GLOBAL TRENDS IN CLINICAL TRIALS OF IVERMECTIN FOR COVID-19 (2026)

Review article

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INTRODUCTION

The authors compiled, organized and analyzed 91 clinical trials of ivermectin, a macrolide anti-infective compound, against the novel coronavirus (SARS-CoV-2) infection (COVID-19). These clinical trials were registered with public registration agencies and conducted in 27 countries around the world as of March 2021, and the results presented in a Japanese[1] and English[2] review published in this journal.

Subsequently, clinical trials of ivermectin for COVID-19 continued to increase worldwide. By November 2023, two years and eight months later, 169 clinical trials in 39 countries had been registered. An additional 54 unregistered clinical trials had been published, bringing the total overview to 223 clinical trials—including the registered trials. The results of 101 of these clinical trials were reported, along with 27 systematic reviews and meta-analyses conducted on 69 clinical trial results papers from 24 countries. The authors summarized and analyzed these findings, presenting them in a review in Japanese [3] and English[4] published in this journal.

Although COVID-19 was treated as a single infectious disease, the causative virus—SARSCoV-2—is unique and mutates rapidly, exhibiting high variability. Mutant strains continued to evolve over time and manifest with different infectivity and pathogenicity. Therefore, it is appropriate to consider the early and later stages of the global pandemic of COVID-19 as an infectious disease with different inherent pathologies. The initial Wuhan strain had limited infectivity, but remarkably high pathogenicity. This resulted in a high mortality rate, due to severe lung inflammation. On the other hand, the Omicron variant, which spread widely around the world from around January of 2022, was highly contagious and caused a significantly large number of cases. With the Omicron variant, however, infection symptoms were primarily limited to the upper respiratory tract—extending to the level of the larynx. Severe lower respiratory tract infections involving the bronchi and lungs rarely occurred. This denoted a weak inherent pathogenicity. Such changes in the pathogenicity of COVID-19 over time are a significant variable behind the conduct and progression of clinical trials involving ivermectin. The authors investigated the global trends of the SARS-CoV-2 mutant strains—up to that time—and published an additional review in this journal in Japanese[5] and English[6], along with the development status of therapeutic drugs.

This review will organize and analyze clinical trial results that were not available at the time of writing the three above-mentioned reviews, and results that have since

been published. We will analyze the outcomes of these clinical trials, as well as summarize and discuss the results of basic research that forms the basis for clinical trials and general discussions.

1. REVIEWS AND GENERAL DISCUSSION OVERVIEWS RELATED TO COVID-19 TREATMENT

In the authors' previously published review article, they analyzed and discussed 430 articles and information collected at the time of the writing. Subsequently, over 300 published papers and additional information have been collected, and each article and piece of information has been classified and organized according to its content. This section provides an overview of 12 general reviews and summaries concerning attempts to treat COVID-19 through the off-label use of existing pharmaceuticals.

In the treatment of COVID-19, the off-label use of existing drugs is termed "repurposing drugs".[7,8] In the United States, the Food and Drug Administration (FDA) granted Emergency Use Authorization (EUA) for hydroxychloroquine on March 20, 2020. This authorization was revoked on June 16th of the same year, due to doubts about the drug's efficacy. This served as the precedent. In the past, chloroquine was approved in Japan in 1955 as an antimalarial drug. Its indications were subsequently expanded, based on its anti-inflammatory properties, to include nephritis, rheumatoid arthritis, bronchial asthma, and epilepsy. However, its use in the treatment of chronic nephritis led to the occurrence of "chloroquine retinopathy" caused by high-dose administrations. This resulted in the discontinuation of its manufacture in 1974. Hydroxychloroquine, on the other hand, was approved in the United States in 1955 for the treatment of malaria, systemic lupus erythematosus (SLE), and rheumatoid arthritis. In Japan, it was approved in July of 2015 as a treatment for both systematic and cutaneous lupus erythematosus. Remdesivir was approved as the second EUA on May 1, 2020. It is an antiviral drug that has been under development since around 2015 as a treatment for Ebola hemorrhagic fever. It was subsequently repurposed for off-label use in COVID-19.

Ivermectin is an oral medication approved in the United States in October of 1998 for the treatment of strongyloidiasis and onchocerciasis. Its off-label use9) rapidly increased around November in 2020, while COVID-19 was rapidly spreading in the United States. As such, it could be considered a typical example of a repurposed drug, although it has not received EUA approval.

Figure 1 shows the progression of COVID-19 pathology as currently elucidated to date. Viral load peaks 2 to 3 days after infection and then declines, largely disappearing by day 5. If recovery begins at this stage, the illness resolves as a mild case. However, when the viral infection progresses

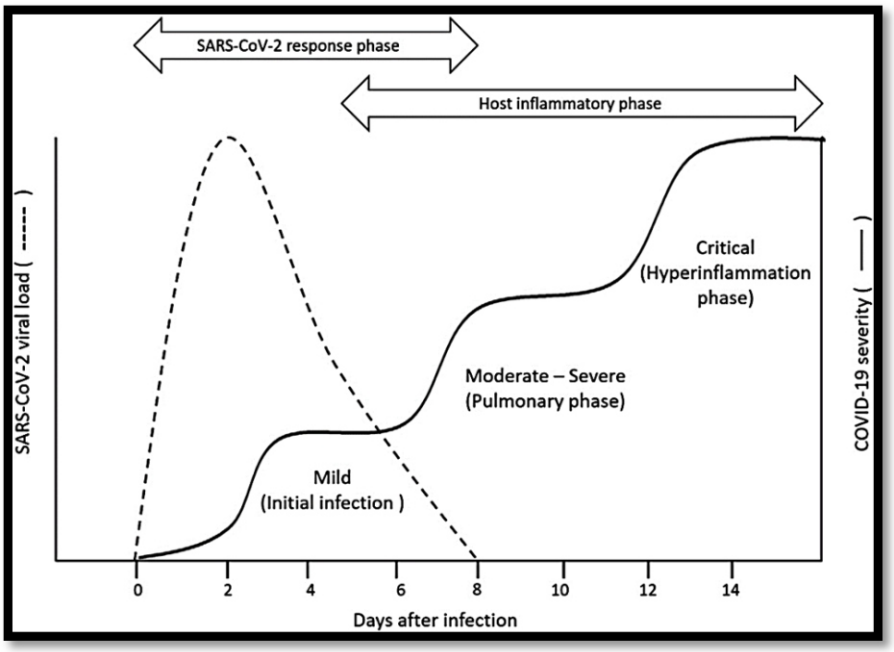

FIG. 1. COVID-19 PATHOLOGICAL CHANGES

to pulmonary inflammation (lower respiratory tract symptoms), the condition worsens to a moderate or severe state that requires medical interventions such as hospitalization, respiratory support, and even intensive care. Furthermore, when suppression of the host's inflammatory response becomes ineffective, the condition progresses to a state of excessive inflammation, leading to a critical state where life-saving measures requiring extracorporeal circulation by use of extracorporeal membrane oxygenation (ECMO) are necessary. This type of pathological progression seen with COVID-19 has not been observed in other conventional viral infections. While the majority of cases present only with mild upper respiratory symptoms and can be managed as outpatients, it is crucial to recognize that if the infection progresses to lower respiratory symptoms, it can quickly become difficult to treat, even intractable, leading to severe consequences due to excessive inflammatory host response. This makes COVID-19 an extremely complex viral infection.

