Exhibit 27

IN COMMON PLEAS COURT
BUTLER COUNTY, OHIO

JULIE SMITH, as Guardian of JEFFREY SMITH	)	**CASE NO. CV 2021 08 1206**
	)	
	)	**Judge Michael A. Oster, Jr.**
Plaintiff,	)	
	)	
v.	)	
	)	
WEST CHESTER HOSPITAL, LLC	)	
	)	
Defendant.	)	

MEMORANDUM OF LAW
IN OPPOSITION TO PLAINTIFF'S COMPLAINT FOR EMERGENCY MEDICAL DECLARATORY JUDGMENT AND EMERGENCY INJUNCTIVE RELIEF AND OBJECTION TO INJUNCTIVE RELIEF

NOW COMES West Chester Hospital, by and through counsel, hereby requests the Court deny the injunctive relief sought by Plaintiff, Julie Smith, in her August 26, 2021, complaint seeking declaratory judgment and injunctive relief. Ohio law requires a particularized process through which a party may seek and obtain injunctive relief in an expedited manner. This process has not been followed by Plaintiff. Rather, Plaintiff has improperly circumvented the process through which expedited injunctive relief can be obtained, namely by failing to file a Motion for a Temporary Restraining Order ("TRO") seeking injunctive relief. Irrespective of Plaintiff's procedural short-comings, West Chester Hospital seeks to provide this Court with a response to Plaintiff's request of injunctive relief and presumed, yet absent, motion for TRO, which has been scheduled for an evidentiary hearing on Thursday, September 2, 2021, at 10:00 a.m. whereby this Court will determine the

appropriateness of a preliminary injunction. In opposition to Plaintiff's requested injunctive relief, West Chester Hospital states the following:

INTRODUCTION & BACKGROUND

On August 26, 2021, Plaintiff filed her Complaint for Emergency Medical Declaratory Judgment and Emergency Injunctive Relief seeking a declaratory judgment from this Court forcing West Chester Hospital to administer Ivermectin to Jeffrey Smith, Plaintiff's husband for which she is guardian of due to COVID-19 related illness and disability.

On July 22, 2021, Mr. Smith was admitted for treatment of a COVID-19 infection. Since July 24, 2021, West Chester Hospital has provided Intensive Care Unit medical treatment to Mr. Smith, with Mr. Smith being on a ventilator since August 3, 2021. Mr. Smith was cleared of COVID-19 infection on or about August 10, 2021, and is presently diagnosed with, among other things, acute hypoxic respiratory failure due to severe acute respiratory distress syndrome.

A Temporary Restraining Order ("TRO") was issued on August 26, 2021, directing West Chester Hospital to provide Ivermectin pursuant to the prescription written by Dr. Fred Wagshul. The TRO is set to expire on September 6, 2021, though a subsequent hearing for preliminary injunction has been scheduled for September 2, 2021 at 10 a.m.

Although Plaintiff has never filed a motion for TRO, an evidentiary hearing for the Plaintiff's requested preliminary injunction has expeditiously been scheduled. Given the timeline between the filing of Plaintiffs complaint and the scheduled hearing, West Chester Hospital has promptly filed an answer in response to Plaintiff's allegations.

ARGUMENT

In short, Plaintiff's request for preliminary injunctive relief disregards Ohio law, medical guidance and scientific information, and the facts and circumstances surrounding Mr. Smith's ongoing treatment at West Chester Hospital. Plaintiff's complaint seeking exceptional and extraordinary injunctive relief has improperly circumscribed the proper procedure for such a matter, limiting West Chester Hospital's ability to respond to Plaintiff's complaint and inform the Court of the realities of the instant matter. Further, Plaintiff relies on hearsay news articles in the form of assertions and limited studies purporting the efficacy and benefits of Ivermectin, while innumerable public health bodies, government agencies, and medical science generally provides directly contradictory guidance to not use Ivermectin for the treatment of COVID-19 or the resulting acute respiratory distress syndrome ("ARDS") continuing once the infection has ceased. Finally, Plaintiff's requested administration of Ivermectin to treat post-infection ARDS is contraindicative to the facts and circumstances of Mr. Smith's present status and the medical expertise of his treating physicians at West Chester Hospital and may result in severe detrimental harm to his medical condition.

I. Preliminary Injunction Standard.

In general, "[t]he purpose of a preliminary injunction is to preserve a status between the parties pending a trial on the merits." *Procter & Gamble Co. v. Stoneham* (2000), 140 Ohio App.3d 260, 267, 747 N.E.2d 268. "The right to an injunction must be clear and the proof thereof clear and convincing, and the right established by the strength of plaintiffs' own case rather than by any weakness of that of his adversary." *White v. Long* (1967), 12 Ohio App.2d 136, 140, 41 O.O.2d 200, 231 N.E.2d 337. In considering a preliminary injunction,

the court considers whether "(1) the movant has shown a strong or substantial likelihood or probability of success on the merits, (2) the movant has shown irreparable injury, (3) the preliminary injunction could harm third parties, and (4) the public interest would be served by issuing the preliminary injunction." *Union Twp. v. Union Twp. Professional Firefighters' Local 3412* (Feb. 14, 2000), Clermont App. No. CA99–08–082, 2000 WL 189959.

As the Twelfth District Court of Appeals has stated, "[a] preliminary injunction is a provisional remedy, which is defined as a 'remedy other than a claim for relief.' " *N. Fairfield Baptist Church v. G129, L.L.C.*, Butler App. No. CA2009–11–281, 2010-Ohio-2543, 2010 WL 2252490, ¶ 16, citing R.C. 2505.02(A)(3); *State ex rel. Butler Cty. Children Servs. Bd. v. Sage* (2002), 95 Ohio St.3d 23, 24, 764 N.E.2d 1027.

II. Plaintiff Failed to Follow the Ohio Rules of Civil Procedure for the Requested Extraordinary Relief of a Temporary Restraining Order and Injunction.

The improper and expeditious route by which Plaintiff has managed to obtain a TRO and evidentiary hearing for injunctive relief runs roughshod over West Chester Hospital's due process rights under the Ohio Rules of Civil Procedure. Plaintiff filed this action on a Friday afternoon, but did not notify undersigned counsel for West Chester Hospital until approximately thirty minutes before this Court held a hearing on the requested relief the following Monday. No copy of the complaint was provided – formally or informally – to West Chester Hospital until its counsel arrived at the Monday afternoon hearing. As the docket reflects, the clerk of courts issued its summons the same day the Judgment Entry was filed. This lack of notice was no doubt an effort at gamesmanship, meant to provide a strategic litigation advantage, given that Plaintiff's counsel and West Chester Hospital's

counsel both appeared at a hearing where Mrs. Smith's petition for guardianship was heard in the Butler County Probate Court, case no. PG21-08-0129. The Plaintiff filed this action shortly thereafter, yet did not alert counsel for West Chester Hospital until minutes before the August 23, 2021 hearing took place.

Rule 65 allows a court to issue a TRO without notice *only* under limited and specific circumstances: "A temporary restraining order may be granted without written or oral notice to the adverse party or his attorney only if . . . the applicant's attorney *certifies to the court in writing* the efforts, if any, which have been made to give notice *and* the reasons supporting his claim that notice should not be required." Civ.R. 65(A) (emphasis added). The plaintiff's attorney failed to do any of that here. Despite that, the trial court issued a temporary restraining order without any meaningful notice to the hospital. This court should reverse the temporary restraining order couched in the Judgment Entry of August 23, 2021.

As the Supreme Court of Ohio has observed: the "'elementary and fundamental requirement'" of due process "'in any proceeding . . . is notice reasonably calculated, under all the circumstances, to apprise interested parties of the pendency of the action and afford them an opportunity to present their objections.'" *Ohio Valley Radiology Associates, Inc. v. Ohio Valley Hosp. Ass'n*, 28 Ohio St. 3d 118, 124–25, 502 N.E.2d 599 (1986) (quoting *Mullane v. Central Hanover Bank & Trust Co.* 339 U.S. 306, 314, 70 S.Ct. 652, 94 L.Ed. 865 (1950)). The lack of notice—and the plaintiff's failure to explain why none was given or why Rule 65 was not otherwise obeyed—deprived West Chester Hospital of even the minimal process it was due under Ohio and federal law.

Rule 65's plain language provides mandatory requirements, not merely suggestions for notice. *N. Elec. Co. v. United Steelworkers of America*, 28 Ohio App.2d 253, 259, 277 N.E.2d 59 (3d Dist.1971) ("We conclude that [the requirements of Rule 65(A)] are mandatory. To hold otherwise would give little meaning to the requirements that a temporary restraining order granted without notice must define the injury and state why it is irreparable and why the order was granted without notice.") (holding trial court erred in issuing injunction that failed to comply with rule's requirements regarding harm, irreparability, and notice). The Judgment Entry merely reiterated the plaintiff's demand for judgment and an order, the appearances of counsel for the parties, and ordered the hospital to administer the plaintiff's requested medication. It did none of the things Ohio law requires, such as explain why relief was granted without notice or why notice could not be provided. The Judgment Entry also failed to define the injury that would occur in its absence or explain why it was irreparable. In light of these deficiencies, the Judgment Entry of August 23, 2021 should be reversed.

III. Temporary restraining order should only preserve the status quo, not compel affirmative relief.

The trial court's order is also improper because it grants affirmative relief—in effect, it entered a judgment that accomplished the plaintiff's ultimate demand on mere minutes' notice to the opposing party and after a half-hour hearing. But "[p]arties should rarely be able to obtain *ex parte* affirmative relief to accomplish the final object of their position in a dispute." *DeLuca v. BankOhio Nat'l Bank, Inc.*, 74 Ohio App.3d 233, 243, 598 N.E.2d 781 (10th Dist.1991). The type of near-total relief the trial court ordered here is not within the province of Rule 65. As *DeLuca* further observed, "the nature of Civ.R. 65(A) temporary

injunctive relief is to preserve the *status quo ante*," and so "is truly extraordinary and should be awarded only with the very greatest caution." *DeLuca v. BankOhio Nat'l Bank, Inc.*, 74 Ohio App.3d 233, 598 N.E.2d 781 (10th Dist. 1991); *see also CS/RW Westlake Indoor Storage, L.L.C. v. Russo*, 2016-Ohio-2845, 64 N.E.3d 396, ¶ 23 (8th Dist.) (citing *Gries Sports Ents., Inc. v. Cleveland Browns Football Co.*, 26 Ohio St.3d 15, 496 N.E.2d 959 (1986)) ("A court issues a temporary injunction when it is necessary to preserve the status quo of the case to prevent any actions of the parties from making null and unenforceable a final judgment.") The order here did not simply preserve the status quo. Rather, it ordered West Chester Hospital to undertake new, affirmative action at the request of Mr. Smith's wife and purported new doctor, and contrary to the clinical judgment of his current medical team. Even acknowledging for Mr. Smith's dire condition, Ohio law and procedure do not contemplate awarding the sort of complete relief and final judgment incorporated by the court's temporary restraining order, particularly absent the notice and process required by the Civil Rules. For this additional reason, the Judgment Entry should be reversed.

IV. Plaintiff's Assertions Regarding the Efficacy and Dangers of Ivermectin Disregard Guidance Provided by Public Health Bodies and the Broader Scientific Community

The mandatory injunctive relief requested by Plaintiff from this Court rejects the reality of science and the medical community's current understanding of acceptable uses for Ivermectin. There is no doubt that the consensus of the medical science community in this country, and others, is that Ivermectin is neither safe nor effective to treat COVID-19 infections, let alone the resulting damage once a COVID-19 infection is cleared.

Governmental Health Bodies Oppose the Use of Ivermectin for COVID-19 Treatment

Governmental health bodies across this country and around the world have provided clear and explicit guidance against the use Ivermectin for COVID-19 related treatment. Nearly the same day that Plaintiff filed her complaint, the federal authorities in the Food and Drug Administration ("FDA") announced: "You are not a horse. You are not a cow. Using the drug Ivermectin to treat COVID-19 can be dangerous and even lethal." *See FDA Tweet* attached hereto as **Exhibit "A".**

The FDA has been forced to provide recurring guidance against the use of Ivermectin to prevent or treat COVID-19. On April 10, 2021, the FDA issued an *FDA Letter to Stakeholders: Do Not Use Ivermectin Intended for Animals as Treatment for COVID-19 in Humans.* This letter was one of the FDAs first attempts to address the vast amount of misinformation surrounding the medical administration of Ivermectin for COVID-19, which includes a research article relied upon by Plaintiff's experts. This FDA Letter is attached hereto as **Exhibit B.**

Then on August 6, 2021, the FDA provided a frequently asked question ("FAQ") section in response to irregular usage of Ivermectin. A copy of the *FDA FAQ: COVID-19 and Ivermectin Intended for Animals* is attached hereto as **Exhibit C.** Within this FAQ the FDA states: (1) "[w]hile there are approved uses for Ivermectin in people and animals, it is not approved for the prevention or treatment of COVID-19"; (2) "[i]vermectin tablets are approved for use in humans for the treatment of some parasitic worms (intestinal strongyloidiasis and onchocerciasis) and Ivermectin topical formulations are approved for human use by prescription only for the treatment of external parasites such as headlice and for skin conditions

such as rosacea"; (3) "[a]ny use of Ivermectin for the prevention or treatment of COVID-19 should be avoided as its benefits and safety for these purposes have not been established"; and (4), important to the instant matter, "[l]aboratory test abnormalities include *decrease in white cell count and elevated liver tests". Id.* (emphasis added). Also on August 21, 2021, the FDA distributed additional guidance via Twitter reiterating the information its previously provided. Within its publication, the FDA states that Ivermectin is not approved for use in treating or preventing COVID-19 and warned Ivermectin can negatively interact with other medications, like blood-thinners.

