



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. During the early phase of the pandemic, when specific antivirals and vaccines were unavailable, hydroxychloroquine (HCQ) and ivermectin (IVM) emerged as widely promoted therapeutic candidates due to their reported *in vitro* antiviral activity, proposed mechanisms of action, and anecdotal clinical observations. Both drugs were rapidly incorporated into clinical practice and national treatment policies despite substantial pharmacological and methodological limitations. Large randomized controlled trials, including RECOVERY Trial, Solidarity Trial, TOGETHER Trial, ACTIV-6, and PRINCIPLE Trial, consistently demonstrated that neither HCQ nor IVM provided meaningful benefit in the prevention or treatment of COVID-19, while HCQ was associated with an increased risk of cardiac adverse events. Regulatory and public health authorities, including the U.S. Food and Drug Administration, the European Medicines Agency, and the World Health Organization, subsequently advised that these agents should be used only within formal clinical trial settings. However, politicization, media amplification, and the publication of low-quality or fraudulent studies contributed substantially to misinformation, inappropriate prescribing practices, and patient harm. These events exposed critical systemic weaknesses in the global response to the pandemic, including the premature adoption of interventions based on weak evidence, insufficient transparency in scientific and public health communication, and the influence of political and commercial interests. The rise and decline of HCQ and IVM underscore the importance of conducting rapid yet methodologically rigorous clinical trials, adhering to evidence-based standards, and implementing proactive strategies to counter misinformation in order to preserve scientific integrity and public trust during future public health emergencies.

Keywords:

drug repurposing; chloroquine; ivermectin; clinical trials; regulatory policy; pandemic preparedness; hydroxychloroquine

1. Introduction

The emergence of coronavirus disease 2019 (COVID-19) created an urgent demand for effective therapeutic interventions at a time when no specific antiviral agents or vaccines were available. Consequently, the repurposing of existing drugs emerged as a practical and rapidly deployable strategy. These agents were already approved for other indications and had relatively well-characterized safety profiles at approved doses, enabling rapid clinical evaluation. Among the earliest proposed candidates

were hydroxychloroquine and ivermectin. Interest in both drugs grew after laboratory studies suggested they might have antiviral effects and after proposed mechanisms appeared biologically plausible in the context of COVID-19.

Hydroxychloroquine, a long-established treatment for malaria and autoimmune disorders, was hypothesized to inhibit viral entry and modulate inflammatory responses. Ivermectin, an antiparasitic agent approved for specific human and veterinary indications, demonstrated inhibition of SARS-CoV-2 replication in cell culture models.

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However, the drug concentrations required to elicit these effects exceeded levels that can be safely achieved in humans. Nevertheless, the absence of established therapies during the early phase of the pandemic contributed to rapid global attention and widespread discussion surrounding both agents.

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

2. Background: Repurposed Drugs in Pandemics

Drug repurposing has been an important strategy during previous infectious disease outbreaks because agents with established safety profiles can be evaluated more rapidly than novel therapeutics. During earlier coronavirus epidemics, several antiviral agents, including lopinavir-ritonavir and favipiravir, were investigated for potential therapeutic benefit, and these prior experiences informed early strategies for 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 following laboratory studies that 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 demonstrated inhibitory effects on SARS-CoV-2 replication in laboratory studies, with substantial reductions in viral RNA levels observed in cell culture models [4]. This effect has been proposed to involve interference with the importin- α/β nuclear transport system, which mediates the intracellular transport of viral proteins into the host cell nucleus [5]. These early in vitro findings, together with the urgent therapeutic demand during the pandemic, generated substantial global interest in the drug.

Subsequent pharmacokinetic studies raised concerns regarding the clinical relevance of these in vitro findings. The concentrations of ivermectin required to achieve antiviral effects in vitro were estimated to be 50–100 times higher than those safely attainable in humans [6]. For hydroxychloroquine, reported antiviral activity occurred near the upper limit of the established safe dosing range, raising early concerns regarding potential toxicity [2]. Despite these limitations, both agents were widely used in several countries prior to the availability of robust clinical trial evidence. This pattern illustrates how preliminary laboratory findings can influence clinical decision-making during periods of scientific uncertainty.

3. Hydroxychloroquine: From Early Promise to Reassessment

3.1. Early Studies and Initial Adoption

Hydroxychloroquine initially received significant attention following early small-scale clinical studies suggesting potential antiviral effects in patients with COVID-19. The study by Gautret et al. reported faster viral clearance associated with hydroxychloroquine treatment, with a more pronounced effect observed when combined with azithromycin; however, this study was later retracted, and its findings should not be interpreted as valid clinical evidence [7]. However, the study was subject to several important methodological limitations, including the absence of randomization, a small sample size, and the exclusion of patients who experienced clinical deterioration during the study period. Despite these weaknesses, the findings received widespread attention and contributed to extensive off-label use of the intervention [8]. Political endorsement further amplified public and clinical interest, and the United States Food and Drug Administration (FDA) issued an Emergency Use Authorization permitting the use of hydroxychloroquine in hospitalized patients with COVID-19 [9].

