



RESEARCH CHALLENGES IN COVID-19 TIMES

This year 2020 will remain in our minds not only because of the onslaught of a new pandemic (1) but also because of the great uncertainty it brought with it, reminding us of our fragility as human beings. As the year dawned, very few things would have been considered unforeseeable or unpredictable. For example, late in 2017 we were made aware of the fact that we lived in a globalized world where the flow of people, information and capital moving across borders was increasingly frequently, to a degree never witnessed before; and, although some threats lurked in the horizon - like Trump's nationalistic stance and Great Britain leaving the European Union in what is known as Brexit - that globalization was not considered to be in jeopardy (2). On the other hand, big data and artificial intelligence-enabled analytical models could be used to predict the possibility of many situations, for example, people's behaviors based on website visits (3), or people's location down to an individual level through the smart phone (4), or the use of text processing to obtain causal inferences (5), among many other applications enabled by these technologies. Very few people could have imagined (6) that a viral infection would unleash the pandemic that still bewilders us since March of this year.

In Colombia, where uncertainty is our bread and butter, the pandemic caught us in the midst of significant social mobilization which had begun in November 2019 as part of a wave of social movements in Latin America (7) characterized by protests fueled by different problems and contexts and which would prevail throughout 2020 (8). Moreover, corruption was rampant. By 2019, Colombia ranked 96 among

180 countries, with a score of 37/10-0 according to Transparency International (9). The State has tried to counteract corruption by means of regulations, decrees, resolutions and oversight agencies, resulting in complex processes that, in "normal times," are time-consuming and have proven ineffectual (10). There are exceptions to every rule, as is the case with the *Colombia compra eficiente* program (11), but there is still a long way to go. On the other hand, workers in both the private and the public sector have not been trained to respond rapidly and creatively to circumstances as uncanny as those created by the pandemic but are rather fearful of not complying with the cumbersome processes surveyed by the oversight mechanisms; or they follow the bureaucratic models designed to heighten the importance of a job (12).

I would like to refer in this editorial to some of the problems that have hindered the process of carrying out a clinical research activity during the Covid-19 pandemic in 2020. This research is designed to find a safe and effective treatment against SARS-CoV-2 (13). Up until now, there is no treatment to fight the virus or to control the overwhelming inflammatory response triggered by the infection, beyond dexamethasone, the synthetic corticosteroid developed in 1958 for the treatment of rheumatoid arthritis (14), which reportedly reduces mortality by 30% in patients requiring invasive ventilation (RR = 0.65; 95% CI: 0.48-0.88) (15).

The problems halting this research are hurdles that will have to be overcome in the near future if we are to respond adequately to similar situations in the field of healthcare research. It is worth noting that, over the past 40 years, we have had to face several epidemics

with dire effects for our population, including the human immunodeficiency virus (HIV), described in 1981 (16). Then, in 2009 in the Americas region, the H1N1 virus (17), followed by chikungunya in 2014 (18) and zika in 2017, as a result of an outbreak in Africa in 2007 (19), with serious repercussions for child health and, finally, the worldwide Covid-19 pandemic in 2020.

By April 2020, in view of the relentless advance of the pandemic, the study had become a priority as a means to offer a treatment option, in particular to the most critically ill patients, and to undertake a careful evaluation of the associated risks and benefits. The hurdles that have delayed the initiation of the study by at least two months, time that could have been saved for the benefit of our patients, are the following:

1. Information and misinformation

Medical research journals have been considered to be of high credibility for the scientific community. This perception is supported by two considerations: peer review process, and scores obtained in metrics used to measure the performance of scientific journals. Peers verify the scientific and methodological quality of the published papers, and metrics describe the average number of citations received by an article published in a specific journal (20). However, perhaps due to the need to look for a solution to a new disease of poor prognosis for some groups of patients, with a huge impact on intensive care units because of respiratory failure cases and unforeseen financial and social consequences, or because of the trend among the media to rush to be the first to publish the news, we found ourselves in a situation where the most important international journals, flooded by large number of manuscripts on Covid-19, had to resort to a simplified peer review process (21); and, not only that, but they began to publish studies with no peer review in preprint sites such as bioRxiv and medRxiv (22). Regrettably, many of these manuscripts have validity issues (23). It is worth mentioning the premise that, in health science, it is important to be

cautious regarding the benefits of rapid transfer of new knowledge as compared to the potential harm that can be caused by studies with a high risk of bias published as part of the accelerated review process, with methodological deficiencies and flaws in the final report (24). This problem of misinformation and study publications had a local effect on research, as will be discussed later.

2. Lack of experience with the management of a pandemic situation, made evident in the decisions of ethics committees and the medical community at large

In the face of unknown viral pandemics, treatments have been based on past experiences with similar infections or *in vitro* results of medications against viruses of the same family. Therefore, it was based on the treatments during the H5N1 and MERS outbreaks, that the use of hydroxychloroquine (25) and lopinavir-ritonavir (26) was considered at the start of this current pandemic. On the basis of this past history, the Colombian consensus for Covid-19 management, published in April 2020, recommended the use of these medications, as well as of azithromycin (27). However, a study published in May by Mehra *et al.* on the safety of hydroxychloroquine presented “real world data” in a cohort of 96,032 patients in 671 hospitals. The results of the study showed a higher risk of death in patients receiving hydroxychloroquine, the risk being even higher when the drug was given in combination with azithromycin (28). Despite low certainty evidence, the publication of the results of this study in the *Lancet* prompted local ethics committees to rush to halt local studies in which those drugs were being used, resulting in delays in the process of initiating the studies. Moreover, the Colombian consensus also excluded these medications as a result of that publication (29). It is worth remembering that the study was the object of retraction by the journal because of the impossibility to confirm the veracity of the data (30). In stark contrast with this attitude, the monitoring committee of the Recovery study

under way in the United Kingdom, which was also assessing those medications, decided not change the treatment arms in response to those results and wait until they reached their own conclusions. It may well be that the English are ahead of us in the study and management of epidemics.

