

# Is clinical effectiveness in the eye of the beholder during the COVID-19 pandemic?

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There is no shortage of clichés being used during the current global pandemic, but none is more striking than the Hippocratic aphorism ‘for extreme diseases, extreme methods of cure’ or, in its modern variants, ‘for desperate times, desperate measures’ or even, ‘take it! What do you have to lose?’.

The current crisis has challenged the erroneous perception that threats to global public health by rapidly spreading infectious diseases were under control. COVID-19 is indeed an extreme disease, not in its nature but due to its global reach and the level of social disruption it is causing. The extent of the direct and indirect adverse effects of the COVID-19 pandemic on the global socioeconomic structures is yet to be ascertained but will probably have systemic and long-lasting repercussions.

In these challenging times, we must consider drastic measures to ensure that clinical practice continues to be rooted in sound evidence. Contrary to those fighting to control the 1918 influenza pandemic, we have at our disposal a body of methodological knowledge to conduct rapid and efficient clinical trials. Furthermore, innovations in information technology, computing and telecommunications have made economic globalisation a reality and enabled a previously unimaginable level of global interconnectedness. As with other sectors of society, science and medicine have significantly benefited from the almost instantaneous speed of communication between different parties involved in medical research, fostering collaboration and information dissemination.

It is thus essential, at a time when global public health response capacities are being put to the test, not to falter through following the path of least resistance, lowering the guard in protecting evidence-based medicine.

A disadvantage of modern telecommunications is the rapid spread of false or inaccurate information. While the former is often produced with malicious intent, the latter is frequently the product of misinterpreting scientific studies and the media’s lack of capacity to appraise different levels of scientific evidence.

Almost 50 years after Archie Cochrane<sup>1</sup> warned us about the dangers of assuming that untested established therapies are effective and the need to test them through randomised controlled trials, it is bewildering to observe the mushrooming of COVID-19-related literature and practices not based on these premises. From methodologically weak studies on potential therapeutic and prophylactic drugs to simple prevention interventions such as mask use, the rules for producing

sound evidence appear to have been suspended or relaxed. Practice-changing trials used to require reasonable control arms, clockwork-like design, stringent ethical clearance, thorough data and safety monitoring committees, reliable statistical analysis methods and accurate reporting. In the era of COVID-19, clinical practice has been influenced by several uncontrolled studies describing results compromised by the vast array of biases commonly taught in introductory courses of clinical study design and statistical analysis.

This rapid adoption of unsound or incomplete evidence is at odds with one of the classic bioethical principals guiding clinical practice. Respecting the principle of non-maleficence requires either doing no harm or causing the least harm to produce a beneficial outcome. While the violation of non-maleficence may not be evident in some of the public health interventions currently in place in various countries (eg, population confinement and mask use by the general population), it is apparent in off-label drug prescription without confirmed effectiveness. No example is more blatant than the widespread use of chloroquine and its derivatives,<sup>2,3</sup> based on in vitro and very tenuous clinical data. While determining its clinical utility in the management of COVID-19 is the object of numerous multinational clinical trials, the associated direct (eg, sudden cardiac arrest due to QT prolongation or toxic retinopathy) and indirect harms (eg, drug shortages for patients afflicted by conditions for which the drug has been approved) are known and should be avoided. Furthermore, mass investment in flawed therapeutic, diagnostic and preventive approaches could pull already strained health systems away from the goal of achieving allocative efficiency, with system-wide consequences and worse population health outcomes.

Information asymmetry characterises the relationships between the different stakeholders in healthcare, most notably between patients and doctors, but also between the scientific community and political decision-makers. In times of increased partisanship, exacerbated as often occurs during times of crisis, results from flawed or weak studies can be captured by political actors and their agendas. Either as the result of succumbing to the pressure of public opinion or as a potential strategy to divert attention from leadership and governing ineptitude, decision-makers may be inclined to portray as valid evidence that is not widely acknowledged as such by the scientific community.



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Tackling this public health crisis will require a concerted global effort in identifying the most effective strategies to contain the virus and its consequences and avoid future outbreaks, as well as in developing and distributing effective treatments and, ultimately, a vaccine.

Until the latter objective is achieved, we will have to rely on important preventive public health interventions. These interventions are being widely implemented and aim at minimising the risk of transmission in the general population (eg, physical and social distancing, environmental disinfection and cleaning, improved hand hygiene and respiratory etiquette),<sup>4</sup> rapid outbreak detection (eg, new digital epidemiological surveillance tools)<sup>5</sup> and protecting the most vulnerable (ie, adapting healthcare delivery methods and clinical guidelines).<sup>6-8</sup>

The transversal reach of the health sector in society was undoubtedly exposed during the COVID-19 pandemic and acting to minimise the intersectoral impact of this public health crisis is crucial. This action will depend on the behaviour of the population in general, but also of the scientific community. Those involved in the process of producing, applying and disseminating scientific knowledge must be conscious of their responsibility in increasing the probability of policymaking being based on the best achievable evidence.

This effort should include, among others, scientific journals responsibly choosing to publish and highlight the most clinically useful studies, and researchers striving for research integrity and efficiency.

Several countries have described the COVID-19 pandemic in military terms, equating it to an armed conflict. It is thus our shared responsibility, as a community, to ensure that evidence-based medicine and the associated population health gains are not collateral damage.

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