The CDC and National Institute of Health, a part of the U.S. Department of Health and Human Services, have also issued guidance in opposition to any use of Ivermectin for COVID-19 treatment. *See* CDC Health Alert, *Rapid Increase in Ivermectin Prescriptions and Reports of Severe Illness Associated with use of Product Containing Ivermectin to Prevent or Treat COVID-19* (Aug. 26, 2021); NIH Publication, *Antiviral Drugs That Are Approved or Under Evaluation for the Treatment of COVID-19* (last updated Jul. 8, 2021); copies of each are attached hereto as **Exhibits D & E.** This guidance opposing the use of Ivermectin generally conforms with the guidance issued by the European Medicines Agency, the agency of the European Union in charge of the evaluation and supervision of medicinal products, and the World Health Organization regarding the use of Ivermectin for the prevention or treatment of COVID-19. *See generally,* European Medicines Agency Publication, *EMA advises against the use of Ivermectin for the prevention or treatment or COVID-19 outside randomized clinical trials* (March 22, 2021); World Health Organization, *Living Guideline: Therapeutics and COVID-19,* (July 6, 2021), copies of which are attached hereto as **Exhibits F & G**

respectively.

This immense volume of public health guidance against the use of Ivermectin for the prevention and treatment of COVID-19 is consistent with the drug's FDA label describing its pharmacology and approved uses, attached hereto as **Exhibit H.** Additionally, Merck & Co., Inc., the initial patent holder for Ivermectin under the brand name STROMECTOL, has provided additional guidance reaffirming the proper use of Ivermectin and cautioning that "[n]o scientific basis for a potential therapeutic effect against COVID-19 from pre-clinical studies; [n]o meaningful evidence for clinical activity or clinical efficacy in patients with COVID-19 disease, and; [a] concerning lack of safety data in the majority of studies [supporting the use of Ivermectin for the treatment of COVID-19]." *See Merck Statement on Ivermectin use During the COVID-19 Pandemic* (Feb. 4, 2021), attached hereto as **Exhibit I**.

V. Plaintiff's Cited Studies Fail to Show the Efficacy of Ivermectin.

Finally, in contradiction to the voluminous guidance provided by public health authorities, the hearsay-laden studies and articles relied upon by Plaintiff are less than definitive and often limited to the laboratory setting. This past summer, the National Institute of Health ("NIH"), the United States agency responsible for medical research, examined many if not all of the studies relied upon by the Front Line COVID-19 Critical Care Alliance and Plaintiff ("FLCCC"). Through a detailed process, the NIH examined each study's design, methods, and results, issuing a statement on the limitations and interpretation of each. Again and again, the NIH found that: (1) the tested Ivermectin treatment "did not improve time to resolution"; (2) "the clinical efficacy of [Ivermectin] is unknown"; (3) "no reduction in

mortality was observed"; (4) "[Ivermectin] did not reduce risk of oxygen requirement, ICU admission, invasive mechanical ventilation, or death in hospitalized patients"; (5) "[Ivermectin] showed no effect on symptom resolution"; (6) "[Ivermectin] did not lead to faster recovery"; and (7) "no difference in viral clearance compared to those who received placebo", amongst interpretations. *See NIH Ivermectin Clinical Data — COVID-19 Treatment Guidelines* (Jul. 19, 2021), attached hereto as **Exhibit J.** The NIH was unable to verify the efficacy of Ivermectin for the treatment of COVID-19 related conditions, firmly contradicting the outlandish assertions advanced by the FLCCC. A private review of many of the same studies touted by FLCCC and Plaintiff came to the same conclusion, namely that it is uncertain whether Ivermectin is safe or effective to use to prevent or treat COVID-19. *See Popp, M, Stegemann, M, Metzendorf; M-I, Gould, S., Kranke, P., Meybohm, P., Skoetz, N., Weibel, S., Ivermectin for preventing and treating COVID-19,* Cochrane Database of Systematic Reviews 2021, Issue 7. Art. No.: CD015017, attached hereto as **Exhibit K.**

Beyond third-party disproval of Ivermectin treatment for COVID-19, studies that have been previously relied upon by Plaintiff have either been retracted or called into question by their own authors. Plaintiff's counsel has previously referenced the findings of Dr. Andrew Hill in support of the administration of Ivermectin. However, Dr. Hill, as recently as August 16, 2021, has expressed concern regarding the study, *Meta-Analysis of Randomized Trials of Ivermectin to Treat SARS-CoV-3 Infection,* that he along with others authored. Specifically, on August 16, Dr. Hill publicly retracted his study and tweeted that "[o]ur meta-analysis of survival for Ivermectin had to be retracted after one of the main studies was suspected of medical fraud." *See* Tweet of Dr. Andrew Hill (Aug. 16, 2021);

Expression of Concern: "Meta-analysis of Randomized Trials of Ivermectin to Treat SARS-CoV-2 Infection", published Jul 6, 2021, copies of which are attached as **Exhibits L & M**. Due to this, Dr. Hill concluded that "there is no statistically significant survival benefit for Ivermectin. So, the original version should not be quoted." *Id.* Dr. Hill's retracted study is included in Exhibit L to Plaintiff's complaint. This is precisely the same body of literature and studies that Plaintiff currently relies on. A study by Ahmed Elgazzar, also referenced within materials previously relied upon by Plaintiff, was withdrawn due to duplication of patient records, inconsistencies in raw data, and records indicating that some participating patients died before the study began. *See Flawed Ivermectin preprint highlights challenges of COVID drug studies,* Nature Portfolio (Aug. 2, 2021), attached hereto as **Exhibit N.**

As previously stated, Plaintiffs asserted efficacy of Ivermectin disregards and contradicts scientific realities. West Chester Hospital is not aware of a single public health body in this nation in support of the use of Ivermectin to treat COVID-19 related conditions. Further, Plaintiffs own admissions and understanding regarding the efficacy of Ivermectin are inapplicable to the instant circumstances. Jeffrey Smith no longer has an active COVID-19 infection. Rather, Mr. Smith is gradually overcoming ARDS since the infection has been cleared.

VI. The Facts and Circumstances at Hand, Medical Expertise, and Mr. Smith's Current Conditions Contraindicate the Administration of Ivermectin

Ohio law requires that West Chester Hospital establish and operate based on Medical Staff Bylaws and the policies, procedures, and protocols therein implemented. West Chester Hospital has established such Medical Staff Bylaws and operated pursuant to the same. Pursuant to these bylaws and in response to the COVID-19 pandemic, a clinical team at West

Chester Hospital composed of doctors and medical professionals of numerous specialties and backgrounds created West Chester Hospital's COVID-19 Protocol. The development of the COVID-19 Protocol has been through numerous iterative improvements as the clinical team strives to improve West Chester Hospital's COVID-19 care. To date, West Chester Hospital has followed its internal operating procedures and protocols and will continue to do so. The Judgment Entry of August 23, if maintained, would further force West Chester Hospital to act in conflict with its protocols and bylaws.

In addition to West Chester Hospital's bylaws and thorough credentialing process, the Judgment Entry violated recently-enacted Ohio law protecting West Chester Hospital's right to decline to perform or participate in any health care service which violates the moral, ethical, or religious beliefs or principles held by it or its practitioners. *See* 134th G.A. Am. Sub. H.B. No. 110, enacting section 4743.10 of the Ohio Rev. Code. "Whenever a situation arises in which a requested course of treatment includes a particular health care service that conflicts with the moral, ethical, or religious beliefs or convictions of a medical practitioner, the medical practitioner shall be excused from participating in the particular health care service to which the practitioner has a conflict." *Id.*

Pursuant to R.C. 4743.10, dispensing or administering a drug – such as Ivermectin – constitutes a health care service. The ethical freedom granted therein extends not only to practitioners, but also health care institutions such as West Chester Hospital. Entities protected by this law enjoy immunity for civil actions where they exercise their right of conscience by declining to participate in a particular health care service. But not only does this immunity protect against civil liability – it shields from ""any other adverse action as a

result of declining to participate in or pay for a particular health care service on the basis of conscience. Moreover, a violation of West Chester Hospital's rights under this statute gives rise to an action for damages, injunctive relief, or any other appropriate relief. *Id.*

Plaintiff's requested administration of Ivermectin to Mr. Smith via injunction violates Ohio law and directly conflicts with West Chester Hospital's policies and procedures, the medical expertise of his treating physicians, and the patient's present medical status. If the Judgment Entry is not reversed, the desired injunctive relief would violate the rights of West Chester Hospital and its attending physicians, and irreparably damage their ability to provide quality medical services to this community. Further, forcing a medical professional to administer a drug in opposition to their own medical expertise would require a physician to violate their Hippocratic Oath and jeopardize their medical license. Finally, administration of Ivermectin is contraindicative to Mr. Smith's medical status.

VII. Granting Plaintiff's Requested Relief Would Violate Public Policy

Plaintiff's Complaint and the relief sought therein would violate public policy if granted. What Plaintiff is seeking will open the floodgates of litigation, place the Courts in the position of making day to day medical decisions, and any type of general release of liability in exchange for contraindicative treatment is counter to the provision of safe and effective treatment.

While Plaintiff alleges in her complaint, she is willing to sign a release in order for West Chester Hospital to administer this medication, such assurance does not advance the provision of safe and effective treatment and such a proposition violates public policy. When an individual sees her physician, she needs to rely upon the proposition that the physician is providing safe and effective treatment. To do a blanket release would invite a physician to

not provide safe and effective treatment and thereby violate her Hippocratic Oath. It is inviting a physician to do harm. What Plaintiff proposes is not protected by the rigorous safeguards of the FDA Drug Development Process, otherwise known as clinical trials. (See https://www.fda.gov/patients/learn-about-drug-and-device-approvals/drug-development-process). This is not something a physician can or should do. It is not something this Court should encourage. Public policy supports the safe and effective development of medications and medical practices, not the practice of mad science at the expense of patient safety.

As pointed out throughout Plaintiff's complaint, her affidavit, and the various attachments thereto, Plaintiff's counsel was able to obtain the sought-after relief in Illinois State Court, specifically DuPage County case 2021-P-542. But that case was fraught with improper filings by Plaintiff's counsel, improper jurisdiction of the third-party hospital, and improper process, including the lack of an evidentiary hearing. Plaintiff states in her affidavit "Elmhurst Hospital appealed [the trial court's] Order and the Appellate Court recently dismissed the appeal in its entirety, but more importantly, upheld Judge Orel's original order." (Complaint, Exhibit A, Plaintiff's affidavit, ¶ 36). What is notably missing from this assertion is how the Illinois Court of Appeals for the Second District actually ruled. The Second District ruled that the appeal was moot as the ward was no longer a patient at Elmhurst Hospital. *See In re Estate of Nurije Fype,* 2021 IL App (2d) 210259-U, ¶ 38 (July 27, 2021). There is no proof or other legal support to be found in the Second District's order for approval of a mandatory injunction requiring a hospital to administer an unproven and disputed medication from a non-privileged physician (or in the case of Elmhurst, allowing a non-privileged physician entry to administer said medication). The Second District's order of dismissal was

based on mootness, not the merits of the trial court's order.

The Second District, in discussing exceptions to the mootness doctrine, disagreed with counsel for Elmhurst on the issues of the likelihood of recurrence of this type of suit. The Second District stated Elmhurst's counsel had "demonstrated, at best, no more than a handful of 'similar' issues have arisen, not a 'flood' of cases." With all due respect to the Second District, the situation presented to this Court proves they were incorrect then, incorrect now, and in fact helped open the floodgates. Plaintiff devotes eight paragraphs of her affidavit and four additional exhibits to the Elmhurst Hospital case, beginning with her discussion of a Chicago Tribune article regarding the case. (Complaint, Exhibit A, Plaintiff's affidavit, Exhibits C-F.) News sources have reported on that particular case. Plaintiff also devoted four paragraphs of her affidavit, and two additional exhibits, to the case of an 80-year-old Buffalo woman. (Complaint, Exhibit A, Plaintiff's Affidavit, Exhibit G, and Exhibit H). Plaintiff further discusses the case of Glenna Dickinson in five paragraphs and two additional exhibits. (Complaint, Exhibit A, Plaintiff's Affidavit, Exhibit I, and Exhibit J). Plaintiff spends two paragraphs and one additional exhibit discussing Jeffery Smith. (Complaint, Exhibit A, Plaintiff's Affidavit, Exhibit M). In total, Plaintiff spends approximately one-third of her sixty-one-paragraph affidavit discussing other cases. These are not simply passing references to other cases; they are the reason this case was filed. If this Court follows down the path Plaintiff and Plaintiff's counsel wish it to, the snowball will gain momentum and there will continue to be more of these cases in this and other jurisdictions based on unsafe and ineffective science as discussed more fully below. Courts should not entertain this dubious invitation to practice pseudo-medicine.