As COVID-19, an emerging infectious disease, spread globally as a pandemic, inflicting severe illness and high mortality rates, repurposed drugs with potential as treatments were investigated. Chowdhury *et al*. (China, 2021) discussed monotherapy and combination therapy with ivermectin, doxycycline, vitamins D and C, zinc, and cannabidiol. Rakedzon *et al*. (Israel, 2021)[11] discussed the potential of nine antiparasitic drugs for COVID-19 treatment, while Kato *et al*. (Japan, 2022)[12] discussed the potential of eighteen existing drugs as repurposed treatments. Baracaldo-Santamaria *et al*. (Colombia, 2022)[13] discussed the efficacy and safety of hydroxychloroquine, nonsteroidal anti-inflammatory drugs, ivermectin, azithromycin, vitamins, aspirin, and chlorine dioxide. Some of these are even commonly used self-medication drugs. Martinez (Spain, 2022)[14] noted that existing antiviral drugs (various anti-HIV drugs and antiviral hepatitis drugs, favipiravir, remdesivir) had not demonstrated clinically proven efficacy against COVID19. It was further argued that developing compounds with mechanisms of action specific to SARS-CoV-2 viral infection is necessary for anti-COVID-19 drugs. Meanwhile, Menéndez (Spain, 2022)[15] discussed the potential for developing COVID-19 therapeutics from a medicinal chemistry perspective. Noting that the pathological state of COVID-19 progresses from an initial viral disease phase of SARS-CoV-2 infection to a more severe pulmonary inflammatory stage, and even further to a state involving the induction of an excessive inflammatory host response, this author advocated for the necessity of therapeutics tailored to different stages of the disease.

Lei *et al*. (China, 2022)[16] explained that for the purpose of treating COVID-19, efforts are underway to repurpose existing drugs that affect each stage of SARS-CoV-2 pathogenicity. Such efforts include: RNA-dependent RNA polymerase and main protease reactions, host cell responses, and immune regulatory pathways involved in disease progression (such as the involvement of the JAK/STAT pathway and NF-κB). They discussed the correlation between this basic research, preclinical studies, and clinical trials. Nabi-Afjadi *et al*. (Iran, 2023)[17] provided comprehensive information on the safety and efficacy of ivermectin for COVID-19 treatment—a topic still generating controversy—based on available data. They provide an overview of research findings of ongoing clinical trials on the mechanisms of action of ivermectin, from the initial stage of SARS-CoV-2 infection to the stage of heightened host inflammatory responses, including the phase of COVID-19-associated energy metabolism abnormalities.

The aforementioned reviews and overviews discuss the efficacy and safety of repurposed drugs in the treatment of COVID-19. On the other hand, Gandhi et al. (USA, 2024)[18] argued that the nirmatrelvir/ritonavir combination therapy, which received EUA in December of 2021, is the only therapeutic with confirmed clinical efficacy. However, as stipulated in COVID-19 treatment guidelines, its use is restricted only to patients who are at a high risk of worsening symptoms— they also discussed the high frequency of COVID-19 recurrence after its use as a treatment. Therefore, they stated that despite gaining extensive knowledge about SARS-CoV-2 infection treatment, a definitive solution has yet to be found.

2. BASIC RESEARCH ON THE EFFICACY OF IVERMECTIN AGAINST COVID-19

Given the sheer number of clinical trials being conducted, one would normally expect foundational research—which provides the theoretical basis for such trials—to be conducted on a scale several times larger

than the number of clinical trials. However, in the case of ivermectin for COVID-19, the number of foundational studies is remarkably low. Under such circumstances, the review article [19] by Zaidi *et al*. from Italy, published in the January of 2022 issue of The Journal of Antibiotics, has received high recognition with over 320,000 page views, 49 citations, and an Altmetric score of 4,643. It highlights the diverse actions of ivermectin against SARS-CoV-2 infection, including: (1) direct effects on SARS-CoV-2, (2) effects on host targets involved in viral replication, (3) effects on host targets involved in inflammation, and (4) effects on other host targets. In particular, regarding ivermectin's anti-inflammatory effects, research findings from 2007 to 2019—prior to the emergence of COVID-19—were also analyzed in relation to the course of SARS-CoV-2 infection, contributing to a better understanding of ivermectin's diverse mechanisms of action.

Using the classification by Zaidi *et al*. as a reference, we organized and analyzed 60 papers on basic research collected by our group, with the results shown in Table 1. In this organization and analysis, papers were first classified based on their primary research topic. Subsequently, the research techniques were categorized into conventional in vitro or in vivo studies (wet studies) and in silico studies (dry studies) using methods such as molecular docking on computers, indicated by the listed reference numbers.

The antiviral effects of ivermectin against SARS-CoV-2 include: (1) inhibiting viral replication, (2) disrupting the process by which the virus binds to the host cell surface and invades the cell, (3) interfering with the processing of polypeptides produced by translating the viral genetic information into multiple active peptides by the main protease (Mpro), (4) the activity of generated NSP13 helicase, NSP12 RNA-dependent RNA polymerase (RdRp), and structural protein N nucleocapsids, and (5) inhibition of the importin transport system that transports multiple proteins essential for viral replication into the cell nucleus. Additionally, ionophore-like effects and inhibition of the virus's ability to evade the host immune system have also been reported. These antiviral mechanisms are being discussed in relation to the early, mild phase of COVID-19 infection.

In contrast, it has been reported that during the progression of COVID-19 beyond the mild phase caused by the viral infection, through the host's inflammatory response leading to moderate to severe illness and ultimately even critical illness, ivermectin inhibits several stages of the processes by which the SARS-CoV-2 virus triggers reactions via various host cell receptors such as TLR-4—ultimately resulting in a cytokine storm in the host. The papers concerning these anti-inflammatory effects—or host immune modulation effects—are categorized and presented in Table 1.

Furthermore, Scheim et al. (USA, 2021–2023) have elucidated [43-45] that ivermectin inhibits red blood cell agglutination and thrombosis caused by the SARS-CoV-2

Action of ivermectin	In vitro/in vivo studies (reference number)	In silico studies (reference number)
Action against SARS-CoV-2		
1) Antiviral action	19~27, 72, 75	70, 71
2) Binding with spike protein	28	47~53
3) Inhibition of invasion into cell	19, 29, 30	54~57, 61
4) Inhibition of peptide processing	19, 29	47, 49, 58~61, 76
5) Inhibition of helicase	24, 25, 31	62, 63
6) inhibition of RNA-dependent RNA polymerase	19, 32	47, 56, 57, 64, 65
7)Inhibition of transfer into nucleus (importin)	9, 23~25, 29, 32~37	49, 63,66, 77,78
8) Ionophore activity	19, 38	
9) Inhibition of viral escape from host immunity		47
Effects on host responses involved in inflammation		
1) Anti-inflammatory action	19, 39, 73, 74	
2) Inhibition of JAK/STA pathway	19, 29, 32, 40	
3) Inhibition of TNF receptor/TRADD pathway	41	
4) Inhibition of TLR-4/NF-κB pathway	19, 41, 42	67
5) Immunomodulation (decrease of IL-6/IL-10) and others	19, 46	
Other actions against host targets		
1) Blood coagulation/CD-147 inhibition	19, 43~45	48, 68, 69
2) Inhibition of α-nicotinic acetylcholine receptor		48
3) Improvement of blood oxygen saturation (SpO2)	44, 45	

TABLE 1. BASIC RESEARCH ON THE EFFECTS OF IVERMECTIN AGAINST COVID-19

spike protein. The mechanism involves the proven inhibition of the spike protein binding to CD-147, which is present on the surface of red blood cells. Moreover, it has been reported[79] in 2024 that ivermectin possesses the ability to dissolve microthrombi formed within blood vessels due to SARS-CoV-2 infection. As a result of these effects, administration of ivermectin to COVID-19 patients with hypoxemia has been shown[80-84] to improve blood oxygen saturation (SpO2) levels.

