A continuation of a timeline of ivermectin-related events in the COVID-19 pandemic

Mika Turkia
M.Sc., mika.turkia@alumni.helsinki.fi, June 30, 2021

Abstract
This review presents a continuation of a previous timeline that described ivermectin-related events in the COVID-19 pandemic from April 2020 to the end of March 2021. The new timeline covers a period from the beginning of April 2021 to the end of June 2021.

In April 2021, the US National Institutes of Health (NIH) announced a new, large clinical trial including ivermectin, with an estimated study completion date in March 2021. A large national trial was also announced in the Philippines, a 1,169-patient trial in the US, and another trial in Ireland.

Trial results published in the period resembled those of previous trials, not producing clinically meaningful changes to the results of existing meta-analyses. Mainstream press of the high-income countries mostly repeated the same arguments as in the previous period, including the warnings against ivermectin by the European Medicine Agency (EMA) and the World Health Organization (WHO). The sparse and one-sided coverage of ivermectin in the press appeared to result from a program called Trusted News Initiative (TNI). The censorship practices of the social media companies, with policies disallowing expression of views differing from the guidelines of the WHO, continued unchanged, apparently organized under a program called International Fact-Checking Network (IFCN).

In contrast to the previous period – during which groups such as the Front Line COVID-19 Critical Care Alliance (FLCCC) and the British Ivermectin Recommendation Development (BIRD) group attempted to influence the decisions of government agencies – in this period these groups began to bypass the agencies and turn directly to clinicians and the public. FLCCC also published two new protocols, I-MASK+ and I-MASK, for mass immunization, and EREC果蔬 for long haul COVID-19 syndrome (LHCS), and a review article which by the end of the period had reached a position in the top 120 of 18 million articles tracked by Altmetric. The BIRD group organized two online conferences on ivermectin and published a meta-analysis which had reached a position in the top 60, respectively.

One of the authors of the in vitro study that initiated the international interest in ivermectin explained that due to, for example, lack of adaptive immune responses in the cell model, their study was unsuitable for making conclusions about in vivo dosing in humans. A review described 20 mechanisms of action of ivermectin in COVID-19.

The parties against and in favor of ivermectin remained in deeply conflicting positions, presenting opposite conclusions on the existing research. The WHO, along with regulatory agencies and national governments of high-income countries, appeared to aim at preserving the value of existing investments in vaccine and investigational therapies-development, as well as questioning the efficacy and safety of repurposed medicines.

Criticism towards excessive influence of Bill Gates in the WHO emerged during the period, as the largest funder of the WHO appeared to be a group of vaccine promotion and intellectual property rights enforcement oriented organizations founded by Gates. There was a noticeable centralization of power, with the pandemic response largely directed by a few public-private partnerships working on commercializable technologies.

Keywords: COVID-19, SARS-CoV-2, WHO, ivermectin

Introduction
Ivermectin is a multifaceted medication invented in collaboration between Japanese professor emeritus Satoshi Omura from Kitasato University and US researcher William Campbell from Merck & Co/MSD between 1973 and 1979 [1, 2]. Each of them received one quarter of the 2015 Nobel Prize in physiology or medicine for their discoveries [3]. Ivermectin is best known as an antiparasitic agent, with approximately four billion doses having been administered since 1981, predominantly in Africa. Merck & Co/MSD’s patent expired in most countries in 1996, and ivermectin preparations are currently available internationally from many sources, with the production cost of a single dose estimated to be less than 0.1 US dollars [4].

This article extends the timeline of ivermectin-related events described in a previous preprint available in two versions, March 30, 2021 and April 3, 2021 [5, 6]. The latter preprint covered the period from April 1, 2020 to March 31, 2021. This preprint extends the timeline to cover April-June 2021, as well as adding a few earlier events. Some caveats of the review are described in the previous preprint. Due to resource limitations, details of many developments are not covered in detail but only mentioned briefly, and omissions have been unavoidable. The focus of this review entails the social, organizational, financial and legal aspects of the situation with ivermectin, with less emphasis placed on presenting clinical trial results and biomedical research.

Some of the main events in the previously covered period from April 2020 to March 2021 were an Australian in vitro study which initiated the interest in ivermectin [5]. This was followed by adoption of ivermectin in several South and Central American countries, the state of Uttar Pradesh in India, and Bangladesh in the second and third quarter of 2020. In late October 2020, the Front Line COVID-19 Critical Care Alliance (FLCCC) published its ivermectin-based outpatient protocol called I-MASK+ [6].

A month later, another group called CoviDAnalysis begun publishing a meta-analysis of ivermectin trials [11] and a list of ivermectin studies [12]. A main event in December 2020 was the US Senate hearing of Pierre Kory of the FLCCC [13]. The hearing raised interest of Lawrie et al. and Bryant et al. who produced additional meta-analyses [14, 15]. In conjunction, another group called British Ivermectin Recommendation Development (BIRD) was founded.

Another main event was the introduction of a preprint of a Unitaid/WHO-funded meta-analysis by Hill et al. [16]. Yet another notable event was the publication of an extensive review by a Japanese group including the discoverer of ivermectin, the Nobel prize winner Satoshi Omura [2, 17]. In the first quarter of 2021, ivermectin had been adopted in several additional countries including Slovakia as the first European Union member country. However, in March 2021 both the European Medicine Agency (EMA) and the World Health Organization (WHO) advised against the use of ivermectin except as the first European Union member country. In conjunction, another group called British Ivermectin Recommendation Development (BIRD) was founded.

In spite of the EMA’s advisory, the US Senate hearing of Pierre Kory of the FLCCC [13], and the recycling of the previously published results and biomedical research, ivermectin was still promoted by both the FLCCC and the BIRD group, which were present in the preprint timeline.

The majority of indications and the safety of ivermectin have been described in the previous preprint [6]. In addition, in April 2021 ivermectin was found to effectively inhibit hepatitis E virus replication [18]. There is also a relatively large amount of research about the treatment of cancers with ivermectin [19, 20, 21, 22, 23, 24, 25], including breast cancer [26, 27, 28, 29, 30, 31, 32], ovarian cancer [33, 34, 35], melanoma [36], breast cancer [37, 38], gastric cancer [39, 40], liver cancer [41] and leukemia [42] (list from [54]).

Recently, mass distribution of ivermectin has been studied for prophylaxis of malaria [35, 56, 57]. Ivermectin has also been found to promote wound healing partly through modulation of the inflammatory process and the levels of transforming growth factor beta 1 (TGF-β1) and vascular endothelial growth factor (VEGF) [58]. Ivermectin has also been proposed for the treatment of autoimmune disorders [59].
an antibacterial, antiviral and anti-cancer agent being particularly extraordinary” [61]. Possible issues include environmental toxicity [62], [63] and the emergence of ivermectin resistance [64].

April 2020

On April 16, Chaccour et al. stated that the recent findings warrant rapidly implemented controlled clinical trials and these trials might open a new field of research on the potential use of avermectins as antivirals but extreme due diligence and regulatory review were needed before testing ivermectin in severe disease. They added that off-label and compassionate use required careful risk-benefit considerations, especially in critically ill patients. The authors suggested trials on early treatment of uncomplicated, low-risk patients [65].

On April 17, a member of the European Parliament asked about the amount of influence of Bill and Melinda Gates Foundation in the WHO [66], [67].

On April 18, a news report described that in the Dominican Republic, pulmonologist Johnny Tavárez Capellán had embarked on an observational trial with 247 patients, observing a favorable response in all cases, with no fatalities [68], [69].

On April 23, Honduras introduced Catracho, a COVID-19 treatment protocol created by Honduran doctors Oscar Díaz, Fernando Valerio and Miguel Sierra-Hoffman, consisting of colchicine, anti-inflammatories, tocilizumab, ivermectin, anticoagulants, and hydroxychloroquine [70], [71], [72].

On April 29, an article by Villar et al. (including Meduri of the FLCCC) provided a rationale for prolonged corticosteroid treatment in COVID-19 [73].

August 2020

On August 2, a news report in a Mexican newspaper described FLCCC’s MATH +: inpatient protocol [74].

On August 5, the New York Times wrote about a “civil war in some hospitals” as a result of disagreements on how much freedom should front-line clinicians have in treating COVID-19 patients with unproven drugs [75]. The article described a conflict over care of a patient involved in a clinical trial, where a clinician was pressured by a head researcher to retain the patient following the trial protocol although the clinician considered adhering to the protocol dangerous for the patient in a critical condition. In this case, the researchers compared relying on the clinician’s judgment to “witchcraft”, insisting the clinician follow “the evidence”. The head researcher mentioned his wife had, however, taken hydroxychloroquine for COVID-19 and recovered. Regardless, the head researcher insisted it was essential to rely on research and anything else was witchcraft.

Another researcher who had spent two weeks in one hospital commented that he was “distressed by how quickly doctors were trying untested therapies outside clinical trials. I mean, it felt like it wasn’t even World War I medicine,” he said. “It was almost like Civil War-level medicine”. He added that he knew his colleagues had been risking their lives, been overwhelmed by their clinical demands and had no research to rely on but was nonetheless surprised to see many of them making decisions “based on the sort of opinion or written protocol of one or a couple of people that was based on kind of nothing that I could see, other than just, ‘This seems like a good idea’”. Pierre Kory of the FLCCC commented that “It became like Republicans and Democrats . . . the two sides can’t talk to each other”. After a 6,000-patient trial indicated benefits from corticosteroids [76], one researcher described as a “research purist” commented that the efficacy “is still unknown” and that even one solitary randomized controlled trial does not settle the question of the use of steroids for patients with Covid-19 as “it needs to be replicated”. Kory commented that “that’s a 6,000-person trial he’s discredit[ing] . . . that’s a person who will never be convinced”.

The article also described the editor of the New England Journal of Medicine commenting that the FLCCC’s recommendation of corticosteroids in the MATH +: inpatient protocol [77], [78] used since January 2020 and made publicly available in the first quarter of 2020 had been just “lucky”. He had opposed corticosteroids but had eventually admitted he had been wrong, yet was still frustrated that doctors were still relying on treatments for which there was no evidence. He had been more positive about tocilizumab for which much less information than that for corticosteroids had been available. He eventually concluded that “I know I seem to be saying opposite things . . . I can’t argue that I was super rational either”.

On August 14, a commentary by Dodge discussed RCT fundamentalism in medicine [79]. He said “the core belief [that only RCTs can decide] is repeated, like a catchism, at times ad nauseam, and contrasting beliefs are treated like heresies. What the RCT fundamentalist is peddling is not a scientific attitude, but rather forcing a tool, the RCT, which was designed for a particular kind of problem to become the only tool we use. In this case, RCT is best understood as standing not for Randomized Controlled Trials, but rather Rigidly Constrained Thinking”. Dodge concluded that “the most prudent option is to allow the professional who knows the patient to have as much flexibility as possible and access to as many medications as possible. If we are to be honest, evidence-based medicine is, in large part, still aspirational. It is an ideal. Clinicians need latitude, and patients assume they have it. But now the RCT fundamentalists are using the absence of RCTs for some drugs to restrict access to them. They have gone too far. This is epistemological hubris, at the expense of lives, and brings to mind the old adage, ‘Absence of evidence is not evidence of absence’. As long as we’ve not got the best studies for all conceivable permutations, medicine will remain both an art and a science”.

September 2020

On September 28, a press release about Catracho, the treatment protocol of Honduras, reported that after the introduction of Catracho on April 23, 2020 the hospital mortality rate had decreased from 14.5% to 2.7% by the end of July, 2020 [70], [71], [72]. One of the creators of the protocol, Sierra-Hoffman, stated that “I am proud that we can tell the world that Honduras has become part of contemporary world history with golden letters . . . we have given the world an answer on how to address the virus in critically ill patients, lowering mortality in Honduras, a country with many limitations and with one of the worst progresses when a scientific point of view it is a great merit and achievement for humanity”. The president of Honduras congratulated the team.

On September 29, a news report from the Dominican Republic described that Dr. José Natalio Redondo had treated at least 6,000 outpatients with ivermectin with promising results [79]. He pointed out the importance of initiating the treatment early.

October 2020

On October 13, Magro et al. published an article describing COVID-19 as a multifaceted viral vasculopathy syndrome [80], [81]. They described that “each of the cytokines (IL-6, TNF-a, IL-1ß, IL-8, and p38) were significantly increased in the endothelia of select extrapulmonary microvascular beds where they each strongly co-localized with the viral spike protein and ACE-2 receptors including the skin”. An earlier 2008 study by Zhang et al. [82] had found that “ivermectin improved mouse survival rate induced by a lethal dose of lipopolysaccharide. In addition, ivermectin significantly decreased the production of TNF-a, IL-1ß and IL-6 in vivo”, matching with the findings of Magro et al.

On October 20, in a video news report, Michael Jacobs, a clinical director of infection at Royal Free Hospital in London, also a co-senior author of WHO’s living guideline for COVID-19 therapeutics and an ivermectin panel member responsible for WHO’s ivermectin guideline [83], presented the hospital’s trial in which volunteers were deliberately exposed to coronavirus in a controlled setting to speed up the development of a successful vaccine [84].

On October 22, Portmann-Baracco et al. commented that “COVID-19 is divided into different phases: asymptomatic, mild symptomatic disease, and severe inflammatory respiratory disease. The first two phases are dependent on viral replication, whereas the latter is attributed to the hyper-inflammatory state called the cytokine storm. Evidence suggests that ivermectin can act at different stages of the disease. Controlled studies must be conducted first to demonstrate the effect of ivermectin against Covid-19, then to determine if this effect is due to its anti viral action and finally to study if its administration is convenient also in hospitalized patients due to its apparent anti-inflammatory effect” [85].
An editorial by Alibhai in the British Medical Journal (BMJ) discussed politicization, “corruption” and suppression of science in the context of COVID-19 pandemic [86]. According to the author, the pandemic had unleashed state corruption on a grand scale, with politicians, industry, scientists and health experts participating in an “opportunistic embezzlement” to manipulate the medical-political complex. As emphasized by Alibhai, there was a lack of transparency, inappropriate involvement of government advisers in a scientific advisory group, blocking of publication of findings about inadequacy of antibody tests, attempted blocking of a press release of a research paper, competing interests such as shareholding in companies manufacturing tests, treatments and vaccines, and cherry-picking of science to advance anticompetitive practices. The author stated that “suppressing science, whether by delaying publication, cherry picking favoring research, or gagging scientists, is a danger to public health, causing deaths by exposing people to unsafe or ineffective interventions and preventing them from benefiting from better ones. When entangled with commercial decisions it is also maladministration of taxpayers’ money. Politicization of science was enthusiastically deployed by some of history’s worst autocrats and dictators, and it is now regrettably commonplace in democracies. The medical-political complex tends towards suppression of science to aggrandize and enrich those in power. And as the powerful become more successful, richer, and further intoxicated with power, the inequitable truths of science are suppressed. When good science is suppressed, people die”.

January 2021

On January 9, a newspaper in Peru reported that the former head of state Martín Vizcarra had recommended the use of ivermectin as prevention and treatment despite the absence of scientific evidence, saying that “it does work . . . ask those who have had the virus and were treated promptly with ivermectin: the symptoms immediately decreased” [87]. The article mentioned opposition by the US FDA and an analysis of possible therapies carried out by the Pan American Health Organization (PAHO) that had concluded that studies on ivermectin presented “a high risk of bias, very little certainty of the evidence, and that the existing evidence is insufficient to reach a conclusion on its benefits and its damage” (in 2014, PAHO did not concern itself with damages from a mass distribution of ivermectin to 1.4 million schoolchildren in Paraguay [88]). Regardless, local authorities had delivered ivermectin throughout several regions for months, but researchers from a social security scientific evidence generation department had raised alarm about ivermectin’s ineffectiveness. The article finished with stating that “without having taken all [opposing] arguments into account, Vizcarra finalized his recommendation as follows: ‘I am an engineer, I am not a doctor, but I met with an expert committee which recommended mass distribution. We have to resume prevention’”.

On January 27, Bill Gates said that the Coalition for Epidemic Preparedness Innovations (CEPI) had helped fund a number of COVID-19 candidates including the Moderna and Oxford/AstraZeneca vaccines. The US United States had included USD 4 billion for Gavi for its latest COVID-19 relief package, and that stopping the next pandemic will require spending tens of billions of dollars per year in for example mega-diagnostic platforms which could test as much as 20 percent of the global population every week [89]. Local authorities had delivered ivermectin throughout several regions for months, but researchers from a social security scientific evidence generation department had raised alarm about ivermectin’s ineffectiveness. The article finished with stating that “without having taken all [opposing] arguments into account, Vizcarra finalized his recommendation as follows: ‘I am an engineer, I am not a doctor, but I met with an expert committee which recommended mass distribution. We have to resume prevention’”.

On January 29, Joel S. Hirschhorn published an ebook titled “Pandemic blunder: Fauci and public health blocked early home COVID treatment” [88]. The author described the handling of the pandemic as “criminal negligence homicide resulting from intentional actions by myriad government officials”. The book concentrated on the actions of the US FDA and NIH. It also analyzed usefulness of RCTs, quoting an article published in the New England Journal of Medicine written by former director of the US Centers of Disease Control and Prevention (CDC) Thomas R. Frieden saying that “elevating RCTs at the expense of other potentially highly valuable sources of data is counterproductive. A better approach is to clarify the health outcome being sought and determine whether existing data are available that can be rigorously and objectively evaluated, independently of or in comparison with data from RCTs, or whether new studies (RCT or otherwise) are needed . . . there is no single, best approach to the study of health interventions; clinical and public health decisions are almost always made with imperfect data . . . there will always be an argument for more research and for better data, but waiting for more data is often an implicit decision not to act or to act on the basis of past practice rather than best available evidence. The goal must be actionable data – data that are sufficient for clinical and public health action that are even derived openly and objectively and that enable us to say, ‘Here’s what we recommend and why’” [91]. Hirschhorn added that “many researchers, like [Didier] Raoult [92], opted for observational studies, in which as many patients as possible are treated. This is not a matter of choosing a design that is ‘fattally flawed’, it is a matter of choosing a design that is not unnecessarily fatal to the patients. It’s not slowness (as some of his critics would allege), but being true to the study question as we saw it: how can we save as many lives as possible. These observational studies could begin almost immediately, and didn’t require the slow approval process that RCTs require”. Hirschhorn also noted that “a study showed that 35 percent of the conclusions of the finest RCTs assessed by peer review and published in the most respected medical journals, could not be replicated on reanalysis of their raw data. Meaning that when researchers gave over their original data sets to another group, they could not come up with the same results 35 percent of the time – in the very best, most-cited journals” [93].