3.2. Evidence from Randomized Controlled Trials

As more rigorous clinical evidence emerged, initial signals of benefit were not substantiated. The RECOVERY Trial, which enrolled more than 4,000 hospitalized patients, demonstrated that hydroxychloroquine did not reduce 28-day mortality, the requirement for mechanical ventilation, or hospital length of stay compared with standard care [10]. The Solidarity Trial, conducted across multiple countries, similarly demonstrated no improvement in survival or other clinical outcomes associated with hy-

droxychloroquine [11]. Additional studies, including the NIH ORCHID trial, were terminated early due to interim analyses indicating a lack of therapeutic benefit [12].

Studies examining hydroxychloroquine in outpatient and 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 either clinical symptoms or virological outcomes [14].

3.3. Safety Considerations

Safety concerns further restricted the use of hydroxychloroquine. Clinical reports documented QT interval prolongation and ventricular arrhythmias, particularly when hydroxychloroquine was co-administered with azithromycin [15]. Large multinational cohort studies subsequently demonstrated an increased risk of cardiovascular adverse events associated with hydroxychloroquine, both alone and in combination with 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; however, the article reporting these findings was subsequently retracted [17].

3.4. Regulatory Reversal

As accumulating evidence consistently demonstrated a lack of clinical benefit alongside ongoing safety concerns, regulatory agencies subsequently revised their recommendations regarding its use. On 15 June 2020, the United States Food and Drug Administration revoked the Emergency Use Authorization for hydroxychloroquine due to lack of demonstrated efficacy and potential cardiac risks [9]. The Solidarity Trial also discontinued the hydroxychloroquine arm following interim analyses that confirmed a lack of clinical benefit [11]. By the end of 2020, major guideline committees recommended against the routine use of hydroxychloroquine for the treatment of COVID-19 outside the context of controlled clinical trials.

4. Ivermectin: The “Second Wave” of Repurposing

4.1. Early Evidence and Uptake

Interest in ivermectin increased following an in vitro study demonstrating marked inhibition of SARS-CoV-2 replication in Vero cell cultures, including a reported 99.8% reduction in viral RNA within 48 h [4]. The proposed mechanism involved disruption of the importin- α/β -mediated

nuclear transport system [5]. However, the concentrations required to achieve these antiviral effects were substantially higher than those that can be safely attained in humans at therapeutic doses [6]. Despite this major limitation, several countries incorporated ivermectin into national treatment guidelines during the early phase of the pandemic, and anecdotal reports of benefit circulated widely.

4.2. Small Trials and Retractions

Early clinical studies yielded inconsistent findings. Many trials were small in scale, employed heterogeneous dosing regimens, and were limited by significant methodological shortcomings. Some studies that initially suggested potential benefit of ivermectin were subsequently retracted due to concerns regarding data quality and research integrity. The widely cited study by Elgazzar et al. was subsequently retracted following the identification of data fabrication and plagiarism [18]. Meta-analyses that incorporated low-quality or flawed studies reported an apparent therapeutic benefit; however, this effect was no longer observed after exclusion of high-risk or retracted trials [19]. These findings highlight how unreliable conclusions can arise when evidence is based on methodologically weak primary studies.

4.3. Evidence from Large Randomized Controlled Trials

Large randomized controlled trials failed to demonstrate any clinical benefit. The TOGETHER Trial, which enrolled more than 3,000 participants, showed no reduction in hospitalization rates with ivermectin compared with placebo [20]. In the United States, the ACTIV-6 platform trial also demonstrated no improvement in time to recovery or other clinical outcomes [21,22]. The PRINCIPLE Trial reported no clinical benefit of hydroxychloroquine in the treatment of high-risk adults in the community setting [23]. A randomized trial conducted in Colombia found no meaningful effect on symptom resolution in patients with mild COVID-19 [24]. Overall, the available randomized evidence did not show meaningful improvement in virological, symptomatic, or hospitalization-related outcomes with ivermectin.