Table 1 shows that 27 papers (46.6%) were classified as "in silico studies." These studies actively employ dry research methods—specifically molecular docking and molecular dynamics simulations—to numerically analyze the binding between target proteins and ligands, thereby elucidating the diverse mechanisms of action of ivermectin against COVID-19. In computer molecular docking analysis, ivermectin has been confirmed to exhibit extremely high binding affinity for the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein, the host cell receptors ACE2 and TMPRSS2 proteins, RdRp, Mpro, and others. Furthermore, some research shows that ivermectin strongly binds to the α subunit of the host cell's nuclear transport system, the importin (IMP) α/β1 system, preventing the β subunit from binding. This inhibits the transport of proteins essential for SARS-CoV-2 viral replication within the host cell into the nucleus. This inhibitory mechanism has also been examined in detail through in silico analysis.

3. PHARMACOLOGICAL AND PHARMACEUTICAL RESEARCH ON IVERMECTIN FOR COVID-19

The dosage of ivermectin has been 150 μg per kg of body weight administered orally once to three times per year since the implementation of onchocerciasis control programs in Africa in 1987. However, in 2001, France began administering 200 μg per kg of body weight orally twice at two-week intervals for the treatment of scabies. Pharmacokinetic studies in humans at these standard doses were summarized[85] as a mini-review by González Canga *et al*. (Spain, 2008); however, at that time, the effect of food on the absorption of ivermectin had not been elucidated. Ivermectin is a lipophilic compound with a macrolide skeleton. During its initial development phase, it was administered on an empty stomach to avoid the influence of food and ensure consistent oral absorption. However, Duthaler *et al*. (Switzerland, 2020) reported [86] that when administered orally after a high-fat meal, it demonstrated 1.2 times the oral absorption compared to administration on an empty stomach.

As off-label use of repurposed drugs such as ivermectin for the prevention and treatment of COVID-19 has become more common, pharmacologic and pharmaceutical findings have begun to be reported. These evaluation techniques are based on pharmacokinetic/pharmacodynamic (PK/PD) theory commonly used in antibacterial chemotherapy and are discussed by comparing the drug concentrations demonstrating antiviral activity obtained in in vitro experiments with the blood concentrations or tissue concentrations achieved during drug administration. Arshad et al. (UK, 2020) compared[87] the maximum plasma concentration (Cmax) and the partition coefficient (KpUlung) of free drug between lung and plasma tissues with the EC50 for 56 existing drugs with reported antiviral activity (EC50) and pharmacokinetics. They reported that the lung tissue concentrations of 8 drugs, including ivermectin, reached 10 times their EC50. On the other hand, it has been debated[88-90] that the Cmax of ivermectin at the standard dose is significantly lower than the EC50 values (2.2–2.8 μM) reported22) by Caly *et al*. (Australia, 2020), requiring 10–50 times the standard dose to cover the EC50 range. Jermain et al. (USA, 2020) estimated[91] human lung tissue concentrations of ivermectin based on concentrations in dairy cows and pharmacokinetic data from phase 1 clinical trials in healthy adults. They concluded that a dose of 120 mg—ten times the standard dose—would be required to achieve the IC50 value (2 μM ＝ 1,750 ng/mL) for suppressing SARS-CoV-2.

These PK/PD discussions regarding ivermectin's effects on SARS-CoV-2 are theoretically sound, but they are limited by the fact that the anti-SARS-CoV-2 activity (PK information) relies solely on the report [22] by Caly et al. As described in the "6. Conclusion" section of our previous reports[1,2], SARS-CoV-2 replication inhibition experiments of Caly et al. were designed with conditions favorable to the virus and unfavorable to the inhibitors, specifically to avoid false positive results. The SARS-CoV-2 strain used in Caly et al.'s experiment was a β variant isolated from a 58-year-old male who arrived in Australia from

Wuhan, China in January of 2020 and developed symptoms. It was designated BetaCoV/Australia/VIC01/2020 and is a highly virulent strain preserved by inoculation into Vero/hSLAM cells. In the replication inhibition experiment using ivermectin, Vero/hSLAM cells, which are suitable for viral growth, were infected at a high MOI of 0.1. After 2 hr of incubation, ivermectin was applied at a concentration of 5 μM. Subsequently, over time, the viral RNA levels in the cell fraction and culture supernatant, E gene RNA levels, and RNA-dependent RNA polymerase gene RNA levels in both the cell fraction and culture supernatant were measured. Results showed a 5,000-fold reduction in viral RNA at 48 hr (IC50 ═2.2–2.8 μM).

Those with experience in viral replication inhibition experiments will readily understand that the IC50 value can vary by a factor of 100 or even 1,000 depending on experimental conditions such as the combination of virus strain and host cell, the timing and amount of inoculation, the culture medium, and the incubation temperature. Adjusting the sensitivity and precision of the experimental system based on what the experiment aims to observe is standard practice in in vitro research. The sensitivity set by Caly et al. at an IC50 of approximately 2 μM appears to be appropriate, yielding neither false positives nor false negatives. Setting the sensitivity of this assay to 10-fold increases the IC50 to approximately 0.2 μM, while setting it to 50-fold increases the IC50 to approximately 0.04 μM. However, assays with high sensitivity are susceptible to various factors, leading to inconsistent results and reduced precision. Therefore, the evaluation of Caly *et al.*'s paper is solely that it demonstrated ivermectin possesses anti-SARS-CoV-2 activity—nothing more, nothing less. It would be an excessive leap to directly extrapolate Caly *et al.*'s experimental results to assess clinical efficacy in humans.

Duenas-Gonzalez (Mexico, 2021) proposed [92] that, regarding the aforementioned PK/PD debate surrounding Caly *et al.*'s paper, since administration of ivermectin at 2 mg/kg—10 times the usual dose—is safe and yields an AUC (5,249 μM·hr) where efficacy is expected, studies should be conducted to examine the correlation between dose and PK/PD, including the high dose of 2 mg/kg, before initiating phase 3 clinical trials.

Ivermectin is a liposoluble compound with a macrolide skeleton. In South America, an oral liquid formulation containing 10% ethanol and 70% propylene glycol is commercially available. Already, in the 2008 paper by González Canga et al., it was stated [85] that the liquid formulation of ivermectin (ethanol solution) exhibits approximately twice the bioavailability compared to tablets or capsules. This indicates that the bioavailability of conventional ivermectin tablets is significantly low at 50% or less, suggesting that formulation studies in the pharmaceutical field are necessary to improve oral absorption. In addition, Ceballos *et al.* (Argentina, 2023) conducted [93] PK analyses in healthy adults after administering ivermectin tablets, capsules, and oral solutions. They reported that the oral solution had an AUC of 1,653 ng hr/mL, compared to 1,056 ng hr/mL for the tablets and 996 ng hr/mL for the capsules.

Ivermectin has been used as a broad-spectrum antiparasitic drug in both veterinary and human medicine, with various dosage forms developed to suit the specific pathophysiology of the disease. Prior to the COVID-19 pandemic, researchers such as Sharun *et al.* (India, 2019)[94] had discussed the need to develop sustained-release formulations of ivermectin that could demonstrate efficacy with a single dose. As ivermectin has become widely used for both the prevention and treatment of COVID-19, active research into improving its dosage forms has intensified.

To improve oral absorption, prototypes of orally disintegrating tablets have been developed using various lubricants and disintegrants as additives in ivermectin tablets [Juan *et al.* (Argentina, 2023)[95]], and attempts have been made to freeze-dry ivermectin as an oil-in-water emulsion [Madawi *et al.* (UAE, 2025) [96]]. Furthermore, studies have been conducted on formulation techniques applying micro/nanotechnology to improve the pulmonary tissue transfer of ivermectin [Formiga *et al.* (Brazil, 2020) [97], Madrid *et al.* (USA, 2021) [98], and Surnar *et al.* (USA, 2020)[99]].

