The Mirage of Miracle Cures: Hydroxychloroquine and Ivermectin in COVID-19

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Abstract

The global coronavirus disease 2019 (COVID-19) pandemic created unprecedented urgency for effective therapeutic interventions. In the absence of specific antivirals or vaccines during the early phase, hydroxychloroquine (HCQ) and ivermectin (IVM) emerged as widely promoted candidates based on in vitro antiviral activity, theoretical mechanisms, and anecdotal reports. Both drugs rapidly entered clinical practice and national policies despite major pharmacological and methodological limitations. Large randomized controlled trials, including RECOVERY, Solidarity, TOGETHER, ACTIV-6, and PRINCIPLE, consistently demonstrated no meaningful benefit of HCQ or IVM in the prevention or treatment of COVID-19, while HCQ was associated with increased cardiac risk. Regulatory authorities such as the FDA, EMA, and WHO subsequently restricted their use to formal clinical trial settings. However, politicization, media amplification, and the publication of low-quality or fraudulent studies contributed to misinformation, inappropriate prescribing, and patient harm. These events exposed systemic weaknesses in global pandemic responses, including premature reliance on poor-quality evidence, limited transparency in communication, and the influence of political and commercial interests. The rise and fall of HCQ and IVM highlight the importance of conducting rapid yet rigorous clinical trials, upholding evidence-based standards, and implementing proactive measures against misinformation to preserve scientific integrity and public trust during future health emergencies.

Keywords: drug repurposing; chloroquine; ivermectin; clinical trials; regulatory policy; pandemic preparedness

1. Introduction

The emergence of coronavirus disease 2019 (COVID-19) created an urgent need for effective treatments at a time when no specific antiviral agents or vaccines were available. Because of this gap, repurposing existing drugs became a practical approach. These agents were already approved for other conditions and had known safety profiles, which allowed them to

be tested quickly. Among the earliest candidates were hydroxychloroquine and ivermectin. Interest in both drugs grew after laboratory studies suggested they might have antiviral effects and after proposed mechanisms appeared relevant to the biology of COVID-19.

Hydroxychloroquine, long used for malaria and autoimmune diseases, was thought to block viral entry and reduce inflammation. Ivermectin, an antiparasitic agent used in both humans and animals, showed inhibition of SARS-CoV-2 replication in cell culture. However, the drug concentrations needed to achieve these effects were higher than what can safely be reached in humans. Even so, the absence of proven therapies at that time led to rapid global attention and widespread discussion of both drugs.

As more clinical evidence became available, early expectations were not confirmed. Randomized controlled trials of hydroxychloroquine and ivermectin in outpatient, inpatient, and prophylaxis settings consistently showed no meaningful clinical benefit. Concerns also emerged regarding inappropriate use, safety issues, and the propagation of misinformation. The rise and subsequent decline of these therapies highlight the challenges of interpreting early, low-certainty evidence during a public health emergency and underscore the importance of relying on robust, well-conducted trials before integrating repurposed drugs into clinical practice.

2. Background: Repurposed Drugs in Pandemics

Drug repurposing has been an important strategy in prior infectious disease outbreaks because agents with established safety profiles can be evaluated more rapidly than novel therapeutics. During previous coronavirus epidemics, several antivirals, including lopinavir–ritonavir and favipiravir, were investigated for potential benefit, and these experiences informed early approaches to COVID-19 management [1]. Consequently, when no proven antiviral therapy was available in the early phase of the COVID-19 pandemic, repurposing became a logical starting point for therapeutic exploration.

Hydroxychloroquine and ivermectin attracted considerable attention after laboratory studies suggested potential antiviral activity. Hydroxychloroquine was proposed to inhibit viral entry by interfering with endosomal acidification and ACE2 receptor glycosylation [2], and its known immunomodulatory properties provided an additional theoretical basis for evaluation [3]. Ivermectin was shown in laboratory experiments to reduce SARS-CoV-2 replication, with large drops in viral RNA levels seen in cell culture [4]. This effect may be related to interference with the importin-α/β nuclear transport system, which plays a role in moving viral proteins inside the cell [5]. These early laboratory results, combined with the urgent need for treatment during the pandemic, created rapid global interest in the drug.

