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HEALTH SCIENCES

COVID-19 pandemic and the answer of science: a year in review

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Abstract: The world is looking forward to a prompt response by the scientific community in order to overcome the first pandemic of the 21st century. This study aimed to provide an overview of scientific output on COVID-19 during its first year. We assembled information regarding 60,830 articles related to COVID-19 indexed in the WoS database from January 24 to December 13, 2020. Only 4 countries accounted for about 60% of the articles (USA, China, Italy, and England) and 12 countries accounted for about 95% of the world scientific output on COVID-19 (USA, China, Italy, England, India, Canada, Germany, Spain, Australia, Brazil, Iran, and Turkey). 25 research centers around the world contributed with more than 500 papers on COVID-19. Papers were scattered throughout 6,133 journals, with 12 journals with > 250 articles. 20 articles (003%) have already received more than the 1,000 citations. The response of the scientific endeavor to this acute global public health emergency has been fast and robust. The overview provided by the analysis of the scientific response to the pandemic may contribute to further studies aiming to evaluate the impact and changes in the scientific endeavor for the next years in light of the forthcoming new world framework.

Key words: COVID-19, research evaluation, scientific production, science policy.

INTRODUCTION

In early December 2019, a cluster of pneumonia cases of unknown origin was identified in Wuhan, the capital city of Hubei province, China (Lu et al. 2020a). On January 7, 2020 a novel coronavirus was identified from a throat swab sample of a patient (Chen et al. 2020), and by January 20, the virus was isolated and sequenced (Zhou et al. 2020). The new virus was then named SARS-CoV-2/human/Wuhan/X1/2019 (SARS-CoV-2) (Coronaviridae Study Group of the International Committee on Taxonomy of Viruses, 2020). On March 11, 2020, the WHO announced that the disease caused by SARS-CoV-2, designated coronavirus disease 2019 (COVID-19), should be considered a global pandemic (WHO 2020).

The first pandemic of the 21st century has been overwhelming healthcare systems and is placing unprecedented economic pressure on global society. Therefore, the entire world is looking forward to a prompt response by the scientific community in order to overcome this unparalleled crisis.

The answer has been quick and robust. The global pandemic stimulated extraordinary amounts of scientific investigation around the world. The virus first appeared in the scholarly literature on January 24, 2020 (Huang et al. 2020), and, since then, medical researchers and virologists have been working to isolate and identify the virus, determine its etiology, and define the risk factors for adverse outcomes, conducting research on drug and vaccine

development (Fry et al. 2020). Since January 2020, the pace of achievements has been astonishing. Nevertheless, this large amount of information produced about COVID-19 is so abundant and dynamic that some concerns have been recently raised regarding some aspects of the scientific enterprise, including research funding and scientific publishing standards. During the pandemic, journals are racing to publish COVID-19 papers and, accordingly, the peer review process has been modified regarding COVID-19 related research submissions (Bauchner et al. 2020).

We developed a database of articles indexed in Web of Science (WoS) during the first sixmonths of the COVID-19 crisis up to December 13 with the aim to understand the scientific impact of the response to the pandemic. We assembled information regarding 60,803 papers published in approximately 6,000 journals, covering an array of disciplines that have already made fundamental contributions to our understanding of the many aspects of this new disease. Based on a comprehensive analysis of this database, this study aimed to provide an overview of the global scientific response to an unparalleled challenge to our society.