February 2021

On February 5, Schellack et al. described the regulatory framework of South Africa, noting the December 22 decision against ivermectin and the January 27 decision to facilitate a controlled, compassionate access program for it [94].

On February 9, an extension to ‘Together’ trial led by McMaster University was announced (NCT04737424) [95], [96], [97], [98]. The evaluation of ivermectin was funded by Fast Grants, with the overall trial infrastructure being supported by the Rainwater Foundation. The ivermectin arm was apparently planned to be carried out in Brazil, with a single dose of 18 mg for participants weighing 40-60 kg and 24 mg for participants over 60 kg. The number of participants was expected to be up to 3,200, with results available within three to six months.

March 2021

On March 9, Kern et al. used pharmaco kinetic modeling to investigate the dynamic impact of timing and dosing regimens of ivermectin [99]. The authors noted that previous clinical trial results of other drugs had been well explained by these models. In this study the greatest benefits were observed when ivermectin was given immediately at the time of diagnosis. The authors wrote that even interventions with minor antiviral effect may reduce host exposure if timed correctly. In contrast to other modeled drugs for which no effect was observed, ivermectin seemed to be at least partially effective: given on positivity, peak viral load dropped by 0.3-0.6 log units and exposure by 8.8-22.3%.

On March 10, Taranuma et al. prospectively assessed environmental of COVID-19 therapeutic solutions, modeling scenarios for predicting levels of pharmaceuticals ending up in the environment through wastewater treatment plants. Their models predicted a very high impact for ivermectin and azithromycin, even at use levels well below the default value of 1% of the population. The authors said the results highlighted fish sublethal effects as the most sensitive target [100].

On March 12, Czech Republic extended the use of ivermectin from hospitals to all general practitioners and distribution to all pharmacies [101]. For hospitalized patients, a dose of 0.2 mg/kg on days 1, 3 and 5 was administered, with a maximum daily dose of 24 mg. For outpatients, it was administered on days 1 and 3.

On March 16, a Czech newspaper wrote an article clarifying “five misunderstandings” about ivermectin, namely that 100 times the standard dosage would be needed, that ivermectin would damage liver and kidneys, that the JAMA study was reliable, that ivermectin was for horses, and that there were no studies about it [102].

On March 16, the National Institutes of Health ACTIV-6 trial of repurposed medicines [103].
On March 16, a news story described some of the background of the adoption of ivermectin in South Africa [104]. A lawyer involved in the process described the compassionate access programme “quite a bureaucratic process, frustrating and completely unworkable” but said the government had agreed to register ivermectin for the treatment of COVID-19 in the next few days, which the lawyer called “a major breakthrough.”

On March 16, an article by Thakrar reported that the South African Health Products Regulatory Authority (SAHPRA) had failed to comply with a court order given on February 2, 2021, and therefore broken the law [105]. This had resulted in ivermectin not having been distributed to COVID-19 patients. On March 23, Mishal Rezek, a head of cardiology clinic in the Czech Republic, commented that he “does not understand the campaign against ivermectin”, most recently demonstrated by the European Medicine Agency’s (EMA) decision against it [106]. Rezek said that for the time being, his hospital was continuing its use. In the news report, Rezek refuted EMA’s arguments against ivermectin.

On March 23, a group of Brazilian medical associations demanded that drugs with no proven efficacy against COVID-19 should be banned, recommending social distancing and hand washing instead [107].

On March 27, the head of the intensive care unit professor Nathie Milladla in South Africa said that ivermectin was widely utilized during the first wave. During the second wave in late 2020, authorities noticed this practice and clamped down on it, threatening doctors who had been prescribing it with sanctions. Milladla believed this response had been unhelpful, and the case was going to appear in a hearing at a high court. Professor Salmi Abdoel Karim, one of the doctors leading South Africa’s coronavirus response, said that the doses being given to people could even be toxic and that “it must be clearly stated that ivermectin does not kill the virus at dosages humans can tolerate. The amount of drug needed to kill the virus is toxic to humans. Whatever it is doing, it is not killing the virus” [108].

On March 27, a Czech expert on clinical studies, Simon Reitz, said that doctors believe in new drugs rather than decades-old antiparasics, and he didn’t understand why people were afraid to use old drugs for new diseases [109].

On March 28, a group of British scientists and medical doctors, Health Advisory and Recovery Team (HART), urged the UK Medicines and Healthcare Products Regulatory Agency (MHRA) to consider granting emergency approval for ivermectin [110].

On March 29, Olufumi Emmanuel Babalola, who had organized an ivermectin RCT in Nigeria in May 2020 [111], was interviewed about the use of ivermectin in Nigeria [112]. Babalola stated that for Nigeria’s population of 210 million inhabitants, there had been only 2,000 deaths, or 10 deaths per million inhabitants. In comparison, for France’s population of 65.4 million inhabitants and 106,000 deaths, the ratio was 1,650 deaths per a million inhabitants, i.e. over 100 times higher. Nigeria was said to have had a special history with ivermectin due to it having been used for a very long time for the treatment of onchocerciasis (river blindness). More ivermectin had likely been used in Nigeria than in any other country in the world. Babalola claimed the reason for ivermectin not being used in Europe was industry influence and ivermectin’s unprofitability in comparison to investigational pharmaceuticals. Babalola highlighted that he had tried to get Covid-19 authors to consider ivermectin in their negotiations for access to 357 million doses of six different vaccines. In 2020, Bingham had served as the Chair of the UK vaccine task force and was currently sitting on the boards of six biotechnology companies [110, 112].

On March 30, Wohlke et al. discussed molecular aspects and therapeutic possibilities of repurposing ivermectin for COVID-19 [114].

April 2021

On April 1, an article by Mourya et al. about a retrospective 100-patient trial in India suggested 89% lower risk of no virological cure (95% vs 94%), RR 0.11, p = 0.0001 [115, 116].

On April 1, a feature by Wadhwa in the BMJ discussed division of the medical community in South Africa [117]. The article described that a lobby group “South Africa Has A Right To Ivermectin” formed on Facebook on January 2, 2021 had reached 72,000 members and was sharing information black market or veterinary ivermectin, reportedly running “an awareness campaign for ‘the people’s medicine’”, physically distributing pamphlets on the benefits of ivermectin at public spaces throughout the country.

On April 1, a Philippines House of Representatives hearing on March 29 about ivermectin was made available online [118, 119].

On April 1, a news report by Horowitz pointed out that data by the WHO indicated a 81% reduction in mortality due to ivermectin, yet the WHO recommended against using it [120].

On April 2, a news report by TriaSite News discussed allegations of scientific misconduct related to the recent Uizardi WHO funded meta-analysis by Hill et al. [121, 126]. The question was about whether or not a third party not named as an investigator had modified or influenced it to downplay ivermectin’s efficacy. The report said a French group, Bon Sens, had sent a demand letter to the University of Liverpool alleging scientific misconduct.

On April 3, an interview of Motozuki Shikhei Naiao, the main researcher in an Iranian clinical trial on ivermectin, discussed the current situation in Iran [122, 123, 124]. Naiao stated that “considering the data and the risk-benefit ratio we should spread the word [about ivermectin’s efficacy] as much as we can because it is our moral and public responsibility . . . we don’t know what the result [of this advocacy] will be . . . but we hope to have a positive influence in the world”.

On April 4, Whiteboard Doctor discussed the ivermectin review published on March 24, 2021 by a Japanese group including the discoverer of ivermectin Satoshi Omura [125, 126].

On April 4, a news report by ABC News suggested that unregulated self-medication with a combination of medications or ivermectin had resulted in cases of liver damage in Brazil [126].

On April 4, Daily Mail (UK) wrote that Britain’s Health Secretary Matt Hancock was setting up an anti-virals task force to produce a “new innovative coronavirus treatments” with one goal to develop a pill suitable for early outpatient treatment, with details expected to be announced in the coming weeks [127]. [129]. Earlier in February 2021, Hancock had been found guilty of unlawful hiding of information about COVID-19 related government spending [129]. The judge called the act “a historic failure”. The anti-viral task force was said to attempt to turn “the latest research on anti-viral therapeutics into approved medical treatments for coronavirus within months”. The report referred to UK’s “success of the vaccine program” saying it “wants to replicate those achievements with anti-viral drugs”. The team was said to be led by a “biochemist turned venture capitalist” Kate Bingham who had previously helped the UK secure agreements for access to 357 million doses of six different vaccines. In 2020, Bingham had served as the Chair of the UK vaccine task force and was currently sitting on the boards of six biotechnology companies [130, 132].

On April 5, in response to a Brazilian physics professor claiming the meta-analyses produced by the CovidAnalysis group were a scam, a blog post in Portuguese investigated the reliability of them [132]. The author noted that some of the world’s most published physicians and researchers had quoted the results of the meta-analyses as valid. A mathematics professor interviewed for the post did not find immediate methodological flaws with the meta-analysis. The author had also been in contact with the CovidAnalysis group directly.

On April 6, a news report indicated that after a judicial process the South African Health Products Regulatory Authority (SAHPRA) and parties in favor of using ivermectin for COVID-19 had reached an agreement, according to which registered medical practitioners may prescribe ivermectin for COVID-19 [133].

On April 6, a news report from the Czech Republic mentioned an ongoing observational trial with 100 patients [134]. Asked about the difference between the ivermectin policy of the Czech Republic and the EMA’s advice against ivermectin, a head of cardiologyology clinic Michal Rezek commented that the contents of EMA’s detailed report were incompatible with the short statement published on the Internet. Rezek said that while EMA admitted the existence of ivermectin studies with positive results they said conclusions could not be made due to ivermectin having been part of a combination of drugs or that the trials had had methodological deficiencies. Rezek said these were just “formal reservations” and that “for them, positive studies are not enough to prove efficacy”. Rezek added that EMA’s recommendation against ivermectin was not indicated by their not commonly available extensive scientific study. In this background document, EMA rejected positive studies due to their various shortcomings but also stated...
that the drug was safe and its efficacy could not be ruled out. Rezak said that “there is no evidence that it did not work.”

On April 6, Syed stated that 54 of his previous YouTube videos mentioning ivermectin had been demonetized, and if he would mention ivermectin in his future videos they would be either removed or demonetized [135].

On April 6, an article about a retrospective cohort study by Mokhtar et al. (n=28,759) concluded that early outpatient treatment of mild COVID-19 with hydroxychloroquine (7,295 treated vs 21,464 not treated) reduced the odds of hospitalization by 35.4% (7.2% vs 11.1%, p<0.001) and mortality by 69.7% (0.4% vs 1.3%, p<0.001) in a six-month follow-up, with no adverse effects [136] [127].

On April 7, an interview of Tos Lawrie discussed the meta-analysis by Bryant et al. and the meta-analysis by WHO, comparing the two [138], [139]. Lawrie mentioned she had not found a protocol for WHO’s review. She mentioned discrepancy between which trials had been classified as high risk and low risk of bias.

On April 7, a preprint from Wiseman and Kory discussed the methodology of the clinical trial of Lopez-Medina et al. and concluded that possible clustering and/or drug switching confounding obscured up to 56% of ivermectin’s effect [140], [141], [142].

On April 7, FLCCC weekly update discussed the situation in Zimbabwe, interviewing Jackie Stone who said ivermectin had “completely changed the landscape for us” with an approximately ten-fold reduction in mortality [143]. Stone had successfully been using colloidal silver, ivermectin and doxycycline protocol for severely hypoxic patients, allowing patients with oxygen saturations under 80% to be treated at home instead of being hospitalized [144]. According to Stone, the components complemented each other. Stone had first been accused of malpractice but later, on January 28, 2021, Zimbabwe had approved ivermectin nationwide [145], [146], [147][148][149]. The presentation detailed the various mechanisms of action of ivermectin in each phase of COVID-19, including the role of C0147 receptor [143].

On April 8, an Italian pharmaceutical website updated its guidance on how to legally prescribe ivermectin for COVID-19 in Italy [150].

On April 8, a preprint by Tsigay et al. indicated that ivermectin inhibited 89% of SARS-CoV-2 spike protein binding to ACE2 [151].

On April 8, a statement by the FLCCC Alliance discussed disappointments related to vaccines, suggesting these indicate an increased need for a medication such as ivermectin which has shown efficacy comparable to vaccines [152]. The statement mentioned adoption of ivermectin in several countries and cities including India, Japan and Mexico City, adding that the WHO and NHF have all the data they need to recommend ivermectin to prevent and treat COVID-19.

On April 8, the Washington Post wrote about increased interest in ivermectin in the US, warning that the drug was safe and its efficacy could not be ruled out. Rezak said that “there is no evidence that it did not work.”

On April 9, a US news article titled “Scientists work toward an elusive dream: a simple pill to treat Covid-19” discussed the possibility of a pharmaceutical for early outpatient treatment of COVID-19, stating that the reason for it not existing yet “is not for lack of trying” [158]. The article included an interview of the US National Institutes of Health director Francis Collins who called this kind of pill a “dream”, adding that “it’s just a damn long pathway... but I will tell you that this is an extremely high priority for Tony Fauci and Francis Collins and the Biden administration, to work with these companies to try to make sure that we speed this up”. Pharmaceuticals in development by Merck & Co, MSD and Ridgeback Biotherapeutics (molnupiravir), Atea Pharmaceuticals (ATX-517 and Pfizer (PF-07321342) were mentioned.

On April 9, a news report wrote that a State Supreme Court in New York, US had ordered a hospital to administer four additional doses of ivermectin to a ventilated patient [159].

On April 9, Garcia et al. published a protocol for a randomized clinical trial comparing ivermectin to placebo in early treatment in Peru (SAINT-Peru, NCT04635943) [160].

On April 10, an article about an in silico analysis by Bello found that the in vitro activity of ivermectin may be explained by acting as an inhibitor of importin-a, dimeric 3C-like protease, and Nafip [161]; [162];

On April 11, the Wall Street Journal published an opinion by Johnson et al., the organizer of US Senate hearings in late 2020 [163]. The authors stated that social media companies had backfired. They said there had been “an extremely limited and unfair coverage” of ivermectin in the US and that the during her forty years in journalism, never before had she encountered such censorship. In her opinion, since the beginning of the hydroxychloroquine controversy involving president Trump there had been a bias in the media against early treatment, leading the mainstream media to become very unwilling to conduct proper investigation and act as journalists were supposed to, instead publishing superficial, erroneous articles. Pfeiffer called for a major congress-led investigation on how the pandemic has been handled in the US but added she was not confident there would be anyone able to conduct it properly. She suggested courts as a good starting point for these investigations and demands. Another journalist, Mariam Mia, described the atmosphere surrounding ivermectin journalism being characterized by fear. A South African journalist, Viasen Soobramoney, described they had become unable to publish their stories on social media platforms, leading them to realign the depiction on this platform, noting it could lead to scary scenarios. In the discussion it was mentioned that in South Africa, 700 medical doctors had joined together to demand adoption of ivermectin and succeeded.

On April 11, the parliament of Italy voted in favor of early treatments [167].

On April 11, Bisoffi said that an interim analysis of an Italian trial (NCT04438850) had been performed but the decision of the steering committee had been to continue the recruitment, leaving the researchers blind as to the preliminary results (personal communication).

On April 11, a news report discussed the situation in Slovakia, noting that after the official authorization, there was no central plan nor efficient market apparatus in place to efficiently and effectively allocate supplies of ivermectin [168]. Therefore, availability remained an issue, with some Austrian pharmacies said to have turned predatory, marking up the prices. Perhaps 10,000 Slovaksians were said to have been treated with ivermectin. Mainstream press was said to avoid the topic or quote physicians with dismissive articles. Pfeiffer commented that these were “an extremely limited and unfair coverage” of ivermectin in the US and that the during her forty years in journalism, never before had she encountered such censorship. In her opinion, since the beginning of the hydroxychloroquine controversy involving president Trump there had been a bias in the media against early treatment, leading the mainstream media to become very unwilling to conduct proper investigation and act as journalists were supposed to, instead publishing superficial, erroneous articles. Pfeiffer called for a major congress-led investigation on how the pandemic has been handled in the US but added she was not confident there would be anyone able to conduct it properly. She suggested courts as a good starting point for these investigations and demands. Another journalist, Mariam Mia, described the atmosphere surrounding ivermectin journalism being characterized by fear. A South African journalist, Viasen Soobramoney, described they had become unable to publish their stories on social media platforms, leading them to realign the depiction on this platform, noting it could lead to scary scenarios. In the discussion it was mentioned that in South Africa, 700 medical doctors had joined together to demand adoption of ivermectin and succeeded.
On April 12, an article by Saha et al. investigated the binding mechanism of ivermectin with the spike protein of SARS-CoV-2 using three different computational modeling techniques, concluding that ivermectin can be a suitable inhibitor for SARS-CoV-2 to enter into the human cell through hACE2 [169].

On April 12, a news report from Indonesia indicated that the WHO was finalizing its evaluation of ivermectin [170].

On April 12, a news report from Lucknow, Uttar Pradesh, India stated that Indian states had simply ignored the WHO recommendation against ivermectin [171].

On April 12, a medical doctor suggested that the ivermectin strategy of the pharmaceutical industry was similar to the earlier strategy of the tobacco industry in denying the harms of smoking [172; 173; 174]. The author seemed to suggest that the SARS-CoV-2 pandemic would have been a part of these strategies to resist introduction of early treatments with repurposed medicines. He also seemed to suggest that the WHO, NIH and FDA were involved in these delaying operations.

On April 12, a German magazine Bild wrote about the ivermectin controversy and the refusal of European and German approval authorities to adopt ivermectin, quoting a German immunologist Peter Schiebler saying “it is completely incomprehensible that there is no approval for this in Germany. We would have thousands fewer deaths to mourn” [175].

On April 12, a news report wrote that ivermectin was going to be tried in Iceland as a part of an international Remap-Cap study [176]. It had already been administered to some critically ill patients before the trial.

