

Science Under Stress. The Pandemic Effects on Research

Ciencia bajo estrés. Efectos de la pandemia sobre la investigación

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It is sometimes surprising to look at the past, in this recent case, and see how facts happen and link together, in a heretofore unimaginable way. This reflection emerges after writing this editorial, whose main purpose was to analyze events that concern biomedical research in an approximately chronological account.

On February 13, 2020, Collins et al., (1) renowned Oxford epidemiologists for their great contribution to cardiovascular therapeutics, published an editorial note (probably written before December 2019), which, to my judgement, was premonitory. In it, the authors questioned the value of large observational studies, referring to them as the “myth of real-world evidence”. The reason for this questioning was that, despite complex statistical adjustments, these studies were still markedly biased, since as it is impossible to control all confounders, they could lead to false conclusions, unacceptable at the time of approving or not a new treatment. The cited authors endorsed controlled clinical trials as the only way of achieving unbiased evidence, though with lower external validity, precisely due to their stringency. Most interestingly, they explained that the difficulty of performing this type of trials is due, to a large extent, to excessive bureaucratization produced by non-scientific regulations. In their editorial note they proposed a series of opportunities improving quality and efficiency to increase the scope of randomized evidence.

When these considerations were coming to light, one of the most extraordinary phenomena lived by humanity in the last hundred years was in full expansion: the SARS-CoV-2 (coronavirus) pandemic, a severe acute respiratory disease, called COVID-19.

The outbreak was reported in December 2019 in the city of Wuhan, China, and the first death was recorded on January 11, 2020, spreading with such speed that on March 11 it was declared a pandemic by the World Health Organization (WHO). During the following two months, it quickly disseminated throughout Europe and America, and has already produced millions of contagions and hundreds of thousands of deaths.

The first and most elemental way of fighting the spread of the disease was “containment and mitigation” (that is, social isolation, hygiene, and drop and contact protection) with the aim of “flattening the curve”, measures that were mostly adopted in Western countries during February and March.

Almost at the same time the pathophysiological process was clarified. This consisted of an initial viral response, followed by an immunological response and, finally, by a hyperinflammatory phase with presence of multiple biochemical markers. The first treatments were empirically aimed at these processes, through the application of inferred previous knowledge.

Thus, different steroid and non-steroid anti-inflammatory, antiviral and macrolide drugs have been used, with uncertain clinical outcomes.

Suddenly becoming aware of the terrifying reality, humanity assisted, shocked, to what the visionary Bill gates defined as the “century pandemic”, (2) as it fulfilled with four defining postulations: 1) it can kill young adults, 2) has high rate of mortality, 3) very efficient dissemination, and 4) can be transmitted by asymptomatic persons. Fauci et al. described this moment of great uncertainty for medical science as an “unchartered navigation”, (3) i.e. with unknown course. The phrase “Never was the gap greater between what we know and what we need to know” masterly describes the helplessness of science before this phenomenon, with the added unusual speed in its development, partly as a result of modern world mobility.

With the phase of containment and mitigation installed, Fineberg proposed several steps to “flatten the curve in ten weeks, (4) including a unified command, millions of diagnostic tests, health care personnel protection and an urgent call for research. But, on this point, the proposal was novel: “Learning while doing, real-time research”.

We could say that the general urgent and mandatory objective to investigate was issued in April, with dedicated funding resources to produce data and adopt conducts based on the emerging results.

(5) By the end of April, Lancet published “A real-time dashboard of clinical trials for COVID-19”. (6) This article reported the ongoing clinical trials evaluating the efficacy and safety of several treatments applied to patients with COVID-19. By that time, around 500 protocols had been published in ClinicalTrials.gov comparing different strategies, though most of them were “head to head” or versus standard treatment designs. Noteworthy, there was absence of controlled studies versus placebo.

After this initial explosion, calls of attention appeared about “out of control” science in times of pandemic, (7) defining it as “a toxic legacy of poor quality research, with excessive media dissemination, lax regulatory control and bias for intentionality, which has emerged within the legitimate search of effective treatments for COVID-19”.

The urgency to investigate and fill the gap in knowledge in times of crisis led to the publication of data that did not have good statistical significance, was methodologically defective, and even of dubious origin. The results thus originated deeply permeated many health professionals (perhaps too naïve or with insufficient methodological training) and also desperate patients, fed by disinformed or extremely sensationalist media.

Since the Spanish flu pandemic, it is known that in these crises research is a true nightmare, as stated by Rupert Blue, in 1918. There is the wish to test different cures or treatments, sometimes ineffective, or even harmful. The media is flooded by miraculous cures and poor studies are reported without adequate criticism.