MATERIALS AND METHODS

A complete dataset of scientific articles on coronavirus-related research between January 1, 2020 and December 13, 2020 was extracted from the Clarivate Web of Science (WoS). The following consistent set of keywords was used in searches in the Title/Abstract/Keywords of each article in the respective databases: "COVID-19" OR "2019-nCoV" OR "coronavirus" OR "Corona virus" OR "SARS-CoV". Using the search procedure outlined, the data comprise a total of 60,803 coronavirus-related articles. Among

these data, 30,152 (42%) were classified by WoS database as "articles', 10,919 (25%) as "editorial material", 10,556 (204%) as "letter", 6,3041 (97%) as "review", and 8,418 as "early access" from each article we retrieved the following data: date of publication, country, address of the institutions, research institutions, journals, and subjects. In addition, we also classified the journals regarding their discipline and scope (for instance, virology, immunology, clinical medicine, and so on). The classification scheme proposed by the WoS was used to assign journals to science fields. In about 8% of the articles, the information about the country and institution involved could not be retrieved. We retrieved data regarding the 2019 scientific output of each country from the SCImago website https://www.scimagojr.com/. SCImago is an online platform that ranks journals and countries in several knowledge fields based on bibliometric indicators, including, among others, the total number of documents per year, citable documents, citations per document, and the H-index.

Statistical analysis

We downloaded to a spreadsheet all the variables of interest from the above-mentioned public databases and integrated all of them into a dedicated database using the Statistical Package for Social Science for Windows (SPSS) version 18.0. We used descriptive statistics analysis. Continuous data were reported as medians and interquartile range (IQ) or means and standard deviation (SD), when appropriate. Graphs were also constructed using Tableau Public, 2019 version (https://public.tableau.com).

RESULTS

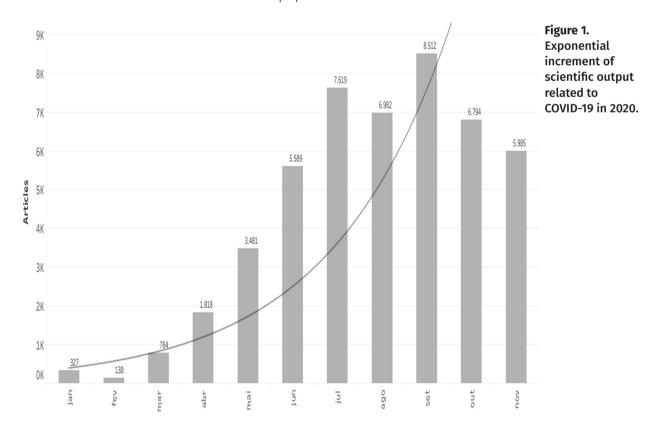
Pace of scientific production about Covid-19

Over the 12-month span, the search retrieved 60,803 articles scattered throughout 6,133 journals covering an array of disciplines. The date of publication was available for 48,029 records (78%). Figure 1 illustrates the exponential increment of scientific production regarding COVID-19 in 2020. it was published Only about 2.6% (1,249/13,451) of the papers were published in the first trimester, while 10,880 (22.6%) were published in the second; 48% in the third, and the remaining 27% in the last. The average output was about 67 papers per day in the first semester compared with a mean of 217 papers per day in the second trimester.

Countries and Research Institutions

Regarding production by country, 3,247 records (53%) did not contain data in the field. There were 179 countries with at least one paper

on COVID-19. However, the distribution of production was heavily skewed. Only 4 countries accounted for about 60% of all articles (USA. China. Italy, and England) and 12 countries accounted for about 95% of the world scientific output on COVID-19 (USA, China, Italy, England, India, Canada, Germany, Spain, Australia, Brazil, Iran, and Turkey). Figure 2 shows the most productive countries, with more than 1,300 papers over the first 12-months. Regarding the production by country, 3,247 records (5.3%) did not contain data in the field. Regarding the research institutions involved in the scientific output, we found 25 research centers around the world that contributed more than 500 articles on COVID-19. The most productive institutions included Harvard University with 1,821 papers (3%), the University of London with 1,795 papers (about 2.9%), the University of California System (2:3%), Huazhong University of Science Technology (22%), and Harvard Medical School



(1.8%). Figure 3 shows the 25 most productive institutions over the first 6-months. The majority of these most productive institutions were from the US (13) and England (4).