Since the filing of the instant complaint NewsChanne120, in Springfield, Illinois, ran a story the evening of August 27, 2021, that included interviews of Plaintiff's counsel. (See https://newschanne120.com/news/local/family-of-auburn-man-hospitalized-with-covid-19-takes-memorial-to-court-to-get-Ivermectin to view video of Plaintiff's counsel). Plaintiff's counsel has described to this Court this type of litigation has been his life since the beginning of the year. He has described being in Court all over the country. Plaintiff's counsel has described to the Court his close association with the FLCCC. He advertises on their website for those seeking legal questions. (See https://covidl9criticalcare.com/Ivermectin-in-covid-19/faq-on-Ivermectin/ under a dropdown labelled "Can the FLCCC help with legal questions?"). He appeared on an FLCCC Expert Panel on May 6, 2021, describing his experience litigating cases like the one at bar, including stating he had "five successes, we have not had any failures." (See https://youtu.be/fWB4nDTr3wo). Plaintiff's counsel has also discussed in open court that he had a Zoom hearing in a similar case in the State of New Jersey. Plaintiff's counsel's website advertises various articles regarding his achievements in relation to Ivermectin. Plaintiff's counsel uses this information as a badge of honor, but this Court should see warning signs instead. The floodgates are open in other areas of this State and Country, and this Court needs to close them.

The idea of litigating day to day medical care should shock and frighten the Court. What Plaintiff, and future potential Plaintiffs, wish for this Court to do is change its J.D. into an M.D. and exchange its black robe for a white coat. Plaintiff wants this Court to decide it has the knowledge, experience, and know-how to make life or death medical decisions on a day-to-day basis. Public policy dictates this Court not do that. This Court cannot and should

not make day to day medical decisions for this patient or any patient. It has neither the training and experience to determine, proactively, which treatments are safe and effective, and which are not. As Plaintiff stated to Illinois Newschannel 20, "Let's just face it. When you're on death's door, and you have no other options, you'll grasp at whatever you can get." If a parent is faced with a severely ill child and disagrees with the trained medical professionals' opinions, it is understandable for that parent to want to take all options to help their child. But the Court should not be placed in a situation to order treatment that is not indicated, is unsafe, is ineffective, and has not been supported by any major public health body. These decisions are best left to the health care professionals on the front line of this or any other health issue. Even in the best of circumstances, it is understood that two similarly situated physicians with the same information could have differences of opinion on the proper course of action. It is not in the interest of the public generally, and the individuals specifically in this case, for the Court to be dragged into the situation and make a decision with no training, education, or experience in making these day-to-day decisions. It is neither safe nor effective.

CONCLUSION

Plaintiff has not articulated, let alone shown with conclusive evidence, that she is entitled to the extraordinary injunctive relief she seeks. This Court need not wade into the highly contentious debate as to the medical efficacy of Ivermectin in treating COVID-19. Plaintiff's procedural deficiencies alone warrant denial of the requested injunction. There is no right to be treated by an unapproved medication, nor a duty of West Chester Hospital to administer the same. Should this Court decline to reverse the Judgment Entry, irreparable

harm to West Chester Hospital and its physicians will continue, and as a matter of public policy, the will of Ohio's General Assembly will be utterly disregarded. Defendant, West Chester Hospital, prays that this Honorable Court enter judgment for West Chester Hospital and against the Plaintiff and for such other and further relief as the Court deems just and proper.

Respectfully submitted,

FROST BROWN TODD LLC

By: /s/ Charles B. Galvin

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CERTIFICATE OF SERVICE

I hereby certify that a copy of the foregoing ***Memorandum*** was served by Electronic Mail this 2nd day of September 2021 upon the following:

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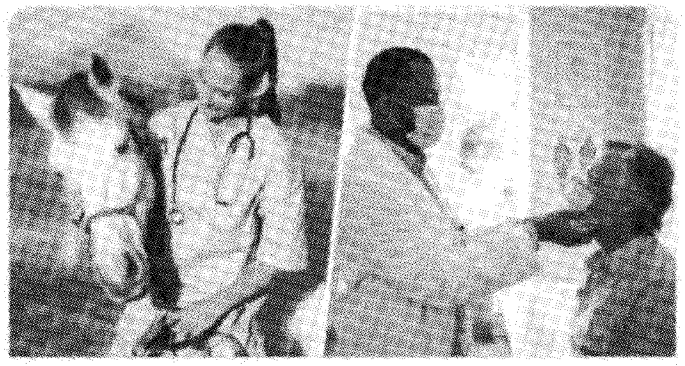
You are not a horse. You are not a cow. Seriously, y'all. Stop it.



Why You Should Not Use Ivermectin to Treat or Prevent COVID-19

Using the Drug Ivermectin to treat COVID-19 can be dangerous and even lethal. The FDA has not approved the drug for that purpose.

fda.gov

12.5K 69.5K 112.9K

EXHIBIT A

FDA Letter to Stakeholders: Do Not Use Ivermectin Intended for Animals as Treatment for COVID-19 in Humans

Español (/animal-veterinary/product-safety-information/carta-de-la-fda-las-partes-interesadas-no-use-ivermectina-destinada-animales-como-tratamiento-para)

April 10, 2020

Dear Stakeholder,

The FDA's Center for Veterinary Medicine has recently become aware of increased public visibility of the antiparasitic drug ivermectin after the announcement of a research article that described the effect of ivermectin on SARS-CoV-2 in a laboratory setting. The *Antiviral Research* pre-publication paper, "The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 *in vitro* (https://www.sciencedirect.com/science/article/pii/S0166354220302011) (http://www.fda.gov/about-fda/website-policies/website-disclaimer)," documents how SARS-CoV-2 (the virus that causes COVID-19) responded to ivermectin when exposed in a petri dish. This type of study is commonly used in the early stages of drug development. Ivermectin was not given to people or animals in this study. Additional testing is needed to determine whether ivermectin might be safe or effective to prevent or treat coronavirus or COVID-19.

Ivermectin tablets are approved for use in people for the treatment of some parasitic worms (intestinal strongyloidiasis and onchocerciasis) and ivermectin topical formulations are approved for human use by prescription-only for the treatment of external parasites such as headlice and skin conditions such as rosacea. Ivermectin is FDA-approved for use in animals for prevention of heartworm disease in some small animal species, and for treatment of certain internal and external parasites in various animal species.

FDA is concerned about the health of consumers who may self-medicate by taking ivermectin products intended for animals, thinking they can be a substitute for ivermectin intended for humans. People should never take animal drugs, as the FDA has only evaluated their safety and effectiveness in the particular animal species for which they are labeled. These animal drugs can cause serious harm in people. People should not take any form of ivermectin unless it has been prescribed to them by a licensed health care provider and is obtained through a legitimate source.

Ivermectin is an important part of a parasite control program for certain species and should only be given to animals for approved uses or as prescribed by a veterinarian in compliance with the requirements for extra-label drug use. Due to potentially elevated interest in ivermectin

following the new research, some products may not be available. If you are having difficulty locating a particular ivermectin product for your animal(s), the FDA recommends that you consult with your veterinarian.

The FDA has established a cross-agency task force dedicated to closely monitoring for fraudulent COVID-19 products that reaches out to major retailers to ask for their help in monitoring online marketplaces. Products that claim to prevent, diagnose, treat, or cure COVID-19 are subject to FDA investigation and potential enforcement action if they have not demonstrated safety and effectiveness for that intended use. The task force has already worked with retailers to remove dozens of these types of product listings online.

Please help us protect public health by alerting FDA of anyone claiming to have a product to prevent or cure COVID-19 and to help safeguard human and animal health by reporting any of these products to FDA-COVID-19-Fraudulent-Products@fda.hhs.gov (mailto:FDA-COVID-19-Fraudulent-Products@fda.hhs.gov) or 1-888-InfoFDA (1-888-463-6332).

We recognize this is a challenging time and urge you to continue practicing social distancing by sharing this information electronically.

Thank you for your support. Please stay safe and healthy.

Dr. Steven Solomon
Director of FDA's Center for Veterinary Medicine

Additional Information

FAQ: COVID-19 and Ivermectin Intended for Animals (/animal-veterinary/product-safety-information/faq-covid-19-and-ivermectin-intended-animals)

Why You Should Not Use Ivermectin to Treat or Prevent COVID-19 (/consumers/consumer-updates/why-you-should-not-use-ivermectin-treat-or-prevent-covid-19)

FAQ: COVID-19 and Ivermectin Intended for Animals

Español (/animal-veterinary/product-safety-information/preguntas-mas-comunes-el-covid-19-y-la-ivermectina-prevista-para-animales)

Q: Should I take ivermectin to prevent or treat COVID-19?

A: No. While there are approved uses for ivermectin in people and animals, it is not approved for the prevention or treatment of COVID-19. You should not take any medicine to treat or prevent COVID-19 unless it has been prescribed to you by your health care provider and acquired from a legitimate source.

A recently released research article (https://pdf.sciencedirectassets.com/271065/AIP/1-s2.0-S0166354220302011/main.pdf?X-Amz-Date=20200406T215853Z&X-Amz-Algorithm=AWS4-HMAC-SHA256&X-Amz-Signature=dfb8133954e6dd01ab978d9288f9036d2b49c25bb0995ff2ca061bc7ea3077fe&X-Amz-Credential=ASIAQ3PHCVTY32VGY2LR%2F20200406%2Fus-east-1%2Fs3%2Faws4_request&type=client&tid=prr-2af71973-98c2-4d5f-954c-02bc9e60ea14&sid=45be74a6676495419c1ba842da478030ef40gxrqa&pii=S0166354220302011&X-Amz-SignedHeaders=host&X-Amz-Security-Token=IQoJb3JpZ2luX2VjEKX%2F%2F%2F%2F%2F%2F%2F%2F%2FwEaCXVzLWVhc3QtMSJHMEUCIAI%2F6GH7KtlFhbG5MZc%2BiCG7X1SV Amz-Expires=300&hash=24d1399e3e67515cfa0c8a128310f04991edd039c80bc29c8a30c84303aa5c67) (http://www.fda.gov/about-fda/website-policies/website-disclaimer) described the effect of ivermectin on SARS-CoV-2 in a laboratory setting. These types of laboratory studies are commonly used at an early stage of drug development. Additional testing is needed to determine whether ivermectin might be appropriate to prevent or treat coronavirus or COVID-19.

Q: Is there an emergency use authorization for ivermectin in the U.S. to prevent or treat coronavirus or COVID-19?

A: No. FDA has created a special emergency program for possible therapies, the Coronavirus Treatment Acceleration Program (/drugs/coronavirus-covid-19-drugs/coronavirus-treatment-acceleration-program-ctap) (CTAP). It uses every available method to move new treatments to patients as quickly as possible, while at the same time finding out whether they are helpful or harmful. We continue to support clinical trials that are testing new treatments for COVID so that we can gain valuable knowledge about their safety and effectiveness.

Q: What is ivermectin approved for in the U.S.?

A: Ivermectin tablets are approved for use in humans for the treatment of some parasitic worms (intestinal strongyloidiasis and onchocerciasis) and ivermectin topical formulations are approved for human use by prescription only for the treatment of external parasites such as headlice and for skin conditions such as rosacea.

Ivermectin is FDA-approved for use in animals for prevention of heartworm disease in some small animal species, and for treatment of certain internal and external parasites in various animal species. People should never take animal drugs, as the FDA has only evaluated their safety and effectiveness in the particular species for which they are labeled. Using these products in humans could cause serious harm.

Q: Is there any danger to humans taking ivermectin?

A: There are approved uses for ivermectin in people and animals but it is not approved for the prevention or treatment of COVID-19. You should not take any medicine to treat or prevent COVID-19 unless it has been prescribed to you by your health care provider and acquired from a legitimate source.

Some of the side-effects that may be associated with ivermectin include skin rash, nausea, vomiting, diarrhea, stomach pain, facial or limb swelling, neurologic adverse events (dizziness, seizures, confusion), sudden drop in blood pressure, severe skin rash potentially requiring hospitalization and liver injury (hepatitis). Laboratory test abnormalities include decrease in white cell count and elevated liver tests. Any use of ivermectin for the prevention or treatment of COVID-19 should be avoided as its benefits and safety for these purposes have not been established. Data from clinical trials are necessary for us to determine whether ivermectin is safe and effective in treating or preventing COVID-19.

Q: What should I do if the ivermectin products I purchase for use in my animals are not available at my typical retailer?

A: Ivermectin is an important part of a parasite control program for certain species and should only be given to animals for approved uses or as prescribed by a veterinarian in compliance with the requirements for extra-label drug use. Due to potentially elevated interest in ivermectin following the new research, some products may not be available. If you are having difficulty locating a particular ivermectin product for your animal(s), the FDA recommends that you consult with your veterinarian.

Q: What is the FDA doing to protect people from fraudulent COVID-19 products?

A: We have established a cross-agency task force dedicated to closely monitoring for fraudulent COVID-19 products. We have reached out to major retailers to ask for their help in monitoring online marketplaces for fraudulent COVID-19 products. Products sold are subject to FDA investigation and potential enforcement action if they claim to prevent, diagnose, treat, or cure COVID-19 and have not demonstrated safety and effectiveness for that intended use. The task force has already worked with retailers to remove dozens of these types of product listings online.

The FDA and the Federal Trade Commission (FTC) issue warning letters to companies that violate federal law and pose significant risks to patient health by selling unapproved products with fraudulent claims to treat or prevent COVID-19. View the warning letters (/consumers/health-fraud-scams/fraudulent-coronavirus-disease-2019-covid-19-products#Warning Letter Table) for more information.