Meanwhile, intranasal ivermectin preparations have been attempted as potential treatments during the initial phase of COVID-19 infection when upper respiratory symptoms are present. Errecalde *et al.* (Argentina, 2021) developed [100] a nasal spray formulation and conducted safety and PK studies in a piglet model, reporting that high nasopharyngeal concentrations were achieved within a

short time. Wissel *et al*. (2025) at HWI Pharma services GmbH in Germany administered [101] a 5% ivermectin nasal spray solution to 14 healthy adults. A randomized, controlled Phase 1 clinical trial comparing a treatment group to 14 cases in a placebo group was conducted (EudraCT No. 2022-002670-82), and the tolerability, safety, and pharmacokinetics were evaluated. As a result, intranasal administration of ivermectin demonstrated excellent tolerability, with no adverse reactions observed beyond local nasal symptoms, and exhibited favorable pharmacokinetic properties. Additionally, attempts have been made to achieve sufficiently high pulmonary tissue concentrations for therapeutic purposes through the administration of inhaled ivermectin formulations, as reported by Mittal *et al*. (India, 2021)[102], Albariqi *et al*. (Australia, 2022),[103] and Saha *et al*. (New Zealand, 2022)[104].

As the clinical use of ivermectin for COVID-19 expands, numerous products are being used worldwide, and the quality control of these formulations is an important consideration in the field of pharmacy. In our previous reports[3,4], we listed the ivermectin preparations commercially available in India—a survey conducted in October 2023 identified 27 products manufactured and sold by 26 companies. Bhorat *et al*. (South Africa, 2021) conducted [105] an analysis combining highperformance liquid chromatography and mass spectrometry on five tablet formulations and two capsule formulations of ivermectin marketed for human use. They found that four tablet formulations contained one or more impurities (substances other than the listed active ingredient) in addition to the two main components. The presence of impurities significantly impacts the efficacy and safety of the drug, necessitating an evaluation of the quality of ivermectin used in any clinical trials.

4. INFORMATION ON IVERMECTIN'S ADVERSE EFFECTS AND TOXICITY IN COVID-19 CLINICAL SETTINGS

Ivermectin, first used in 1987 for onchocerciasis control programs in West Africa, has since been employed to treat lymphatic filariasis, intestinal strongyloidiasis, and scabies. By 2022, it was reported to have been administered to 3.7 billion people across more than 50 countries worldwide. Due to its low dosage per administration and the small number of required doses, it has been considered a drug with extremely few side effects. As such, ivermectin, which has been considered highly safe, has been used in a remarkably large number of cases across many countries worldwide for the prevention and treatment of COVID-19—under circumstances where there are no established guidelines for its administration or dosage. Consequently, a significant amount of information regarding its side effects and toxicity has been reported. The most serious problem arises when individuals purchase over-the-counter veterinary ivermectin formulations due to the unavailability of human-use preparations and ingest them in excessively large quantities, leading to the onset of side effects. The use of veterinary formulations in humans must be strictly prohibited.

In the WHO Onchocerciasis Control Program, which distributed ivermectin on a large scale across a wide area, De Sole *et al*. (Burkina Faso, 1989) reported [106] that 9% of the participants experienced side effects. However, only 2.4% were moderate and 0.24% were severe. The majority of these were attributed to a drop in blood pressure caused by the rapid death of microfilariae parasitizing the skin and subcutaneous tissues. That is, the primary adverse effects were found to occur as a result of ivermectin exerting its therapeutic effect and killing the parasites. The frequency of adverse effects caused by ivermectin itself was shown to be remarkably low.

An interesting paper [107] is the study by Guzzo *et al*. (2002) from Merck & Co., Inc., the developer of ivermectin, which examined the safety, tolerability, and pharmacokinetics of highdose, frequent administration in 68 healthy adults. In trials involving a single dose of 60 mg (five times the usual dose) administered three times weekly or a single dose of ten times the standard dose (120 mg) three times weekly, no adverse effects were observed, including those affecting the central nervous system. In the pharmacokinetic analysis, AUC and Cmax showed a near-linear correlation with dose. Tmax was observed at 4 hr, and the plasma half-life was approximately 18 hr. The AUC was found to be 2.6 times higher after administration with food compared to administration on an empty stomach. Thus, while the safety of high-dose frequent administration was confirmed by the company's own clinical trials, the company still stated concerns about ivermectin's safety in its February 4, 2021 company statement [108] regarding the use of ivermectin for

COVID-19, creating a clear contradiction.

In Brazil, de Castro Jr. *et al*. (2020) administered high-dose ivermectin (1 mg/kg/day) for 14–15 days to a series of pediatric patients with poorly defined acute myeloid leukemia. They observed [109] no particular side effects and confirmed its safety, arguing that ivermectin can therefore be administered for COVID-19 without concern for side effects. On the other hand, regarding the use of ivermectin for the prevention or treatment of COVID-19, Zaheer *et al*. (Pakistan, 2021) argue [110] that appropriate regimens (dosage and administration methods) have not been established. Given the current lack of confirmed safety in patients with impaired renal or hepatic function, chronic diseases, pregnant women, and children, they argue that trials to establish appropriate dosing regimens are necessary, with careful attention to potential side effects affecting the central nervous system and liver function.

Campillo *et al*. (France, 2021 and 2022) examined [111,112] adverse events of ivermectin reported to the WHO's pharmacovigilance database (VigiBase®), and discussed that reports after 2020 —when COVID-19 emerged— increased compared to those before 2019. From the 1st of May 2020 to the 21st of December 2021, there were 1,777 reports, most of which were gastrointestinal and neurological adverse events. Among them, 35 cases, including 6 deaths, were suspected to be caused solely by ivermectin and considered serious. Based on this paper's presentation, Montastruc (France, 2022) stated [113] in an "Editorial" that ivermectin should not be used for the treatment of COVID-19. Johnson-Arbor (USA, 2022) reviewed approximately 50 papers on the mechanism of action, pharmacokinetics, antiviral effects, and side effects of ivermectin, and argued [114] that due to the potential for central nervous system side effects, ivermectin should not be used too readily for the prevention or treatment of COVID-19. Shirazi *et al*. (USA, 2022) reviewed approximately 20 clinical trial results of ivermectin for COVID-19. They argued [115] that at the standard dosage used in these trials (0.2–0.4 mg/kg), adverse events were virtually nonexistent, but the dosage was too low to demonstrate significant efficacy.

Ngan et al. (USA, 2022) proposed [116] using inhibition of human delayed rectifier potassium channel (hERG) activity and induction of drug-induced phospholipidosis as toxicological evaluation indicators for repurposed drugs used for COVID-19. The study discussed the potential for cardiotoxicity due to hERG inhibition among 331 compounds showing activity against SARSCoV-2, but concluded that the likelihood of adverse events occurring with ivermectin is low.

Ivermectin was approved for COVID-19 treatment in India, and governments in Latin American countries undertook widespread distribution. Additionally, when it became possible to obtain ivermectin over-the-counter without a prescription in various countries and regions, it resulted in its widespread use for preventing or treating COVID-19. Meanwhile, in the United States, the Centers for Disease Control and Prevention (CDC), FDA, and NIH strictly regulated the off-label use of human-grade ivermectin for COVID-19. This created an extremely dangerous situation where people purchased and ingested veterinary-grade ivermectin formulations, which were available without regulation. If human-use ivermectin preparations had been used off-label for COVID-19 under a physician's guidance, at the prescribed dosage and frequency, adverse effects from overdose could have been avoided. However, by purchasing veterinary preparations without medical supervision and self-administering them at arbitrary dosages, unexpected side effects are inevitable.
In August of 2021, the CDC issued [117] an "Official CDC Health Advisory" titled "Rapid Increase in Ivermectin Prescriptions and Serious Illness Associated with the Use of IvermectinContaining Preparations for the Prevention or Treatment of COVID-19." Data from outpatient pharmacies indicate that prior to the COVID-19 pandemic, weekly prescriptions for ivermectin averaged around 3,600. However, during the week of August 7–13, 2021—when the Delta variant caused approximately 120,000 weekly cases—prescriptions surged to 88,000, representing a 24-fold increase. The article stated a correlation between the sharp increase in prescriptions and severe side effects from ivermectin. However, such serious side effects occurred in cases involving massive ingestion of veterinary formulations. The title presented these entirely unrelated incidents—which had nothing to do with prescriptions dispensed by the aforementioned outpatient pharmacies—as if they resulted from ingestion of human-use ivermectin formulations.