Journals and Categories

The scientific output was distributed through 6,133 journals from all over the world. Figure 4 shows the 12 journals with more than 250 articles published in 2020. These journals accounted for about 11% of the papers concerning the novel coronavirus, led by the Lancet family (21%), BMJ

(18%), Nature family (15%), J Med Virol. (12%), and the JAMA family (11%).

The articles about COVID-19 belonged to 238 different categories in the WoS database. As expected, the main categories of the articles concerning this new disease were those dealing with fundamental aspects of the clinical and epidemiological issues of the pandemic. The journals included in the Medicine (General and Internal) category accounted for 7,728 papers (12-7%), followed by journals included in the category of Public Environmental Occupational Health (4,697; 77%), Infectious diseases (3,066;

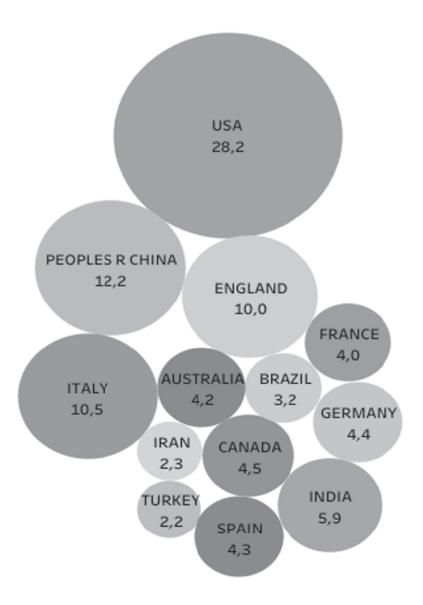


Figure 2. Output of scientific articles related to COVID-19 by the 12 most productive countries.

5%), Cardiology (2,631; 43%), and Surgery (2,539; 41%). Other frequent categories were Virology, Pharmacology, Emergency/critical care, and medical specialties such as Radiology, Oncology, and Pediatrics. Figure 5 displays the main categories that contributed to the literature about the novel coronavirus, highlighting those with more than 600 papers (1%).

Citations

Over the 12-month period, 20 articles (0.03%) had already received more than the 1,000 citations. Table I presents the 15 papers most cited up to December 2020. Of the 20 papers, 10 were from China, 2 from the US, and 1 each from Germany, the United Kingdom, and France. The majority of

the most cited articles were published in Lancet and affiliated journals (33%) and in NEJM (27%). Most of these articles dealt with the clinical features (47%) and pathophysiology (40%) of the new disease.

Subjects

Regarding the title contents, the most frequent terms included impact (2,952, 48%), clinical (2,900, 47%), case (2,723, 45%), response (2,252, 37%), risk (2,142, 35%), management (2,019, 33%), treatment (1,973, 32%), testing (1,731, 28%), immunity/immunology (1,650, 27%), cancer (1,506, 25%), and mental health (1,471, 24%). Of note, among the 60,830 articles only 757 (124%) and 736 (120%) had the terms vaccine and clinical

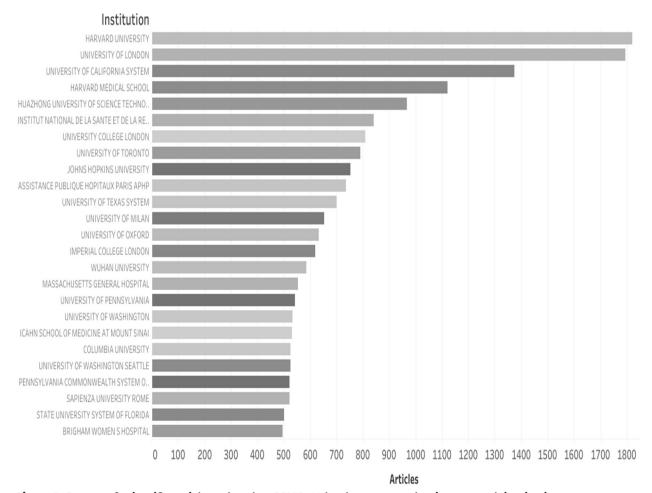


Figure 3. Output of scientific articles related to COVID-19 by the most productive research institutions.