As with everything, the problem forces the return to the sources. Several authors have already emphasized the concept with which this editorial started: without a randomized controlled study with placebo there is no way of knowing whether a specific drug is better than its absence. Failure to use an appropriate control branch has historically led to false conclusions. The drive to offer treatments not based in well-designed studies erodes high-quality science and condemns us to repeat ancient errors.

By the month of April, the ClinicalTrials.gov base showed more than 450 studies with hydroxychloroquine or chloroquine associated or not to macrolides, with well-designed studies sponsored by WHO, destined to answer the question of their efficacy and safety on COVID-19. On May 22, Mehra et al. published in Lancet (8) a retrospective analysis of 671 hospitals in five continents with 14,888 patients treated with these drugs or their combinations, compared with a control group of 81,144 patients infected with coronavirus. The study not only showed no benefit, but an increase in mortality and fatal arrhythmias.

As a consequence of these results, ongoing randomized studies were suspended by WHO (considering that the published data was sufficient evidence) and Anthony Fauci declared in CNN that the drug was not

effective.

The scientific world quickly mistrusted this study because there was no access to the pool of data, which threatened the integrity and safety of findings. (9) Many researchers questioned with harshness the legitimacy of the study and a possible ethical deviation due to conflicts of interest was observed. The publication was retracted on June 4.

The analysis of Rome and Avorn (10) shed an important light concerning drug assessment during a pandemic. The need to develop, test and distribute drugs during a pandemic constitutes a challenge as well as an opportunity. Sometimes, the media and political pressure is intense and forces emergency authorizations that later must be reviewed. The promotion of drugs without randomized evidence goes against evidence-based data and, what is worse, damages public credibility in control organisms. The cited authors recommend acting as efficiently as possible, but keeping standards. Drugs, massively administered without solid bases and which might produce damage eliminate the ethical claim of the “right to try”. The temptation to use untested therapies is understandable, but, generally, the results have been neutral or bad (having certain data is sometimes worse than having nothing). Paul P Glasziou, in his BMJ editorial, analyses the great “waste” of information. (11)

Research at great speed “under stress” has produced an initial chaos, from which some positive facts can nevertheless be saved, as open access to data, greater collaboration among groups, expeditious regulation and faster ethical resolutions. But also, the amount of negative consequences is high: 85% of waste information due to poor research questions, inadequate designs, bad reports, great increase in pre-prints and duplicate information.

On this ground, we have the challenge of achieving a balance between the need of learning while doing and of having exact data during the pandemic. An exploitation vs. exploration trade-off has been defined. (12) Exploitation refers to acting on current knowledge, habits, or beliefs despite uncertainty, that is the “just do it” option. Exploration refers to actions taken to generate new knowledge, that is “to learn something”. Their balanced combination would be to learn while doing. But this is more a statement or wish than a feasible reality. Clinical practice (“exploitation”) and clinical research (“exploration”) are addressed in different contexts (institutions, procedures, regulations and funding) limiting their compatibility.

It is very important for the medical community to be minimally prepared for a critical review of information, to avoid errors and waste of time. It should always be recalled that when analyzing data there is an interplay between the effect size and the statistical power (probability of a significant effect), which requires an adequate sample size within the selected significance level. When looking at data, it is better

to look for “hard outcomes” (death, ventilation, etc.) and that the study is randomized, especially versus placebo. We should be more skeptical of very flexible designs, lax definitions and subgroup or per protocol analyses. We should also be very critical of composite outcomes, small samples or series of cases or clusters.

There are potential solutions to this problem: in the first place, it is necessary to look for scientific designs that favor randomization, and develop initiatives that promote regulatory simplification, funding and international coordination (as the Research Project Tracker, Epidemic Preparedness Innovation, CEPI Multicenter Trial Infrastructure, CTTI Clinical Trials Transformation Initiative, etc.). The health systems and their means (electronic clinical history) can be applied to randomization.

There is a false dichotomy between fast drug approval and rigorous data. It is also true that randomized controlled trials can be done quickly and with hard endpoints, evaluated in a few days (the ritonavir/lopinavir study, with thousands of patients, was completed in two months).

To end this analysis, I believe it is appropriate to remember the deep conclusion of Rome and Avorn in their perspective about drug evaluation, which I transcribe verbatim: “The pandemic will inevitably leave considerable morbidity, mortality, and loss in its wake. Damage to the country’s medication-assessment process -and the public’s respect for it- should not be part of its legacy”. (10)

We hope that the confusion generated by the impending need to fill the gap of uncertainty will henceforth be an opportunity for a qualitative leap in research excellence.

Ethical approval

Not applicable.

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