Similar to CDC recommendations, despite the toxicity primarily stemming from the administration of veterinary ivermectin formulations, a paper with a title implying

adverse events from human formulations was published [118] by Temple *et al.* (USA, 2021). Of the 21 adverse event reports submitted to the Oregon Poison Center, 17 cases (80.9%) involved individuals who purchased and ingested over-the-counter veterinary ivermectin formulations. While the ingestion of veterinary formulations should be the focus of concern, there is misleading information suggesting that the clinical use of ivermectin for COVID-19 is the problem. It appeared to be a response to critical comments on the Temple et al. paper, that, in an update paper [119] by Hoang *et al.* (2022) from the same research group, the title explicitly states that the toxicity observed was induced by veterinary formulations. Adverse events associated with veterinary ivermectin formulations have also been discussed in reports by Lorente *et al*. (South Africa, 2022)[120] , Porubcin *et al*. (Slovakia, 2022)[121], and Akhlaq *et al*. (USA, 2023)[122]. Thereafter, the U.S. FDA has published [123] a Consumers Update, after the declaration ending the COVID-19 pandemic, stating that it has neither authorized nor approved the use of ivermectin for preventing or treating COVID-19. The FDA also noted that it had received reports of multiple individuals who self-administered veterinary formulations requiring medical intervention, including hospitalization.

Idonije *et al*. (Nigeria, 2011) reported [124] the emergence of sperm dysfunction as one of the side effects of ivermectin. This paper has been cited as an adverse event associated with the administration of ivermectin for COVID-19, and concerns have been raised regarding reduced sperm count and impaired sperm motility. The paper [125] by Collins *et al*. (USA, 2022) dispelled such concerns, stating that Idonije *et al*.'s survey research lacked a control group and that its findings and conclusions lacked credibility. In fact, among the 385 onchocerciasis patients studied by Idonije et al., only 37 (9.6%) had normal sperm function, indicating that onchocerciasis itself is associated with sperm dysfunction. The study discussing sperm function in these 37 apparently healthy men treated with ivermectin, conducted without a comparative control group, is deemed scientifically unreliable. Regarding this sperm dysfunction, a long-term clinical observation study by Yuan *et al*. (China, 2025) reported [126] that sperm function was significantly impaired in men who had contracted COVID-19.

The development of inhalation formulations of ivermectin was discussed in the previous section. Preclinical tolerability test results for this formulation have been reported [127] by Mansour *et al*. (Egypt, 2021). The safety of a soluble freeze-dried powder containing hydroxypropylβ-cyclodextrin was evaluated by administering 0.05 to 0.8 mg/kg to rats via pulmonary administration for three consecutive days. Dose-dependent increases in inflammatory markers such as TNF-α and IL-6 were observed. Lung tissue damage was noted at doses of 0.2 mg/kg or higher, but no abnormalities were observed in the 0.05 mg/kg and 0.1 mg/kg dose groups, confirming safety.

5. TREATMENT AND PREVENTION OF COVID-19 WITH IVERMECTIN

We collected the results of COVID-19 clinical trials of ivermectin that were either unavailable at the time of the writing of our previously published reviews1–4) or published after their completion. Ten trials registered with public clinical trial registries were identified, as shown in Table 2.

First author	Country	Year*	Registration number	Subject of trial	Ref.
Hirsch RR	Argentina	2020	NCT04425850 NCT04425863	Adoption of protocol for prophylaxis and therapy	128
Bernigaud C	France	2021	NCT02841215	Prophylaxis in long-care facility	129
Gonzalez JLB	Mexico	2022	NCT04391127	RCT in severe cases	130
Ochoa-Jaramillo F	Columbia	2022	NCT04602507	RCT in severe cases	131
Mikamo H	Japan	2024	NCT05056883	RCT for phase 3 trials in Japan and Thailand	132
Salama HAESA	Egypt	2024	NCT05930002	RCT in moderate cases	133
Siripongboonsitti T	Thailand	2024	TCTR20230403007	RCT for phase 2 with 3 drugs combination	134
Vamaseri M	Iran	2024	IRCT20200404046937N4	RCT in mild/moderate cases	135
Wijewickrema A	Sri Lanka	2024	SLCTR/2021/020	RCT in mild/moderate cases	136
Wagstaff KM	Australia	2025	ACTRN12621001535864	RCT for prophylaxis in close contact persons	137

TABLE 2. CLINICAL TRIALS OF IVERMECTIN FOR COVID-19: PUBLICLY REGISTERED TRIALS

Year: year of publication*
RCT: randomized control trial
NCT: U.S. National Library of Medicine, ClinicalTrials.gov identifier
TCTR: Thai Clinical Trials Registry
IRCT: Iranian Registry of Clinical Trials
SLCTR: Sri Lanka Clinical Trials Registry
ACTRN: Australia and New Zealand Clinical Trials Registry

Among the 10 clinical trials registered with public institutions [128-137]), 8 were randomized controlled trials (RCTs). Three reports—by Varnaseri *et al.* (Iran, 2024)[135]; Wijewickrema *et al*. (Sri Lanka, 2024)[136], and Wagstaff *et al*. (Australia, 2025)[137]—demonstrated the clinical efficacy of ivermectin, but five other reports130–134) did not show a significant effect compared to the control group.

On the other hand, 11 clinical trials not registered with public registries were collected, as shown in Table 3. The content of these trials was diverse, and none were RCTs.

Ascencio-Montiel *et al*. (Mexico, 2022)[143] examined the risk ratio for hospitalization or death through telephone follow-up after distributing treatment kits containing ivermectin and azithromycin. The hospitalization rate was 6.14% in the kit distribution group and 11.71% in the non-distribution group, indicating that the kit distribution group showed significantly better results.

Shimizu et al. (Japan, 2022)[145] reported highly intriguing clinical trial results. The study compared the incidence of gastrointestinal disorders—a side effect of mechanical ventilation—in 88 critically ill COVID-19 patients on ventilators in the ICU. The patients were divided into an ivermectin treatment group (39 patients) and a non-treatment control group (49 patients). According to the report, the group taking ivermectin had a significant reduction in the incidence of gastrointestinal issues. Furthermore, the duration of mechanical ventilation was also shortened in this group.