Additional Information

FDA Letter to Stakeholders: Do Not Use Ivermectin Intended for Animals as Treatment for COVID-19 in Humans (/animal-veterinary/product-safety-information/fda-letter-stakeholders-do-not-use-ivermectin-intended-animals-treatment-covid-19-humans)

Why You Should Not Use Ivermectin to Treat or Prevent COVID-19 (/consumers/consumer-updates/why-you-should-not-use-ivermectin-treat-or-prevent-covid-19)

This is an official
CDC HEALTH ADVISORY

Distributed via the CDC Health Alert Network
August 26, 2021, 11:40 AM ET
CDCHAN-00449

Rapid Increase in Ivermectin Prescriptions and Reports of Severe Illness Associated with Use of Products Containing Ivermectin to Prevent or Treat COVID-19

Summary
Ivermectin is a U.S. Food and Drug Administration (FDA)-approved prescription medication used to treat certain infections caused by internal and external parasites. When used as prescribed for approved indications, it is generally safe and well tolerated.

During the COVID-19 pandemic, ivermectin dispensing by retail pharmacies has increased, as has use of veterinary formulations available over the counter but not intended for human use. FDA has cautioned about the potential risks of use for prevention or treatment of COVID-19.

Ivermectin is not authorized or approved by FDA for prevention or treatment of COVID-19. The National Institutes of Health's (NIH) COVID-19 Treatment Guidelines Panel has also determined that there are currently insufficient data to recommend ivermectin for treatment of COVID-19. ClinicalTrials.gov has listings of ongoing clinical trials that might provide more information about these hypothesized uses in the future.

Adverse effects associated with ivermectin misuse and overdose are increasing, as shown by a rise in calls to poison control centers reporting overdoses and more people experiencing adverse effects.

Background
The Centers for Disease Control and Prevention (CDC) confirmed with the American Association of Poison Control Centers (AAPCC) that human exposures and adverse effects associated with ivermectin reported to poison control centers have increased in 2021 compared to the pre-pandemic baseline. These reports include increased use of veterinary products not meant for human consumption.

Ivermectin is a medication that is approved by FDA in oral formulations to treat onchocerciasis (river blindness) and intestinal strongyloidiasis. Topical formulations are used to treat head lice and rosacea. Ivermectin is also used in veterinary applications to prevent or treat internal and external parasitic infections in animals. When used in appropriate doses for approved indications, ivermectin is generally well tolerated.

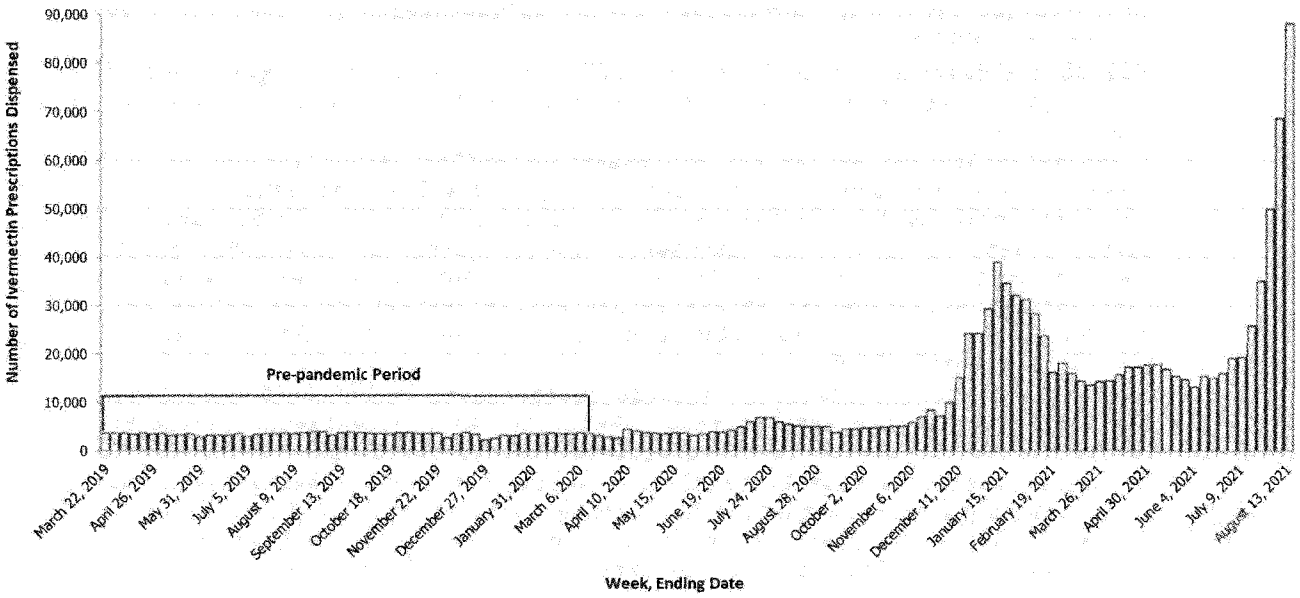
Clinical trials and observational studies to evaluate the use of ivermectin to prevent and treat COVID-19 in humans have yielded insufficient evidence for the NIH COVID-19 Treatment Guidelines Panel to recommend its use. Data from adequately sized, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin in the treatment of COVID-19.

A recent study examining trends in ivermectin dispensing from outpatient retail pharmacies in the United States during the COVID-19 pandemic showed an increase from an average of 3,600 prescriptions per week at the pre-pandemic baseline (March 16, 2019–March 13, 2020) to a peak of 39,000 prescriptions in the week ending on January 8, 2021.[1] Since early July 2021, outpatient ivermectin dispensing has again

begun to rapidly increase, reaching more than 88,000 prescriptions in the week ending August 13, 2021. This represents a 24-fold increase from the pre-pandemic baseline. (**Figure**)

Figure: Estimated number of outpatient ivermectin prescriptions dispensed from retail pharmacies — United States, March 16, 2019–August 13, 2021*

*Data are from the IQVIA National Prescription Audit Weekly (NPA Weekly) database. NPA Weekly collects data from a sample of approximately 48,900 U.S. retail pharmacies, representing 92% of all retail prescription activity. Ivermectin dispensed by mail order and long-term care pharmacies, prescriptions by veterinarians, and non-oral formulations were not included.



In 2021, poison control centers across the U.S. received a three-fold increase in the number of calls for human exposures to ivermectin in January 2021 compared to the pre-pandemic baseline.
In July 2021, ivermectin calls have continued to sharply increase, to a five-fold increase from baseline. These reports are also associated with increased frequency of adverse effects and emergency department/hospital visits.

In some cases, people have ingested ivermectin-containing products purchased without a prescription, including topical formulations and veterinary products. Veterinary formulations intended for use in large animals such as horses, sheep, and cattle (e.g., "sheep drench," injection formulations, and "pour-on" products for cattle) can be highly concentrated and result in overdoses when used by humans. Animal products may also contain inactive ingredients that have not been evaluated for use in humans. People who take inappropriately high doses of ivermectin above FDA-recommended dosing may experience toxic effects.

Clinical effects of ivermectin overdose include gastrointestinal symptoms such as nausea, vomiting, and diarrhea. Overdoses are associated with hypotension and neurologic effects such as decreased consciousness, confusion, hallucinations, seizures, coma, and death. Ivermectin may potentiate the effects of other drugs that cause central nervous system depression such as benzodiazepines and barbiturates.

Examples of recent significant adverse effects reported to U.S. poison control centers include the following:

- An adult drank an injectable ivermectin formulation intended for use in cattle in an attempt to prevent COVID-19 infection. This patient presented to a hospital with confusion, drowsiness, visual hallucinations, tachypnea, and tremors. The patient recovered after being hospitalized for nine days.
- An adult patient presented with altered mental status after taking ivermectin tablets of unknown strength purchased on the internet. The patient reportedly took five tablets a day for five days to treat COVID-19. The patient was disoriented and had difficulty answering questions and following commands. Symptoms improved with discontinuation of ivermectin after hospital admission.

Recommendations for Clinicians and Public Health Practitioners

- Be aware that ivermectin is not currently authorized or approved by FDA for treatment of COVID-19. NIH has also determined that there are currently insufficient data to recommend ivermectin for treatment of COVID-19.
- Educate patients about the risks of using ivermectin without a prescription, or ingesting ivermectin formulations that are meant for external use or ivermectin-containing products formulated for veterinary use.
- Advise patients to immediately seek medical treatment if they have taken any ivermectin or ivermectin-containing products and are experiencing symptoms. Signs and symptoms of ivermectin toxicity include gastrointestinal effects (nausea, vomiting, abdominal pain, and diarrhea), headache, blurred vision, dizziness, tachycardia, hypotension, visual hallucinations, altered mental status, confusion, loss of coordination and balance, central nervous system depression, and seizures. Ivermectin may increase sedative effects of other medications such as benzodiazepines and barbiturates. Call the poison control center hotline (1-800-222-1222) for medical management advice.
- Educate patients and the public to get vaccinated against COVID-19. COVID-19 vaccination is safe and the most effective means to prevent infection and protect against severe disease and death from SARS-CoV-2, the virus that causes COVID-19, including the Delta variant.
- Educate patients and the public to use COVID-19 prevention measures including wearing masks in indoor public places, physical distancing by staying at least six feet from other people who don't live in the same household, avoiding crowds and poorly ventilated spaces, and frequent handwashing and use of hand sanitizer that contains at least 60 percent alcohol.

Recommendations for the Public

- Be aware that currently, ivermectin has not been proven as a way to prevent or treat COVID-19.
- Do not swallow ivermectin products that should be used on skin (e.g., lotions and creams) or are not meant for human use, such as veterinary ivermectin products.
- Seek immediate medical attention or call the poison control center hotline (1-800-222-1222) for advice if you have taken ivermectin or a product that contains ivermectin and are having symptoms. Signs and symptoms include gastrointestinal effects (nausea, vomiting, abdominal pain, and diarrhea), headache, blurred vision, dizziness, fast heart rate, and low blood pressure. Other severe nervous system effects have been reported, including tremors, seizures, hallucinations, confusion, loss of coordination and balance, decreased alertness, and coma.
- Get vaccinated against COVID-19. COVID-19 vaccination is approved by FDA and is the safest and most effective way to prevent getting sick and protect against severe disease and death from SARS-CoV-2, the virus that causes COVID-19, including the Delta variant.
- Protect yourself and others from getting sick with COVID-19. In addition to vaccination, wear masks in indoor public places, practice staying at least six feet from other people who don't live in your household, avoid crowds and poorly ventilated spaces, and wash your hands often or use hand sanitizer that has at least 60 percent alcohol.

For More Information

NIH COVID-19 Treatment Ivermectin Guidelines

FDA Consumer Alert on Use of Ivermectin to Treat or Prevent COVID-19

FDA MedWatch Adverse Event Reporting program

CDC Coronavirus (COVID-19) website

U.S. Government Coronavirus (COVID-19) website

American Association of Poison Control Centers

Press Release: American College of Medical Toxicology Reports Data on Adverse Effects and Toxicity from Unapproved Use of Ivermectin for the Prevention or Treatment of COVID-19

Treatments Your Healthcare Provider Might Recommend if You Are Sick

References

1 Lind JN, Lovegrove MC, Geller AI, Uyeki TM, Datta SD, Budnitz DS. Increase in Outpatient Ivermectin Dispensing in the US During the COVID-19 Pandemic: A Cross-Sectional Analysis. J Gen Intern Med. 2021 Jun 18:1–3. doi: 10.1007/s11606-021-06948-6.

The Centers for Disease Control and Prevention (CDC) protects people's health and safety by preventing and controlling diseases and injuries; enhances health decisions by providing credible information on critical health issues; and promotes healthy living through strong partnerships with local, national, and international organizations.

Categories of Health Alert Network messages:

Health Alert	Requires immediate action or attention, highest level of importance
Health Advisory	May not require immediate action; provides important information for a specific incident or situation
Health Update	Unlikely to require immediate action; provides updated information regarding an incident or situation
HAN Info Service	Does not require immediate action; provides general public health information

##This message was distributed to state and local health officers, state and local epidemiologists, state and local laboratory directors, public information officers, HAN coordinators, and clinician organizations##

Antiviral Drugs That Are Approved or Under Evaluation for the Treatment of COVID-19

Last Updated: July 8, 2021

Summary Recommendations

Remdesivir is the only Food and Drug Administration-approved drug for the treatment of COVID-19. In this section, the COVID-19 Treatment Guidelines Panel (the Panel) provides recommendations for using antiviral drugs to treat COVID-19 based on the available data. **As in the management of any disease, treatment decisions ultimately reside with the patient and their health care provider.** For more information on these antiviral agents, see Table 2e.

Remdesivir

- See Therapeutic Management of Hospitalized Adults with COVID-19 for recommendations on using remdesivir with or without dexamethasone.

Ivermectin

- There is insufficient evidence for the Panel to recommend either for or against the use of ivermectin for the treatment of COVID-19. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin in the treatment of COVID-19.

Nitazoxanide

- The Panel **recommends against** the use of **nitazoxanide** for the treatment of COVID-19, except in a clinical trial **(BIIa)**.