On April 12, New Republic published a news report by Zaitchik, titled “How Bill Gates impeded global access to Covid vaccines” [177]. According to Zaitchik, Gates was using his foundation to defend monopoly medicine. Initially in February 2020, a WHO expert group had drafted outlines for pandemic responses, assuming that the world would unite against the virus and that intellectual property issues would not be allowed to slow things down. In May 2020, WHO Covid-19 Technology Access Pool (CTAP) was launched. However in March 2020, Gates had first launched Therapeutics Accelerator, a joint initiative with MasterCard and Welcome Trust, then in April 2020 a larger initiative inside the WHO called Access to COVID-19 Tools Accelerator (ACT-Accelerator), which was a public-private partnership based on charity and industry enticements. According to Zaitchik, it “undermined Gates’s long-standing commitment to respecting exclusive intellectual property claims . . . [the idea that intellectual property] must be protected, even during a pandemic, carried the enormous weight of Gates’s reputation as a wise benefactor, and prophetic leader that he himself nurtured” [178]. The ACT-Accelerator was a “Gates operation, top to bottom”. It included a vaccine arm called COVID-19 Vaccines Global Access (COVAX) which aimed at providing a small amount of vaccines to low-and-middle-income countries for a lower price [179]. Zaitchik wrote that Gates actively sought to undermine all challenges to his authority and ACT-Accelerator’s intellectual property-based charity agenda. Pharmaceutical companies, through International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), strongly supported Gates. C-TAP was manipulatively sidelined in favor of ACT-Accelerator COVAX which later completely failed to meet its stated goals. Gates also prevented Oxford University’s plan to place the rights to its vaccine candidate in the public domain. Subsequently, the rights were sold to Astra Zeneca.

On April 13, an open letter by US doctors described the ivermectin trial by López-Medina et al. published in JAMA on March 4, 2021 as “fatally flawed” [179; 181].

On April 13, a preprint by Al Sulaiman et al. of a multicenter, non-interventional, retrospective cohort study of 786 critically ill patients at ICUs found a significant association between thiamine use with mortality rate of over one hundred ivermectin-treated inpatients had been around 10 percent, in contrast to a general level of around 20 percent in the Czech Republic [187]. He said a small proportion of patients do not respond to any treatment, and that ivermectin probably has a greater meaning and effect in the outpatient setting and in the early stages of the disease. He said ivermectin is being used in only 10 percent of patients in the hospital. He said they don’t have convincing results of other antivirals. He added that no-one understood why they attack us when our patients receive the same treatment as in other developed countries . . . [allegations about a pharmaceutical lobby] are illogical, because if ivermectin took up, it would become a gold mine for pharmaceutical companies. It would be used by tens or hundreds of millions of people”. He said they were mainly used against enteric protozoa, hepatic and vitamins C and D as a supportive treatment, and had tested monoclonal antibodies. Ivermectin was usually used “because we don’t know how the drug behaves in a COVID-19 patient receiving a number of other medications” and they had several cases of ivermectin-treated patients had been around 10 percent, in contrast to a general level of around 20 percent in the Czech Republic [187]. He said a small proportion of patients do not respond to any treatment, and that ivermectin probably has a greater meaning and effect in the outpatient setting and in the early stages of the disease. He said ivermectin is being used in only 10 percent of patients in the hospital. He said they don’t have convincing results of other antivirals. He added that no-one in the EU has applied for ivermectin’s approval for COVID-19 because in order to do that successfully...
On April 17, a presentation by FLCCC's Marik focused on methylprednisolone and ivermectin. [200]

On April 17, a retrospective cohort study by Morgenstern et al. indicated 74.0% lower risk of infection randomized controlled studies. We must never allow anonymous censors to determine what is medical safeguard the entire region”.

of ivermectin is being regarded as a political fanaticism, which could be punished by international tribu-
the meta-analysis of the CovidAnalysis group was based on. The author concluded that “in Brazil, the use
in the shape of COVID-19 curves when comparing groups of treated and untreated people from the same
area, adding that ivermectin might have contributed to a terrible situation in Manaus, with allegedly
increasing reports in the last two decades. The recent COVID-19-related widespread self-medication was
numerous positive results reported in smaller studies”. About the WHO decision, Rezek commented that
for other medicines that the WHO had recommended against there had been large studies to back up
for trying to bring up exactly the same things Lawrie had just stated. The interviewer cited the comment
and a statement by professor Robert Clancy saying Kelly had been right to raise awareness about ivermectin and hydroxychloroquine and that due to limitations of vaccines they need to
by Peter Schleicher [175] and a statement by professor Robert Clancy saying Kelly had been right to raise to either promote or refute the efficacy of ivermectin, dexamethasone, or their combination in COVID-19 management [188]. There were no new safety signals of concern. The quality of studies was said to vary widely, with five studies having a “good” methodological quality [189], [190], [191], [192] and two studies having a “fair” quality [193], [194].

On April 16, an article by Domingo-Echaburu et al. discussed ivermectin’s ecotoxicity [62]. They wrote that available risk assessments confirm extremely high toxicity for invertebrates and that the use of wastewater treatment plant sludge as soil fertilizer in agricultural soils should be approached cautiously. On April 19, an article by DiNicolantonio et al. suggested that the efficacy of ivermectin in the cytokine storm phase of COVID-19 may be, at least in part, an anti-inflammatory effect mediated by increased activation of gynecoid receptors on leukocytes and possibly vascular endothelium [207], [208]. On April 19, a review by DiNicolantonio et al. suggested that the effectiveness of ivermectin in the cytokine storm phase of COVID-19 may be, at least in part, an anti-inflammatory effect mediated by increased activation of gynecoid receptors on leukocytes and possibly vascular endothelium.

On April 16, a scoping review by Bkowimbik et al. concluded that evidence is not sufficiently strong to either promote or refute the efficacy of ivermectin, dexamethasone, or their combination in COVID-19 management [188]. There were no new safety signals of concern. The quality of studies was said to vary widely, with five studies having a “good” methodological quality [189], [190], [191], [192] and two studies having a “fair” quality [193], [194].

On April 16, an article by Molento described “unprecedented consequences in Latin America”. [195]. The author said endo- and ectoparasites had developed a strong tolerance to ivermectin since the 1980s with increasing reports in the last two decades. The recent COVID-19-related widespread self-medication was said to have been adopted based on false promises against any medical, pharmacological and epidemiolo-
gical recommendations. The article stated that ivermectin distribution did not result in any modification in the shape of COVID-19 curves when comparing groups of treated and untreated people from the same

On April 18, a review by DiNicolantonio et al. suggested that the efficacy of ivermectin in the cytokine storm phase of COVID-19 may be, at least in part, an anti-inflammatory effect mediated by increased activation of gynecoid receptors on leukocytes and possibly vascular endothelium.

On April 16, an opinion published in the Wall Street Journal [196] said: “how shocking it is to read in your editorial that YouTube’s standard for medical misinformation is information that contradicts authorities [196]. Modern medicine doesn’t believe in authorities but in evidence based on data analyzed from random controlled studies. We must never allow anonymous censors to determine what is medical misinformation and cancel scientific inquiry and discussion with which they disagree”.

On April 17, a retrospective cohort study by Moeggenstern et al. indicated 74.0% lower risk of infection [197], [198]. On April 17, an open-label nonrandomized case study with 10 ivermectin-treated patients and 15 controls in a French care home suggested (results not statistically significant) 70.0% lower risk of death (10.0% vs 33.3%), RR 0.30, 95% CI 0.13–0.69 and 55% lower risk of severe disease (30.0% vs 66.7%), RR 0.45, p = 0.11 [199], [200]. On April 17, a presentation by FLCCC’s Marik focused on methylprednisolone and ivermectin [201].
On April 19, a report discussed politicization of ivermectin, mentioning lack of availability of remdesivir and vaccines in resources-limited settings, adoption of ivermectin in Slovakia, the Czech Republic and parts of Latin America, the warnings of FDA, EMA, Merck & Co., MSD and EMA, pro-ivermectin campaign in South Africa, pressure to adopt ivermectin in the Philippines, and the Surrogace scandal [16]. The author concluded that “consequences of global healthcare inequality are clear: if life-saving vaccines aren’t available, people will be driven to take matters into their own hands – with potentially catastrophic results”.

On April 20, a news report in the Guardian discussed the new UK antiviral task force, reviewing six medicines (dexamethasone, tocilizumab, budesonide, favipiravir, remdesivir, convalescent plasma) having “shown promise in treating Covid” [217]. Ivermectin was not mentioned.

On April 20, Cochrane Collaboration published a protocol for a systematic review about ivermectin for preventing and treating COVID-19 [226].

On April 21, the State Institute for Drug Control of the Czech Republic was threatening a Czech newspaper with a fine of approximately USD 25,000 for illegal advertising of ivermectin’s efficacy by publishing stories with a claim assigned to Paul E. Marik that ivermectin reduced mortality or a claim assigned to Michael Heuk that Czech inpatients had been improved by ivermectin treatment [229]. The threat was described as “shocking” and illegitimate by some parliament members who also accused the Ministry of Health of reluctance in easing patients’ access to ivermectin [220].

On April 21, the FLCCU Weekly Update discussed “the WHO’s denial of ivermectin: ‘Big Science’, disinformation and their impacts on human rights”, in which “Big Science” represented a concept similar to “Big Pharma” [221]. Kory described how the FLCCU recommendations with regard to COVID-19 had consistently been months to a year ahead of recommendations of other entities, and now wanted to discuss “what we as a group are now finding with our advocacy of good evidence-based medicine: we are now what I think is actually beyond the science. We are running to an area which I knew little about before Covid happened and which I’m quickly becoming an expert on”. He said “the WHO most clearly demonstrates what we are up against”. According to him, the FLCCU had been accused of spreading disinformation (advocacy of “unproven therapies”). Kory introduced the concept of disinformation to describe the practices of, among others, the WHO. He noted the converging expert opinions from the 18 April 2021 meeting of the IQS group [222], UNITAID/WHO [16] and Spain, in contrast to the opposing recommendations issued by agencies including the European Medicine Agency (EMA), SAIHPRA and CADTH. He said the FLCCU had tried to pursue data-based arguments with these organizations but it had been futile. Initially, the FLCCU had assumed the barrier was the “Big Science”, a societal constellation that requires that treatments are proven by large RCTs, the fact that only large agencies or pharmaceutical companies are able to finance trials of this magnitude, and premiums journals publishing results of these trials and ignoring small clinician-initiated trials, resulting in a monopolization of “re- sions” science to large, well-funded actors only. Recently in the case of ivermectin, however, the FLCCU had changed its view, no longer seeing the “Big Science” as the only barrier with respect to ivermectin. Instead, a more prominent barrier appeared to be a targeted disinformation campaign against ivermectin specifically, pursued predominantly through the WHO.

On corticosteroids, Kory said most hospitals were still adhering to WHO’s guidance based on University of Oxford’s Recovery dexamethasone trial [76]. According to Kory, it was “an anemic dose” of wrong current vaccine manufacturer”. ACTIV project program had organized six trials on ivermectin [229]. ACTIV- I had included three patent-protected pharmaceuticals, ACTIV-III six investigational pharmaceuticals. ACTIV-IV four antithrombotics including aspirin and heparins, ACTIV-5 two investigational monoclonal antibodies, and ACTIV-6 ivermectin. In addition, there had been NIH-funded studies on, for example, remdesivir and convalescent plasma.

On disinformation, Kory said that commonly used tactics included conducting counterfeit science and trying to pass it off as legitimate research, harassing scientists, manufacturing uncertainty where little or none exists, buying credibility through alliances with academia or professional societies, and manipulating government officials or processes to influence policy. As examples, he mentioned Merck & Co., MSD obscuring the risks of tocilizumab [230] and GlaxoSmithKline trying to silence a scientist researching the safety of ransiglumab [231], both of which were later withdrawn from the market; the US opioid crisis having been created or exacerbated by webs of influence woven by several pharmaceutical companies involving health professionals, patient advocacy groups, medical professional societies, research universities, teaching hospitals, public health agencies, policymakers and legislators [242]. Pfizer pressuring FDA to downplay the risks of ronaviruse [239], counterfeit science on the safety of aslosterol [224], tobacco industry practices [237] and a few other examples. About WHO’s past track record, Kory commented that “that was then, this is now” and that most of the budget now “has strings attached . . . [WHO is a] very compromised organization particularly susceptible to external influences”, especially the Bill and Melinda Gates Foundation through Gavi The Vaccine Alliance, CRIP and COVAX. Also, the “revolution door” phenomena was said to have a large effect. According to Kory, the recent failures of the WHO included handling of the Chernoby [216] and Fukushima (2011) nuclear disasters, the Ebola epidemic in 2014, the H1N1 pandemic in 2009-2010, and the COVID-19 pandemic. On ivermectin’s evidence base, Kory said WHO had failed to publish a pre-established protocol for data exclusion, excluded trials from their original Unitaid search protocol, excluded two quasi-randomized RCTs with lower mortality, two RCTs in which ivermectin was combined with other medications, seven other RCTs, all RCTs about prophylaxis, 13 observational trials with more than 5,500 patients, and numerous epidemiological studies.

Among possible interests against the adoption of ivermectin, Kory said, were in effect everything related to investments in vaccines and investigative pharmaceuticals, including sovereign nations producing them, with “the scale of the market also being incalculable”. In closing, Kory asked clinicians to “stop looking for that was then, this is now” and that most of the budget now “has strings attached . . . [WHO is a] very compromised organization particularly susceptible to external influences”, especially the Bill and Melinda Gates Foundation through Gavi The Vaccine Alliance, CRIP and COVAX. Also, the “revolution door” phenomena was said to have a large effect. According to Kory, the recent failures of the WHO included handling of the Chernoby [216] and Fukushima (2011) nuclear disasters, the Ebola epidemic in 2014, the H1N1 pandemic in 2009-2010, and the COVID-19 pandemic. On ivermectin’s evidence base, Kory said WHO had failed to publish a pre-established protocol for data exclusion, excluded trials from their original Unitaid search protocol, excluded two quasi-randomized RCTs with lower mortality, two RCTs in which ivermectin was combined with other medications, seven other RCTs, all RCTs about prophylaxis, 13 observational trials with more than 5,500 patients, and numerous epidemiological studies.

On April 22, FLCCU’s article published as a preprint in 2020 [236], provisionally accepted to Frontiers of Pharmacology peer-reviewed but subsequently retracted post-peer-review [247], [237], [238], was published in American Journal of Therapeutics [240].

On April 22, Philippe Duneton, the chief of Unitaid, the sponsor of the meta-analysis by Hill et al. [216], [241], said there was a need to “double down on research and development for COVID-19 treatment” [242]. In March 2021, Hill had allegedly said Unitaid had forced him to alter the conclusion of his meta-analysis [233], [234]. In the April 22 interview, Duneton said “I think that there is a need . . . not just to look [at] old drugs, but to double down [on] the effort in terms of screening of potential new drugs . . . people at the beginning thought that it was possible to repurpose drugs, so from hydroxychloroquine, to ivermectin, to colchicine, to remdesivir. A long list. But . . . I think that we can say that we don’t see . . . a real opportunity for old drugs . . . except dexamethasone”. However, Unitaid had apparently included ivermectin in its funded trials “to fill in the gap in evidence”. Duneton said “we need to finish the job, because I think that we have seen that people, for whatever good reason, I suspect, want to use drugs without evidence of benefit”. That’s the situation. And I think it’s quite important to fix this. Duneton was said to “hope for better outcomes for new antivirals in development, such molnupiravir, which is being developed by Ridgeback Biotherapeutics and Merck & Co and is advancing to Phase 3 trials” [243]. He also highlighted that the second generation of monoclonal antibodies would be efficacious against the new COVID-19 variants and would be easier to administer. Next, the report mentioned an agreement between the Bill and Melinda Gates Foundation and Eli Lilly to develop a monoclonal antibody to treat COVID-19 in low- and middle-income countries. The agreement was said to be a part of the COVID-19 Therapeutics Accelerator, which
worked with but was separate from the ACT Accelerator, of which Unitaid was part. Unitaid was said to typically provide funding for late-stage research and development of new drugs and diagnostics and to bring more affordable formulations to low- and middle-income countries (LMICs), adding that these efforts had not been fully maximized. Duneton explained that Unitaid and its partners were working in parallel to ensure access for LMICs when and if new treatments prove to have a significant benefit. “So what kind of incentive, how can we push for access in LMICs?” Can we organize volume guarantees [of medication]? Can you pay more up front, for example that Unitaid and its partners in Brazil, with the Gates Foundation, or incentivize generic manufacturers so we can have access for LMICs in all continents? It’s a lot of money, but that’s the kind of tool that we need to consider”, Duneton said.

On April 22, Indian Council of Medical Research COVID-19 National Task Force published clinical guidance for management of adult COVID-19 patients [214]. For mild disease, as an option “based on low certainty of evidence”, the guideline suggested 0.2 mg/kg ivermectin for three days, with the suggestion to avoid it in pregnant and lactating women. For moderate and severe disease the guideline suggested predominantly methylprednisolone and low molecular weight heparin.

On April 22, an opinion by Gazregnani et al. stated that research related to ivermectin in COVID-19 has serious methodological limitations resulting in very low certainty of the evidence, and continues to grow [215].

On April 22, a post on the website of Gavi The Vaccine Alliance discussed why ivermectin isn’t recommended for use, mentioning the Surgisphere scandal, the case of rejection of FLCCC’s article by Frontiers of Pharmacology, the EMA’s and NIH’s lack of support due to insufficient evidence, and the ongoing Together trial co-sponsored by Bill and Melinda Gates Foundation [216]. The author concluded that “it would therefore be premature to conclude absolutely that ivermectin has no place in COVID-19 treatment. On the basis of current evidence, however, its use cannot be recommended” [217].

On April 24, a full interview of Jackie Stone talking about ivermectin in Zimbabwe was made available [218].

On April 24, Shankara Chetty from South Africa discussed alternative therapy options for COVID-19 treatment in patients with non-severe illness who might have an allergic reaction due to virus particles [219]. Chetty case a parallel to inflammatory responses in COVID-19, using ivermectin for immunomodulation of dyspepsia which he considered an allergic reaction in the lung due to virus particles [219]. He said there had been no reports of ivermectin for oxygenation and no cases of long haul COVID-19 syndrome among his 4,000 patients and that his method “has stood up to the test of time far better than vaccines would”. He said in some countries medicine was very regulated with people taught to follow protocols and not to step out of the box. Conversely in India doctors are taught to think outside the box, to try anything, to diagnose patients with their clinical skills, and to only use diagnostic laboratory tests to verify or clarify their clinical diagnosis, never to come to a diagnosis. He also referred to arrogance and stubbornness, saying it was difficult to convince someone when they are closed in their ways.