First author	Country	Year*	Subject of trial: Result	Ref.
Núñez AC	Mexico	2020	Outpatient/inpatient 107 cases, open trial: effective	138
Prasad A	India	2020	Case report: combination therapy in severe case: effective	139
Chuang TY	Taiwan	2021	Case report: combination with tocilizumab in severe case: effective	140
Pedroso C	Brazyl	2021	Prophylaxis in medical staff: effective (multiple dose)	141
Annie FH	USA	2022	Database analysis of mortality: not effective	142
Ascencio-Montiel IJ	Mexico	2022	Distribution of therapeutic kit: effective (mortality)	143
Ozer M	USA	2022	Inpatient 286 cases (IVM 60 cases): not effective	144
Shimizu K	Japan	2022	Intubated patients 39 cases vs 49 controls: effective	145
Llenas-Garcia J	Spain	2023	Inpatients with strongyloidiasis 96 cases: not effective	146
Corral RH	Columbia	2024	Nursing facility 475 cases (combination): effective	147
Elgohary MA	Egypt	2025	Inpatients (moderate) 310 cases: effective	148

TABLE 3. CLINICAL TRIALS OF IVERMECTIN FOR COVID-19: TRIALS NOT PUBLICLY REGISTERED

Year: year of publication*

Corral *et al*. (Columbia, 2024)[147] administered, at the time the first case of COVID-19 occurred among 475 residents at two elderly care facilities, ivermectin (0.6 mg/kg twice on days 1 and 7), nitazoxanide (500 mg twice daily for 6 days), and aspirin (100 mg every other day for 7 days). Eighty-seven individuals (18.3%) were found to be positive for SARS-CoV-2, and among them, 1 individual (1.1%) died. This mortality rate is significantly lower than the 24–45% mortality rate documented in the literature for elderly care facilities, indicating that early administration of these drugs was effective.

6. COVID-19 SEQUELAE AND IVERMECTIN

The long-term effects following COVID-19 infection are referred to as long COVID (Long COVID) or post-acute sequelae of COVID-19 (PASC). Fatigue and lethargy, joint and muscle pain, cough and shortness of breath, chest pain, hair loss, memory impairment, difficulty concentrating, headaches, depression, taste disorders, smell disorders, sleep disorders, autonomic nervous system dysfunction, and other extremely diverse symptoms appear and persist for more than two months.

Dysautonomia[149-151] in and of itself presents as dysfunction of the autonomic nervous system with symptoms such as dysregulation of heart rate, blood pressure, body temperature, respiration, digestion, etc. Postural orthostatic tachycardia syndrome (POTS)[152-156] is a specific form of dysautonomia and is considered one of the typical pathologies (a cardiovascular phenotype) of long COVID. POTS is characterized by an abnormal increase in heart rate upon rising from a lying position, causing orthostatic intolerance symptoms such as palpitations, dizziness, and fatigue.

The diverse range of symptoms and varying degrees of severity made it difficult to establish a definitive definition for the disease. However, in 2024, a committee of the National Academies of Sciences, Engineering, and Medicine (NASEM) proposed[157-160] a unified definition. Meanwhile, the National Institutes of Health (NIH) in the United States launched[149] a research initiative called RECOVER (Researching COVID to Enhance Recovery) in 2021 with a budget of $1.15 billion. This initiative aims to advance the understanding of the pathophysiology of long COVID, as well as its diagnosis, prevention, and treatment. Ramonfaur *et al*. (USA, 2024)[161], noting that RECOVER alone is insufficient, provide an overview of the status of clinical trials for long COVID being conducted worldwide.

Research into the pathogenesis of Long COVID has continued to move forward. Elliott *et al*. (USA, 2024)[162] stated that while viral persistence or reactivation may also be contributing factors, the primary mechanism is thought to be the inflammatory response triggered by COVID-19 and the resulting dysregulated immune response. This dysregulation of the immune response relates to the function of "regulatory T cells," which was recognized with the 2025 Nobel Prize in Physiology or Medicine and will be discussed in detail later. Meanwhile, Westman et al. (Sweden, 2025)[163] reported that microthrombi formed by the fibrinolytic-resistant SARS-CoV-2 spike protein are involved in the development of long COVID.

Scholkmann et al. (Switzerland, 2023)[164] cited numerous papers arguing that the SARSCoV-2 spike protein is a factor in PASC. They proposed calling the long-term symptoms occurring after COVID-19 mRNA vaccination, similar to PASC, "post-COVID-vaccine syndrome: PCVS," and discussed the similarities and differences between PASC and PCVS.

It should be noted that SARS-CoV-2, the virus causing COVID-19, has undergone temporal changes, transitioning from the initially highly virulent Wuhan strain through the α-, β-, and δ-variants to the o-variant. Rosen (USA, 2024)[165] and Xie *et al*. (USA, 2024)[166] discussed the incidence of long COVID associated with these variant transitions.

Trials on the therapeutic effects of ivermectin for PASC or long COVID have been conducted since early on—Aguirre-Chang *et al*. (Peru, 2020)[167], Al-kuraishy *et al*. (Iraq, 2022)[168], and Aref *et al*. (Egypt, 2022)[169] reported that post-COVID-19 symptoms such as fatigue, muscle weakness, autonomic dysfunction, and olfactory dysfunction improved following ivermectin treatment. Krumholz *et al*. (USA, 2023)[170] investigated the actual treatment practices for 241 cases of post-vaccine syndrome (PVS) following COVID-19 vaccination and reported that ivermectin was used in 44 cases (18%).

Hulscher *et al*. (USA, 2023)[171] discuss the spike protein as the cause of PASC occurring after COVID-19 infection or COVID-19 mRNA vaccination. They further state that ivermectin binds to the spike protein and allows for its detoxification. Clancy and Borody (Australia, 2024)[172] proposed calling the long-term effects of COVID-19 infection and vaccination "spikopathy," defining it as a T-cell-mediated autoimmune disorder caused by the prolonged presence of the SARS-CoV-2 spike protein in the body. Ivermectin demonstrates an effect that reverses the symptoms caused by this spikopathy. Treatment with ivermectin may block the host's humoral and cellular immune mediator responses upon exposure to the spike protein. Therefore, it is predicted that ivermectin will improve long-term symptoms associated with COVID in patients. The authors proposed a protocol involving administration of 12 mg of ivermectin daily for 14 days (in combination with vitamin D).

Furthermore, Yang et al. (Taiwan, 2023)[173] analyzed the effects of ivermectin and six antioxidants from a pharmacogenomic perspective. Their approach is based on the hypothesis that antioxidants are effective in improving long COVID symptoms, and they have elucidated the possibility of potential genome-level

Country	First author (Year of publication)
USA	McCullough PA (2020)[187], Jahan Z (2020)[188], DiNicolantonio JJ (2020)[189], Santin AD (2021)[190], Kory P (2021)[191, 192], Efimenko I (2022)[193], Pincus SH (2022)[194], Gkioulekas E (2023)[195], Scheim DE (2024)[196], Gkioulekas E (2025)[197, 198], Chamie JJ (2023)[199]
Mexico	Abreu JL (2020)[200]
Peru	Salvador-Carrillo J (2024)[201]
Argentina	Hirsch RR (2020)[202]
Spain	Cobos-Campos R (2021)[203]
Iran	Khanghah RR (2022)[204], Barati N (2022)[205]
Lebanon	Wehbe Z (2021)[206]
UAE	Awad H (2022)[207]
Israel	Schwartz E (2022)[208, 209]
Egypt	Masoud HH (2020)[210]
Tanzania	Osati EFO (2024)[211]
South Africa	Aldous C (2024)[212]
India	Pareek RP (2020)[213], Dixit A (2020)[214], Mathachan SR (2021)[215], Sharma SK (2022)[216], Eerike M (2022)[217], Karim A (2024)[218]
Pakistan	Chaudhry MW (2021)[219]
Bangladesh	Alam S (2021)[220]
Malaysia	Munir MZ (2023)[221]
China	Yang S (2022)[222]
Japan	Ohe M (2021)[223]
Australia	Kalfas S (2020)[224]
New Zealand	Boretti A (2022)[225]

TABLE 4. REVIEW ARTICLES ON THE CLINICAL USE OF IVERMECTIN FOR COVID-19 [WITH POSITIVE CONLUSIONS]

examined the preventive effects of nationwide mass distribution and evaluated the protocols involved for preventive administration. Chamie *et al*. (USA, 2023)[199] analyzed the impact of mass distribution of ivermectin in Peru on excess death during the COVID-19 pandemic. They confirmed that among individuals aged 60 and older across 25 regions of the country, excess death decreased to one-fourteenth during distribution but increased 13-fold two months after distribution ceased, prompting debate over ivermectin's efficacy.