Later, pharmacokinetic studies questioned whether these findings were meaningful for clinical use. The concentrations of ivermectin needed to produce antiviral effects in vitro were fifty to one hundred times higher than the levels that can be safely achieved in humans [6]. For hydroxychloroquine, the antiviral activity occurred close to the highest safe dose, which raised concerns about toxicity early on [2]. Despite these issues, both drugs were used widely in many countries before strong clinical trial evidence was available. This pattern shows how early laboratory signals can influence clinical practice during times of uncertainty.

3. Hydroxychloroquine: From Promise to Discredit

3.1 Early Studies and Initial Adoption

Hydroxychloroquine received early attention after small clinical studies suggested that it might have antiviral effects in patients with COVID-19. The study by Gautret et al. reported improvements in viral clearance, especially when hydroxychloroquine was combined with azithromycin [7]. However, this study had several important limitations. It did not use randomization, involved a small number of patients, and excluded individuals who worsened during treatment. Despite these weaknesses, the results gained wide publicity and led to extensive off-label use [8]. Political endorsement further increased interest, and the United States Food and Drug Administration issued an Emergency Use Authorization allowing hydroxychloroquine to be used in hospitalized patients with COVID-19 [9].

3.2 Evidence from Randomized Controlled Trials

As more rigorous studies became available, early signals of benefit were not supported. The RECOVERY trial, which included more than four thousand hospitalized patients, found that hydroxychloroquine did not reduce twenty-eight-day mortality, the need for mechanical ventilation, or length of hospital stay compared with standard care [10]. The WHO Solidarity trial, conducted in multiple countries, also showed no improvement in survival or clinical outcomes with hydroxychloroquine [11]. Other trials, such as the NIH ORCHID study, were stopped early because interim results showed no benefit [12].

Studies examining hydroxychloroquine in outpatient or prophylaxis settings produced similar findings. In a post-exposure prophylaxis trial, Boulware et al. reported no reduction in symptomatic COVID-19 compared with placebo [13]. Additional outpatient trials assessing early treatment found no improvement in symptoms or virological outcomes [14].

3.3 Safety Considerations

Safety concerns further limited the use of hydroxychloroquine. Reports documented QT interval prolongation and ventricular arrhythmias, particularly when the drug was combined with azithromycin [15]. Large multinational cohort studies later showed increased risks of cardiovascular adverse events with hydroxychloroquine, with or without macrolide therapy [16]. There were also documented cases of overdose and fatal cardiac events, highlighting the narrow safety margin of this drug when used outside its approved indications [17].

3.4 Regulatory Reversal

As evidence consistently showed lack of benefit and ongoing safety concerns, regulatory agencies revised their recommendations. On 15 June 2020, the United States Food and Drug Administration revoked the Emergency Use Authorization for hydroxychloroquine due to lack of efficacy and potential cardiac risks [9]. The WHO also discontinued the hydroxychloroquine arm of the Solidarity trial after interim analyses confirmed no clinical benefit [11]. By the end of 2020, major guideline committees advised that hydroxychloroquine should not be used for COVID-19 treatment except within controlled clinical trials.

4 Ivermectin: The “Second Wave” of Repurposing

4.1 Early Evidence and Uptake

Interest in ivermectin increased after an in vitro study showed a strong reduction in SARS-CoV-2 replication in Vero cell cultures, with a 99.8 percent drop in viral RNA within forty-eight hours [4]. The proposed mechanism involved interference with the importin-α/β nuclear transport system [5]. However, the drug levels needed to achieve these antiviral effects were far higher than the doses that can be safely used in humans [6]. Despite this major limitation, several countries added ivermectin to their national treatment guidelines early in the pandemic, and anecdotal reports of benefit circulated widely.