On April 24, a petition to the Government of Canada suggesting adoption of ivermectin for COVID-19 opened on March 25 ended with 4,825 signatures [220].

On April 24 and 25, the BIRD group organized the First International Ivermectin for Covid Conference [221]. The speakers included Moosen Syed (US), Tesfaw Iwerie (UK), Pierre Kory (US), Hector Carvalho (Argentina), Juan Chamin (US), Andrew Bryant (UK), David Chesser (US), Eli Schwartz (Isr), Waisi Khan (Bangladesh), Manjul Medhi (UK) and Marta Zwick (Speedenia). Syed described five mechanisms of action of ivermectin. Iwerie described the principles of assessment of research evidence, the role of systematic reviews, details of the meta-analyses carried out by the BIRD group [221], [15], and issues with WHO’s meta-analysis. Iwerie referred to the Hippocratic oath and the Helsinki Declaration as fundamental rights of clinicians, adding that BIRD membership was intended for doctors in need of peer support. Chamin compared changes in case fatality rates of some countries before and after the introduction of ivermectin. Bryant provided an overview of ongoing trials. Chamin described handling of scaleable and COVID-19 outbreaks in nursing homes in the US involving 514 high-risk residents with 399 confirmed COVID-19 cases treated with multi-drug approach (12 mg of ivermectin on days 1 and 8, doxycycline, azithromycin, enoxaparin, zinc, vitamins C and D).

Schuwa described final results of their double-blinded RCT in Brazil initiated in March 2020 to study reduction of viral shedding in isolated non-pregnant adult outpatients with mild to moderate or asymptomatic disease. Due to the massive vaccination campaign there was no longer a need for ivermectin treatment and the population could not possibly continue ivermectin prophylaxis. Kory discussed recent changes to FLCCC’s MATH+ protocol and the L-MASK: prophylaxis and early outpatient protocol. Khan described his ivermectin trial conducted in Bangladesh [222]. Carvalho described his experience with ivermectin in the long haul COVID-19 syndrome (LHCS). Peers described LIHCs as a mast cell activation issue [223]. Medhi discussed ivermectin in patients at risk of disseminated strongyloidases infection. Zwitter discussed medical ethics related to ivermectin in COVID-19.

On April 23, a cluster randomized trial about repurposing ivermectin for outpatients with a mild disease (IVER-Lever) sponsored by the Argentinian Ministry of Public Health completed in Argentina (NCT04718481), indicating that a higher proportion of outpatient discharge was observed in treated patients (98.2% vs 86.1%, p=0.0007) and that the treated patients showed eight timeshigher chance of discharge (OR 8.71, 95% CI 1.99-38.12, p=0.004) even in the presence of comorbidities [224] [225] [226] [227] [228]. The authors concluded that the treatment with ivermectin could significantly prevent the evolution to serious stages since no treated patients deteriorated to a severe disease.

On April 23, an letter by Roche et al. stated that despite reported antiviral effects at supratherapeutic doses in vitro, there is neither clinical evidence nor a plausible biologic mechanism to support ivermectin as an effective prophylactic or therapeutic agent against SARS-CoV-2, and that it is important that healthcare professionals understand the lack of evidence for its application to COVID-19, and continue to refute and rebut misleading health information [229].

On April 26, an article about prophylaxis by Bartoszko et al., a group involved with WHO’s living guideline, included one trial of ivermectin combined with iota-carrageenan (n=234) [230] and two trials of ivermectin alone (n=540) [231] [232], all compared with standard of care or placebo. The authors concluded that it was highly uncertain whether ivermectin combined with iota-carrageenan or ivermectin alone reduced the risk of SARS-CoV-2 infection [233]. The authors noted that “the data are consistent with three meta-analyses [234] [235] [236] and one network meta-analysis [237] evaluating ivermectin as treatment for COVID-19. In contrast with other meta-analyses, we rated the certainty as very low because of serious risk of bias and very serious imprecision”. On April 26, a news report in a Canadian newspaper said Pfizer’s was testing its investigational drug PF-07321322, developed from scratch during the current pandemic, which, if successful, could become first-ever COVID-19 outpatient treatment [238]. Pfizer said it had demonstrated potent in vitro antiviral activity against SARS-CoV-2 and it was soon going to be given to 60 volunteers in a phase I trial.

On April 27, the CEO of Pfizer said that an oral drug PF-07321322 for COVID-19 outpatients could be ready by the end of the year 2021. Pfizer had begun an early-stage clinical trial of the oral drug in March 2021. It was working on two antivirals, an oral and an injectable [239]. The report said the drug “could become first-ever home cure for COVID-19… . . for Pfizer and PF-07321322, it is a ‘race against time’”, [J supposed in pharmaceutical medicine] said. They not only need to produce a drug that works but need to do it while SARS-CoV-2 still presents a major public health threat” [240].

On April 27, Merek & Co/MSD announced that it had entered into non-exclusive voluntary licensing agreements for mohupavir (EIDD-2803/MK-4482) in an investigation oral therapeutic intended for treatment of COVID-19 outpatients, with five established Indian generics manufacturers [241].


On April 28 in the Philippines, two lawmakers were planning to distribute three doses of ivermectin at no cost at an event in which those hoping to get ivermectin could present their medical prescriptions or get a prescription from doctors present at the event. FDA director Eric Domingo commented that “It is very difficult to convince someone when they are closed in their ways.”
checked before issuing a prescription. He added FDA was not for or against any medicine and that it only prohibited unregulated and unregistered drugs. A doctor estimated over 100,000 people were to be given ivermectin over the next few weeks and regularly monitored afterwards. The Philippines Department of Health maintained there was still no concrete evidence of efficacy in mild to moderate COVID-19 [272].

On April 28, an article in The Scientist by Noel discussed events subsequent to the retraction of FLCCC’s ivermectin review by Frontiers of Pharmacology in the beginning of March 2021 [273]. The review was intended to be a part of a special issue on drug repurposing for COVID-19, produced by guest editors. Noel wrote that on April 23, following disagreements about other submissions and more than a month of failed negotiations between Frontiers and the guest editors about how to proceed, the editors had followed through on previous threats to resign, while the publisher pulled the special issue page from its website. The editors stated that “the actions of Frontiers in this matter clearly violated well established norms and procedures for peer review and publication of scientific works and intellectual contributions . . . in our opinion, these unfortunate events constitute gross editorial misconduct” [274].

On April 28, MedPage Today reviewed the history of the development of Merck & Co’s molnupiravir (MK-4482/EIDD-2801) [275].

On April 29, a news report stated that the Christian Social Union in Bavaria (CSU) had called for the federal government in Berlin to help with the adoption of ivermectin [276]. The proposal mentioned that ivermectin had already been adopted in Slovakia as the first EU country, and that two expert groups at the Robert Koch Institute already considered ivermectin a potentially active substance.

On April 30, version 66 of the CovidAnalysis group’s meta-analysis of ivermectin studies was made available [277]. 24 peer-reviewed RCTs and observational studies indicated 85% improvement for prophylaxis (RR 0.15, 95% CI 0.05-0.30, n=6,356), 84% improvement for early treatment (RR 0.16, 95% CI 0.08-0.31, n=882), 36% improvement for late treatment (RR 0.64, 95% CI 0.43-0.94, n=1,338), and 72% overall improvement (RR 0.28, 95% CI 0.18-0.41, n=8,576).

On April 30, a preprint by Aguiri-Chang et al. described a therapeutic plan for patients with persistent symptoms [278].

On April 30, an interview with parliamentary managing director of the CSU, Tobias Reiss, called for the federal government to help with the adoption of ivermectin in Germany [279]. Reiss mentioned that unlike in the Czech Republic, ivermectin was not discussed in the German media. Reiss also said the FLCCC protocols which included ivermectin were used with favorable results at the Academic Hospital Brothers of Mercy in Munich. Reiss indicated he put more trust in the views of FLCCC, BIRD, and German and Czech scientists using ivermectin than the guidance of EMA and Merck & Co/MSD. According to Reiss, German scientists with experience on ivermectin had stated that “negative evaluations are not based on a thorough analysis of the current state of knowledge”. Also Bernhard Steinken, the chairman of the committee for health and care in the Bavarian state parliament announced CSU had begun campaigning for ivermectin to be trialed for COVID-19 in Germany [280].

In April, Bharti et al. published a qualitative analysis of seven ivermectin formulations in South Africa indicating that two of seven formulations contained altered active pharmaceutical ingredients such as paracetamol, diclofenac, telmisartan, diclofenac, hydroxyquine, mebeverine, nor-triptaline, ornipazolic, pregabaline, cephalexin and etizolam [281].

May 2021

On May 1, a medical doctor using a pseudonym Justus R. Hope published an ebook “Ivermectin for the Human” [282]. The book introduced pioneering of early human ivermectin use in the Dominican Republic, a statement by Jean-B Jacques Rajter, articles about court proceedings about ivermectin treatments in the US and in South Africa, an article about YouTube’s censorship practices, an open letter and a statement by Lawrie, an article about India, and several other articles.

On May 3, an analysis of the results of early treatment with an ivermectin-based medical kit in Mexico City by Merino et al. indicated a significantly lower hospitalization with ivermectin use, with approximately 70% lower risk of hospitalization [283], [284].

On May 4, a preprint by Karale et al. describing a systematic review and a meta-analysis of 30 studies indicated an overall mortality benefit (OR 0.39, 95% CI 0.22-0.70) and an even more significant mortality benefit in mild/moderate cases (OR 0.19, 95% CI 0.03-0.33) [285], [286].

On May 4, an article by Okumug et al. (the preprint of which had been made available on January 12) about a randomized controlled trial (n=66) about late treatment in Turkey compared low dose hydroxychloroquine, azithromycin and favipiravir with and without ivermectin, indicating 90% lower risk of no virological cure (15% vs 63%, p=0.002) on day 10 (NCT04646109) [287], [288].

On May 4, MedPage Today discussed cases in the US in which judges had ordered hospitals to give ivermectin to patients despite no evidence of efficacy and even though it wasn’t endorsed by federal health agencies [289]. The story mentioned potential side effects of the drug include nausea, vomiting and diarrhea, as well as facial or limb swelling, neurologic adverse events, a sudden drop in blood pressure, and liver injury, according to the FDA, as well as FDA’s warning against the use of veterinary forms of ivermectin and its stance that more studies are needed.

On May 4, a news story by Pfeiffer described the situation in the United States where hospitals were refusing to treat patients with ivermectin but in multiple cases, family members of the patients taking the hospitals to courts had resulted in the judges to order the hospitals to use ivermectin for those individual patients [290]. As a reason for their initial refusal, a hospital had stated that ivermectin use was not ethical because it was “not standard of care”, in addition to “not being an anti-viral medication”. Another had stated that ivermectin was not consistent with their guidelines based on “recommendations of professional societies, international government agencies and infectious disease expert opinions”. Asked about a specific patient not having receiving the treatment, a doctor was quoted saying: “That’s one life. I have a license to protect”. [291]

On May 5, referring to March 2021 guideline by the US National Institutes of Health and the studies by Lopez-Medina et al. and Beltran-Gonzalez et al., the European Centre for Disease Prevention and Control stated that ivermectin had not been shown to be effective against COVID-19 in clinical studies so far as it had not shown any statistically significant difference in neither outpatienta with mild disease nor in hospitalized patients with a non-critical disease [292], [293], [294].

On May 5, an insulino study by Qureshi et al. explored the inhibition of insulin-a by ivermectin with several computational methods [295].

On May 5, a review by Abdelgawad et al. mentioned that there was no published data about ivermectin’s efficacy or safety [296].

On May 6, the president of the Philippines had reportedly ordered a 1,200-patient, six-to-eight month RCT on the efficacy of ivermectin on the early treatment of mild-to-moderate disease [297], [298].

On May 6, FLCCC organized an expert panel discussion about standing up for human rights in COVID-19 care [299]. Panel members were Barend Yus (South Africa), Michael Defensor (Philippines), Jackie Stone (Zimbabwe), Ralph C. Lorigo (US) and Jean-Charles Teissedre (France). Kory said that “we are working in a system which is not working for us . . . in which therapies are being restricted and deprived from patients . . . ivermectin is probably the most absurd example of a system that is completely dysfunctional and failing . . . we have to try to figure out how to correct that”. Teissedre, a criminal law attorney working in Bon Sens [300] and also working for an alliance of 900 doctors in favor of ivermectin, had been working on obtaining a recommendation for ivermectin in France since October 2020. The problem was that France and similar countries had “lost their power to decide”. It was not a problem of supply or manufacturing but of prescribing and lack of a national guideline. According to Teissedre, creating such a guideline appeared “blocked” by the health authorities which was “difficult to understand”, yet in France judges didn’t want to legislate on matters that they thought of as science and medicine. The legal action for a guideline had ended unsuccessfully but another legal action for freedom of prescribing was ongoing. In addition, Teissedre was collecting evidence of scientific fraud for a judge to investigate on. Teissedre said the doctors pay attention to national guidelines only; he
acked that “maybe they don’t read studies, maybe they can’t do that. maybe they don’t know [how to], it’s a big problem” that “if doctors would be a little bit brave, the pandemic would be over now with ivermectin”. He said there is not only the corruption by the industry but also “a psychological effect of the doctors”.

Lorigo, an US lawyer, had been litigating against US hospitals in order for patients to obtain ivermectin in hospital settings since January 2021. Utilizing FLCCC research materials he had successfully represented at least one patient in federal court, and the result had been threatened by expulsion from a national research group if she had mentioned ivermectin there again. Stone wanted to encourage physicians to stand up to the regulators; in her hearing, it had become apparent that her well-prepared legal team had an opportunity to sue the regulator which, after presentation of all the evidence by Stone’s team, had become unable to argue against ivermectin.

Kory said that “the fact that we are at war against COVID-19 and [public health authorities] are putting up those peacetime regulations: it’s not how war works. You don’t follow peacetime regulations at war . . . we all keep talking about guidelines as if the guidelines are how we are going to win this . . . NIH guidance clearly state that they are not mandates . . . physicians don’t have to follow the guidelines . . . they invite you in a doctor’s decision model to use your expertise, ability, your understanding of the evidence . . . you still have autonomy . . . many physicians see them as mandates and are very fearful of straying from them . . . it’s not what those documents are for . . . it’s time to recognize that and take back some of that autonomy”. Kory concluded that “we are progressing . . . it’s time for civic, social organizations around the world to step up and lead”.

On May 6, a preprint by Marhamick described the conclusions of the FLCCC’s review in the American Journal of Therapeutics [248], [236] as “a cruel hoax” [244].

On May 6, an article by Shahbaznejad et al. describing a multicenter double-blind randomized controlled trial with 69 hospitalized patients administered a single dose of 0.2 mg/kg of ivermectin in Iran (IRCT2011122440987N73) [305], [306]. Ivermectin reduced the frequency of lymphopenia, the duration of dyspnea and persistent cough and the mean length of hospital stay. One critical patient in the treatment group died within 24 hours of admission, causing the result to indicate increased mortality for ivermectin.

On May 7, the Bill and Melinda Gates Foundation announced that in contrast to its previous policy on defining COVID-19 vaccine related intellectual property of pharmaceutical companies, it had begun to support a “narrow waiver for COVID-19 vaccines during the pandemic” [307].

On May 7, an editorial by Nardelli et al. presented a meta-analysis of seven ivermectin studies, indicating lower mortality (2% vs 9%, OR 0.19, 95% CI 0.10-0.34, p<0.01, n=1,323) [308]. The authors noted that lower mortality may have been due to resolution of Strongyloides hyperinfection. They said that in an emergency situation, the use of a cheap medication without major side effects may be reasonable even if strong verification of its efficacy is still lacking, and that results from the reported trials all point in the same direction and cannot be overlooked.

On May 8, FLCCC announced a new protocol, L-MASS, for mass prophylaxis of populations [309]. For prevention, 18 mg of ivermectin once a week, and 50 μg of vitamin D3 and a multivitamin daily were suggested. For outpatient treatment, 18 mg of ivermectin daily for five days, 6 mg of melatonin at night and vitamin D3. For post-exposure prevention, 18 mg of ivermectin on days 1 and 3 were suggested.

On May 10, a report stated that the rationale for a decision made in France by French medical authorities to reject ivermectin was undocumented, breaking transparency laws and making it impossible to trace who made the decision and through what kind of process [310], [311], [312], [313]. In response, 1,500 French physicians had signed a letter in protest. The organizer of the protest commented that ivermectin was subject to “special treatment . . . the ASNM [French Agency for the Safety of Health Products], WHO, EMA, NIH openly cheat, unreasonably, with the blessing of so-called democratic governments”.

On May 10, an article by Faisal et al. about a RCT with 100 participants in Pakistan indicated 6.4% lower risk of no recovery (12.0% vs 18.8%), RR 0.32, p<0.005 on days 6-8 (mid-recovery) [314].

On May 18, the state of Goa in India announced ivermectin will be distributed to all adults for prophylaxis [315]. The dosing was said to be 12 mg for five days. Some experts commented that five days was not enough and the medicine should instead be administered continuously until the pandemic was brought under control.

On May 11, the state of Karnataka in India announced one million ivermectin tablets had been procured and their supply was to begin on May 14 [315]. A further 2.5 million tablets were going to be procured for state hospitals.
On May 13, an interview of Didier Raoult discussed vaccines and corruption [331], [332]. Raoult noted that among the vaccinated there were fewer hospitalizations but not fewer deaths, adding that because the proportion of asymptomatic carriers remained extremely high the current data did not confirm that vaccination significantly reduced circulation of SARS-CoV-2. Corruption, he said, was an old as the world, and all of the current producers of vaccines had been convicted of corruption. Gilead had been fined USD 97 million, Pfizer USD 60 million, AstraZeneca USD 5.5 million, and also GSK. He described scientific publishing as a profitable business with profits of 35% per year, saying that a significant part of the revenue of premium journals comes directly from pharmaceutical industry, and as soon as a scientific journal reached a large enough audience it became a target of science akin to marketing. Raoult said it necessary to recreate the seal between public interest activities and the industry, and said he did not think that participating in industry-led trials contributed to knowledge, adding “it is not research to include patients in a trial carried out by the pharmaceutical industry, whose analysis is made by the pharmaceutical industry, whose methodology was decided by the pharmaceutical industry and even the publication of which was written by the pharmaceutical industry and then offered to and accepted in one of the biggest journals . . . we must return to science that contributes to knowledge . . . it is also necessary that ethics committees rather than looking at the methodology, should ask themselves questions about the ethics of clinical trials”.