3. Hiring fieldwork staff for research

For a long time in Colombia, service agreements have been used to hire freelance workers who pay for their own fringe benefits (health and pension fund) and who have no direct working relationship with the hiring company (31). Additionally, the contractor must pay the work-related risk coverage charges under categories I, II and III (minimum to intermediate risk) while the hiring company pays for level IV or V risks (high or maximum). Research assistants have been retained under this modality in Colombia during this pandemic. For the study in question, researchers are required to identify patients with a confirmed diagnosis of Covid-19 and explain to them the objective of the research and ask whether they are willing to participate by signing an informed consent. With the rate of infection being close to 12% (32), researchers are at risk of contagion, hence the need to provide them with the full protection kit, including elements for use in areas with aerosol exposure, in order to ensure their personal protection as well as that of their families. To the question of what would happen in the event they acquired the infection and required isolation, the answer was that the contract would be placed on hold and no payment of professional fees would be made. As to the level of risk according to the view of the insurance company, it was classified as intermediate or level III. Consequently, the option of life insurance plus coverage for sick leave was considered in order to ensure compensation for their work; however, no public organization was able to provide this coverage. This resulted in the resignation of several research assistants which, in turn, delayed patient recruitment in some institutions. It is also worth noting that the hiring process in State organiza-

tions is very slow and hampered by red tape, taking up to 15 or 30 days. In some cases, hiring processes are conflicting: for example, the medications regulatory authority requires a third-party liability policy containing all the clauses and issue date in order to grant approval for the protocol, but sponsors do not authorize payments based on that particular date, delaying authorization by the regulatory authority for the initiation of the study.

4. Timelines in the participating centers

Although the ethics committees of the participating centers and the regulatory authority expressed their willingness to expedite the process as much as possible, reality showed that, at times, formalities are more important than triggering a quick response to situations like the current pandemic. By way of example, the initially drugs included for assessment in the study were hydroxychloroquine and azithromycin. These two drugs are associated with electrocardiographic (EKG) prolongation of the QT segment as an adverse effect (33), hence the exclusion of patients with this finding on EKG screening, because of the high risk of cardiac death. Because of the evidence of lack of effectiveness of these medications as well as of the lopinavir/ritonavir combination derived from Recovery study (34,35), they were replaced by emtricitabine/tenofovir, colchicine and rosuvastatin, which are not associated with this adverse effect. A letter was sent to the ethics committees requesting to waive that entry requirement since it was no longer needed and would otherwise delay treatment initiation by up to 24 hours in patients who had agreed to participate. However, in one center, the ethics committee stated that such change would not be approved until the revised protocol was submitted. The formality trumped over the relevance of the change in terms of benefit for the patients. On the other hand, the regulatory agency took four weeks before authorizing patient inclusion in one of the participating centers. By the time the request was sent, the figures of infected patients and deaths in Bogota had reached 201,919 and

5,398, respectively. By the time the authorization was issued, those figures had increased to 256,136 newly infected patients and close to 6,753 deaths (36). It is impossible to understand these delayed responses in a situation like the current one.

This pandemic has pushed us to accelerate processes previously considered impossible to implement in the short-term, as is the case of working from home with the help of mass use of information and communication technologies, or other transformations unimagined just one year ago, like the way to relate with other human beings. The State, society as a whole, and we as individuals are required to change the rigid mindset that keeps us anchored in underdevelopment so that an individual and collective transformation is unleashed. For this to happen, we need to learn from our mistakes and avoid repeating them in the future, and overcome these hurdles because it would appear at times that we are doomed to an irrevocable fate, similar to the paradox portrayed in *Dark*, the TV series (37).

As a society, we need to be capable of mounting an articulated response when it comes to searching for a solution or at least a way to mitigate crises like the one we are facing now, working towards a common goal in order to offer prompt and valid answers to exceptional circumstances like the present one. This requires learning to drop rigid stances regarding such things as hiring and procurement of goods and services or compliance with administrative formalities that bring us to a halt; but it also requires being critical of the avalanche of information we are buried in, many times originating in vested commercial or political interest which are alien to us. Perpetuation of our equivocal development model awaits us if these hurdles are not overcome.

These reflections are probably applicable in other areas such as healthcare, education, food security, work and others which were seriously affected not only by the significance of the pandemic and the fear and uncertainty it brought with it, but also by the low ability to respond and, possibly, the inexperience of our society.

The 2019 Mission of Scholars discussed the emblematic missions that should bring us together as a society or as country. Life has presented us with a challenge around which to unite in order to protect the future of our country in areas like food security for children 2-5 years of age. Let us not miss this opportunity.

Hernando Gaitán Duarte, MD, MSc.

Editor

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