Table I. The 15 most cited COVID-19 articles until December 13, 2020.

Authors	Country	Journal	Date	Theme	Citations	Mean Citations month
Guan, WJ et al.	China	N Engl J Med	2020/02/29	Clinical	5,095	526
Zhou, FT et al.	China	Lancet	2020/03/15	Clinical	4,335	481
Zhu, N. et al	China	N Engl J Med	2020/03/28	Clinical	4,301	474
Zhou, P. et al	China	Nature	2020/03/02	Clinical	3,303	367
Wu, Z. et al.	China	JAMA	2020/02/25	Clinical	2,518	252
Hoffmann, M. et al	Germany	Cell	2020/04/16	Pathophysiology	2,338	311
Lu, R. et al	China	Lancet	2020/02/22	Genomic	2,169	217
Mehta, P. et al.	UK	Lancet	2020/03/21	Pathophysiology	1,764	207
Xu, Z. et al	China	Lancet Respir Med	2020/05/10	Pathophysiology	1,707	262
Yang, X. et al	China	Lancet Respir Med	2020/05/10	Clinical	1,701	261
van Doremalen, N. et al	USA	N Engl J Med	2020/04/16	Pathophysiology	1,591	198
Gautret, P. et al	France	Int J Antimicrob Agents	2020/07/01	Treatment	1,319	239
Wrapp, D. et al	USA	Science	2020/03/13	Pathophysiology	1,214	134
Zou, L. et al.	China	N Engl J Med	2020/02/20	Pathophysiology	1,165	117
Wu, C.	China	JAMA Internal Med	2020/07/15	Clinical	1,154	192

trials in the title, respectively. Of note, most of these articles were comments or protocols regarding vaccine and clinical trials. The first results of a randomized clinical trial (RCT) on COVID-19 treatment were reported on March 18, involving a trial with Lopinavir-Ritonavir, both of them antiviral HIV medications repurposed as experimental drugs for SARS-CoV-2. The first RCT with an effective repurposed drug was reported on July 17, involving a trial with dexamethasone which showed a reduction of mortality of severely affected patients. Figure 6 illustrates the timeline of the milestones regarding drugs and vaccine trials. Interestingly, trials of possible repurposed drugs first predominated, followed by trials of candidate vaccines culminating with the beginning of phase 1 vaccination for

healthcare professionals in the United Kingdom on 12/8/2020.

National Contribution

Brazil is part of the 12 countries group accounting for 95% of the world scientific output on COVID-19, adding up to 2,582 papers on WoS database in 2020. Regarding affiliations, the most frequent institution was University of São Paulo, accomplishing for 21.0% of Brazilian papers and placing 29th in the international ranking on the number of papers published in 2020. The other representative institutions are Oswaldo Cruz Foundation (7.9% of national research), Federal University of São Paulo (7.8%), Federal University of Rio de Janeiro (6.6%), Federal University of Minas Gerais (5%) and

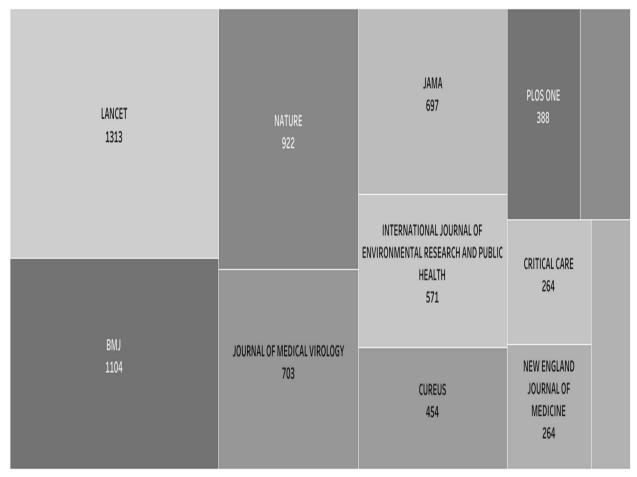


Figure 4. Output of scientific articles related to COVID-19 by the most productive journals.