On May 13, a news report from Hungary described that ivermectin tests in Hungarian hospitals had been going well and in a few months ivermectin would likely be prescribed off-label for COVID-19 outpatients in Hungary. The article said this would be a “major breakthrough”, as the pharmaceutical institute had so far explicitly banned anyone from using the drug for COVID-19, with the government even prosecuting a woman who had ordered a dose from South Asia. A local pharmaceutical company was beginning to produce generic ivermectin, and a 78-patient phase II clinical trial managed by the University of Debrecen was ongoing [333].

On May 13, an article by Konne et al. reviewed ivermectin and concluded that it could be a remarkable medical breakthrough for the lasting treatment of COVID-19 [334].

On May 14, Bogaizy et al., a group that in 2020 had carried out an ivermectin RCT in Egypt [335], [261], published a review of ivermectin and suggested that ivermectin could be used for mass chemoprophylaxis of populations with minimal risk [336].

On May 16, a commentary titled “Who’s advising WHO on the pandemic?” by a former president of Jamaica Medical Doctors Association criticized WHO for the hypocrisy of claiming to be attempting to save lives and ending the pandemic while at the same time recommending against the use of prophylactic and therapeutic options [337].

On May 17, a news report described a strong disagreement on whether the state of Goa in India should distribute ivermectin against the advice of the WHO [338].

On May 17, a presentation by Bryant et al. provided an updated version of the BIRD group’s ivermectin meta-analysis [339]. Twenty-four RCTs involving 3,466 participants met review inclusion. Meta-analysis of 15 trials found ivermectin reduced risk of death by 62% (95% CI 27%-81%) compared with no ivermectin (RR 0.38, 95% CI 0.19-0.73, n=2438, I² 2%); 2 trials found ivermectin reduced infections by an average 86% (95% CI 79%-91%). Estimates of moderate-certainty evidence found large reduction in mortality to be possible.

On May 13, the WHO’s chief scientist Soumya Swaminathan reiterated her and the WHO’s opposition to India’s ivermectin plan, linking to a statement by Berk & Co.-MSD claiming there is no evidence of efficacy but considerable safety risks [316], [154]. The report also said doctors across India were being pressured into giving drugs despite knowing that they are not effective against all forms of COVID-19 and irrespective of the patient’s medical history. The head of critical care of one hospital said that there was no evidence and that only two very poor quality studies studies exhibiting a very strong bias existed.

On May 12, in the FLCCC weekly update, Roxy again criticized the WHO saying they were hurting the global public health but stated he saw “a sea change” happening, with more attention paid to the failures of public health agencies, this criticism “supercharged” by the publication of the FLCCC’s review in the American Journal of Therapeutics which, in about three weeks, had reached a position in the top 250 of over 17,700,000 articles ever tracked by Altmetric, and the first position among approximately 1,200 articles of similar age in all journals [317]. The review was available on PubMed Central (PMC) with PMCID PMC8088823 but could not be found in the PubMed search portal and had no PMID assigned [318].

On May 12, the FLCCC issued a statement “on the irregular actions of public health agencies and the widespread disinformation campaign against ivermectin” [319], detailing flaws in WHO’s meta-analysis.

On May 12, a commentary by Bannister stated that an efficient medicine for COVID-19 would halt the international vaccine rollout under Emergency Use Authorization (EUA), endangered the profits of approximately USD 100 billion expected from vaccine sales in 2021 [320]. The author said that the WHO had either made serious mistakes or deliberately undermined early treatment drugs in favor of vaccinations, adding it was a huge windfall for vaccine manufacturers, with Pfizer set to receive approximately USD 70 billion from vaccines over the next five years according to Morgan Stanley. He said that an extension to the Trusted News Initiative (TNI) [321] in December 2020 had led to censorship of early treatments, adding that “almost every media house around the world has contributed to the marginalisation of ivermectin”.

On May 12, a news report stated that the state of Uttarakhand in India will mass distribute ivermectin as prophylaxis [315]. The dosing for people over 15 was said to be 12 mg twice daily for three days, a total of 72 mg. For children between 10 and 15 years the dosing was half of that. For children between 2 and 10 years ivermectin was to be administered only by prescription, and not administered at all to children below 2 years. Pregnant women and people suffering from liver diseases.

On May 13, a new report stated that the state of Odisha in India was to buy 720,000 ivermectin tablets for patients in isolation [322]. Despite the WHO guidance against ivermectin the state health department strongly recommended its use. A prophylaxis trial carried out at the All India Institutes of Medical Sciences (AIIMS) in Odisha in mid-2020 had indicated a 75% reduction of SARS-CoV-2 infection among healthcare workers for the following month after administration of 0.3 mg/kg ivermectin on days 1 and 4 (preprint published on November 3, 2020 [323], [324], peer-reviewed article published on February 16, 2021 [325]). A local professor commented that “there is no time to wait for a clinical trial during the ongoing emergency situation . . . ivermectin is an immune-regulatory and anti-parasite drug. It has proven to be effective in the given circumstances, it should continue to be used as certain studies show promising results”. The suggested dosing was 12 mg twice daily for three days.

On May 13, an article by Mahmud et al. described a randomized trial with mild-to-moderate disease treated with a combination of ivermectin and doxycycline with 185 patients in the treatment group and 138 control patients [326]. The results of which were initially published on October 9, 2020 [327], [328]. According to the Covid19Analysis group, the trial indicated 96% lower risk of no recovery on day 12 (23.0% vs 37.2%, RR 0.04, p<0.001), 57% lower risk of disease progression (8.7% vs 17.8%, RR 0.43, p<0.001) and 19.6% lower risk of no virological cure (7.7% vs 20.0%, RR 0.41, p<0.002) [329].

On May 13, ivermectin was officially included in the ACTIV-6 trial with 15,000 patients (NCT04885530) [320]. The estimated start date was May 2021, the estimated primary completion date December 2022, and the estimated study completion date March 2023.

On May 13, Campbell discussed the plans of the state of Goa in India to distribute prophylactic ivermectin for all adults [330].
of tweets posted by WHO African Region in the latter half of May; a majority concerned vaccines and the COVAX program. WHO African Region also retweeted posts by Gavi The Vaccine Alliance, and by Tedros Adhanan Ghebreyesus which celebrated WHO’s partnership with COVAX.

On May 18, the Times (UK) wrote that Bill Gates had sought the help of the convicted sex criminal Jeffrey Epstein to help connect influential people in order to improve chances of winning the Nobel Peace Prize [342] [343]. Another report wrote that what a former employee had said was the prize “what Bill wants more than anything else in the world” [344].

On May 19, an opinion article by Mookim in Wired magazine wrote about Bill Gates “vaccine colonialism” and “intellectual property shibboleth”, saying “the question is not whether people in rich Western countries will be prioritized over people in the Global South. Rather, it’s whether large Western corporations will benefit to the detriment of people everywhere” [345]. Mookim noted that the Biden administration had recently come out in support of waiving intellectual property rights to coronavirus vaccines, after which the Bill and Melinda Gates Foundation also had reversed course and endorsed the patent waiver [307] but Bill Gates himself had not. The article described that a WHO initiative, a patent-free technology sharing pool C-TAP announced in early 2020 would have removed intellectual property barriers for accessing COVID-19 treatments and vaccines but Gates, “maintaining his steadfast commitment to intellectual property rights”, had blocked the plan in order for companies to retain exclusive rights through Gates-initiated COVAX program, regardless of the vaccines and medicines having been developed largely with public funding. Mookim described that COVAX “enshrines monopoly patent rights and relies on the charitable whims of rich countries and pharmaceutical giants . . . should we be surprised that a monopolist-turned-philanthropist maintains his commitment to monopoly patent rights as a philanthropist too?” Mookim recounted Gates’ anticompetitive practices at Microsoft, calling him a “ruthless monopolist”, adding that “he chose to launder his reputation by tried and true philanthropic giving. But as he pivoted to global health, his faith in exclusive IP rights remained unchanged”. Mookim also recounted Gates’ opposition to generic AIDS medicines for Africa, his two-decade advocacy of anticompetitive public health policies, and the Gates Foundation’s continuing acquisitions of substantial intellectual property, also throughout the pandemic. In 2020, Gates was said to have leveraged his USD 750 million donation to Oxford University to convince it not to open-license its COVID-19 vaccine. As anticompitive public health policies, and the Gates Foundation’s continuing acquisitions of substantial intellectual property, also throughout the pandemic. In 2020, Gates was said to have leveraged his USD 750 million donation to Oxford University to convince it not to open-license its COVID-19 vaccine.

On May 23, the First International Ivermectin Summit was organized online by the BIRD group (Brazil, Canada, Malaysia, South Africa, Vietnam) with the stated completion date December 2021. The report also covered recent experiences in India, quoting an Indian official from the Ministry of Health of Malaysia presented current research evidence on ivermectin and criticized Malaysia’s lack of adoption of it [349].

On May 20, a news report stated that the University of Minnesota was adding ivermectin to an ongoing outpatient trial with hypoxia, emergency department utilization and post-COVID-19 syndrome prevalence as primary endpoints (NCT04510194) [352]. The trial, with an estimated enrollment of 1,100 patients, included arms for metformin, fluvoxamine, ivermectin, metformin and fluvoxamine, metformin and ivermectin, and placebo. Estimated primary completion date was October 2021 and estimated study completion date December 2021.

On May 23, the First International Ivermectin Summit was organized online by the BIRD group [353] [354]. The speakers included Martin Gill (South Africa), Jackie Stone (Zimbabwe), Sabine Hanan (US), David Scheim (US), Jennifer Hibberd (Canada), Lucy Kerr (Brazil), Kylie Wagstaff (Australia), Tess Lawrie (UK) and Thomas Borryco (Australia).
Gill said the front line doctors are left to what they have, and have to repurpose drugs and come up with protocols that will work. As soon they find one that is working they do a small trial because they need to get information out so that it will be further researched and used around the world. Gill said these small studies that can be used for decision makers but for researchers to have a guideline of what to research. He said the situation with ivermectin was unique due to data on ivermectin being way beyond the point of needing further data since no further data was unlikely to change the conclusion that ivermectin worked so well that it could change the course of the pandemic.

Stone presented her experiences with severe cases and described that early treatment with high doses with titration to effect and with a combination therapy utilizing zinc and doxycycline had improved results in comparison to ivermectin only. She said combination therapy reduced oxygen requirements, an important factor since they often did not have access to oxygen. She said their “hospital at home” approach had resulted in a mortality rate approximately 90% lower in state hospitals, adding that the mortality rate in moderate to severe inpatients should be less than 1%. She described a few patient cases, stressing the importance of early anticoagulation, aggressive diabetes control, and home nursing on oxygen, adding that the response was a dose dependent. She also said D-imer was a marker of clot breakdown and an increase in D-imer indicated recovery instead of deterioration. They had developed a treatment protocol (0.3-0.6 mg/kg ivermectin, ceftiraxone, dexamethasone, zinc, doxycycline, prednisolone, enoxaparin) that had been widely distributed in Zimbabwe so that nurses had learnt to treat patients following the protocol. A January 26, 2021 statement from Zimbabwe Ministry of Health had stated it was important to not deny patients effective treatment regimes. Stone said it was “perhaps time we stood away from what the Northern hemisphere is doing because to be perfectly honest it doesn’t really look like it’s working”.

Hanan said her team had carried out one of the first ivermectin trials. Hanan had used “Ziverdom” protocol consisting of 12 mg of ivermectin on days 1, 4 and 8, 100 mg doxycycline BID, 50 mg of zinc, 3000 IU of vitamin D, and 3,000 mg of vitamin C. Some of her patient cases had been described in the local press [355]. She stressed the importance of “making the patients feel that you are trying to save them” and the importance of combination therapy. Sheem presented an analysis of ivermectin distribution in Peru, describing that introduction of ivermectin had first caused a 14-fold reduction in excess deaths of people over 60 years old, and subsequent restrictions introduced by a new president had caused a 13-fold increase; respectively. Community mobility, household densities and seropositivity rates were considered as confounding factors. One state with ivermectin distribution differed sharply from states with distribution (74% vs 25% reductions in excess deaths. p<0.02).

Hilbreed presented world data on ivermectin collected by her and Juan Jose Chamie. According to her, India’s second wave started from the city of Mumbai in the state of Maharashtra, and from the state of Punjab (originating from Pakistan). Migrant workers fleeing from Mumbai spread the virus especially to the city of Lucknow in the state of Uttar Pradesh. New viral variants were detected in regions where ivermectin had been implemented in pattern also noted for other countries including the UK, South Africa and Brazil. The media represented these as very effective and ivermectin as unproved and outdated. On April 21, 2021, the national guideline was updated to include ivermectin. Initially death rates stabilized and case counts dropped in Maharashtra and Uttar Pradesh. In Tamil Nadu, a state without ivermectin distribution, deaths and case counts had continued increasing. In Mexico, according to Hilbreed, the pandemic was under control, with ivermectin being the main factor in enabling India’s second wave to happen.

Kerr reviewed the pathophysiology of COVID-19 and mechanisms of action of ivermectin. Kerr was the leader of a group “Doctors for Life” with 12,000 members in Brazil. The group was teaching principles of anticoagulation and with a combination therapy utilizing zinc and doxycycline had improved results in comparison to ivermectin only. She explained that since ivermectin was a host acting agent it was effective and ivermectin as a host acting agent it was required. Ivermectin also accumulated in the lungs and other tissues. She said they were looking whether ivermectin analogues possessed similar effects.

Lawrie said researchers had a fundamental moral obligation to share preliminary results through pre-publication mechanisms. Journals were not to hinder the sharing of data, and WHO’s normative guidance was on health emergencies also encouraged sharing. According to Lawrie, in the case of ivermectin there had been no support to low-and-middle income countries and their clinician-researchers, no editorial support from journals, nor financial support from public health authorities. Instead, the response had been characterized by a systematic denigration of the quality of studies, systematic handiencing to publication, and systematic disinformation and censorship from public health authorities, pharmaceutical companies and the “big tech”. In the UK, National Institute for Health and Care Excellence (NICE) had been silent on ivermectin although according to Lawrie evidence for it had existed at every level of the evidence pyramid. In contrast, the use of remdesivir and some other pharmaceuticals had been authorized in the UK on very little evidence. She said the latest meta-analysis by Karale et al. [265] supported the conclusions of the BIRD group. She also mentioned the Cartaeh protocol of Honduras [70] and the experience of Mexico [294]. International doctors’ groups in favor of ivermectin included FLCCC, BIRD, Doctors for Life (Brazil), Canadian Covid Care Alliance, UK Medical Freedom Alliance, Association of American Physicians and Surgeons (AAPS), Johnsorganate, United Health Alliance, and HART. According to Lawrie, major opponents to ivermectin were the ALT-Accelerator with USD 38.1 billion funding, and the Trusted News Initiative (TNI).

On May 24, a Finnish company Therapeutica Borealis got a US patent for a nasal spray containing ivermectin, hydroxychloroquine and aprotinin, a protease inhibitor [356]. The company said active ingredients were used in a new, targeted manner on the upper respiratory mucous membrane, so that the concentrations of the active ingredients throughout the body remained very low but were sufficient locally to prevent the passage and replication of the virus, making the drug safer and more effective. On May 24, FLCCC announced that they had been locked out of their Twitter account for “violation of Twitter rules” [357].

On May 24, a Belgian virologist with experience in vaccine research and development in several pharmaceutical companies, the Bill and Melinda Gates Foundation, Gavi The Vaccine Alliance and the WHO, Geert Vanden Bossche, presenting a review of unsolved issues in COVID-19 vaccine related immunology, proposed early multifrug treatment (with e.g. ivermectin as one of the components of an early treatment kit) as a way out of the “mismatched pandemic” [355, 359]. Bossche said it was “difficult to imagine how [‘updating’ vaccines] could solve the problem of immune escape SARS-CoV-2 variants”. Bossche referred to a steadily growing community of world-class scientists and experts calling for an immediate halt to the mass vaccination campaigns as the only method. Instead, early treatment proven highly efficient, practical and cost-effective should have been made widely available. He said quick ‘updates’ of the current Covid-19 vaccines would most likely fail to solve the pandemic because they were still based on an immunological concept and mechanism that didn’t address the risk of evolutionary immune escape. He predicted SARS-CoV-2 to become resistant to current vaccines and asked the vaccine community to develop vaccines with a different mechanism of action. Regardless, he predicted that it would be impossible to rely on an asymptomatic viral large scale community spread that can be made available in high quantities at low cost, adding that ivermectin would seemingly qualify. He concluded that “a well-coordinated and targeted drug treatment program could be a game-changer and turn the tide of this pandemic in that it could drastically reduce the chain of viral transmission, not least in vaccines. Whether sensitively targeted virucidal chemoprophylaxis will provide populations with sustained protection from COVID-19 in the post-pandemic era and hence, serve as a full-fledged substitute for herd immunity is likely but uneven. Virucidal chemoprophylactics seems, however, a promising option, the effectiveness of which could rapidly be explored at low cost and without raising the type of safety concerns that are associated with the ongoing mass vaccination campaigns”.

On May 24, entrepreneur Steve Kirsch, who had earlier founded a COVID-19 Early Treatment Fund (CETF) which had funded fluvoxamine trials [346], offered his US$ 1 million purse for any peer-reviewed, licensed physician, medical journal editor, NIH or WHO employee, mainstream media reporter, elected official, public health official, or YouTube or Twitter CEO who would provide a convincing argument working in conjunction with immune system. Therefore, 1:1 ratio of drug to virus was unlikely to be required. Ivermectin also accumulated in the lungs and other tissues. She said they were looking whether ivermectin analogues possessed similar effects.
null
On May 28, a news report in Forbes India said that drugs such as ivermectin continued to be on India’s health ministry’s treatment protocol despite evidence not inspiring confidence, and that the regulator was approving medicines without following due scientific process, experts had said [398]. According to a director of critical care at a major hospital and a member of state of Maharashtra’s COVID-19 task force, only corticosteroids and oxygen were backed by evidence. A pulmonologist said hydroxychloroquine and ivermectin needed to be taken out of the treatment protocol and called for an all-India committee with government, private players and central institutes to finalize treatment protocols. He saw promise in two new antibody cocktails that had recently received emergency use authorizations. These products were said to be priced at approximately USD 900.