4.2 Small Trials and Retractions

Early clinical studies provided mixed results. Many trials were small, used different dosing schedules, and had important methodological problems. Some studies that initially appeared to support ivermectin were later retracted because of concerns about data quality. The well-known study by Elgazzar et al. was withdrawn after evidence of data fabrication and plagiarism was found [18]. Meta-analyses that included such flawed studies reported apparent benefit, but when high-risk or fraudulent trials were removed, the effect disappeared [19]. These issues show how unreliable conclusions can be when primary studies are of poor quality.

4.3 Evidence from Large Randomized Controlled Trials

Large randomized controlled trials did not show clinical benefit. The TOGETHER trial, which included more than three thousand participants, found no reduction in hospitalization rates with ivermectin compared with placebo [20]. In the United States, the ACTIV-6 platform trial also showed no improvement in time to recovery or other clinical outcomes [21,22]. The PRINCIPLE trial in the United Kingdom reported no benefit in community treatment for high-risk adults [23]. A randomized trial in Colombia found no meaningful effect on symptom resolution in mild COVID-19 [24]. Overall, these trials showed that ivermectin did not improve virological, symptom-related, or hospitalization outcomes.

4.4 Safety and Pharmacological Considerations

Ivermectin is usually safe at approved antiparasitic doses, but misuse increased during the pandemic. Some people used veterinary formulations, leading to cases of toxicity. Poison control centres reported neurological symptoms, low blood pressure, and other adverse events, some severe enough to require hospitalization [25]. These events were often linked to inappropriate dosing and the mistaken belief that higher doses would increase antiviral activity. Pharmacokinetic studies confirmed that drug concentrations achievable in humans are not high enough to inhibit SARS-CoV-2 replication [6].

4.5 Regulatory Guidance

Regulatory agencies advised against the use of ivermectin for COVID-19 outside formal research. In March 2021, the European Medicines Agency concluded that current evidence did not support ivermectin for prevention or treatment and recommended restricting use to randomized trials [26]. The World Health Organization issued similar guidance, noting the very low certainty of the available evidence and the absence of proven clinical benefit [27]. The United States Food and Drug Administration also warned against off-label or veterinary use and emphasized the lack of efficacy and potential safety risks [25].

5 Regulatory Responses and Global Variability

The regulatory course of hydroxychloroquine and ivermectin illustrates the importance of scientific rigor and highlights the global inconsistency that emerged in the absence of definitive evidence. In high-income countries, regulatory agencies such as the United States Food and Drug Administration authorized hydroxychloroquine under an Emergency Use Authorization in March 2020, but revoked it in June 2020 after data demonstrated lack of efficacy and potential cardiac toxicity. Ivermectin was never authorized for COVID-19 at any stage [9,25]. The European Medicines Agency adopted a cautious approach by restricting the use of both agents to clinical trial settings because of insufficient evidence and emerging

safety concerns [18,26]. The World Health Organization discontinued the hydroxychloroquine arm of the Solidarity trial in June 2020 after interim analyses showed no clinical benefit, and later advised against the use of ivermectin outside research settings in March 2021 [11,27].

In contrast, the regulatory trajectory in low and middle income countries differed considerably. In India, both hydroxychloroquine and ivermectin were incorporated into early national treatment guidelines for prophylaxis and mild disease, influenced by local research efforts and the limited availability of established antiviral therapies. These recommendations remained in place until 2021, when the Indian Council of Medical Research and the Ministry of Health withdrew them following the publication of large negative trials. In Peru, ivermectin was added to national treatment protocols in 2020 but was later removed after independent evaluations identified data inconsistencies in several influential studies that had supported its use. In Bolivia, community distribution of ivermectin persisted into 2021, sustained by political endorsement and public demand during a period of restricted vaccine access.