State University of Campinas (4.8%). Collectively, the six institutions comprise more than 50% of Brazilian contribution to the scientific research on COVID-19. The most frequent categories in the WoS database were Public Environmental Occupational Health (323; 12.5%), Medicine (General and Internal) (281; 10.9%), Infectious Diseases (116; 4.5%), Tropical Medicine (93; 3.4%) and Multidisciplinary Sciences (88; 3.3%). The most cited paper up to December 2020 received 555 citations and exposed about Fair Allocation of Scarce Medical Resources in the Time of Covid-19. Among the 2,582 articles, only 16 (0.59%) and 17 (0.65%) had the terms vaccine and clinical trials in the title, respectively. The three most important funding agents were the

National Council for Scientific and Technological Development (CNPq), supporting 12.7% of the 2,582 papers, followed by the Coordination for the Improvement of Higher Education Personnel (CAPES) (9.6%) and the São Paulo Research Foundation (FAPESP) (5.2%).

DISCUSSION

The findings of this descriptive study of the scientific production related to COVID-19 highlight the impressive pace of the response of the world scientific community to this unparalleled challenge posed by the first pandemic of the 21st century. In 2020, about

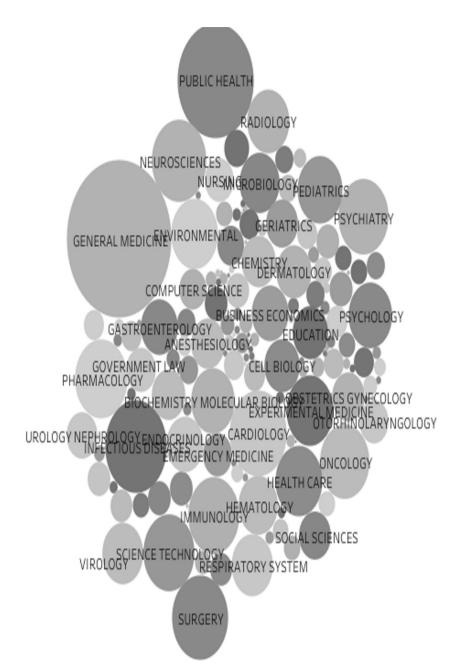


Figure 5. Subject categories of the scientific articles related to COVID-19 indexed by WoS

60,0000 articles were indexed in WoS, not to mention 11,000 additional articles that were deposited in preprint repositories such as the medRxiv website. Thus, the pace of the global scientific output on COVID-19 averaged 110 papers a day, mostly concentrated in the second trimester of 2020. In a recent editorial regarding the development of a vaccine against COVID-19, Heaton (2020) pointed out that the

world has now witnessed the compression of 6 years of work into 6 months. We believe that this observation is also pertinent to the pace of the overall scientific production on COVID-19. For instance, during the same period, this output was greater than that regarding other current highly productive traditional topics such as hypertension (10.120 papers indexed by WoS) and obesity (12,220 papers).

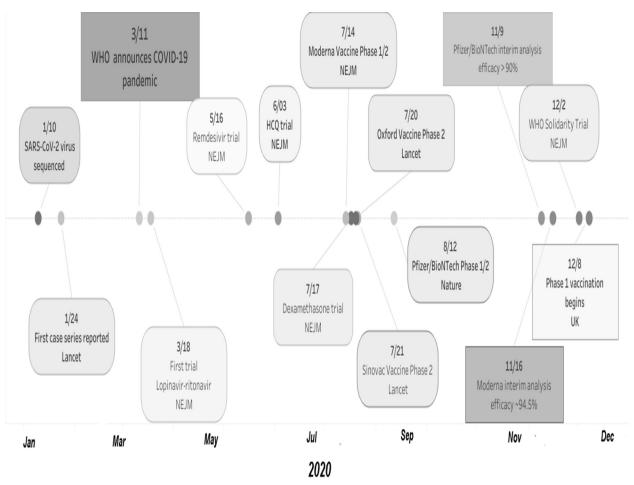


Figure 6. Timeline of the milestone events of the COVID-19 pandemic and related scientific production.