On May 29, an American weekly wrote about ivermectin, describing it as having a high efficacy, yet being opposed by WHO and the “mainstream” [391].

On May 29, a news report from Spain interviewed José Muñoz who was initiating an 800-patient clinical trial on ivermectin [392]. Muñoz said they had been trying various drugs for 1.5 years and so far the success had not been equivalent to that of vaccines and that they now wanted to trial high-dose ivermectin.

On May 30, in a blog post citing FLCCC materials, bishop Thomas Schirrmacher, the president of the International Council of the International Society for Human Rights (ISHR) and the secretary general of the World Evangelical Alliance (WEA) which networks churches with 600 million conservative Protestant Christians, stated that ivermectin treatments are safe and effective and could save many lives and speed economic recovery [393].

On May 31, the FLCCC announced it had regained access to its Twitter account but Cision PRWeb and PR NewsWire had announced they would no longer distribute FLCCC’s press releases. YouTube had also removed two more videos by FLCCC.

On May 31, version 85 of the CoriCatalysis group’s meta-analysis indicated that all 17 RCTs for prophylaxis and early treatment reported positive effects, with an estimated 85% improvement for prophylaxis (RR 0.17, 95% CI 0.05-0.61, n=1,974) and 75% improvement for early treatment (RR 0.27, 95% CI 0.18-0.41, n=1,820) [394]. For late treatment, eleven RCTs indicated 42% improvement (RR 0.58, 95% CI 0.38-0.90, n=1,197). Together, all 28 RCTs indicated 66% improvement (RR 0.34, 95% CI 0.24-0.50, n=922). Together, the nine mortality trials indicated 66% improvement (RR 0.34, 95% CI 0.17-0.67, n=1,798). Together, all of the 56 RCTs and observational studies indicated 72% improvement (RR 0.28, 95% CI 0.21-0.36, p<0.000000000000044, n=18,447).

June 2021

On June 2, the FLCCC updated its e-IHASS protocol intended for mass prophylaxis [395, 396]. Ivermectin dose for outpatient treatment (daily for five days) was raised from 18 mg to 24 mg.

On June 2, a RCT with 164 patients by Abd-Elsalam et al. failed to produce statistically significant results [397].

On June 3, Wang et al. (a group including Andrew Hill) reviewed production costs of potential repurposed drugs for COVID-19, including dexamethasone, ivermectin, dolutegravir, budesonide and colchicine [398]. They noted that repurposed therapies could be generally manufactured at very low per-course costs, for example USD 0.12 for ivermectin. They concluded that the analyzed drugs were widely available and affordable, and that successful management of COVID-19 required equitable access to treatment for all populations, not just those able to pay high prices.

On June 6, a systematic review and meta-analysis of 19 RCTs with 2,768 patients by Haryanto et al. indicated that ivermectin was associated with 69% reduction in mortality (RR 0.31, 95% CI 0.15-0.62, p=0.001), 57% reduction in severity of COVID-19 (RR 0.43, 95% CI 0.23-0.81, p=0.008), higher negative test result rate (RR 1.23, 95% CI 1.01-1.51, p=0.04), shorter time to negative test result (mean difference -0.68, 95% CI -1.07 to -0.29, p=0.007) and shorter time to hospital discharge (mean difference -2.66, 95% CI -4.49 to -0.82, p=0.004) [399]. The authors concluded that more randomized clinical trial studies were still needed to confirm the results.

On June 7, in a blog post in the Science Magazine, Lowe wrote that while it was not important to know the mechanism of action, the trials he had reviewed had used doses far too low in comparison to the required level in vitro [397], the WHO had done a solid job in evaluating the literature [400], the JAMA study [411] had found no benefit, the issue reminded him of the hydroxychloroquine situation, and he was “not having it with people going the conspiracy theory route” [400].

On June 7, the Union Health Ministry and Family Welfare’s directorate general of health services (DGHS) issued revised guidelines to stop the use of ivermectin and dexamethasone in India [401]. The new guidelines dropped all medicines, except antipyretic and antiviral, for asymptomatic and mild cases, while remdesivir was reserved only for patients hospitalized with moderate or severe disease receiving supplemental oxygen [402]. The guidelines of the Indian Council for Medical Research (ICMR), the country’s leading health agency in the fight against COVID-19, remained unchanged, optionally suggesting ivermectin for outpatient.

On June 7, an article by Gluchowska et al. discussed whether parasitic diseases were protective agents or risk factors in COVID-19, noting lower incidence of COVID-19 in most African countries, especially those where malaria is endemic, and speculating that parasites might have also beneficial immunomodulatory effects but also noting that the difference may be due to hydroxychloroquine and chloroquine prophylaxis [403]. They however did not mention the possible effect of ivermectin prophylaxis pointed out by Guerrero et al. [404].

On June 7, in Malaysia, a news report said a complaint had been filed accusing the health minister and the health director-general of refusing to adopt ivermectin for COVID-19 [405].

On June 8, a news report by Birrell discussed conflicts of interest of scientific journals, suggesting that open access journals published by Springer Nature and Elsevier depended on donations of China and access to the Chinese market, which may have led to publication bias [406].

On June 8, in Japan, Constitutional Democrats submitted a bill to the House of Representatives to allow use of existing drugs including ivermectin to treat COVID-19 [407].

On June 9, a news report said the US government had agreed to pay USD 1.2 billion for 1.7 million courses (USD 709 per course) of Merck & Co/MSD’s molnupiravir, if it is proven to work in an 1,850-patient trial expected to complete in the fall of 2021, and emergency use authorized by U.S. regulators [408]. Other drugs in development included Pfizer’s PF-07321332 and Roche Holding AG’s AT-527.

On June 9, the chief minister of the state of Goa in India said that the government of Goa had not purchased a single tablet of ivermectin and that it had been dropped from the treatment protocol, despite an earlier announcement of the Health Ministry on May 10 to distribute it for mass prophylaxis in Goa [409] [410]. Instead, a plan to vaccinate as many people as possible in the age group 18-44 years was announced [411].

On June 12, an article by Zaheer et al. stated that potential toxicity and careful dosage analyses are urgently required before declaring ivermectin as an anti-SARS-CoV-2 drug candidate [412].

On June 14, a Canadian newspaper published an interview of Edward Mills, the principal investigator in the Canadian Together trial led by McMaster University, with funding for ivermectin and fluoronamidine provided by Faust Grant [413]. Mills discussed the possibility of repurposing medicines, and the possible role of repurposed medicines, criticized the FLCCC for overcalling the importance of what they were doing, and held a neutral stance about ivermectin. He expected the ivermectin trial to complete in a few months.

On June 14, an editorial commentary by Siesler introduced a meta-analysis by Hill et al. to be published in the same issue [414]. The meta-analysis was said to include 24 studies and 2,127 participants for mortality outcome. Siesler described the results as “compelling, … suggesting a modest to large benefit of a low-cost, widely available, well-tolerated therapy for COVID-19 – a dream scenario” – but based on studies with small sample sizes, design flaws, incomplete results, or some combination thereof. He worried about possible “erosion of trust in the scientific community” due to “early support for therapies based on studies with small sample sizes, design flaws, incomplete results, or some combination thereof”.
prior to a solid evidence base" and stressed the need for larger trials, mentioning that “the best we can do is guess the mechanism of action”. He concluded that ivermectin might be best considered as an extremely promising therapy not quite ready for public use; otherwise, there would be “a real risk that the scientific community will once again be befooled by over-enthusiasm and forced to answer to a public that will not be shy about holding us to account”.

On June 15, a review by Zaidi et al. provided an extensive review of 20 mechanisms of action of ivermectin for SARS-CoV-2 on four levels: first, direct action on SARS-CoV-2, including action on SARS-CoV-2 cell entry, action on importin superfamily, and action as an ionophore; second, action on host targets important for viral replication, including action as an antiviral, action on viral replication and assembly, action on post-translation processing of viral polyproteins, and action on karyopherin (KPNA, KPNI) receptors; third, action on host targets important for inflammation, including action on interferon (INF) levels, action on toll-like receptors (TLR), action on nuclear factor-XB (NF-XB) pathway, action on the JAK-STAT pathway, PAL-1 and COVID-19 sequelae, action on P21 activated kinase 1 (PAK-1), action on interleukin-6 (IL-6) levels, action on allostERIC modulation of P2X4 receptor, action on high mobility group box 1 (HMGB1), action as an immunomodulator on lung tissue and olfaction, and action as an anti-inflammatory; fourth, action on other host targets, including action on plasmin and annexin A2, action on CD347 on the red blood cells, and action on mitochondrial ATP under hypoxia on caracal function. [415], [416]

On June 15, an article by Aref et al. about a RCT with ivermectin containing nasal spray in Egypt (n=114) indicated 63.2% lower relative duration of fever (relative time 0.37, p=0.001) and 78.6% lower risk of no virological cure [HR 0.21, p<0.004, 5.7% vs 24.4%] (NCT03715809) [417], [418].

On June 15, a commentary by Thakur in an Australian newspaper questioned the “lack of alternative treatments” required for emergency authorization of vaccines, suggesting that a significant number of specialists have pointed out benefits of prophylaxis and early treatment with ivermectin [419].

On June 15, adoption of ivermectin had been recently petitioned for in Namibia [420].

On June 16, a private clinic was raided in Malaysia for offering ivermectin to COVID-19 patients [421].

On June 16, FLCCC introduced a new protocol, I-RECOVER, for long haul COVID-19 syndrome (LHCS) [422], [423]. The protocol consisted of an initial therapy with 2-0.4 mg/kg of ivermectin for 3-5 days, added with 50 mg of fluvoxamine twice daily for 15 days if the patient was presenting with neurological symptoms. If not all symptoms resolved with ivermectin, an additional corticosteroid protocol was introduced. Early corticosteroids did not produce a resolution, suspected mast cell activation was to be treated with low histamine diet, antihistamines and mast cell stabilizers and possibly other drugs. For all patients, vitamin C, omega-3 fatty acids, atorvastatin and melatonin were suggested.

On June 17, a news story by Zimmer in the New York Times said the U.S. government was to invest USD 3.2 billion to develop antiviral pills for Covid-19 and other viral diseases [424]. The new influx of money was to speed up the clinical trials of a few promising drug candidates which were said to become available within a few years.

On June 17, an article by Gordon et al. suggested that many long haul COVID-19 syndrome (LHCS) symptoms may not be a direct result of the SARS-CoV-2 virus but the result of COVID-19 inflammation-induced Epstein–Barr virus reactivation [425].

On June 18, an analysis by Lind et al. from the COVID-19 response team of the US Centers for Disease Control and Prevention (CDC) analyzed ivermectin prescriptions in the US during the pandemic and found that ivermectin dispensed from outpatient retail pharmacies increased from an average of 3,569 prescriptions per week at the pre-pandemic baseline to a peak of 39,102 prescriptions in the week ending on January 8, 2021 (989% relative percent increase) [426]. The authors stated that clinicians should be aware of the stances of FDA and NIH, and that better trials are needed.

On June 18, an opinion article by Reyes discussed the situation in Jacmel, with the government wanting to follow WHO’s advice in order to protect the public against possible dangers of ivermectin [431].

On June 18, an opinion article by Gordon discussed the situation in South Africa, indicating that while ivermectin was approved for COVID-19, the process of applying for an individual permit for each patient was unreasonably restrictive and as a result ivermectin was not being widely used [422].

On June 18, in a WHO media briefing, in a reply to a question about the possible relationship between ivermectin home treatment kit distribution in Mexico and the decline in COVID-19 cases and deaths (study by Merino et al. [284]), COVID-19 technical lead Maria Van Kerkhove said that the decline was likely a result of a combination of factors, that WHO only recommends ivermectin in clinical trials, that WHO’s clinical management team led by Janet Diaz were constantly looking at all ivermectin studies, there were meta-analyses adding more studies as their results were becoming available, those meta-analyses being updated regularly, and after the meta-analyses providing “robust, comprehensive review” were updated the WHO would be looking at the recommendations again to decide what the guideline development group “can and cannot, should and should not recommend”. She said the process was underway and updates would be coming soon [433]. Also the chief Scientist Soumya Swaminathan pointed out that epidemiological changes were usually due to combinations of things, never due to a single intervention, and peaks in infections had fallen for various reasons, also in countries not using ivermectin. She said it was important to undertake properly designed studies, adding that “we must have an open mind, and the WHO certainly has an open mind to look at each and every intervention that could be beneficial”. Unfortunately there are not very high quality trials yet conducted about the role of ivermectin in either prevention or treatment, and this is what our guideline development group pointed out. When they looked at the meta-analysis, the studies were all very low quality, and therefore what is needed is more evidence. … we encourage more research on this … the jury is still out on this.”

On June 20, a news report by Jaswal analyzed the failure of Goa’s ivermectin distribution plan [434]. Earlier, the ICMR had allowed optional use of ivermectin for outpatients with a mild disease. Subsequently, with the intention of prophylaxis, the health minister of Goa had announced a mass distribution of ivermectin. Goa’s political opposition soon framed the operation as a financial scam. WHO’s chief scientist Swaminathan and a group of prominent medical institutes of hospitals announced ivermectin should only be used in clinical trials. Petitions were filed in the high court against the plan, leading the scientist Swaminathan and a group of prominent medical institutes of hospitals to announce that ivermectin was available over-the-counter. ivermectin was available over-the-counter.

On June 20, a news report stated that Goa’s directorate of health services has instructed health centres and hospitals across the state to remove ivermectin, zinc and doxycycline tablets from COVID-19 home isolation kits [435].

On June 20, a 16-minute television report on Fox News featured US senator Ron Johnson and FLCCC’s Kory presenting their view on ivermectin and censorship. Commenting the week’s announcements of US government investing USD 3.2 billion in new antivirals for early treatment, Kory said “they will never develop a drug that is more effective than ivermectin” [436].

On June 22, a systematic review by Murch et al. about the effectiveness and safety of various pharmacological and nonpharmacological interventions in the ambulatory setting, aimed at preventing severe COVID-19, found very low certainty evidence of effect for ivermectin plus doxycycline and insufficient evidence of effect for ivermectin monotherapy [437].
On June 22, a news report said that the National Agency of Drug and Food Control of Indonesia (Badan POM) had licensed ivermectin for the treatment of COVID-19 [438]. General Moeldoko, the chief of staff of the Executive Office of the President of the Republic of Indonesia, was said to have celebrated the decision. In the previous weeks he had already distributed tens of thousands of doses to various red zone locations.

On June 22, a news report from Argentina described monitoring results of 4,000 patients provided by the ministry of health of the province of Misiones, saying that in comparison to untreated population, ivermectin had reduced hospitalization from 4.7% to 1.2%, and mortality from 1.7% to 0.2% [439]. The effect was dose dependent.

On June 23, a news report said Oxford University was testing ivermectin in its large-scale ‘Principle’ trial [440]. The intent to include ivermectin in the trial had initially been reported on January 23 [441].

On June 23, Warren Buffett announced his resignation as the trustee at the Bill and Melinda Gates Foundation, describing his previous role as the trustee as “inactive” [442].

On June 24, an article by Yuce et al. determined ivermectin as a MMP9 inhibitor candidate to be evaluated against SARS-CoV-2 infections [443].

On June 25, an article by Días de Molo et al. about an animal study showed that standard doses of ivermectin prevented clinical deterioration, reduced oedema deficit, limited the inflammation of the upper and lower respiratory tracts but had no effect on viral load in the airways in SARS-CoV-2-infected hamsters [444]. It dampened type-1 interferon responses, and dramatically reduced the IL-6, IL-10 ratio in lung tissue and promoted macrophage M2 polarization.

On June 25, in a video interview professor of biochemistry and molecular biology Gordan Lauc, an official advisor to the Croatian government on pandemic management strategy, discussed, among other subjects, COVID-19 testing [445]. Lauc commented that he continuously wondered what the reason was for the fall in SARS-CoV-2 respiratory viral load, which is the major driving force behind the pandemic from an economic perspective. He said that many people in the world were counting on this fall, which was a significant factor for the economy. The test result was virtually zero, so the test producers, distributors, laboratories make a profit. There is a 99% profit margin on all levels. Lauc also said that he had a PCR laboratory, he knew the technology. The raw cost of testing is virtually zero, so the test producers, distributors, laboratories make a profit. There is a 99% profit margin on all levels. Lauc also said that he had a PCR laboratory, he knew the technology. The raw cost of testing is virtually zero, so the test producers, distributors, laboratories make a profit. There is a 99% profit margin on all levels. Lauc also said that he had a PCR laboratory, he knew the technology. The raw cost of testing is virtually zero, so the test producers, distributors, laboratories make a profit. There is a 99% profit margin on all levels. Lauc also said that he had a PCR laboratory, he knew the technology. The raw cost of testing is virtually zero, so the test producers, distributors, laboratories make a profit. There is a 99% profit margin on all levels.
had adopted ivermectin previously; including Slovakia, implicitly disregarded the March 2021 guideline set by the WHO [171] [457]. India adopted ivermectin nationally after the announcement of the WHO guideline, then mostly dropped it, with the current situation being somewhat unclear. Legal action against WHO was initiated in India. At the end of the period, Indonesia also adopted ivermectin.

With regard to researchers and clinicians, medical professionals whose practices appeared to be predominantly based on following existing regulations and protocols appeared to feel engaged against them unjustified and unfair. Similarly, medical professionals whose interest was in the further development of their profession were driven against them unjustified and unfair. The former group may have perceived the latter group as deviants, whereas the latter group may have perceived the first group as anti-innovative. Presumably, both groups saw each others’ practices as somewhat unethical and antisocial. The difference was possibly due to different perspectives on collegiality and the perception of the role of patients. The first group appeared to put more weight on collegial cohesion and rule-adherence, with less weight put on individual patient outcomes, assumedly perceiving that patient outcomes were predominantly the product of the inflexible regulations which lay beyond their responsibility. The second group appeared to put less weight on collegial cohesion and regulations, placing more weight on individual patient outcomes, assumedly perceiving that patient outcomes superseded the rules and that validation of rules was the responsibility of individual clinicians.