Hydroxychloroquine or Chloroquine and/or Azithromycin

- The Panel **recommends against** the use of **chloroquine** or **hydroxychloroquine** and/or **azithromycin** for the treatment of COVID-19 in hospitalized patients **(AI)** and in nonhospitalized patients **(AIIa)**.

Lopinavir/Ritonavir and Other HIV Protease Inhibitors

- The Panel **recommends against** the use of **lopinavir/ritonavir** and **other HIV protease inhibitors** for the treatment of COVID-19 in hospitalized patients **(AI)** and in nonhospitalized patients **(AIII)**.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

Antiviral Therapy

Because SARS-CoV-2 replication leads to many of the clinical manifestations of COVID-19, antiviral therapies are being investigated for the treatment of COVID-19. These drugs inhibit viral entry (via the angiotensin-converting enzyme 2 [ACE2] receptor and transmembrane serine protease 2 [TMPRSS2]), viral membrane fusion and endocytosis, or the activity of the SARS-CoV-2 3-chymotrypsin-like protease (3CLpro) and the RNA-dependent RNA polymerase.[1] Because viral replication may be particularly active early in the course of COVID-19, antiviral therapy may have the greatest impact before the illness progresses to the hyperinflammatory state that can characterize the later stages of disease, including critical illness.[2] For this reason, it is necessary to understand the role of antiviral medications in treating mild, moderate, severe, and critical illness in order to optimize treatment for people with COVID-19.

The following sections describe the underlying rationale for using different antiviral medications, provide the COVID-19 Treatment Guidelines Panel's recommendations for using these medications to treat COVID-19, and summarize the existing clinical trial data. Additional antiviral therapies will be added to this section of the Guidelines as new evidence emerges.

References +

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA advises against use of ivermectin for the prevention or treatment of COVID-19 outside randomised clinical trials

News 22/03/2021

EMA has reviewed the latest evidence on the use of ivermectin for the prevention and treatment of COVID-19 and concluded that the available data do not support its use for COVID-19 outside well-designed clinical trials.

In the EU, ivermectin tablets are approved for treating some parasitic worm infestations while ivermectin skin preparations are approved for treating skin conditions such as rosacea. Ivermectin is also authorised for veterinary use for a wide range of animal species for internal and external parasites.

Ivermectin medicines are not authorised for use in COVID-19 in the EU, and EMA has not received any application for such use.[1]

Following recent media reports and publications on the use of ivermectin, EMA reviewed the latest published evidence from laboratory studies, observational studies, clinical trials and meta-analyses. Laboratory studies found that ivermectin could block replication of SARS-CoV-2 (the virus that causes COVID-19), but at much higher ivermectin concentrations than those achieved with the currently authorised doses. Results from clinical studies were varied, with some studies showing no benefit and others reporting a potential benefit. Most studies EMA reviewed were small and had additional limitations, including different dosing regimens and use of concomitant medications. EMA therefore concluded that the currently available evidence is not sufficient to support the use of ivermectin in COVID-19 outside clinical trials.

Although ivermectin is generally well tolerated at doses authorised for other indications, side effects could increase with the much higher doses that would be needed to obtain concentrations of ivermectin in the lungs that are effective against the virus. Toxicity when ivermectin is used at higher than approved doses therefore cannot be excluded.

EMA therefore concluded that use of ivermectin for prevention or treatment of COVID-19 cannot currently be recommended outside controlled clinical trials. Further well-designed, randomised

studies are needed to draw conclusions as to whether the product is effective and safe in the prevention and treatment of COVID-19.

This EMA public health statement has been endorsed by the COVID-19 EMA pandemic Task Force (COVID-ETF), in light of the ongoing discussions on the use of ivermectin in the prevention and treatment of COVID-19.

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[1] Czechia and Slovakia, have allowed the temporary use of the medicine for COVID-19 within the remit of their national legislation.

References

1. Elgazzar, A., et al., *Efficacy and safety of ivermectin for treatment and prophylaxis of COVID-19 pandemic.* Research Square, 2020.

2. Ahmed, S., et al., *A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness.* Int J Infect Dis, 2021. 103: p. 214-216.

3. Alam, M.T., et al., *Ivermectin as pre-exposure prophylaxis for COVID-19 among healthcare providers in a selected tertiary hospital in Dhaka – an observational study*. European Journal of Medical Health and Sciences, 2020.

4. Arévalo, A.P., et al., *Ivermectin reduces coronavirus infection in vivo: a mouse experimental model.* Biorxiv, 2020.

5. Babalola, O.E., et al., *Ivermectin shows clinical benefits in mild to moderate COVID19: a randomised controlled double-blind, dose-response study in Lagos.* QJM, 2021.

6. Behera, P., et al., *Prophylactic role of ivermectin in SARS-CoV-2 infection among healthcare workers.* Research Square, 2021.

7. Bray, M., et al., *Ivermectin and COVID-19: a report in antiviral research, widespread interest, an FDA warning, two letters to the editor and the authors' responses.* Antiviral Res, 2020. 178: p. 104805.

8. Caly, L., et al., *The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro.* Antiviral Res, 2020. 178: p. 104787.

9. Camprubí, D., et al., *Lack of efficacy of standard doses of ivermectin in severe COVID-19 patients.* PLoS One, 2020. 15(11): p. e0242184.

10. Carvallo, H., et al., *Safety and efficacy of the combined use of ivermectin, dexamethasone, enoxaparin and aspirin against COVID 19.* MedRxiv, 2020.

11. Carvallo, H., et al., *Study of the efficacy and safety of topical ivermectin + iota-carrageenan in the prophylaxis against COVID-19 in health personnel.* Journal of Biomedical Research and Clinical Investigation, 2020.

12. Castañeda-Sabogal, A., et al., *Outcomes of ivermectin in the treatment of COVID-19: a systematic review and meta-analysis.* Medrxiv, 2021.

13. Chaccour, C., et al., *Nebulized ivermectin for COVID-19 and other respiratory diseases, a proof of concept, dose-ranging study in rats.* Sci Rep, 2020. 10(1): p. 17073.

14. Chaccour, C., et al., *The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with non-severe COVID-19: a pilot, double-blind, placebo-controlled, randomized clinical trial.* EClinicalMedicine, 2021: p. 100720.

15. Chachar, A.Z.K., et al., *Effectiveness of ivermectin in SARS-CoV-2/COVID-19 patients.* International Journal of Sciences, 2020. 9(09): p. 31-35.

16. Chowdhury, A.T.M.M., et al., *A randomized trial of ivermectin-doxycycline and hydroxychloroquine-azithromycin therapy on COVID19 patients.* Research Square, 2020.

17. de Melo, G.D., et al., *Anti-COVID-19 efficacy of ivermectin in the golden hamster.* BioRxiv, 2020.

18. Elalfy, H., et al., *Effect of a combination of nitazoxanide, ribavirin, and ivermectin plus zinc supplement (MANS.NRIZ study) on the clearance of mild COVID-19.* J Med Virol, 2021.

19. Errecalde, J., et al., *Safety and pharmacokinetic assessments of a novel ivermectin nasal spray formulation in a pig model.* J Pharm Sci, 2021.

20. Espitia-Hern, G., et al., *Effects of ivermectin-azithromycin-cholecalciferol combined therapy on COVID-19 infected patients: A proof of concept study.* Biomedical Research, 2020.

21. Formiga, F.R., et al., *Ivermectin: an award-winning drug with expected antiviral activity against COVID-19.* J Control Release, 2020.

22. Gonzalez, J.L.B., et al., *Efficacy and safety of ivermectin and hydroxychloroquine in patients with severe COVID-19. A randomized controlled trial.* Medrxiv, 2021.

23. Gorial, F.I., et al., *Effectiveness of ivermectin as add-on therapy in COVID-19 management (pilot trial).* Medrxiv, 2020.

24. Hashim, H.A., et al., *Controlled randomized clinical trial on using ivermectin with doxycycline for treating COVID-19 patients in Baghdad, Iraq.* Medrxiv, 2020.

25. Hellwig, M.D., and Maia, A., *A COVID-19 prophylaxis? Lower incidence associated with prophylactic administration of ivermectin.* Int J Antimicrob Agents, 2021. 57(1): p. 106248.

26. Hill, A., et al., *Meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection.* Research Square, 2021.

27. Jermain, B., et al., *Development of a minimal physiologically-based pharmacokinetic model to simulate lung exposure in humans following oral administration of ivermectin for*

COVID-19 drug repurposing. J Pharm Sci, 2020. 109(12): p. 3574-3578.

28. Kalfas, S., et al., *The therapeutic potential of ivermectin for covid-19: a systematic review of mechanisms and evidence.* Medrxiv, 2020.

29. Khan, M.S.I., et al., *Ivermectin treatment may improve the prognosis of patients with COVID-19.* Arch Bronconeumol, 2020. 56(12): p. 828-830.

30. Kim, M.S., et al., *Comparative efficacy and safety of pharmacological interventions for the treatment of COVID-19: a systematic review and network meta-analysis.* PLoS Med, 2020. 17(12): p. e1003501.

31. Kory, P., et al., *Review of the emerging evidence demonstrating the efficacy of ivermectin in the prophylaxis and treatment of COVID-19.* FICCC.net, 2021.

32. Krolewiecki, A., *Antiviral effect of high-dose ivermectin in adults with COVID-19: a pilot randomised, controlled, open label, multicentre trial.* Lancet preprint, 2020.

33. Lehrer, S., and Rheinstein, P.H., *Ivermectin docks to the SARS-CoV-2 spike receptor-binding domain attached to ACE2.* In Vivo, 2020. 34(5): p. 3023-3026.

34. Lima-Morales, R., et al., *Effectiveness of a multidrug therapy consisting of ivermectin, azithromycin, montelukast and acetylsalicylic acid to prevent hospitalization and death among ambulatory COVID-19 cases in Tlaxcala, Mexico.* Int J Infect Dis, 2021.

35. López-Medina, E., et al., *Effect of ivermectin on time to resolution of symptoms among adults with mild COVID-19: a randomized clinical trial.* JAMA, 2021.

36. Mittal, N. and Mittal, R., *Inhaled route and anti-inflammatory action of ivermectin: Do they hold promise in fighting against COVID-19?* Med Hypotheses, 2021. 146: p. 110364.

37. Mohan, A., et al., *Ivermectin in mild and moderate COVID-19 (RIVET-COV): a randomized, placebo-controlled trial.* Research Square, 2021.

38. Niaee, M.S., *Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: a randomized multi-center clinical trial.* Research Square, 2020.

39. Okumuş, N., et al., *Evaluation of the effectiveness and safety of adding ivermectin to treatment in severe COVID-19 Patients.* Research Square, 2021.

40. Patel, A., Desai, S., et al, RETRACTED, *Ivermectin in COVID-19 related critical illness.* 2020.

41. Podder, C.S., et al., *Outcome of ivermectin treated mild to moderate COVID-19 cases: a single-centre, open-label, randomised controlled study.* IMC J Med Sci, 2020.

42. Rajter, J.C., et al., *Use of ivermectin is associated with lower mortality in hospitalized patients with coronavirus disease 2019: the ivermectin in covid nineteen study.* Chest, 2021.

159(1): p. 85-92.

43. Ravikirti, R., et al., *Ivermectin as a potential treatment for mild to moderate COVID-19 – a double blind randomized placebo-controlled trial.* Medrxiv, 2021.

44. Bukhari, S.K.H.S., et al., *Efficacy of ivermectin in COVID-19 patients with mild to moderate disease.* Medrxiv, 2021.

45. Soto-Becerra, P., et al., *Real-world effectiveness of hydroxychloroquine, azithromycin, and ivermectin among hospitalized COVID-19 patients: results of a target trial emulation using observational data from a nationwide healthcare system in Peru.* Medrxiv, 2020.

46. Spoorthi, V., and Surapaneni, S., *Utility of ivermectin and doxycycline combination for the treatment of SARS-CoV-2.* International Archives of Integrated Medicine, 2020.

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- Trial Site News: Slovakia Becomes the First EU Nation to Formally Approve Ivermectin for Both Prophylaxis and Treatment for COVID-19 Patients
- Státní ústav pro kontrolu léčiv: Informace o povolení používání neregistrovaného léčivého přípravku HUMEVEC (ivermektin)

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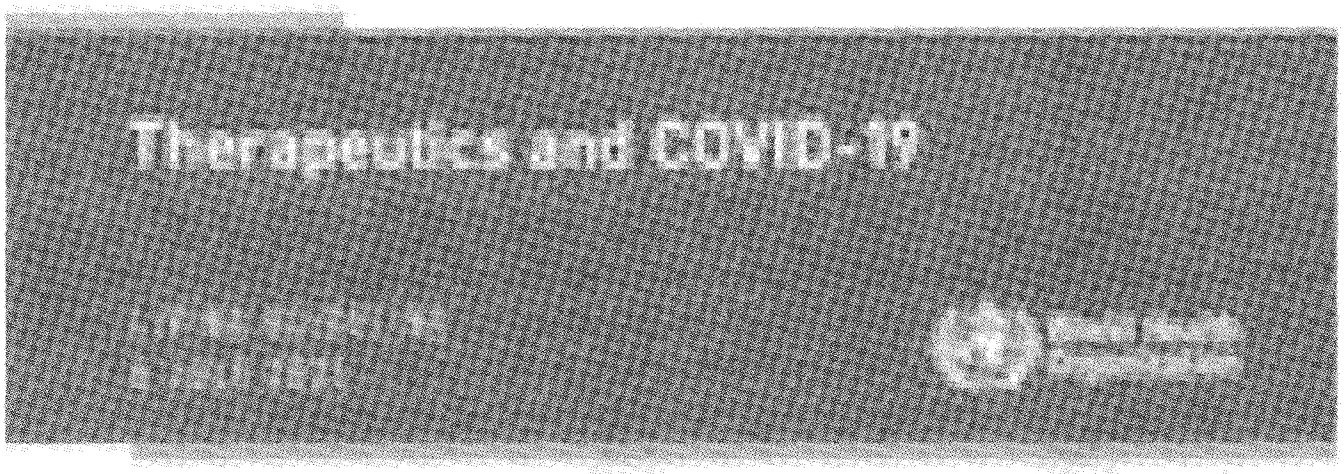
Therapeutics and COVID-19: living guideline

6 July 2021 | COVID-19: Clinical care


Therapeutics and COVID-19

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Overview

The WHO *Therapeutics and COVID-19: living guideline* contains the Organization's most up-to-date recommendations for the use of therapeutics in the treatment of COVID-19. The **latest version** of this living guideline is available in pdf format (via the 'Download' button) and via an online platform, and is updated regularly as new evidence emerges.