Regarding the countries with the greatest COVID-19 scientific output, the scenario is comparable to that of the overall global scientific production. Among the 11 countries with the greatest share of the global scientific production in 2019, 9 are also among those with the largest production on COVID-19. Only Japan and Russia were not included in the two rankings, being replaced by Spain and Brazil. Interestingly, three countries that were heavily hit by COVID-19, i.e., the US, Italy, and England, have shown the capacity to increase their scientific production, with a relevant increment in the share of scientific output. Together, these three countries account for about 25% of the global scientific production and have contributed

about 50% of the scientific output on COVID-19. This impressive increment might reflect the presence of cutting-edge research institutes and universities in these countries, which allowed a rapid response to this unparalleled crisis. For instance, among the 20 most productive institutions, 60% are from these countries (6 from the US, 5 from England, and one from Italy). China also had three institutions among the 20 most productive research institutes. We believe that this fast pace and huge amount of scientific production simultaneously involving many countries and institutions somewhat reflects the state of collaboration and healthy competition in the current world scientific output. Moreover, these leader countries have the concentration

of scientific skill, technical knowledge and productive capacity that has allowed them to engage in an immediate response to an acute public health emergency. Unfortunately, the information regarding multicenter studies was not readily available in the WoS database. However, we found about 90,000 registries of countries for these 60,803 articles. Thus, we may infer that about one third of these studies are collaborative efforts involving the participation of research institutions from two or more countries. Interestingly, Fry et al. (2020) evaluated the trends in international collaboration during the first months of the COVID-19 pandemic and demonstrated that the event shifted the geographic loci of coronavirus research, as well as the structure of scientific teams, narrowing team membership and favoring consolidated structures.

This huge amount of scientific output is scattered through about 6,133 journals including a vast array of disciplines from basic science to the clinical front line. The first report from Chinese physicians in the front line was published online in Lancet on January, 24 (Huang et al. 2020). The authors described a cohort of 41 patients who were identified as having laboratory-confirmed 2019-nCoV infection. This report was followed by several papers that described the clinical and epidemiological features of patients in China (Guan et al. 2020). On February 3, Zhou et al. (2020) reported the identification, characterization, and full-length genome of a new coronavirus (2019-nCoV) obtained from five patients at an early stage of the outbreak. Subsequently, as expected, the most prestigious journals took the leadership in the process. Among 6,133 journals, 12 (0.2%) have already published more than 250 articles. Interestingly, 6 of these journals are among those with the highest impact factor in Medicine or Multidisciplinary Sciences: NEJM (IF 2019, 76),

Lancet (60), JAMA (45), Nature (42), Science (41), and BMJ (30). An aspect of particular concern was raised regarding the impact of this fast increment in the volume of scientific production on journal standards. A number of manuscripts have been submitted to journals within such a short time that some leading journals have changed their process of evaluation. For example, Bauchner et al. (2020) reported that from January 1 to June 1, 2020, more than 11,000 manuscripts were submitted to JAMA, compared to approximately 4,000 manuscripts submitted during the same period in 2019. Consequently, in the midst of the pandemic, the process of manuscript evaluation has been modified by many journals. For instance, in JAMA, for manuscripts that were judged as essentially descriptive, review has primarily been internal, by JAMA editors. External peer review has been conducted only for research manuscripts whose results were likely to "influence clinical practice or public health policy" (Bauchner et al. 2020). Since the pandemic began, an atypical volume of manuscripts has overwhelmed other prestigious journals. The Lancet is receiving three times the usual number of papers and the NEJM has fielded as many as 200 submissions in a day, according to their editors. In the context of a rapid increase in cases, hospitalizations, and deaths from COVID-19, clinicians, patients, policymakers, and the public at large are understandably eager for results of studies of prognosis, diagnosis, and treatment (Saitz & Schwitzer 2020). Although rapid publication of clinically relevant information during a pandemic is obviously pivotal, publishing results that are not valid can do much harm. In this regard, for instance, two of the most prestigious clinical journals (NEJM and Lancet) were victims of a fraud with an immense repercussion in the press and social media (Ledford & Van Noorden 2020, Servick & Enserink 2020). The same research