4.4. Safety and Pharmacological Considerations

Ivermectin is generally safe when used at approved antiparasitic doses; however, its inappropriate use increased during the COVID-19 pandemic. In some cases, individuals used veterinary formulations, resulting in reported

cases of toxicity. Poison control centers reported neurological symptoms, hypotension, and other adverse events, some of which were severe enough to require hospitalization [25]. These events were frequently associated with inappropriate dosing practices and the misconception that higher doses would enhance antiviral efficacy. Pharmacokinetic studies confirmed that drug concentrations achievable in humans are insufficient to inhibit SARS-CoV-2 replication [6].

4.5. Regulatory Guidance

Regulatory agencies advised against the use of ivermectin for COVID-19 outside the context of formal clinical research. In March 2021, the European Medicines Agency concluded that available evidence did not support the use of ivermectin for the prevention or treatment of COVID-19 and recommended that its use be restricted to well-designed randomized clinical trials [26]. The World Health Organization issued similar guidance, citing very low certainty in the available evidence and the absence of demonstrated clinical benefit [27]. The United States Food and Drug Administration also issued warnings against off-label and veterinary use of ivermectin, emphasizing the absence of demonstrated efficacy against COVID-19 and the potential for significant safety risks [25].

5. Regulatory Responses and Global Variability

The regulatory trajectory of hydroxychloroquine and ivermectin underscores the importance of scientific rigor in clinical decision-making and highlights the global inconsistencies that emerged in the absence of definitive evidence. In high-income countries, the United States Food and Drug Administration (FDA) granted Emergency Use Authorization for hydroxychloroquine in March 2020; however, this authorization was revoked in June 2020 following emerging evidence demonstrating a lack of clinical efficacy and potential cardiac toxicity. Ivermectin was never authorized for COVID-19 at any stage [9,25]. The European Medicines Agency adopted a precautionary approach by advising that these agents should not be used routinely outside clinical trial settings due to insufficient evidence of efficacy and emerging safety concerns [26]. The Solidarity Trial discontinued the hydroxychloroquine arm in June 2020 following interim analyses demonstrating no clinical benefit, and the World Health Organization later advised in March 2021 against the use of ivermectin outside research settings [11,27].

In contrast, regulatory responses in several low- and middle-income countries varied 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 trials demonstrating no clinical benefit. In Peru, ivermectin was incorporated into national treatment protocols in 2020 but was later removed following independent evaluations that identified data inconsistencies in several influential studies supporting its use. In Bolivia, community-level distribution of ivermectin continued into 2021, supported by political endorsement and sustained public demand during a period of limited vaccine availability.

Taken together, these examples illustrate how variations in regulatory capacity, domestic political pressures, and unequal access to evidence-based therapies influenced 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, evaluation, and interpretation of clinical evidence. Numerous small, methodologically weak, and poorly controlled trials generated misleading signals of benefit, while the accelerated pace of scientific dissemination—particularly through widespread use of preprint servers—amplified unverified findings. The Surgisphere incident, in which a study published in *The Lancet* reporting harm associated with hydroxychloroquine was retracted after its underlying data were found to be unverifiable, further undermined public and scientific trust [28].

Meta-analyses that incorporated low-quality or fraudulent ivermectin studies contributed to a misleading impression of therapeutic efficacy. After exclusion of retracted or high-risk studies, the observed treatment effect was no longer evident [19]. Subsequent re-analyses consistently demonstrated that exclusion of such studies eliminated any statistically significant mortality benefit associated with ivermectin and substantially reduced heterogeneity across trials. These observations indicate that early signals of efficacy were largely driven by flawed or fabricated data. Collectively, these findings 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 factors. Hydroxychloroquine, in particular, received public endorsement from prominent political leaders, notably in the United States and Brazil, which shifted its evaluation from a scientific issue to a symbol of political identity [8,28]. Ivermectin was subsequently adopted by anti-vaccination groups and conspiracy-driven communities, which portrayed it as an inexpensive but deliberately suppressed treatment.

Social media played a substantial role in amplifying misinformation, with personal testimonials and unsupported claims often overshadowing evidence from clinical trials. 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 [29]. These developments illustrate how scientific discourse can be distorted by political agendas, social media dynamics, and commercial incentives. They also underscore the importance of transparent communication and ethical stewardship in maintaining public trust during public health emergencies.

8. Lessons for Future Pandemics

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

In vitro findings must be interpreted within their pharmacological context. Although laboratory studies provide an important initial step in evaluating therapeutic potential, they do not establish clinical efficacy. Both hydroxychloroquine and ivermectin inhibited SARS-CoV-2 replication in cell cultures only at concentrations exceeding those safely achievable in humans. This limitation underscores the importance of evaluating pharmacokinetics, tissue distribution, and dose–response relationships prior to advancing candidates to clinical trials or informing public health recommendations.