This fifth version of the WHO guideline now contains seven recommendations, including a new recommendation regarding interleukin-6 (IL-6) receptor blockers, including both tocilizumab and sarilumab. This latest update was initiated in response to publication of the RECOVERY and REMAP-CAP trials addressing IL-6 receptor blockers as a potential treatment for COVID-19. No further updates to the previous existing recommendations were made in this latest version.

CORRIGENDUM

The WHO *Therapeutics and COVID-19: living guideline* currently includes a:

- **** NEW ** strong recommendation to use IL-6 receptor blockers (tocilizumab or sarilumab) in patients with severe or critical COVID-19 (published 6 July 2021);**
- **recommendation not to use ivermectin in patients with COVID-19 except in the context of a clinical trial (published 31 March 2021);**
- **strong recommendation against hydroxychloroquine in patients with COVID-19 of any severity (published 17 December 2020);**
- **strong recommendation against lopinavir/ritonavir in patients with COVID-19 of any severity (published 17 December 2020);**
- **conditional recommendation against remdesivir in hospitalized patients with COVID-19 (published 20 November 2020);**
- **strong recommendation for systemic corticosteroids in patients with severe and critical COVID-19 (published 2 September 2020);**
- **conditional recommendation against systemic corticosteroids in patients with non-severe COVID-19 (published 2 September 2020).**

Other COVID-19 therapeutics that are currently under consideration by WHO include colchicine, monoclonal antibodies and anticoagulants. This guideline will be updated if/when sufficient new evidence warrants this.

Guidelines regarding the use of drugs to prevent (rather than treat) COVID-19 are included in a separate document, *WHO Living guideline: Drugs to prevent COVID-19*, that can be accessed via an online platform and in pdf format (or click 'PDF' in top right corner of online platform).

Guidelines regarding the clinical management of COVID-19 patients are included in a further document, *COVID-19 Clinical management: Living guideline*, that can be accessed via an online platform and in pdf format (or click 'PDF' in top right corner of online platform).

To view **previous (now outdated) versions** of this guideline, please see the links below:

- **First version, published 2 September 2020 (accessible as pdf only)**
- **Second version, published 20 November 2020 (access as pdf or via online platform)**
- **Third version, published 17 December 2020 (access as pdf or via online platform)**
- **Fourth version, published 31 March 2021 (access as pdf or via online platform)**

This document was updated on 6 July 2021

WHO TEAM

WHO Headquarters (HQ)

EDITORS

World Health Organization

REFERENCE NUMBERS

WHO REFERENCE NUMBER: WHO/2019-nCoV/therapeutics/2021.2

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Ivermectin Tablets

Dosage form: tablet
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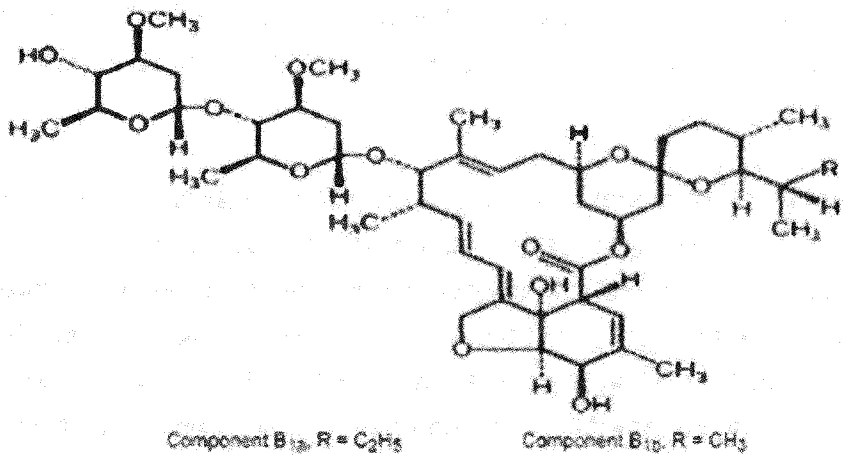
On This Page

Ivermectin Tablets Description

Ivermectin is a semisynthetic, anthelmintic agent for oral administration. Ivermectin is derived from the avermectins, a class of highly active broad-spectrum, anti-parasitic agents isolated from the fermentation products of Streptomyces avermitilis. Ivermectin is a mixture containing at least 90% 5-O-demethyl-22,23-dihydroavermectin A_{1a} and less than 10% 5-O-demethyl-25-de(1-methylpropyl)-22,23-dihydro-25-(1-methylethyl)avermectin A_{1a}, generally referred to as 22,23-dihydroavermectin B_{1a} and B_{1b}, or H_2B_{1a} and H_2B_{1b}, respectively. The respective empirical formulas are $C_{48}H_{74}O_{14}$ and $C_{47}H_{72}O_{14}$, with molecular weights of 875.10 and 861.07, respectively. The structural formulas are:



Ivermectin is a white to yellowish-white, nonhygroscopic, crystalline powder with a melting point of about 155°C. It is insoluble in water but is freely soluble in methanol and soluble in 95% ethanol.

Ivermectin Tablets are available as 3-mg tablets containing the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and pregelatinized starch.

Ivermectin Tablets - Clinical Pharmacology

Pharmacokinetics

Following oral administration of ivermectin, plasma concentrations are approximately proportional to the dose. In two studies, after single 12-mg doses of ivermectin in fasting healthy volunteers (representing a mean dose of 165 mcg/kg), the mean peak plasma concentrations of the major component (H_2B_{1a}) were 46.6 (±21.9) (range: 16.4 to 101.1) and 30.6 (±15.6) (range: 13.9 to 68.4) ng/mL, respectively, at approximately 4 hours after dosing. Ivermectin is metabolized in the liver, and ivermectin and/or its metabolites are excreted almost exclusively in the feces over an estimated 12 days, with less than 1% of the administered dose excreted in the urine. The plasma half-life of ivermectin in man is approximately 18 hours following oral administration.

The safety and pharmacokinetic properties of ivermectin were further assessed in a multiple-dose clinical pharmacokinetic study involving healthy volunteers. Subjects received oral doses of 30 to 120 mg (333 to 2000 mcg/kg) ivermectin in a fasted state or 30 mg (333 to 600 mcg/kg) ivermectin following a standard high-fat (48.6 g of fat) meal. Administration of 30 mg ivermectin following a high-fat meal resulted in an approximate 2.5-fold increase in bioavailability relative to administration of 30 mg ivermectin in the fasted state.

In vitro studies using human liver microsomes and recombinant CYP450 enzymes have shown that ivermectin is primarily metabolized by CYP3A4. Depending on the in vitro method used, CYP2D6 and CYP2E1 were also shown to be involved in the metabolism of ivermectin but to a significantly lower extent compared to CYP3A4. The findings of in vitro studies using human liver microsomes

suggest that clinically relevant concentrations of ivermectin do not significantly inhibit the metabolizing activities of CYP3A4, CYP2D6, CYP2C9, CYP1A2, and CYP2E1.

Microbiology

Ivermectin is a member of the avermectin class of broad-spectrum antiparasitic agents which have a unique mode of action. Compounds of the class bind selectively and with high affinity to glutamate-gated chloride ion channels which occur in invertebrate nerve and muscle cells. This leads to an increase in the permeability of the cell membrane to chloride ions with hyperpolarization of the nerve or muscle cell, resulting in paralysis and death of the parasite. Compounds of this class may also interact with other ligand-gated chloride channels, such as those gated by the neurotransmitter gamma-aminobutyric acid (GABA).

The selective activity of compounds of this class is attributable to the facts that some mammals do not have glutamate-gated chloride channels and that the avermectins have a low affinity for mammalian ligand-gated chloride channels. In addition, ivermectin does not readily cross the blood-brain barrier in humans.

Ivermectin is active against various life-cycle stages of many but not all nematodes. It is active against the tissue microfilariae of Onchocerca volvulus but not against the adult form. Its activity against Strongyloides stercoralis is limited to the intestinal stages.

Clinical Studies

Stongyloidiasis

Two controlled clinical studies using albendazole as the comparative agent were carried out in international sites where albendazole is approved for the treatment of strongyloidiasis of the gastrointestinal tract, and three controlled studies were carried out in the U.S. and internationally using thiabendazole as the comparative agent. Efficacy, as measured by cure rate, was defined as the absence of larvae in at least two follow-up stool examinations 3 to 4 weeks post-therapy. Based on this criterion, efficacy was significantly greater for ivermectin (a single dose of 170 to 200 mcg/kg) than for albendazole (200 mg b.i.d. for 3 days). Ivermectin administered as a single dose of 200 mcg/kg for 1 day was as efficacious as thiabendazole administered at 25 mg/kg b.i.d. for 3 days.

Summary of Cure Rates for Ivermectin Versus Comparative Agents in the Treatment of Strongyloidiasis		
	Cure Rate* (%)	
	Ivermectin†	**Comparative Agent**

*Number and % of evaluable patients
†170 to 200 mcg/kg
‡200 mg b.i.d. for 3 days

§25 mg/kg b.i.d. for 3 days

Albendazole‡ Comparative		
International Study	24/26 (92)	12/22 (55)
WHO Study	126/152 (83)	67/149 (45)
Thiabendazole§ Comparative		
International Study	9/14 (64)	13/15 (87)
US Studies	14/14 (100)	16/17 (94)

In one study conducted in France, a non-endemic area where there was no possibility of reinfection, several patients were observed to have recrudescence of Strongyloides larvae in their stool as long as 106 days following ivermectin therapy. Therefore, at least three stool examinations should be conducted over the three months following treatment to ensure eradication. If recrudescence of larvae is observed, retreatment with ivermectin is indicated. Concentration techniques (such as using a Baermann apparatus) should be employed when performing these stool examinations, as the number of Strongyloides larvae per gram of feces may be very low.

Onchocerciasis

The evaluation of ivermectin in the treatment of onchocerciasis is based on the results of clinical studies involving 1278 patients. In a double-blind, placebo-controlled study involving adult patients with moderate to severe onchocercal infection, patients who received a single dose of 150 mcg/kg ivermectin experienced an 83.2% and 99.5% decrease in skin microfilariae count (geometric mean) 3 days and 3 months after the dose, respectively. A marked reduction of >90% was maintained for up to 12 months after the single dose. As with other microfilaricidal drugs, there was an increase in the microfilariae count in the anterior chamber of the eye at day 3 after treatment in some patients. However, at 3 and 6 months after the dose, a significantly greater percentage of patients treated with ivermectin had decreases in microfilariae count in the anterior chamber than patients treated with placebo.

In a separate open study involving pediatric patients ages 6 to 13 (n=103; weight range: 17 to 41 kg), similar decreases in skin microfilariae counts were observed for up to 12 months after dosing.

Indications and Usage for Ivermectin Tablets

Ivermectin is indicated for the treatment of the following infections:

Strongyloidiasis of the intestinal tract

Ivermectin is indicated for the treatment of intestinal (i.e., nondisseminated) strongyloidiasis due to the nematode parasite Strongyloides stercoralis. This indication is based on clinical studies of both

comparative and open-label designs, in which 64-100% of infected patients were cured following a single 200-mcg/kg dose of ivermectin (See CLINICAL PHARMACOLOGY, Clinical Studies).

Onchocerciasis

Ivermectin is indicated for the treatment of onchocerciasis due to the nematode parasite Onchocerca volvulus.

This indication is based on randomized, double-blind, placebo-controlled and comparative studies conducted in 1427 patients in onchocerciasis-endemic areas of West Africa. The comparative studies used diethylcarbamazine citrate (DEC-C).

NOTE: Ivermectin has no activity against adult Onchocerca volvulus parasites. The adult parasites reside in subcutaneous nodules which are infrequently palpable. Surgical excision of these nodules (nodulectomy) may be considered in the management of patients with onchocerciasis, since this procedure will eliminate the microfilariae-producing adult parasites.

Contraindications

Ivermectin Tablets are contraindicated in patients who are hypersensitive to any component of this product.