On the other hand, a review of multiple papers concluding that ivermectin is effective against COVID-19 reveals that 12 such papers, as shown in Table 5, ultimately refrain from judging its efficacy due to reasons such as insufficient trial protocols or sample sizes. This group of 12 papers provides objective and/or neutral commentary.

Among these, four papers addressed multiple repurposed drugs, while eight focused exclusively on ivermectin; the majority of these were commentaries based on literature searches or citations from other review articles. Among these commentaries, a noteworthy point raised is the concern that, overall, no trials have been conducted to evaluate the appropriate dosage and administration of repurposed drugs for clinical use against COVID-19. Instead, clinical trials for COVID-19 are being conducted using the dosage and administration intended for the drugs' original indications. Furthermore, the commentary states that since the clinical trials of these repurposed drugs for COVID-19 are not trials conducted by pharmaceutical companies—many are mostly small-scale, physician-led studies—they cannot be considered high-quality trials. Therefore, it is not possible to conclude whether or not efficacy has been demonstrated.

Seven papers presenting negative reviews of ivermectin's clinical efficacy against COVID19 were collected, as shown in Table 6. One paper covered multiple repurposed drugs, while the other six reviews focused exclusively on ivermectin.

Among these seven papers, the study [241, 242] by Hill *et al*. (UK, 2022 and 2021) contains highly unusual content and has sparked controversy. The controversy stems from the fact that when their meta-analysis paper[242] was first published in July of 2021 after peer review, it described results indicating that among the 24 RCTs included, 11 targeted moderate/severe cases, and in those cases, ivermectin demonstrated a favorable effect, significantly reducing mortality by 56%. However, when published in print in November of that same year, it concluded that based on 23 meta-analyses, ivermectin did not show a statistically significant increase in survival rates.

involvement. Additionally, attempts at treatment with ivermectin are described in review articles[174-177]) discussing the etiology, pathogenesis, and treatment of long COVID.

On the other hand, Koc *et al*. (China, 2022)[178] have expressed skepticism that ivermectin can suppress the onset of long COVID, citing methodological limitations in the clinical trials of ivermectin for COVID-19 found in the literature. Additionally, Manu (USA, 2023)[179] stated that no trials of ivermectin for long COVID had been conducted and, based on the results of the Active-6 and COVID OUT trials conducted in the USA, no clinical efficacy of ivermectin for COVID-19 had been demonstrated, leading to the inference that it was also ineffective for long COVID.

Nevertheless, Lee *et al*. (USA, 2025)[180] note that, mitochondria are involved with the regulation of the NLRP3 inflammasome; when the former are stressed or damaged, the latter is activated by the release of mitochondrial reactive oxygen species (mtROS)—the resultant dysfunction can be a central driver to inflammation, immune response, and overactivation seen in chronic diseases. Lee et al. further note that "ivermectin resulted in a reduction in biomarkers of oxidative stress" and "suppressed NLRP3", thereby "supporting the antioxidant and anti-inflammatory effects of ivermectin."

It is speculated that the function of regulatory T cells may be involved in the progression of COVID-19 disease and the onset of long COVID. Haunhorst et al. (Germany, 2022)[181] proposed that dysregulation of Treg composition in COVID-19 patients during recovery is involved in the development of long COVID. Dhawan *et al*. (India, 2023)[182] argued that a smaller Treg/Th17 ratio in COVID-19 patients correlates with worsening disease severity and an increased likelihood of developing long COVID. Liu *et al*. (China, 2024)[183] emphasized the importance of the Th17/Treg balance in inflammatory diseases and Korobova et al. (Russia, 2025)[184] discussed the dynamics of various regulatory T cells (Th1, Th2, Th17, Tfh, etc.) during the course of COVID19 and long COVID.

Regarding the effect of ivermectin on the Th17/Treg balance, Xie *et al*. (China, 2023)[185] reported that in a mouse model of autoimmune encephalomyelitis, that ivermectin prevents the infiltration of inflammatory cells into the central nervous system, promotes Treg cell activity, and inhibits the secretion of IFN-γ and IL-17 by inflammatory Th1 and Th17 cells. Hazan *et al*. (USA, 2025)[186] speculated that ivermectin influences intestinal immunity by promoting the cholinergic anti-inflammatory pathway, a component of the "gut-brain axis," thereby increasing beneficial gut microbiota such as Bifidobacterium and improving the pathophysiology of COVID-19 and long COVID.

The Th17/Treg balance is implicated in the onset and suppression of PASC or long COVID. Therefore, it is desirable to conduct appropriate clinical trials to evaluate the efficacy of ivermectin's involvement in the promotion of Treg cell activities and COVID-19 sequelae.

7. REVIEWS RELATED TO CLINICAL TRIALS OF IVERMECTIN FOR COVID-19

We organized and analyzed 57 published materials[187-244], mainly review articles, that provide an overview of individual clinical trials of ivermectin for COVID-19. Thirty-seven studies discussed the efficacy of ivermectin, twelve presented neutral opinions stating it was premature to conclude if it was effective, and eight offered negative opinions, such as suggesting bias in the trials claiming efficacy.

Literature discussing the efficacy of ivermectin includes, as shown in Table 4, a review[187] by McCullough *et al*. in the United States. Thirteen papers covered multiple drugs, including combination therapy, while 24 focused exclusively on ivermectin. The scope of the literature is diverse, encompassing studies limited to COVID-19 treatment versus those including prevention, and those restricted to mild disease versus those addressing hospitalization and severe cases.

In treatment-related papers, many conclude or discuss that while the efficacy of ivermectin has been recognized, large-scale RCTs are necessary to obtain definitive evidence. It has been proposed that, when evaluating the therapeutic efficacy of ivermectin, improvement in the patient's SpO2 should be used as an indicator. It has also been proposed that emphasis should be placed on ivermectin's activity in inhibiting red blood cell agglutination caused by SARS-CoV-2 infection.

Regarding preventive administration, studies have

Country	First author (Year of publication)
USA	Parvathaneni V (2020)[226], Kaur B (2024)[227], Halma M (2025)[228]
Mexico	Castillejos-López M (2022)[229]
Peru	Farfán-Castillo AM (2022)[230]
Brazil	Marques LLM (2024)[231]
Egypt	Salama HAESA (2022)[232]
India	Rao MVV (2021)[233], Kaur H (2021)[234]
Indonesia	Alfaqeeh M (2023)[235]
Japan	Watari T (2022)[236]
Australia	Jans DA (2021)[237]

TABLE 5. REVIEW ARTICLES ON THE CLINICAL USE OF IVERMECTIN FOR COVID-19 [WITH OBJECTIVE AND/OR NEUTRAL CONCLUSIONS]

Country	First author (Year of publication)
USA	Siedner MJ (2021)[238], Van Scoy LJ (2023)[239], Toussi SS (2023)[240]
UK	Hill A (2022) [241], Hill A (2021)[242]
South Africa	Schellack N (2021)[243]
Malaysia	Ministry of Health Malaysia (2022)[244]

TABLE 6. REVIEW ARTICLES ON THE CLINICAL USE OF IVERMECTIN FOR COVID-19 [WITH NEGATIVE CONCLUSIONS]

Furthermore, it is noted that this paper[242] was retracted in February of 2022. Hill et al. stated that, in their January 2022 paper [241], the studies on ivermectin included in their meta-analysis were biased—with some involving medical fraud.

