific knowledge (such as the duplication of research works or the sharing of clinical data). The COVID-19 pandemic will undoubtedly contribute to reshaping the way we think about research during health emergencies and encourage us to approach them in terms of alternate phases of preparation, response and learning instead of disconnected outbreak events.

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Tables:

	Efficient Use of Information	Safety of Trial Participants	Avoiding Trial Downtime	Fusing Research with Care	Determining Optimal Disease Management	Learning Healthcare System
Multifactorial	✓	—	✓	✓	✓	—
Response adaptive randomization	✓	✓	—	✓	—	✓
Embedding	—	—	—	✓	—	✓
Frequent adaptive analyses	✓	✓	—	—	✓	✓
Analysis by stratum/subgroup	✓	✓	—	—	✓	—
Evaluation of interaction	—	✓	—	—	✓	—
Substitution of new interventions	✓	—	✓	—	✓	—

Table 1: REMAP design advantages. Retrieved from Angus, D. C., et al. (2020). The remap-cap (Randomized embedded multifactorial adaptive platform for community-acquired pneumonia) Study rationale and design. Annals of the American Thoracic Society, 17(7), 879–891. https://doi.org/10.1513/AnnalsATS.202003-192SD[112].