team published the papers about controversial aspects of COVID-19 treatment (Mehra et al. 2020a, b). Both papers were rapidly retracted, but in a polarized political atmosphere this fact ultimately contributed to undermining the public trust in science.

Regarding the subjects of the papers, our search has shown that the timeline follows the flow of the classic description of a new disease. At the outset, there was a predominance of papers with the description of the clinical characteristics and epidemiological data derived from the first cases series in China (Chen et al. 2020, Lu et al. 2020b). Soon after, from the epidemiological perspective, articles emerged reporting predictive models of the spread of the disease and stressing the risk of the worldwide collapse of the health systems (Flaxman et al. 2020, Dehning et al. 2020). On the clinical front, many of the elusive pathophysiological mechanisms involved have been investigated and the groups at risk for severe disease were identified (Williamson et al. 2020). Concomitantly, studies of the molecular aspects of the virus and its mechanisms of transmission have also emerged (Moghadas et al. 2020). The biology of SARS-CoV-2 has been intensively scrutinized. and its pivotal proteins have been described (Cyranoski 2020). In addition, the fundamental aspects of the human immune response to the virus have been progressively elucidated (Gussow et al. 2020, Barnes et al. 2020, Yang et al. 2020). With the disease spreading across Europe and North America, papers describing large case series from these regions came out, adding some new insights on risk factors and patient management (Cummings et al. 2020, Grasselli et al. 2020).

Brazil consolidated its place as a highquality scientific producer during the COVID-19 pandemic, being one of the 12 countries accounting for 95% of the world scientific output

in 2020. For instance, genome sequencing and analysis of SARS-CoV-2 occurred only 48 hours after the first confirmed COVID-19 case in Brazil (Jesus et al. 2020). Affiliation ranking showed the overwhelming predominance of federal institutions, pointing to the undeniable role of public funding to national research and development. Indeed, the three most important funding agents - CNPq, CAPES and FAPESP are public institutions strictly, persevering on scientific development despite the continuous scrapping of higher education in the country (Oliveira et al. 2020). The importance of Brazilian federal institutions and public funding is highlighted by the seventeen ongoing vaccine development research, all taking place or being associated with federal institutions, according to the Ministry of Health. Because of chronic underfunding, vaccine-developing programs experience important limitations and delays, with poor literature being published on vaccine and clinical trials in 2020 even though Brazil stands out internationally for its vaccine production and vaccination program. In addition to the underfunding of scientific research, pandemic management by the federal government put Brazilian Unified Health System to collapse several times. Endorsement of drug relocations without scientific evidence, contempt for social distance measures and a general disregard for the seriousness of the pandemic by the federal government got Brazil on the worse scenario in 2021, breaking daily records on death numbers and becoming an international threat on variant development (Palmeira et al. 2020). That is why the most cited Brazilian article in 2020 is so representative, as it deals with the fair allocation of scarce medical resources.