Taken together, these examples demonstrate how differences in regulatory capacity, domestic political pressures, and unequal access to evidence-based therapies shaped national policy decisions. The heterogeneity of these responses contributed to public uncertainty, reinforced misinformation, and highlighted broader inequities in governance and healthcare access during the COVID-19 pandemic.

6 Methodological and Evidence-Quality Issues

Both controversies exposed systemic weaknesses in the generation and interpretation of clinical evidence. Numerous small and poorly controlled trials produced misleading signals of benefit, and the accelerated pace of scientific publication, particularly the widespread use of preprint servers, amplified unverified findings. The Surgisphere incident, in which a Lancet study reporting harm from hydroxychloroquine was retracted after its underlying data were deemed unverifiable, further undermined public and scientific trust [28].

Meta-analyses that included fraudulent or low-quality ivermectin studies also created a false impression of efficacy. Once retracted or high-risk studies were removed, the apparent treatment effect disappeared [19]. Subsequent re-analyses consistently showed that excluding such studies eliminated any statistically significant mortality benefit associated with ivermectin and markedly reduced heterogeneity across trials. These observations indicate that early signals of efficacy were largely driven by flawed or fabricated data. Collectively, these episodes reinforce the principle that rigorous evidence synthesis cannot compensate for deficiencies in the quality of primary research.

7 Sociopolitical and Misinformation Dimensions

The debates surrounding hydroxychloroquine and ivermectin were strongly shaped by political and social forces. Hydroxychloroquine received public endorsement from prominent political leaders, including the Presidents of the United States and Brazil, which transformed it from a scientific question into a marker of political identity [8,29]. Ivermectin was later adopted by anti-vaccination groups and conspiracy communities that portrayed it as an inexpensive but deliberately suppressed treatment.

Social media played a substantial role in amplifying misinformation, where personal testimonials and unfounded claims often overshadowed clinical trial evidence. In the United States, misuse of veterinary ivermectin products became widespread, prompting the United States Food and Drug Administration to issue the now widely cited warning, “You are not a horse. You are not a cow. Seriously, y’all. Stop it” [25]. Commercial exploitation also emerged as telemedicine networks and informal suppliers profited from large-scale prescribing of ivermectin and hydroxychloroquine, raising significant patient safety concerns [30]. These developments illustrate how scientific debate can be distorted by political agendas, social media dynamics, and commercial interests. They also highlight the importance of transparent communication and ethical stewardship in sustaining public trust during health emergencies.

8. Lessons for Future Pandemics

The experience with hydroxychloroquine and ivermectin provides important lessons for global health preparedness and for future outbreak responses.

In vitro findings must always be interpreted within their pharmacological context. Laboratory results represent an initial step in the exploration of therapeutic potential, but they do not establish clinical utility. Both hydroxychloroquine and ivermectin inhibited SARS-CoV-2 replication in cell cultures only at concentrations far higher than those safely achievable in humans. This limitation highlights the need to evaluate pharmacokinetics, tissue distribution, and dose–response relationships before advancing to clinical trials or issuing public health recommendations.

Small and uncontrolled studies should remain exploratory and should not influence policy decisions. The adoption of hydroxychloroquine and ivermectin was driven by studies that lacked randomization, adequate blinding, and sufficient statistical power. These trials produced weak and unreliable signals of potential benefit, yet they were rapidly translated into treatment guidelines and political advocacy. Future responses must recognise that

early data are intended to support hypothesis generation and further investigation rather than guide clinical practice.

Rapid implementation of large, well-designed randomized controlled trials is essential during public health emergencies. The RECOVERY and Solidarity trials demonstrated that adaptive, multicenter trial platforms can generate reliable evidence at scale and with exceptional speed [10,11]. These initiatives showed that robust data can be obtained within weeks or months, even under pandemic conditions. Investments in such research infrastructure before crises occur are critical to ensure readiness for future outbreaks.