CONCLUSION

Regarding clinical trials of ivermectin for COVID-19, our review articles1–4) published in 2021 and 2024 have already cited over 430 papers and other references. In compiling this current review article, over 230 papers were collected, including those previously overlooked in earlier reports—as well as newly published works. The fact that such a large number of basic and clinical studies are being conducted worldwide on the efficacy of a single drug, ivermectin, against a single disease, COVID-19, is an extremely unique situation. It vividly illustrates how people around the world were desperately hoping for the development of an effective treatment for COVID-19.

This review provides a detailed analysis of the basic research findings that were briefly explained in the previous reviews. The clinical efficacy of ivermectin against early-stage COVID-19 has been elucidated to arise not only from suppressing replication of the causative virus SARSCoV-2, but also from inhibiting multiple reactions required for the virus to invade and replicate within host cells. As shown in Table 1, ivermectin (1) exhibits antiviral activity, (2) binds to the spike protein on the viral surface, (3) inhibits viral binding to host cell surface receptors, (4) inhibits proteases that process viral polypeptides generated within the host into functional individual peptides, (5) inhibits helicase involved in viral RNA replication, and (6) inhibits importins involved in the nuclear transport of functional peptides. It is argued that these multiple inhibitory actions suppress the initial symptoms of COVID-19 caused by SARS-CoV-2.

Furthermore, in cases where SARS-CoV-2 infection progresses to moderate to severe COVID-19 symptoms, abnormal host immune responses related to inflammation are triggered. Ivermectin is proposed to: (1) exhibit anti-inflammatory effects, (2) inhibit NF-κB production via pathways such as the JAK/STAT pathway mediated by IL-6 receptors, (3) inhibit NF-κB production via the TRADD pathway mediated by TNF receptors, and (4) TLR-4-mediated pathways— thereby suppressing cytokine storm development. Other proposed actions of ivermectin on host targets include: (1) inhibition of blood coagulation/thrombogenesis by blocking CD147 on red blood cells, (2) modulation of immune responses by inhibiting acetylcholine receptors, and (3) improvement of blood oxygen saturation.

Research findings in the pharmacology and pharmaceutical sciences field concerning ivermectin were analyzed, including insights obtained prior to the COVID-19 pandemic. Since ivermectin is an existing drug already on the market, when considering its repurposing for COVID19, many clinical trials were conducted using existing approved treatments for other conditions. This meant that Phase 1 trials—which explore pharmacokinetics and safety in healthy adults, as in typical new drug trials—and Phase 2 trials—which explore optimal dosing and treatment regimens in a small number of cases—were not sufficiently conducted. On the other hand, clinical trials have also been conducted to test high-dose multiple administrations, based on the judgment that the previously approved dosage regimen (a single dose of 0.2 to 0.4 mg/kg/day administered on an empty stomach) was insufficiently effective. However, all collected pharmacology papers concluded that efficacy based on conventional pharmacokinetics/pharmacodynamics (PK/PD) theory could not be expected, as they relied solely on Caly et al.'s in vitro test results [22] for ivermectin against SARS-CoV-2 replication. The mechanism of action (pharmacodynamics) of ivermectin involves inhibiting multiple processes necessary not only for viral replication but also for viral entry into cells and intracellular viral proliferation. However, no in vitro test results applicable to PK/PD analysis exist beyond viral replication, leaving this aspect unresolved.

In pharmaceutical research papers, the improvement of ivermectin's oral bioavailability is discussed, and the development of new dosage forms based on nanotechnology applications is proposed. For early-stage COVID-19, inhalation formulations targeting the oropharynx are expected to be effective, while for later stages of infection, the development of formulations that increase concentrations within lung tissue is desired. In addition, concerns exist regarding the quality of the ivermectin formulations used in COVID-19 clinical trials, and it appears necessary to evaluate clinical efficacy in consistent clinical trials from Phase 1 to Phase 3 using formulations with assured quality.

No active research has been conducted on the side effects and toxicity of ivermectin in the clinical setting of COVID-19; inferences are based solely on safety data incidentally obtained from clinical trials conducted under diverse

protocols. Scheim *et al*. (USA, 2021) [245] cite dizziness, visual disturbances, and blurry vision as characteristic side effects of high-dose ivermectin administration. The collected data did not include any discussion of such characteristic adverse effects occurring following administration of human-use ivermectin formulations. However, cases of neurological adverse effects occurring after ingestion of high-dose veterinary formulations were reported.

Among the individual clinical trials of ivermectin for COVID-19, 3 trials out of the 7 randomized controlled trials (RCTs) registered with public registries demonstrated the efficacy of ivermectin. The study [135] by Varnaseri *et al*. in Iran was conducted from July of 2020 to June of 2021; the dominant viruses during this period were B.1.36, B.1.1.413, and B.1.1.7 (Alpha variant). The study [136] by Wijewickrema *et al*. in Sri Lanka was conducted from July of 2021 to March of 2022; during the period from July to October of 2021, the predominant causative virus was the Delta variant (AY.28 and AY.104 sub-lineages). Given the high pathogenicity of the Delta variant and the severe condition of patients, the clinical efficacy of ivermectin was notably evident. Meanwhile, a study [137] by Wagstaff *et al*. in Australia examined the efficacy of infection prevention among close contacts of COVID-19 patients conducted from November of 2021 to May of 2024. Since the predominant causative virus during this specific period was the Omicron variant, PCR or rapid antigen testing could not demonstrate a difference between ivermectin and placebo in confirming infection. However, the ivermectin group showed a significant prolongation in the time to confirmed infection and the onset of symptomatic infection.

Post-acute sequelae of COVID-19 has become a serious issue domestically and large-scale studies are being conducted in the United States. Therefore, we have included it as a chapter in this review. The primary cause of this pathological manifestation is the "excessive inflammatory response in the host" shown in the progression of COVID-19 pathology in Fig. 1. The involvement of "regulatory T cells" in this process is suspected. One known effect of ivermectin is to promote Treg cell activity and regulate the Th17/Treg balance, and its potential application in treating long COVID or PASC, the post-COVID-19 syndrome, has been discussed.

As a summary of this review, we compiled and analyzed general discussions and reviews concerning clinical trials of ivermectin for COVID-19. As shown in Tables 4–6, 37 studies reported positive conclusions regarding the efficacy of ivermectin, 12 studies reached neutral conclusions stating it was too early to conclude efficacy, and 7 studies reported negative conclusions indicating no recognized efficacy of ivermectin. As these are general discussions and reviews, the papers cited to draw conclusions and the analytical perspectives employed differ in each case. It is therefore natural that different conclusions are reached.

However, as we described in our 2023 review articles [5,6] on the trajectory of COVID-19, since the first cases were identified in the fall of 2019, the pandemic has seen the following peaks: the Alpha variant peaked in January of 2021, the Delta variant peaked in India in April of 2021 and globally outside India in August of 2021, and the Omicron variant showed a fourth peak in October, and a fifth peak in December of the same year. Each of these outbreaks was comprised and driven by different variants of concern (VOCs) sub-lineages—involving viruses with distinct infectivity and pathogenicity.

Consequently, despite being collectively termed COVID19, the disease manifestations actually evolved over the course of each outbreak. The infection presented with different clinical features in its early versus late phases, leading to varying responses to therapeutic drugs. In other words, while the efficacy of the treatment was relatively easy to assess in moderate to severe cases involving lower respiratory symptoms caused by the Alpha and Delta variants, it became difficult to determine treatment effectiveness in mild cases involving only upper respiratory symptoms confined to the pharynx and larynx caused by the Omicron variant. It is necessary to consider that the assessment of trial results varies significantly depending on the time period of the cases included in the papers reviewed. Consequently, in the aforementioned general discussions and reviews, the conclusions differ.

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CONFLICTS OF INTEREST

There is no conflict of interest.

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