Warnings

Historical data have shown that microfilaricidal drugs, such as diethylcarbamazine citrate (DEC-C), might cause cutaneous and/or systemic reactions of varying severity (the Mazzotti reaction) and ophthalmological reactions in patients with onchocerciasis. These reactions are probably due to allergic and inflammatory responses to the death of microfilariae. Patients treated with ivermectin for onchocerciasis may experience these reactions in addition to clinical adverse reactions possibly, probably, or definitely related to the drug itself (See ADVERSE REACTIONS, Onchocerciasis).

The treatment of severe Mazzotti reactions has not been subjected to controlled clinical trials. Oral hydration, recumbency, intravenous normal saline, and/or parenteral corticosteroids have been used to treat postural hypotension. Antihistamines and/or aspirin have been used for most mild to moderate cases.

Precautions

General

After treatment with microfilaricidal drugs, patients with hyperreactive onchodermatitis (sowda) may be more likely than others to experience severe adverse reactions, especially edema and aggravation of onchodermatitis.

Rarely, patients with onchocerciasis who are also heavily infected with Loa loa may develop a serious or even fatal encephalopathy either spontaneously or following treatment with an effective microfilaricide. In these patients, the following adverse experiences have also been reported: pain (including neck and back pain), red eye, conjunctival hemorrhage, dyspnea, urinary and/or fecal incontinence, difficulty in standing/walking, mental status changes, confusion, lethargy, stupor, seizures, or coma. This syndrome has been seen very rarely following the use of ivermectin. In individuals who warrant treatment with ivermectin for any reason and have had significant exposure to Loa loa-endemic areas of West or Central Africa, pretreatment assessment for loiasis and careful posttreatment follow-up should be implemented.

Information for Patients

Ivermectin Tablets should be taken on an empty stomach with water (See CLINICAL PHARMACOLOGY, Pharmacokinetics).

Strongyloidiasis

The patient should be reminded of the need for repeated stool examinations to document clearance of infection with Strongyloides stercoralis.

Onchocerciasis

The patient should be reminded that treatment with ivermectin does not kill the adult Onchocerca parasites, and therefore repeated follow-up and retreatment is usually required.

Drug Interactions

Post-marketing reports of increased INR (International Normalized Ratio) have been rarely reported when ivermectin was coadministered with warfarin.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of ivermectin.

Ivermectin was not genotoxic in vitro in the Ames microbial mutagenicity assay of Salmonella typhimurium strains TA1535, TA1537, TA98, and TA100 with and without rat liver enzyme activation, the Mouse Lymphoma Cell Line L5178Y (cytotoxicity and mutagenicity) assays, or the unscheduled DNA synthesis assay in human fibroblasts.

Ivermectin had no adverse effects on the fertility in rats in studies at repeated doses of up to 3 times the maximum recommended human dose of 200 mcg/kg (on a mg/m^2/day basis).

Pregnancy

Teratogenic Effects

Pregnancy Category C

Ivermectin has been shown to be teratogenic in mice, rats, and rabbits when given in repeated doses of 0.2, 8.1, and 4.5 times the maximum recommended human dose, respectively (on a mg/m^2/day basis). Teratogenicity was characterized in the three species tested by cleft palate; clubbed forepaws were additionally observed in rabbits. These developmental effects were found only at or near doses that were maternotoxic to the pregnant female. Therefore, ivermectin does not appear to be selectively fetotoxic to the developing fetus. There are, however, no adequate and well-controlled studies in pregnant women. Ivermectin should not be used during pregnancy since safety in pregnancy has not been established.

Nursing Mothers

Ivermectin is excreted in human milk in low concentrations. Treatment of mothers who intend to breast-feed should only be undertaken when the risk of delayed treatment to the mother outweighs the possible risk to the newborn.

Pediatric Use

Safety and effectiveness in pediatric patients weighing less than 15 kg have not been established.

Geriatric Use

Clinical studies of ivermectin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, treatment of an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Strongyloidiasis in Immunocompromised Hosts

In immunocompromised (including HIV-infected) patients being treated for intestinal strongyloidiasis, repeated courses of therapy may be required. Adequate and well-controlled clinical studies have not been conducted in such patients to determine the optimal dosing regimen. Several treatments, i.e., at 2-week intervals, may be required, and cure may not be achievable. Control of extra-intestinal strongyloidiasis in these patients is difficult, and suppressive therapy, i.e., once per month, may be helpful.

Adverse Reactions

Strongyloidiasis

In four clinical studies involving a total of 109 patients given either one or two doses of 170 to 200 mcg/kg of ivermectin, the following adverse reactions were reported as possibly, probably, or definitely related to ivermectin:

Body as a Whole: asthenia/fatigue (0.9%), abdominal pain (0.9%)

Gastrointestinal: anorexia (0.9%), constipation (0.9%), diarrhea (1.8%), nausea (1.8%), vomiting (0.9%)

Nervous System/Psychiatric: dizziness (2.8%), somnolence (0.9%), vertigo (0.9%), tremor (0.9%)

Skin: pruritus (2.8%), rash (0.9%), and urticaria (0.9%).

In comparative trials, patients treated with ivermectin experienced more abdominal distention and chest discomfort than patients treated with albendazole. However, ivermectin was better tolerated than thiabendazole in comparative studies involving 37 patients treated with thiabendazole.

The Mazzotti-type and ophthalmologic reactions associated with the treatment of onchocerciasis or the disease itself would not be expected to occur in strongyloidiasis patients treated with ivermectin (See ADVERSE REACTIONS, Onchocerciasis).

Laboratory Test Findings

In clinical trials involving 109 patients given either one or two doses of 170 to 200 mcg/kg ivermectin, the following laboratory abnormalities were seen regardless of drug relationship: elevation in ALT and/or AST (2%), decrease in leukocyte count (3%). Leukopenia and anemia were seen in one patient.

Onchocerciasis

In clinical trials involving 963 adult patients treated with 100 to 200 mcg/kg ivermectin, worsening of the following Mazzotti reactions during the first 4 days post-treatment were reported: arthralgia/synovitis (9.3%), axillary lymph node enlargement and tenderness (11.0% and 4.4%, respectively), cervical lymph node enlargement and tenderness (5.3% and 1.2%, respectively), inguinal lymph node enlargement and tenderness (12.6% and 13.9%, respectively), other lymph node enlargement and tenderness (3.0% and 1.9%, respectively), pruritus (27.5%), skin involvement including edema, papular and pustular or frank urticarial rash (22.7%), and fever (22.6%) (See WARNINGS).

In clinical trials, ophthalmological conditions were examined in 963 adult patients before treatment, at day 3, and months 3 and 6 after treatment with 100 to 200 mcg/kg ivermectin. Changes observed were primarily deterioration from baseline 3 days post-treatment. Most changes either returned to baseline condition or improved over baseline severity at the month 3 and 6 visits. The percentages of patients with worsening of the following conditions at day 3, month 3 and 6, respectively, were: limbitis: 5.5%, 4.8%, and 3.5% and punctate opacity: 1.8%, 1.8%, and 1.4%. The corresponding percentages for patients treated with placebo were: limbitis: 6.2%, 9.9%, and 9.4% and punctate opacity: 2.0%, 6.4%, and 7.2% (See WARNINGS).

In clinical trials involving 963 adult patients who received 100 to 200 mcg/kg ivermectin, the following clinical adverse reactions were reported as possibly, probably, or definitely related to the drug in ≥1% of the patients: facial edema (1.2%), peripheral edema (3.2%), orthostatic hypotension (1.1%), and tachycardia (3.5%). Drug-related headache and myalgia occurred in <1% of patients (0.2% and 0.4%, respectively). However, these were the most common adverse experiences reported overall during these trials regardless of causality (22.3% and 19.7%, respectively).

A similar safety profile was observed in an open study in pediatric patients ages 6 to 13.

The following ophthalmological side effects do occur due to the disease itself but have also been reported after treatment with ivermectin: abnormal sensation in the eyes, eyelid edema, anterior uveitis, conjunctivitis, limbitis, keratitis, and chorioretinitis or choroiditis. These have rarely been severe or associated with loss of vision and have generally resolved without corticosteroid treatment.

Laboratory Test Findings

In controlled clinical trials, the following laboratory adverse experiences were reported as possibly, probably, or definitely related to the drug in ≥1% of the patients: eosinophilia (3%) and hemoglobin increase (1%).

Post-Marketing Experience

The following adverse reactions have been reported since the drug was registered overseas:

Onchocerciasis

Conjunctival hemorrhage

All Indications

Hypotension (mainly orthostatic hypotension), worsening of bronchial asthma, toxic epidermal necrolysis, Stevens-Johnson syndrome, seizures, hepatitis, elevation of liver enzymes, and elevation of bilirubin.

Overdosage

Significant lethality was observed in mice and rats after single oral doses of 25 to 50 mg/kg and 40 to 50 mg/kg, respectively. No significant lethality was observed in dogs after single oral doses of up to 10 mg/kg. At these doses, the treatment-related signs that were observed in these animals include ataxia, bradypnea, tremors, ptosis, decreased activity, emesis, and mydriasis.

In accidental intoxication with, or significant exposure to, unknown quantities of veterinary formulations of ivermectin in humans, either by ingestion, inhalation, injection, or exposure to body surfaces, the following adverse effects have been reported most frequently: rash, edema, headache, dizziness, asthenia, nausea, vomiting, and diarrhea. Other adverse effects that have

been reported include: seizure, ataxia, dyspnea, abdominal pain, paresthesia, urticaria, and contact dermatitis.

In case of accidental poisoning, supportive therapy, if indicated, should include parenteral fluids and electrolytes, respiratory support (oxygen and mechanical ventilation if necessary) and pressor agents if clinically significant hypotension is present. Induction of emesis and/or gastric lavage as soon as possible, followed by purgatives and other routine anti-poison measures, may be indicated if needed to prevent absorption of ingested material.

Ivermectin Tablets Dosage and Administration

Strongyloidiasis

The recommended dosage of Ivermectin Tablets for the treatment of strongyloidiasis is a single oral dose designed to provide approximately 200 mcg of ivermectin per kg of body weight. See Table 1 for dosage guidelines. Patients should take tablets on an empty stomach with water (See CLINICAL PHARMACOLOGY, Pharmacokinetics). In general, additional doses are not necessary. However, follow-up stool examinations should be performed to verify eradication of infection (See CLINICAL PHARMACOLOGY, Clinical Studies).

Table 1: Dosage Guidelines for Ivermectin Tablets for Strongyloidiasis

Body Weight (kg)	**Single Oral Dose Number of 3-mg Tablets**
15 to 24	1 tablet
25 to 35	2 tablets
36 to 50	3 tablets
51 to 65	4 tablets
66 to 79	5 tablets
≥80	200 mcg/kg

Onchocerciasis

The recommended dosage of Ivermectin Tablets for the treatment of onchocerciasis is a single oral dose designed to provide approximately 150 mcg of ivermectin per kg of body weight. See Table 2 for dosage guidelines. Patients should take tablets on an empty stomach with water (See CLINICAL PHARMACOLOGY, Pharmacokinetics). In mass distribution campaigns in international treatment programs, the most commonly used dose interval is 12 months. For the treatment of individual patients, retreatment may be considered at intervals as short as 3 months.

Table 2: Dosage Guidelines for Ivermectin Tablets for Onchocerciasis

Body Weight (kg)	Single Oral Dose Number of 3-mg Tablets
15 to 25	1 tablet
26 to 44	2 tablets
45 to 64	3 tablets
65 to 84	4 tablets
≥85	150 mcg/kg

How is Ivermectin Tablets Supplied

Ivermectin Tablets USP, 3 mg are white, round, flat, bevel-edged tablets debossed with "806" on one side and plain on the other side. They are supplied as follows:
NDC 42799-806-01 unit dose packages of 20.

Storage

Store at temperatures below 30°C (86°F).

Manufactured for:
Edenbridge Pharmaceuticals, LLC
Parsippany, NJ 07054

Rev. 01/14

PRINCIPAL DISPLAY PANEL - 3 mg Tablet Carton

NDC 42799-806-01

Ivermectin
Tablets USP

3 mg

20 Tablets
(2 Foil Strips of 10 tablets each)

Rx Only

Edenbridge
Pharmaceuticals

IVERMECTIN
ivermectin tablet

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG LABEL	**Item Code (Source)**	NDC:42799-806
Route of Administration	ORAL	**DEA Schedule**	

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
IVERMECTIN (IVERMECTIN)	IVERMECTIN	3 mg

Inactive Ingredients	
Ingredient Name	**Strength**
SILICON DIOXIDE	
CROSCARMELLOSE SODIUM	
MAGNESIUM STEARATE	
MICROCRYSTALLINE CELLULOSE	
STARCH, CORN	

Product Characteristics			
Color	WHITE	**Score**	no score
Shape	ROUND	**Size**	6mm
Flavor		**Imprint Code**	806
Contains			

Packaging		
#	**Item Code**	**Package Description**

1	NDC:42799-806-01	2 BLISTER PACK in 1 CARTON
1		10 TABLET in 1 BLISTER PACK

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA204154	11/15/2014	

Labeler - Edenbridge Pharmaceuticals, LLC (948715060)

Edenbridge Pharmaceuticals, LLC

Frequently asked questions

- Can Ivermectin be used to treat COVID-19?