With regard to COVID-19 knowledge about the mechanisms and treatments was somewhat scarce especially in the early phase of the pandemic. A recent study described in such a situation, it would be adaptive to seek further information to resolve uncertainty and obtain a more accurate worldview but biases in such information-seeking behavior could contribute to the maintenance of inaccurate views [458]. The study indicated that more dogmatic individuals were less likely to seek out new information to refine an initial perceptual decision, leading to a reduction in overall belief accuracy despite similar initial decision performance. In addition, dogmatic participants placed less reliance on internal signals of uncertainty, rendering them less likely to seek additional information to update beliefs derived from weak or uncertain initial evidence. Dogmatism is often defined as a viewpoint or system of ideas based on insufficiently examined premises. Thus, differences in openness to research evidence may have been due to differences in personalities and habits which, in turn, may be seen as products of the life experiences (environments) of the individuals, including their medical education.

At times, the views appeared to differ up to a point in which the existence of a shared reality could be questioned, and the practice of presenting opposite conclusions on the same, existing data was in effect making further research irrelevant.

Validity of statistics-based research

In the context of clinical trials, the fundamental validity of the statistics-based research in general is rarely discussed. In 2011, Penston said that the extent and depth of the criticisms of statistics-based research usually comes as a surprise to investigators, doctors and other health care professionals who use the data from large-scale RCTs and epidemiological studies, as they rarely have the time, inclination and skill to read the related literature [459]. He questioned the large size of a study as a sign of strength, saying that as the number of patients recruited to a study increases, statistical significance may be achieved but causal inference is weakened, adding that the source of the problem was the belief that causal relationships of value can be derived from extremely heterogeneous samples. He also said that the methodology of statistics-based research cannot be tested independently of statistics; therefore it is unknown whether the causal inferences drawn from the data of large-scale RCTs and epidemiological studies are valid. According to him, lack of understanding of diseases and the properties of drugs, i.e. ignorance, were driving up the size of studies, and we had witnessed “an inexorable increase in the size of epidemiological studies and RCTs over the past 50 years without any concern for the consequences”.

Saint-Mont discussed the effect of randomization, detailing various false assumptions related to it, concluding that randomization does not lift experimental procedures in the medical and social sciences to the level of classical experiments in the natural sciences but may still hinder researchers into a false sense of security instead [460]. Both Saint-Mont and Penston stressed the importance of the existence of sound background theory as crucial for the success of science. Theory allows for stricter definitions of concepts and the identification of homogeneous reference classes that ensure regularity and, hence, reliable causal inference. In the context of COVID-19, the FLCCC appeared to present their conclusions more in the context of background theory (especially the MATH+ protocol [271]), while most others appeared to rely more on statistics.

An alternative or adjunct to RCTs to investigate could be causal modeling [461], [462], [463], [464]. According to Sgaier et al., causal modeling allows testing for causality in individuals and population groups faster and more efficiently, along with the ability to unravel the underlying complexity, and allows researchers and program designers to simulate an intervention and infer causality by relying on already available data. [461] Karvonen has provided examples of causal models for a case-control study, a nested case-control study, a clinical trial and a two-stage case-cohort study [463].

Journalistic ethics

With regard to journalistic ethics, the censorship discussion of April 11 appeared to indicate that journalistic principles that should have been self-evident no longer were, such as the responsibility of the media “to tell the truth” [165]. As described already for the period preceding April 2021, the financial press (e.g. the Wall Street Journal [168] and the Financial Express [173]) seemed to be more in favor of repurposed medicines, whereas the generalist press mostly continued to ignore or oppose them [217].

MacLeod has written about practices of the mass media in the United States, stating that corporate shareholders have no interest in the veracity of the news, only in short-term profits, and that reporting that challenges corporate profits is strongly discouraged [465]. A key factor shaping the content of the media is its reliance on advertising from large businesses for revenue. Advertisers wish to appeal to the groups and individuals with a greater spending power and to avoid controversial and critical content. Also, the collapse in advertising revenue in the traditional media has led to an increasing dependence on official sources, government and corporations which effectively subsidize the media by providing free content but expect something in return. In addition, in many cases, journalists are preselected based on their obedience to authority and their credentials, and they increasingly come from the elite themselves [466]. The media houses also depend on social media for visibility which may be easily denied of them. Yet another factor are ideologies which in the United States were traditionally anti-communist but more recently anti-Trump and anti-Russian, for example. In the US media, ivermectin was often associated with hydroxychloroquine, and hydroxychloroquine with president Trump [467].

The dismissal of ivermectin in the press appeared to be related to the Trusted News Initiative (TNI) founded by Associated Press (AP), Agence France-Presse (AFP), British Broadcasting Corporation (BBC), Canadian Broadcasting Corporation (CBC), European Broadcast Union (EBU), Facebook, Financial Times, First Draft, Google, YouTube, The Hindu, Microsoft, Reuters, Twitter and Washington Post [321]. TNI appeared to function as some kind of peer-to-peer structured censorship mechanism.

Social media fact-checkers

In its COVID-19 medical misinformation policy, YouTube explicitly forbade treatment misinformation including “content that recommends use of ivermectin or hydroxychloroquine for the treatment of COVID-19” and “claims that ivermectin or hydroxychloroquine are effective treatments for COVID-19” [468]. The policy forbade also a large amount of peer-reviewed medical publications, in effect making YouTube an anti-science organization.

In a similar manner the policy forbade “prevention misinformation”, explicitly defined as “content that promotes prevention methods that contradict local health authorities or WHO”, specifically mentioning “content that recommends use of ivermectin or hydroxychloroquine for the prevention of COVID-19.” It also explicitly disallowed discussions of efficacy and possible adverse effects of vaccines which “contradict expert consensus from local health authorities or WHO”. Also diagnostic, transmission, social distancing and self-isolation information contradicting local health authorities or WHO were banned. The definitions of “expert” and “consensus” remained undefined, making the policy arbitrary, subsequently making YouTube an unpredictable promoter and enforcer of possibly arbitrary or authoritarian practices. In addition, technically, where local health authorities and WHO disagreed, application of the “or” operator in a similar manner the policy forbade “prevention misinformation”, explicitly defined as “content that promotes prevention methods that contradict local health authorities or WHO”, specifically mentioning “content that recommends use of ivermectin or hydroxychloroquine for the prevention of COVID-19.” It also explicitly disallowed discussions of efficacy and possible adverse effects of vaccines which “contradict expert consensus from local health authorities or WHO”. Also diagnostic, transmission, social distancing and self-isolation information contradicting local health authorities or WHO were banned. The definitions of “expert” and “consensus” remained undefined, making the policy arbitrary, subsequently making YouTube an unpredictable promoter and enforcer of possibly arbitrary or authoritarian practices. In addition, technically, where local health authorities and WHO disagreed, application of the “or” operator
banned content contradicting with either of them. Therefore in countries such as Slovakia and India, YouTube could not be used for content that recommended either for or against ivermectin for prophylaxis of COVID-19.

Clarke mentioned that YouTube and Facebook were relying on third-party fact checkers funded partly by Charles Koch Institute [372, 374, 372]. Koch was listed as one of the 18 major funders of Poynter Institute, each with an undisclosed sum of at least US$ 50,000, making it impossible to compare funders’ contributions [409, 478]. The International Fact-Checking Network (IFCN) is a unit of the Poynter Institute [472]. In May 2020, Facebook stated that all of its fact-checking partners were certified by IFCN [472]. IFCN stated it held an alliance of over 100 fact-checkers [473]. Poynter Institute described that the alliance was launched in January in response to “sensational misinformation globally” which the WHO classified as an “infodemic”, with the alliance “on the front lines in the fight against it”. IFCN and the alliance also maintained a database of checked facts [474]. The database was updated daily, with members collaborating on the “massive crowdsourcing project” by using a shared spreadsheet and instant messaging apps. Poynter said the international collaboration had allowed the members to respond faster and reach larger audiences. All of the over 80 items found in the database with search term “ivermectin” dated between April 2020 and May 2021 were labeled either as no evidence, unproven, exaggerated, misleading, missing context, partly false, or false (the most common label), with two items labeled as explanatory [474]. Most of the items originated from South American partners such as Estudio Verifica in Brazil. Some of the other major funders of Poynter included Facebook, Google News Initiative [475], Foundation to Promote Open Society (FPOS) of George Soros, a primarily US government funded agency National Endowment for Democracy (NED) [476], Democracy Fund created by ebay founder Pierre Omidyar, funding especially PointFact [477], and the Omicur Network Luminate also of Omidyar, Craig Newmark Foundation of Craigslist founder Craig Newmark, with at least USD 6 million donated to Poynter Institute [478], and Rita Allen foundation involved in medical research, with its stated goal of “investing in transformative ideas in their earliest stages to promote breakthrough solutions to significant problems” [479]. It was of note that the main funders of Poynter included several individuals who were billionaires. Anonymously, they may have possessed influence over guidelines for what qualified as “facts”. While there was not enough information to ascertain whether the observed patterns of social media censorship were related to the values and previously observed practices of the any of the funders specifically, it was also not possible to rule out such influences. An example may illustrate what kind of issues may arise from the use of donations as a tool for gaining political influence. With regard to funding by Koch, a report by Mayer in the New Yorker described the Koch brothers as “longtime libertarians who believe in drastically lower personal and corporate taxes, punctuating such policies with lawsuits for the newly, and much less oversight of industries”. Their combined fortune of thirty-five billion dollars is exceeded only by those of Bill Gates and Warren Buffett … many of the organizations funded by the Kochs employ specialists who write position papers that are subsequently quoted in Congress and, in some cases, published on the company’s websites. … Their combined fortune of thirty-five billion dollars is exceeded only by those of Bill Gates and Warren Buffett … many of the organizations funded by the Kochs employ specialists who write position papers that are subsequently quoted in Congress and, in some cases, published on the company’s websites.

A republican political consultant commenting Kochs’ strategies for opposing climate change related oil industry reforms said that “the key … was to question the science – a public-relations strategy that the tobacco industry used effectively for years to forestall regulation”. As an example of health related interests, David Koch had served on the US National Cancer Advisory Board without disclosing his conflicts of interests as a major producer of formaldehyde, while simultaneously lobbying to prevent the US Environmental Protection Agency (EPA) from classifying formaldehyde as a carcinogen, and funding members of Congress who had stymied the EPA, requiring it to defer new regulations until more studies would be completed. Mayer’s article described Kochs’ operations as “covert”, referring to David Koch’s description of their businesses as “the largest company that you’ve never heard of”. According to SourceWatch, in addition to denying climate change, other issues on the Kochs’ agenda included repealing health reform (Obamacare), dismantling collective bargaining rights, fighting reductions in carbon emissions, keeping corporate money in elections and fighting internet neutrality [482]; [483]. With regard to COVID-19, Koch Industries were producing test kit materials, sanitizers, alerting systems, healthcare IT systems related to COVID-19 diagnostic testing, ventilators, and personal protective equipment [484]. Poynter’s largest custom training partners in 2019-2021 included Facebook, Huffington Post, Marketplace, MRC Media, Middle East Broadcasting Network, National Public Radio (NPR), Newsweek, New York Times, Southern Newspapers Publishers Association, Washington Post, TikTok, USA Today Network, Vice and Voice of America [469].

Academic journals

Regarding the academic journal publisher Frontiers Media SA’s, one of the members of its board of directors responsible for the financial and governance oversight of the company was Steve Kolton, founder and co-chairman of CVC Capital Partners Ltd [485]. In 2019, CVC Capital Partners, one of the world's largest private equity and investment advisory firms, was said to have USD 75 billion of assets under management [486]. CVC announced that a group of its executives had helped fund University of Oxford’s vaccine research [487]; [488]. CVC had also invested in System C, a company providing key software being used for planning and managing the UK’s COVID-19 vaccination programme [489]. The Times described CVC as “powerful, successful and extremely low profile” [490].

In 2015, Frontiers had removed 31 editors after the editors had complained that company staff were interfering with editorial decisions and violating core principles of medical publishing [491].

The WHO

During the period, an intensifying critique of the WHO emerged as a result of the March 2021 ivermectin guideline lacking transparency and breaking established practices of meta-analysis and research. Presenting criticism towards the feasibility of the vaccines-only approach and its possible relationship to financial interests of the pharmaceutical industry, or possible failures of entities such as WHO, FDA, NIH and EMA, has been difficult during the pandemic. Regardless, it is necessary to consider whether funding-related biases might exist with regard to the current practices of these agencies, especially the WHO.

First we may note that the main funders of the WHO for the 2018/2019 biennium were United States (USD 893 million), Bill and Melinda Gates Foundation (USD 531 million), United Kingdom (USD 435 million), Gavi the Vaccine Alliance (USD 371 million), Germany (USD 292 million), Japan (USD 214 million), UN Office for the Coordination of Humanitarian Affairs (UNOCHA) (USD 192 million), Rotary International (USD 143 million), World Bank (USD 133 million), European Commission (USD 131 million), National Philanthropic Trust (USD 108 million), Canada (USD 101 million), China (USD 86 million), Norway (USD 86 million), UN Central Emergency Response (USD 86 million), Sweden (USD 77 million), France (USD 76 million), Kuwait (USD 70 million), Republic of Korea (USD 70 million) and Australia (USD 67 million) [492] [493] [494].

The Bill and Melinda Gates Foundation stated that its focus was on vaccine equity [307]. Also Gavi The Vaccine Alliance had been founded by the Bill and Melinda Gates Foundation in 1999, and the Gates foundation had invested a total of USD 4 billion in Gavi [495]. Gavi described the Gates foundation as “a key Gavi partner in vaccine market shaping”. The Gates Foundation also had long-term partnerships with Rotary International (polio vaccinations), National Philanthropic Trust, and the World Bank. Together, the USD 902 million contributions of the Gates Foundation and Gavi exceeded the United States contributions of USD 893 million, making the Gates-Gavi cluster the largest funder of the WHO in the 2018/2019 biennium (in April 2020, president Trump announced that US halted funding to the WHO, the effects of this remained unclear [496]; [497]. In addition, the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) contributed 33 million. Co-founded by the Bill and Melinda Gates Foundation in 2002, the foundation has contributed a total of USD 2.49 billion to GFATM [498].
Considering the recent USD 4 billion donation by the United States government to Gavi [89], one interpretation of the situation might be that the US outsourced a large part of its public health policy setting to Gavi and, subsequently, to Gates.

Yet another member of the Gates cluster was the Seattle-based PATH (Program for Appropriate Technology in Health), one of the largest nonprofit organizations in global health [89]. In 2021, its website was presented with a banner saying “900 million people are vaccinated. 7 billion haven’t had a shot. Help PATH today!” PATH’s CEO Nikolaj Gilbert, previously the global partnerships director for the United Nations Office for Project Services (UNOPS) and an employee of Néstor Nolisk, described PATH’s priorities: “the partnership with the Bill and Melinda Gates Foundation and the U.S. government has shaped what this organization is all about today . . . so one of my key priorities will be to see how we can sustain and grow those relationships that we have, how we can continue to be the preferred partner for those donors, and how can we also help them with their priorities?” [499].

A 2017 Politico article described Gates as “the world’s most powerful doctor”, saying his sway over the WHO spared criticism about misplaced priorities and undue influence [500, 501]. The article quoted Gates’ critics saying that “Gates’ priorities have become the WHO’s . . . he is treated like a head of state, not only at the WHO, but also at the G20.” Top WHO officials were said to have raised concerns that the foundation was distorting research priorities. Over three quarters of the WHO’s budget was coming from voluntary contributions which were usually earmarked for specific projects or diseases so that the WHO could not freely decide how to use them. The article stated that the Gates foundation’s focus on delivering vaccines, rather than on building resilient health systems, had drawn criticism. Changes had been made to the WHO’s budget approval process to in order to decrease the foundation’s influence. Yet a senior fellow for global health at the Council on Foreign Relations commented that “the foundation’s impact on the WHO is enormous . . . if they weren’t there, if they walked away with their money, the deleterious impact would be profound, and everyone is all too aware of that”.

It is important to note that it should also be noted that the other top 20 funders predominantly represent high-income countries of the North America and Europe. None of the countries that had officially adopted invermectin country-wide for COVID-19 up to April 2021 were represented [502]. Similarly, Coalition for Epidemic Preparedness Innovations (CEPI), an organization aiming to develop vaccines against emerging infectious diseases and enable equitable access to those vaccines for people during outbreaks was founded by the governments of Norway and India, Bill and Melinda Gates Foundation, UK Wellcome Trust, and the World Economic Forum [503]. It had later secured financial support from Australia, Austria, Belgium, the Bill and Melinda Gates Foundation, Canada, Denmark, the European Commission, Ethiopia, Finland, Germany, Hungary, Iceland, Indonesia, Italy, Japan, Kuwait, Lithuania, Luxembourg, Malaysia, Mexico, Netherlands, New Zealand, Norway, Panama, Romania, Saudi Arabia, Serbia, Singapore, Switzerland, The Republic of Korea, United Kingdom, USAID, and UK Wellcome Trust. Of these countries, as of June 2021, invermectin had been officially adopted in Mexico, Panama and Indonesia, as well as mixed use or occasional off-label use in some other countries [502].

Additionally, CEPI had received support from undisclosed private sector entities as well as public contributions through the UN Foundation COVID-19 Solidarity Response Fund [503]. Each investor was to get one representative to an investors Council providing guidance and oversight of CEPI activities, with investors expected to remain on the CEPI board. Another entry was a Joint Coordination Group was intended to discuss how to best enhance CEPI’s efforts to deliver and deploy vaccines, and had a role in planning for rapid response to a priority pathogen or an unknown pathogen. The Joint Coordination Group included the WHO, Geneva European Medicine Agency (EMEA), United States Food and Drug Administration Agency (FDA), Médecins Sans Frontières (MSF), UNICEF, International Federation of Red Cross and Red Crescent Societies (IFRC), African Vaccine Regulatory Forum (AVAREF), UK National Institute for Biological Standards and Control (NIASC) and UK Wellcome Trust. The Wellcome trust had been previously found out to secretly invest in companies that contributed to the same problems the trust said it wanted to solve [504]. The trust’s known investments through offshore companies in the Cayman Islands amounted to USD 901 million in 2018. In 2010, the Bill and Melinda Gates Foundation, Gavi, WHO, US NIH-NIAID, CDC, UNICEF, PAHO and several research organizations launched a Decade of Vaccines collaboration, initiated by the Gates Foundation [505]. The intention was to enable greater coordination across all stakeholder groups –

national governments, multilateral organizations, civil society, the private sector and philanthropic organizations. The five-member leadership council included the director general of WHO, Anthony S. Fauci of the National Institute of Allergy and Infectious Diseases (NIAID), executive director of UNICEF, a representative of African Leaders Malaria Alliance, and the president of global health at the Bill and Melinda Gates Foundation. All the relevant organizations had thus intimately and for the long term participated in the vaccine-centric collaboration initiated by Gates.