It is undeniable that several of these studies have already made fundamental contributions to our understanding of the many aspects of this novel highly contagious virus and of

the virulent disease it causes, i.e., COVID-19. Moreover, based on the aforementioned epidemiological studies, the adoption of public health measures labeled nonpharmaceutical interventions (NPIs) may have spared many lives by preventing the collapse of health systems worldwide. For instance, based on data from 149 countries, Islam et al. (2020) reported that the incidence of COVID-19 decreased by an average of 13% in association with physical distancing interventions. Nevertheless, with the disease leaving in its wake millions of infected patients, thousands of deaths, and an economic toll in the trillions of dollars to date, an effective treatment and vaccine are urgently needed (Heaton 2020). In this regard, on March 18th, 2020, the Director-General of the WHO announced the launch of a multinational Phase III-IV clinical trial called SOLIDARITY to facilitate a rapid worldwide comparison of unproven treatments. Unfortunately, the SOLIDARITY trial revealed that remdesivir, hydroxychloroguine, lopinavir, and interferon regimens had little or no effect on hospitalized patients with Covid-19 (Consortium WHOST 2021). In the United Kingdom, investigators designed the RECOVERY trial involving hospitalized patients with COVID-19 in order to assess the efficacy of different treatments using a single endpoint, i.e., mortality within 28 days after randomization (Normand 2020). In addition, several other ongoing trials are investigating efficient treatment for the disease and its complications (Fauci et al. 2020). Using the terms COVID-19, SARS-CoV-2, 2019-nCov, and 2019 novel coronavirus in the ClinicalTrials.gov database, we identified 1,829 studies registered as clinical trials aiming to evaluate several drugs against COVID-19. Nevertheless, Pundi et al. (2020) reviewed these studies registered in ClinicalTrials.gov and demonstrated that, among the RCTs, only 29% were placebo-controlled, blinded studies and had the potential to result

in a high level of evidence. In our analysis, we found only about 2.5% papers with the terms "vaccine" and "clinical trials" in the title. The first trial was published online on March 18 and evaluated the combination of two drugs (lopinavir-ritonavir) in hospitalized adult patients with severe COVID-19 in China (Cao et al. 2020). Of note, only one of these trials has reported so far a drug with clinical benefits against COVID-19 (Group et al. 2021). In addition, research centers across the globe are racing to develop a SARS-CoV-2 vaccine based on many strategic approaches such as the entire virus, a recombinant protein subunit, and an mRNA vaccine (Shin et al. 2020). After July 2020, the first reports of phase 1/2 RCT of candidate vaccines were published showing promising results concerning safety and immunogenicity (Folegatti et al. 2020, Jackson et al. 2020, Zhu et al. 2020, Sahin et al. 2020). Remarkably, in December 2020, the reports of phase 3 RCT of two vaccines with a combined number of 67,000 participants were released (Polack et al. 2020, Voysey et al. 2020).

In conclusion, the response of the scientific endeavor to this global acute public health emergency has been impressively fast and robust. Many collaborative coordinated efforts have contributed to a reliable answer to this unprecedented challenge in modern times. This has been a truly collective effort by researchers all around the world, as a global community, struggling to bring knowledge to the front lines. In the context of scientific publishing, a welcome initiative at the onset of the COVID-19 crisis was the decision by the most prestigious publishers and journals to provide open access to the entire material concerning COVID-19 to the scientific community. The scientific and social impact of this decision need to be evaluated in further studies, but we may already infer that this large

available material has contributed to enhance research around the world.

We are living through an unprecedented biopsychosocial crisis. COVID-19 continues to spread throughout the world, resulting in major disruptions of business, education and transportation, and permeating virtually every aspect of daily life (Fontanarosa & Bauchner 2020). Millions of people have been affected by COVID-19, hundreds of thousands have experienced critical illness, and tens of thousands have died. Physicians, health care professionals, and health care systems around the world have been challenged like never before in recent times. As we approach the end of 2020, it is time to consider a balance of the achievements of science during this extraordinary year. The emblematic pace of events, from the first case series in China described on January 24 to the report of an impressively effective vaccine on December, 10, is a testament to the work of so many dedicated scientists and health care workers. This is perhaps an opportunity for the governments and general population to definitively understand the importance of science in their daily lives. We believe that the overview provided by the analysis of the first months of scientific response to the pandemic may contribute to further studies aiming to evaluate the impact and changes in the scientific endeavor for the next years in light of the forthcoming new world framework.

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