Small, uncontrolled studies should be regarded as exploratory and should not be used to inform clinical

guidelines or policy decisions. The adoption of hydroxychloroquine and ivermectin was driven by studies that lacked randomization, adequate blinding, and sufficient statistical power. These trials generated weak and unreliable signals of potential benefit; nevertheless, they were rapidly incorporated into treatment guidelines and amplified through political advocacy. Future interpretations of early data should recognize their primary role in generating hypotheses and guiding subsequent investigation, rather than directly informing clinical practice.

Rapid implementation of large, well-designed randomized controlled trials is essential during public health emergencies. The RECOVERY Trial and Solidarity Trial demonstrated that adaptive, multicenter trial platforms can generate robust evidence at large scale and with exceptional speed [10,11]. These initiatives showed that robust clinical evidence can be generated within weeks to months, even under pandemic conditions. Investment in such research infrastructure prior to public health emergencies is therefore critical to ensuring preparedness for future outbreaks.

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

Regulatory flexibility is essential during public health emergencies but must remain firmly grounded in robust and evolving scientific evidence. Emergency use authorizations may be appropriate when therapeutic options are limited; however, they must remain provisional and subject to timely revision as new evidence emerges. The United States Food and Drug Administration’s revocation of the hydroxychloroquine Emergency Use Authorization, following the publication of large randomized trials, reflects a science-based regulatory response despite surrounding political controversy [9]. Effective regulation requires balancing urgency with caution to prevent premature endorsement of unproven therapies.

Effective communication is equally important in countering misinformation. Misleading narratives regarding hydroxychloroquine and ivermectin often disseminated more rapidly than formal clinical trial results and evidence-based guidance. Clear, timely, and consistent communication from trusted health authorities is essential for maintaining public trust.

Scientific decision-making must remain independent of political influence. The premature promotion of hydroxychloroquine and ivermectin was strongly shaped by political leaders and ideological groups rather than by robust scientific evidence. 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 for ensuring patient safety and sustaining public trust in health systems.

Public communication should clearly articulate the evolving nature of scientific evidence, explicitly acknowledge inherent uncertainties, and directly and transparently address misinformation disseminated through media platforms and social networks. Clear, consistent, and evidence-based communication is essential to prevent premature public acceptance of unproven therapies and to maintain confidence in public health decision-making.

9. Conclusions

Hydroxychloroquine and ivermectin were initially regarded as promising therapeutic candidates for the management of COVID-19, based on early laboratory findings and proposed mechanistic rationale that appeared plausible during a period of global clinical urgency. As evidence from large randomized controlled trials accumulated, it became evident that neither drug showed meaningful improvement in clinical outcomes or reliable prevention of infection. In response, health authorities restricted their use to clinical trial settings due to safety concerns and the absence of demonstrated therapeutic benefit. The experience with these agents illustrates how rapidly optimism can outpace evidence when fear, uncertainty, and political influences converge. The rapid adoption of unproven therapies revealed vulnerabilities in the interpretation and communication of scientific evidence during public health 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. Premature promotion of therapies before their safety and efficacy are established can result in patient harm, erosion of public trust, and diversion of resources away from interventions with proven clinical benefit. Future pandemic preparedness should prioritize the rapid initiation of large, well-designed clinical trials, adherence to the principles of evidence-based medicine, and clear, transparent communication of emerging findings.

List of Abbreviations

ACE2	Angiotensin-Converting Enzyme 2
ACTIV-6	Accelerating COVID-19 Therapeutic Interventions and Vaccines-6 Trial
COVID-19	Coronavirus Disease 2019
EMA	European Medicines Agency
EUA	Emergency Use Authorization
FDA	United States Food and Drug Administration
HCQ	Hydroxychloroquine
IVM	Ivermectin
NIH	National Institutes of Health
ORCHID	Outcomes Related to COVID-19 treated with Hydroxychloroquine among Inpatients with symptomatic Disease
PRINCIPLE	Platform Randomized Trial of Interventions against COVID-19 in Older People
QT interval	Interval between Q and T Waves on Electrocardiography
RECOVERY	Randomized Evaluation of COVID-19 Therapy
RNA	Ribonucleic Acid
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
WHO	World Health Organization

Author Contributions

The author is solely responsible for conceptualization, literature review, analysis and interpretation of the evidence, writing—original draft preparation, writing—review and editing of the manuscript. The author has read and agreed to the published version of the manuscript.

Conflicts of Interest

The author declares no conflicts of interest. The Editor-in-Chief is affiliated with the same institution as the author. To ensure transparency and avoid any potential conflict of interest, the Editor-in-Chief was not involved in the peer-review process, editorial assessment, or decision-making for this manuscript. The manuscript was handled independently by an alternate editor.

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