According to a recent study, in 2020, governments had spent a total of EUR 93 billion on COVID-19 vaccines and therapeutic development projects, with 95% allocated to vaccines and 5% on therapeutics [506]. 32% of the funds came from the US, 24% from the EU, and 13% from Japan and South Korea (a total of 69%). Only 7% of funds were preferred loans or conventional grants. 93% were advance market commitments (AMCs), i.e. binding agreements to subscribe to vaccines of doses prior to availability. Interestingly, 71% of the vaccine funding was allocated to Small and Medium Enterprises (SMEs) and MidsCaps, with only 18% allocated to large pharmaceutical manufacturers. The figures did not include private sector investments.

The Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public-private partnership program initiated by the US National Institutes of Health aimed at developing a coordinated research strategy for prioritizing and speeding development of the most promising treatments and vaccines [229]. Its public partners included Biomedical Advanced Research and Development Authority (BARDA), Centers for Disease Control and Prevention (CDC), Department of Defense, Department of Veterans Affairs, European Medicines Agency (EMA), National Institutes of Health (NIH), The Operation (formerly known as Operation Warp Speed), and US Food and Drug Administration (FDA). Industry partners included AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, DepoTherapeutics, Eisai, Eli Lilly and Company, Glaxo, GlaxoSmithKline, Johnson & Johnson, Merck & Co, MSD, Moderna, Novartis, Novavax, Pfizer, Rhythm Therapeutics, Roche-Genevetech, Sanofi, Takeda, and Vir Biotechnology. Non-profit partners included Bill and Melinda Gates Foundation, Fred Hutchinson Cancer Research Center, Foundation for the National Institutes of Health, and RTI International.

According to the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), as of February 2021, there were approximatly 382 vaccine candidates in development for COVID-19 related industries [507]. The IFPMA also noted that Wellcome Trust had invested USD 1.25 billion to benefit low- and middle-income countries. Both funders were thus positioned to potentially gain from the pandemic. Wellcome’s director had a position on the Scientific Advisory Group for Emergencies (SAGE), the UK government’s board on COVID-19, as well as a board seat on the Coalition for Epidemic Preparedness Innovations (CEPI). Earlier, the UK’s Scientific Advisory Group for Emergencies had failed to publicize disbelief competing interests related to COVID-19. A Canadian professor emeritus of public health policy and management commented that “The availability of Covid-19 vaccines to certain high-income countries is almost like a race where the people with the most money win. The wealthy in these countries are likely to have access to the vaccines that are approved by their countries, while the poorer countries may have to wait longer due to their limited access to finances.” The professor further added that the competition among vaccine manufacturers could lead to increased prices and reduced availability. Some experts argue that this competition among vaccine manufacturers could be seen as contributing to global inequality in access to vaccines, as high-income countries are more likely to have access to the latest and most advanced vaccines, while lower-income countries may struggle to access even basic vaccines.

According to Schwab, in five years up to 2020 the Gates Foundation had invested at least USD 270 million in companies that were currently working on COVID-19 vaccines, therapies, diagnostics or manufacturing. The Gates Foundation had invested USD 1.25 billion to benefit low- and middle-income countries. Both funders were thus positioned to potentially gain from the pandemic. Wellcome’s director had a position on the Scientific Advisory Group for Emergencies (SAGE), the UK government’s board on COVID-19, as well as a board seat on the Coalition for Epidemic Preparedness Innovations (CEPI). Earlier, the UK’s Scientific Advisory Group for Emergencies had failed to publicize disbelief competing interests related to COVID-19. A Canadian professor emeritus of public health policy and management commented that “The availability of Covid-19 vaccines to certain high-income countries is almost like a race where the people with the most money win. The wealthy in these countries are likely to have access to the vaccines that are approved by their countries, while the poorer countries may have to wait longer due to their limited access to finances.” The professor further added that the competition among vaccine manufacturers could lead to increased prices and reduced availability. Some experts argue that this competition among vaccine manufacturers could be seen as contributing to global inequality in access to vaccines, as high-income countries are more likely to have access to the latest and most advanced vaccines, while lower-income countries may struggle to access even basic vaccines.

The Gates Foundation had also donated almost USD 2 billion to for-profit businesses, including USD 99 million to Novavax Inc., USD 65 million to GlaxoSmithKline Biologicals, USD 63 million to Evotec and Just Biotechnologies, USD 61 million to Biologial E. Limited, USD 53 million to LG Chem Ltd., USD 44 million to Denmark Inc, USD 40 million to Inventive, USD 38 million to Bharat Biotech International Ltd., USD 37 million to Janssen Vaccines and Prevention BV, and USD 35 million to A3 Vaccines AS [510]. Schwab claimed the foundation was subsidizing private companies’ research costs, opening up

41

42
markets for their products, and tankrolling their bottom lines. He also claimed the foundation had funded groups pushing for industry-friendly government policies and regulation, including the Drug Information Association. He was also said to have funded nonprofit think tanks and advocacy groups that wanted to limit the role of government or direct its resources toward helping business interests. Schwab also noted that despite having given away USD 23.5 billion in the last five years up to 2020, Bill and Melinda Gates Foundation’s income from its investments had exceeded USD 25.5 billion in the same period [510].

Other commentators asked whether the Gates Foundation was addressing or reinforcing systemic problems raised by COVID-19, citing lack of transparency, dogmatic defence of intellectual property rights and monopolies, and intimate involvement with large pharmaceutical corporations as the main issues [511]. A 2016 report by Curtis gave details about Microsoft’s tax avoidance practices and its monopolistic nature; the foundation’s excessive global influence and support to various questionable practices including industrial agriculture with patented genetically modified seeds, Gates family’s “considerable personal access to senior levels of the WHO”. Gavi’s alleged overpaying for vaccines leading to excessive increases in vaccine prices, Gates’ dismissal of the issue, and the foundation’s agenda skewing health priorities and distorting health programmes [512]. Curtis wrote that one problem with the foundation’s heavy focus on developing new vaccines was that it detracted from other, more vital health priorities such as building resilient public health systems. As a rationale, Gates was said to have provided the following: “Vaccines are an extremely elegant technology. They are inexpensive, they are easy to deliver, and they are proven to protect children from disease. At Microsoft, we dreamed about technologies that were so powerful and yet so simple... all 193 member states, you must make vaccines a central focus of your health systems”. Curtis commented that Gates had “a fixation on vaccines”. He also claimed the foundation was stifling criticism through its media and NGO influence built on donations. An US professor of media, culture and communications was quoted saying the foundation “wielded enormous propaganda power”. A 2009 editorial in the Lancet, describing the foundation’s governance principle of being “driven by the interests and passions of the Gates family” as “whimsical”, proposed that the foundation should be more transparent and accountable and listen to opinions of external parties [513, 514].

In April 2020, the Bill and Melinda Gates Foundation awarded a five-year grant of USD 50 million to Unitaid to fight against HIV, tuberculosis and malaria, in addition to previous contributions of USD 100 million since 2006. Unitaid’s budget for the year 2021 was approximately USD 32 million [515]. In late 2020, Unitaid partially funded the ivermectin meta-analysis by Hill et al. published as a preprint [18]. This meta-analysis was later ignored by the WHO in its March 2021 decision against the use of ivermectin except in clinical trials [6]. On April 22, the chief of Unitaid stressed the need to increase commercial research and development of new pharmaceuticals for the treatment of COVID-19 [516]. A core function of Unitaid is Medicines Patent Pool, a tool or practice to negotiate patents for low-income countries; this emphasis may have made unpatentable products seem foreign to the organisation [516, 517]. Gates foundation was the chair of Unitaid’s Finance and accountability committee and a member of its policy and strategy committee [518].

Comparing the countries most heavily involved in the development and funding of vaccines to the countries with interest in ivermectin it can be noted that the two sets of countries have little overlap. Also, it can be noted that if influence is related to the amount of funding given, the first set of countries likely had more influence in the WHO in comparison to the rest of the countries.

Comparing the countries most heavily involved in the development and funding of vaccines to the countries with interest in ivermectin it can be noted that the two sets of countries have little overlap. Also, it can be noted that if influence is related to the amount of funding given, the first set of countries likely had more influence in the WHO in comparison to the rest of the countries.

The WHO, the philanthropic entity Bill and Melinda Gates Foundation, the public-private partnership Gavi The Vaccine Alliance, and the philanthropic-commercial entity CEPI appeared to be strongly interconnected with each other and with high-income nation states. Major financial investments and commitments likely created propensities for various biases and a vulnerability to the sunk cost fallacy [519]. A handful or ideological commitment solely to vaccines (93%) of government spending may have overlooked considerations of cost-effectiveness and feasibility, such as vaccines likely being more expensive and more vulnerable to viral variants than repurposed medicines, their long-term safety being unclear, and vaccines likely requiring constant redevelopment and revaccinations, in addition to not being suitable for self-administration and requiring refrigerated delivery systems. With regard to the sunk cost fallacy, it would be more economical for the governments to reconsider the vaccine and investigate pharmaceuticals dominated pandemic policy and at least adjust it with broad-spectrum repurposed medicines.

Comparisons to the H1N1 pandemic

After the H1N1 ‘swine flu’ pandemic of 2009-2010, the WHO was accused of malpractice when conflicts of interests of key WHO scientists led to unsuitable WHO recommendations which in turn led to billions of public money spent on ineffective antivirals for H1N1 influenza [520]. In her book, Abyegahye has written about the role of the WHO [524]. A review by Andreas summarizes key points, including the monopoly of the WHO to declare a pandemic [525]. In the case of H1N1, the WHO was retrospectively criticized for unnecessarily declaring a pandemic, as for example the European Centre for Disease Control (ECDC) did not agree that the disease should be qualified as severe (measured by mortality), which at the time was considered a requirement for a pandemic but is no longer mentioned.

At the time, an epidemiologist commented that the WHO, public health officials, virologists and pharmaceutical companies had “built this machine around the impending pandemic... there’s a lot of money involved, and influence, and careers, and entire institutions... all it took was one of these influenza viruses to mutate to start the machine grinding” [526].

WHO was later criticized by the Council of Europe for giving too much importance to vaccination and for not sufficiently emphasising other measures such as the use of antivirals even though some arguments suggested that other measures, such as taking antivirals preventively, could be at least as efficacious as vaccines [520], [521], [522]. WHO emphasized mass vaccination as the most effective strategy against H1N1 [524]. According to Abyegahye, this emphasis was a result of the path-dependent institutional reaction of the organization, where prior experience with infectious disease (including notable victories using mass vaccination strategies) resulted in the favoring of this reaction, whereas other potential actions were disregarded or underevaluated.

In June 2020, the rapporteur of Council of Europe Parliamentary Assembly described the acts of the WHO as foolish, saying “this is not going to go away” [524]. The rapporteur assumingly meant the criticism was not going to go away; yet it appears instead that the organizational patterns did not go away, leading the WHO and the national governments to repeat the same issues a decade later in the COVID-19 pandemic.

Legal responsibility of public-private partnerships and the WHO

Clarke has noted that the regulation of global health has partially shifted from the hands of states and international organizations into the hands of public-private partnerships such as Gavi The Vaccine Alliance and the Global Fund [527] [528]. These partnerships then become capable of also adversely impacting the rights of individuals, leading to concerns of responsibility under international law. However, the private entities in public-private partnerships typically fall outside the framework of responsibility under international law, and thus cannot be held responsible under it. In addition, in certain instances the partnerships have been granted immunity from the jurisdiction of domestic courts. This immunity applies to the staff, funds, properties and assets of these partnerships. The situation regarding Gavi and the Global Fund appeared especially complicated and the legal details were therefore considered out of the scope of this review.

With regard to the WHO, Gustin has described WHO’s regulatory powers as extraordinary, noting that it may set regulations on a broad range of health topics including the safety, potency, and advertising of biologicals and pharmaceuticals, and a nomenclature for diseases, causes of death, and public health practices [529], [530]. These regulations, unlike most international law, are binding on member states unless they proactively “opt out”. In addition, also the WHO enjoys several privileges and legal immunities. Regardless of the original purpose of these privileges, the possibility of abuse of these privileges by the WHO also exists. Also here the details were considered out of the scope of this review.
Private philanthropy, society and science

In his recent book, Callahan discussed the role of private philanthropy, noting the rising influence and political power of elite philanthropy, asking who is making choices over public life and who actually benefits from those choices [531]. Callahan described “today’s era of austerity” as a result of an orchestration of the upper class to reduce its taxes and the size of government, even so that in some US states, cuts to higher education specifically helped finance tax reductions for the wealthy and corporations. He noted that in a decade, Bill Gates and Warren Buffett, the main funders of the Bill and Melinda Gates Foundation, had added USD 25 billion and USD 80 billion, respectively, to their wealth, and that the Koch brothers had increased their wealth from USD 9 billion in 2005 to USD 85 billion in 2015.

In a book review, Saunders-B Hastings asked whether elite philanthropists are a counterweight to other, self-interested elites or to democracy itself, and noted that the distance between elite “charity” and elite political influence is small and shrinking, and that donors’ motivations matter less than the results of their actions [512].

Broad wrote that due to cuts to public funding and increase in private donations, “American science, long a source of national power and pride, is increasingly becoming a private enterprise” and quoted a policy analyst commenting that “the practice of science in the 21st century is becoming shaped less by national priorities or by peer-review groups and more by the particular preferences of individuals with huge amounts of money” [533].

Callahan proposed putting some curbs in place against the private philanthropy, yet noted that foundations and nonprofit trade groups are strongly against any new restrictions, partly due to their dependency on philanthropy. He noted that “rethinking philanthropic freedom is a Pandora’s box that almost nobody wants to open”, saying the current situation was a result of “yesterday’s mantras about philanthropic freedom and the dated regulation upholding it”.

Vaccines vs repurposed medicines

In Finland, a team led by two leading Finnish professors, Kari Alitalo and Seppo Ylä-Herttuala, had a patent and intellectual property free adenovirus-based nasal spray COVID-19 vaccine ready in May 2020. Despite taking approximately EUR 18 billion of public debt to mitigate damages caused by societal lockdowns and using hundreds of millions of Euros on diagnostic tests only, the Finnish government refused the approximately EUR 50 million needed to fund a phase III patient trial for the vaccine [534] [535].

The above case illustrates that the issue at hand is fundamentally not even about vaccines versus repurposed medicines or new pharmaceuticals versus repurposed medicines. Based on this data it is difficult to say whether it is about excessive adherence to inflexible regulations, subconscious biases present in national priorities or by peer-review groups and more by the particular preferences of individuals with huge amounts of money” [533].

The exact causes of the situation remained unclear. Regardless, the consequences remain to be seen and felt. One way forward might entail the majority of governments halting their funding to the WHO in order to dissolve the whole organization which appeared beyond repair. Another necessary change might be the eviction of the so-called philanthropic entities from healthcare contexts. In the long term, another beneficial action might be a worldwide conversion of the pharmaceutical industry into a non-profit operation. Continuing on the current path may result in a further polarization or destabilization of societies.

Near-future objections to adoption of ivermectin will undoubtedly include the possible environmental impacts. In the mid-to-long term, due to the need to reduce water usage and enable better retention of nitrogen, phosphorus and ammonia [539], transition from water based sewer systems to toilet systems not using water and not requiring wastewater processing but utilizing for example composting and new kind of treatments to degrade pharmaceuticals will become inevitable in many areas in any case.

Conclusions

During this period, ivermectin was officially adopted in South Africa but not widely used, adopted but later dropped in most of India, and adopted in Indonesia. In the United States and the United Kingdom, projects with involvement of both the governments and commercial companies were announced for development of new pharmaceuticals for early outpatient treatment of COVID-19, indicating nuclear boundaries between these entities. The dismissal of repurposed medicines including ivermectin continued in high-income countries due to very differing views on what constituted evidence of efficacy. The divide between ivermectin proponents and opposers remained mostly unchanged during the period, indicating a stagnated situation.

There was a noticeable centralization of power, with pandemic response and public discussions largely directed by a few organizations that were largely funded by a few billionaires which, in turn, were affected by their own personal preferences and biases such as obsessive-compulsive attachment to testing and new technologies, primarily vaccines. Legal responsibilities of these organizations appeared, in the words of one researcher, “obscure”.

industry and protecting its interests against those of the public, with the result of government failing to protect the public [536]. Whether rejection of ivermectin may be seen as an example of “regulatory capture” depends on how the vaccines-only policy was selected: primarily to align with the interests of the pharmaceutical industry, or because a better option could not be imagined. Curiously, options could be imagined early on in many low-income countries, but not in the high-income countries, possibly as a result of “technological capture”, where access to advanced technology exists, every problem looks like a problem that can be solved with advanced technology, even though other solutions would be substantially cheaper due to being overly complex and unnecessarily expensive. For example, the idea of spending tens of billions of dollars per year for testing 20 percent of the global population every week assumedly for a single pathogen (SARS-CoV-2) appeared irrational at best [56]. Gates’s speeches repeated terms such as “war” and “battle plan” [537], those talks may easily be interpreted as priming fear in the public. Gates is also famous for regularly predicting the next pandemics [538].
Commercial interests appeared to override public health interests during this period. As a result, several low- and middle-income countries and regions either explicitly or implicitly disregarded the WHO guidance, accelerating an erosion of WHO’s credibility.

Abbreviations

Acknowledgements
The author wishes to thank Simon Barber for a grammar check.

Authors’ contributions
The author was responsible for all aspects of the manuscript.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials
Not applicable.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The author declares that he has no competing interests.

Author details
Independent researcher, Helsinki, Finland. ORCID iD: 0000-0002-8575-9838

References
17. Dr. Satoshi Omura, the discoverer of ivermectin, says a special approval should not be required. Daily Shincho. 2021. https://www.dailyshincho.jp/article/20210314034254.html


217. The drugs that have shown promise in treating Covid. http://www.theguardian.com/world/2021/apr/20/the-drugs-that-could-stop-covid-causing-serious-illness


357. Bill Gates thought Je-


