Embracing the Uncertainty: an Important Lesson from COVID-19

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The past year will be remembered as the one in which the world had to face an unknown enemy, the SARS-CoV-2, and the disease it caused, COVID-19. For almost all health care workers, it will also be remembered among the most challenging periods of their lives: caught between increasing workloads and the fear of infecting themselves, their loved ones, and their patients; overwhelmed by double shifts, stress, and sometimes forced separation from their families.

Beyond these evident sources of frustration, others, more subtle, hit physicians during the COVID-19 outbreak. Early in 2020, an editorial published in the *New England Journal of Medicine* underlined the need for critical and rational thinking—a “reminder to reason”, according to the authors.¹ The crisis of our certainties has revealed itself, more disruptive than ever, in front of this unknown disease. How can we treat our sick patients? How much can we rely on a single nasopharyngeal swab test? Why do some patients present with mild symptoms and others with severe disease or death? These are only some questions that physicians ask themselves every day; most of these doubts remain unresolved, and leave us suspended in our frustration and a deep sense of precariousness.

As human beings, we hold on to what we know and avoid uncertainties. Often in our profession, we are tempted to overtrust the protocols we use or the guidelines we follow. We often forget the degree of uncertainty behind recommendations; what level of evidence supports the treatment we administer almost every day; that real-world patients may differ from those enrolled in clinical trials. We tend towards oversimplification to deal with the enormous number of doubts we are surrounded by. In many of us, the COVID-19 pandemic hit that nerve: we are not used to doubt; we are not comfortable with the unknown, in the face of which we feel lost. Sometimes,

we are unwilling to communicate our uncertainty to patients, or their relatives, fearing that this would project ourselves as weak or—even worse—unable to provide the best care they deserve.

During this pandemic, we experienced many of the most frightening uncertainties that belong to our profession: an unknown spreading disease, with an often unpredictable evolution, for which we are still struggling to find treatment. Caught in the middle of this storm, many physicians started to do what is furthest from modern medicine: treating patients without the support of evidence, or blindly relying on diagnostic tests with limited sensitivity and specificity. We made use of several drugs, in the absence of definitive and convincing proof of efficacy,² and when more robust evidence proved the inefficacy of those treatments,³ some of us continued to prescribe them, in a desperate attempt to cling to those evanescent beliefs, built with so much effort amid the pandemic.

Neglecting the uncertainty, and overtrust in ephemeral (or outdated) knowledge, did not originate with COVID-19, and is similar to what happens when new studies or guidelines are published: adoption in clinical practice is often slow and incomplete.⁴ This is related not only to inadequate information or sluggish update, but also to our resistance to questioning beliefs and certainties that we matured over time. Likewise, our confidence in diagnostic tests is often inappropriate, and our ability to interpret results limited:⁵ often, we do not acknowledge limitations in sensitivity and specificity, and do not consider the pre-test and post-test probabilities when deciding to perform, interpret or even repeat one test. During this pandemic, some of us have found ourselves surprised in front of an unconfirmed result of a single nasopharyngeal swab, without accounting for the obvious chance of false-negative or false-positive results.

This pandemic has escalated our conflicted relationship with uncertainty, to a higher level: some physicians transitioned from an “unconscious ignorance” of the uncertainty to a resolute urge to “do something”, irrespective of the many doubts arising. Why did this happen? How did we find ourselves moving away from evidence and method? We should interpret these questions from the perspective from which we were thrown into. Most front-line physicians were overwhelmed by logistical challenges (including the shortage of equipment and hospital beds,

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especially for critical patients). The fear of the unknown, anxiety, and the sense of powerlessness that many doctors experienced during this pandemic may have pushed them to go the extra mile in the decision-making process, even forgetting their commitment to rigorous evidence in front of an unknown disease. The ethical dilemma between trying to do something and sticking to scientific rigor has led many of us to see ourselves in the shoes of Martin Arrowsmith, the young physician narrated by Sinclair Lewis, who was swept away, together with his ideals, by a pandemic: this novel, written a century ago, sounds now extremely contemporary.⁶ Among the most neglected issues of this pandemic, emotional distress and personal feelings of frontline physicians, and political pressures (also on the use of some hyped treatments)² further inflated the sense of uncertainty in the medical community.

On the other side, this pandemic harshly revealed many of the limitations of the current approach to evidence-based medicine and medical communication. The need for prompt answers to urgent clinical questions caused significant issues to the peer review process, dissemination of subsequently retracted data, and a great dispersion of relevant information among a myriad of articles and pre-print manuscripts.⁷ The public has often been bombarded with misinformation, myths, and “easy answers”, in a jumble of announcements of new miraculous drugs, regularly denied thereafter. This led to additional discouragement and mistrust.

How should we have responded in a scenario dominated by doubts? The solution to this dilemma is pivotal in shaping our response to new challenges (including COVID-19), improving the care we deliver to our patients, and strengthening the doctor-patient relationship. The answer lies in accepting the uncertainty, to which medicine is inevitably bound: we need to increase the awareness of both our limits and the incompleteness of current knowledge. Being transparent with ourselves as physicians and our patients about the challenges and difficulties in our decision-making process will help us deal rationally and ethically with the unknown; even when a novel disease threatens us. Our role in a pandemic, indeed, goes far beyond patient care: we must provide information and guidance, without neglecting the “grey zones”; presenting facts more than opinions, avoiding oversimplification and easy answers if there is no room for them. This is also the way that we, as scientists, can build trust with the community, fighting misinformation and distrust: explaining the limits of our knowledge, guiding our patients across the uncertainties, sharing our arguments and thesis rather than merely delivering them. Gaining patients’ trust represents one key challenge of our times, and we will not achieve that without being able to deal with and communicate the uncertainty. The vaccination campaign will be the next milestone in the fight against COVID-19, and its success will depend very much on this.

Accepting uncertainty in everyday clinical practice may also improve the way we treat and manage our patients. Remember how tests with limited sensitivity and specificity may bias our decisions, and considering the pre-test probability of our patients would eventually reduce misdiagnosis and unnecessary further exams; a clear understanding of the evidence behind one therapeutic recommendation would definitely help weigh potential risks and benefits, inform patients about what to expect from a given treatment, and, ultimately, reduce costs and treatment failures. Finally, greater awareness of our limits can improve the way we cope with hard choices, work-related stress, and bad outcomes when these occur.

Among these uncertainties, administration of treatments without a solid background of evidence has represented one of the most complex ethical dilemmas during this pandemic. Is it justified (or even acceptable) to treat patients with an unknown disease with drugs of uncertain benefits, even if with low to virtually no risk of harm? Are we really able to weigh the possible benefit against all the potential adverse effects accurately? Treating patients based on hypotheses or assumptions may provide little to no benefit, but at a much higher cost than it appears: it may distract from delivering the best supportive care that we can, or performing trials that may help improve our knowledge of the disease. Moreover, on a large scale, unexpected side effects may emerge, these being completely unacceptable in the absence of proof of benefit. In our decision-making process, we should also consider false hopes, and additional costs that may arise.^{1, 7}

Hopefully, this pandemic will eventually end: science and medicine will beat this enemy, and we all will return to our lives. However, uncertainty will not leave us: perhaps in a less evident fashion, it will remain one essential trait of our profession. As physicians, we should take one big lesson, among others, from these challenging times: we need to remember to doubt; we need to accept, deal with and communicate the uncertainty that naturally belongs to our beloved profession. Embracing the uncertainty is how we can improve, as physicians, while facing current and future challenges.

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