Transparency, data integrity, and methodological rigor must be upheld at all times. The controversy surrounding ivermectin illustrated how fraudulent or poorly conducted studies can distort evidence synthesis when incorporated into meta-analyses. Preregistration of clinical trials, adherence to predefined outcomes, and transparent data sharing are essential safeguards that strengthen scientific credibility. Consistent reinforcement of these standards protects both the reliability of the evidence base and public confidence in research outcomes.

Regulatory flexibility is necessary during emergencies but must remain guided by evidence. Emergency use authorizations can be appropriate when treatment options are limited, yet they should be provisional and subject to rapid revision as new data emerge. The United States Food and Drug Administration's revocation of the hydroxychloroquine Emergency Use Authorization, following the publication of large randomized trials, reflects an appropriate regulatory response despite political controversy [9]. Effective regulation requires balancing urgency with caution to prevent premature endorsement of unproven therapies.

Effective communication is equally important for countering misinformation. Misleading narratives regarding hydroxychloroquine and ivermectin spread more rapidly than formal trial results and evidence-based guidance. Clear, timely, and consistent communication from trusted health authorities is essential for maintaining public trust. Public messages should explain the evolving nature of scientific evidence, acknowledge uncertainty, and address misinformation circulating through media and social networks directly and transparently.

Science must remain independent of political influence. The premature promotion of both hydroxychloroquine and ivermectin was shaped strongly by political leaders and ideological groups rather than by scientific data. Policy decisions must be grounded in impartial expert evaluation that is free from political or commercial interests. Protecting the independence of scientific institutions is essential to ensuring patient safety and maintaining trust in health systems.

As effective COVID-19 vaccines became widely available, the perceived need and ethical justification for the continued use of unproven therapeutics declined substantially. This shift altered the balance between potential risks and benefits and marked a turning point in global treatment priorities. It also demonstrated how evolving preventive strategies can influence the relevance and acceptability of experimental therapies during public health emergencies.

9. Conclusion

Hydroxychloroquine and ivermectin were once viewed as promising treatments that might help control COVID-19, based on laboratory findings and theoretical mechanisms that appeared plausible at a time of global urgency. As evidence from large randomized controlled trials accumulated, it became clear that neither drug improved outcomes nor prevented infection. Health authorities responded by limiting their use to clinical trials because of safety concerns and the lack of proven benefit. The experience with these agents shows how quickly optimism can outpace evidence when fear, uncertainty, and political influence converge. The rapid adoption of unproven therapies revealed vulnerabilities in how scientific data are interpreted and communicated during emergencies. It also demonstrated the damage that misinformation can cause when it spreads faster than formal guidance or trial results.

The most important lesson is that reliable treatments emerge only through rigorous scientific investigation. When drugs are promoted before their safety and efficacy are established, patients may be harmed, public confidence declines, and valuable resources are diverted from drugs that are already proven to work. Future pandemic preparedness must focus on launching large, well-designed trials quickly, maintaining the principles of evidence-based medicine, and communicating results clearly and transparently.

List of Abbreviations

- ACE2 – Angiotensin-converting enzyme 2
- ACTIV-6 – Accelerating COVID-19 Therapeutic Interventions and Vaccines-6 trial
- COPE – Committee on Publication Ethics
- COVID-19 – Coronavirus disease 2019
- EMA – European Medicines Agency
- EUA – Emergency Use Authorization
- FDA – United States Food and Drug Administration

- HCQ – Hydroxychloroquine
- HIV-1 – Human immunodeficiency virus type 1
- IVM – Ivermectin
- NIH – National Institutes of Health
- ORCHID – Outcomes Related to COVID-19 treated with Hydroxychloroquine among Inpatients with symptomatic Disease
- PRINCIPLE – Platform Randomised trial of Interventions against COVID-19 In older peoPLE
- QT interval – Interval between Q and T waves on electrocardiography
- RCT – Randomized controlled trial
- RECOVERY – Randomised Evaluation of COVID-19 Therapy
- RNA – Ribonucleic acid
- SARS-CoV-2 – Severe acute respiratory syndrome coronavirus 2
- WHO – World Health Organization

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