MERCK

Menu

Media > Company statements > Company statement

Merck Statement on Ivermectin use During the COVID-19 Pandemic

Save

February 4, 2021 11:45 am ET

KENILWORTH, N.J., Feb. 4, 2021 – Merck (NYSE: MRK), known as MSD outside the United States and Canada, today affirmed its position regarding use of ivermectin during the COVID-19 pandemic. Company scientists continue to carefully examine the findings of all available and emerging studies of ivermectin for the treatment of COVID-19 for evidence of efficacy and safety. It is important to note that, to-date, our analysis has identified:

- No scientific basis for a potential therapeutic effect against COVID-19 from pre-clinical studies;
- No meaningful evidence for clinical activity or clinical efficacy in patients with COVID-19 disease, and;
- A concerning lack of safety data in the majority of studies.

We do not believe that the data available support the safety and efficacy of ivermectin beyond the doses and populations indicated in the regulatory agency-approved prescribing information.

Indications and Usage for STROMECTOL® (ivermectin)

Ivermectin is approved in the United States under the brand name STROMECTOL. STROMECTOL is indicated for the treatment of intestinal (i.e., nondisseminated) strongyloidiasis due to the nematode parasite *Strongyloides stercoralis* and for the treatment of onchocerciasis due to the nematode parasite *Onchocerca volvulus*.

STROMECTOL has no activity against adult *Onchocerca volvulus* parasites.

SELECTED SAFETY INFORMATION FOR STROMECTOL® (ivermectin)

Contraindications

STROMECTOL is contraindicated in patients who are hypersensitive to any component of this product.

EXHIBIT I

Warnings and Precautions

Patients treated with STROMECTOL for onchocerciasis may experience cutaneous and/or systemic reactions of varying severity (the Mazzotti reaction) and ophthalmological reactions.

After treatment with microfilaricidal drugs, patients with hyperreactive onchodermatitis (sowda) may be more likely than others to experience severe adverse reactions, especially edema and aggravation of onchodermatitis.

Rarely, patients with onchocerciasis who are also heavily infected with *Loa loa* may develop a serious or even fatal encephalopathy either spontaneously or following treatment with an effective microfilaricide. In these patients, the following adverse experiences have also been reported: pain (including neck and back pain), red eye, conjunctival hemorrhage, dyspnea, urinary and/or fecal incontinence, difficulty in standing/walking, mental status changes, confusion, lethargy, stupor, seizures, or coma. In individuals who warrant treatment with ivermectin for any reason and have had significant exposure to *Loa loa*-endemic areas of West or Central Africa, pretreatment assessment for loiasis and careful post-treatment follow-up should be implemented.

STROMECTOL should be taken on an empty stomach with water.

Strongyloidiasis: The patient should be reminded of the need for repeated stool examinations to document clearance of infection with *Strongyloides stercoralis*.

Onchocerciasis: The patient should be reminded that treatment with STROMECTOL does not kill the adult *Onchocerca* parasites, and therefore repeated follow-up and retreatment is usually required.

Adverse Reactions

Strongyloidiasis

In four clinical studies involving a total of 109 patients given either one or two doses of 170 to 200 mcg/kg of STROMECTOL, the following adverse reactions were reported as possibly, probably, or definitely related to STROMECTOL: Body as a Whole: asthenia/fatigue (0.9%), abdominal pain (0.9%); Gastrointestinal: anorexia (0.9%), constipation (0.9%), diarrhea (1.8%), nausea (1.8%), vomiting (0.9%); Nervous System/Psychiatric: dizziness (2.8%), somnolence (0.9%), vertigo (0.9%), tremor (0.9%); Skin: pruritus (2.8%), rash (0.9%), and urticaria (0.9%).

Onchocerciasis

In clinical trials involving 963 adult patients treated with 100 to 200 mcg/kg STROMECTOL, worsening of the following Mazzotti reactions during the first 4 days post-treatment were reported: arthralgia/synovitis (9.3%), axillary lymph node enlargement and tenderness (11.0% and 4.4%, respectively), cervical lymph node enlargement and tenderness (5.3% and 1.2%, respectively),

inguinal lymph node enlargement and tenderness (12.6% and 13.9%, respectively), other lymph node enlargement and tenderness (3.0% and 1.9%, respectively), pruritus (27.5%), skin involvement including edema, papular and pustular or frank urticarial rash (22.7%), and fever (22.6%).

In clinical trials, ophthalmological conditions were examined in 963 adult patients before treatment, at day 3, and months 3 and 6 after treatment with 100 to 200 mcg/kg STROMECTOL. Changes observed were primarily deterioration from baseline 3 days post-treatment. Most changes either returned to baseline condition or improved over baseline severity at the month 3 and 6 visits. The percentages of patients with worsening of the following conditions at day 3, month 3 and 6, respectively, were: limbitis: 5.5%, 4.8%, and 3.5% and punctate opacity: 1.8%, 1.8%, and 1.4%. The corresponding percentages for patients treated with placebo were: limbitis: 6.2%, 9.9%, and 9.4% and punctate opacity: 2.0%, 6.4%, and 7.2%.

In clinical trials involving 963 adult patients who received 100 to 200 mcg/kg STROMECTOL, the following clinical adverse reactions were reported as possibly, probably, or definitely related to the drug in ^{3}1% of the patients: facial edema (1.2%), peripheral edema (3.2%), orthostatic hypotension (1.1%), and tachycardia (3.5%). Drug-related headache and myalgia occurred in <1% of patients (0.2% and 0.4% respectively).

The following ophthalmological side effects do occur due to the disease itself but have also been reported after treatment with STROMECTOL: abnormal sensation in the eyes, eyelid edema, anterior uveitis, conjunctivitis, limbitis, keratitis, and chorioretinitis or choroiditis. These have rarely been severe or associated with loss of vision and have generally resolved without corticosteroid treatment.

Drug Interactions

Post-marketing reports of increased INR (International Normalized Ratio) have been rarely reported when ivermectin was co-administered with warfarin.

Use in Specific Populations

Ivermectin should not be used during pregnancy since safety in pregnancy has not been established.

Ivermectin is excreted in human milk in low concentrations. Treatment of mothers who intend to breast-feed should only be undertaken when the risk of delayed treatment to the mother outweighs the possible risk to the newborn.

Safety and effectiveness in pediatric patients weighing less than 15 kg have not been established.

Clinical studies of STROMECTOL did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

In immunocompromised (including HIV-infected) patients being treated for intestinal strongyloidiasis, repeated courses of therapy may be required. Adequate and well-controlled clinical studies have not been conducted in such patients to determine the optimal dosing regimen.

About Merck

For 130 years, Merck, known as MSD outside of the United States and Canada, has been inventing for life, bringing forward medicines and vaccines for many of the world's most challenging diseases in pursuit of our mission to save and improve lives. We demonstrate our commitment to patients and population health by increasing access to health care through far-reaching policies, programs and partnerships. Today, Merck continues to be at the forefront of research to prevent and treat diseases that threaten people and animals – including cancer, infectious diseases such as HIV and Ebola, and emerging animal diseases – as we aspire to be the premier research-intensive biopharmaceutical company in the world. For more information, visit www.merck.com and connect with us on Twitter, Facebook, Instagram, YouTube and LinkedIn.

Forward-Looking Statement of Merck & Co., Inc., Kenilworth, N.J., USA

This news release of Merck & Co., Inc., Kenilworth, N.J., USA (the "company") includes "forward-looking statements" within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs and expectations of the company's management and are subject to significant risks and uncertainties. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.

Risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of the global outbreak of novel coronavirus disease (COVID-19); the impact of pharmaceutical industry regulation and health care legislation in the United States and internationally; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; the company's ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of the company's patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

The company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in the company's 2019 Annual Report on Form 10-K and the company's other filings with the Securities and Exchange Commission (SEC) available at the SEC's Internet site (www.sec.gov).

Please see Prescribing Information for STROMECTOL at
https://www.merck.com/product/usa/pi_circulars/s/stromectol/stromectol_pi.pdf.

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Table 2c. Ivermectin: Selected Clinical Data

Last Updated: July 19, 2021

The Panel has reviewed other clinical studies of IVM for the treatment of COVID-19.[1-16] However, those studies have limitations that make them less definitive and informative than the studies discussed here. The studies summarized below are those that have had the greatest impact on the Panel's recommendations.

Study Design	Methods	Results	Limitations and Interpretation
Ivermectin Versus Placebo for Treatment of Mild COVID-19[17]			
Randomized, double-blind, placebo-controlled trial in Cali, Colombia (n = 476)	**Key Inclusion Criteria:** • Positive SARS-CoV-2 PCR result or positive antigen test result • Symptoms began ≤7 days prior to randomization • Mild disease (defined as receiving outpatient or inpatient care, but not receiving HFNC oxygen or mechanical ventilation) **Key Exclusion Criteria:** • Asymptomatic disease • Severe pneumonia • Receipt of IVM within previous 5 days • Hepatic dysfunction/abnormal liver function tests **Interventions:** • Oral IVM 300 µg/kg per day in solution for 5 days, taken primarily on an empty stomach • Placebo **Primary Endpoints:** • Time from randomization to resolution of symptoms within the 21-day follow-up period. Resolution of symptoms was defined as the first day a patient reported a score of 0 (no clinical evidence of infection) on an 8-point ordinal scale.	**Number of Participants:** • IVM (n = 200) and placebo (n = 198) in primary analysis **Participant Characteristics:** • Median age was 37 years; 4% of patients in IVM arm and 8% in placebo arm were aged ≥65 years. • 39% of patients in IVM arm and 45% in placebo arm were male. • 79% of patients had no known comorbidities; median BMI in both arms was 26. • Median time from symptom onset to randomization was 5 days (IQR 4–6 days). • 62% of patients in IVM arm and 55% in placebo arm were not hospitalized and had no limitations of activities at baseline (ordinal scale 1); 38% and 44% were not hospitalized but had some limitations on activities, or they were receiving oxygen at home, or both (ordinal scale 2). • 1% of patients in both arms were hospitalized at baseline. **Primary Outcomes:** • No difference in time to resolution of symptoms (median 10 days in IVM arm vs. 12 days in placebo arm; HR 1.07; 95% CI, 0.87–1.32; $P = 0.53$) • Symptoms resolved in 82% of patients in IVM arm and 79% in placebo arm by Day 21. **Other Outcomes:**	**Key Limitations:** • Relatively small sample size • Primary endpoint was modified during the trial due to lower than expected event rates. • The first 65 patients received a placebo that smelled and tasted different from IVM. • The study enrolled a younger, healthier demographic than those who typically experience more serious cases of COVID-19. • Study included 4 hospitalized patients (out of 398). • The IVM dose used in this study was higher than the dose that is usually administered (IVM 200 µg/kg per day). **Interpretation:** • A 5-day course of IVM did not improve time to resolution of symptoms in patients with mild COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
		• No significant difference between arms in proportion of patients who showed clinical deterioration of ≥2 points on the ordinal scale (3.5% in IVM arm vs. 2.0% in placebo arm; absolute difference -1.5%; 95% CI, -4.8% to 1.7%) • No significant difference between arms in the odds of improvement in ordinal scale score and the proportion of patients who sought medical care or required escalation in care. • 8% of patients in IVM arm and 3% in placebo arm discontinued treatment due to an AE. None of the reported SAEs were considered to be related to study interventions.	
Ivermectin Versus Ivermectin Plus Doxycycline Versus Placebo for Treatment of COVID-19[18]			

Study Design	Methods	Results	Limitations and Interpretation
Randomized, double-blind, placebo-controlled trial of hospitalized adults in Dhaka, Bangladesh (n = 72)	**Key Inclusion Criteria:** • Aged 18–65 years • Laboratory-confirmed SARS-CoV-2 infection with fever, cough, or sore throat • Admitted to hospital within previous 7 days **Key Exclusion Criteria:** • Chronic cardiac, renal, or liver disease **Interventions:** • IVM 12 mg PO once daily for 5 days • Single dose of IVM 12 mg PO plus DOX 200 mg PO on Day 1, then DOX 100 mg every 12 hours for 4 days • Placebo **Primary Endpoints:** • Time to virologic clearance, measured by obtaining an NP swab for SARS-CoV-2 PCR on Days 3, 7, and 14, then weekly until PCR result was negative • Resolution of fever and cough within 7 days	**Number of Participants:** • IVM (n = 24; 2 withdrew), IVM plus DOX (n = 24; 1 withdrew), and placebo (n = 24; 1 withdrew) **Participant Characteristics:** • Mean age was 42 years. • 54% of patients were female. • Mean time from symptom onset to assessment was 3.83 days. • No patients required supplemental oxygen. **Primary Outcomes:** • Shorter mean time to virologic clearance with IVM than placebo (9.7 days vs. 12.7 days; $P = 0.02$), but not with IVM plus DOX (11.5 days; $P = 0.27$). • Rates of virologic clearance were greater in IVM arm at Day 7 (HR 4.1; 95% CI, 1.1–14.7; $P = 0.03$) and at Day 14 (HR 2.7; 95% CI, 1.2–6.0; $P = 0.02$) compared to placebo, but not in the IVM plus DOX arm (HR 2.3; 95% CI, 0.6–9.0; $P = 0.22$ and HR 1.7; 95% CI, 0.8–4.0; $P = 0.19$). • No statistically significant difference in time to resolution of fever, cough, or sore throat between IVM and placebo arms ($P = 0.35$, $P = 0.18$, and $P = 0.35$, respectively) or IVM plus DOX and placebo arms ($P = 0.09$, $P = 0.23$, and $P = 0.09$, respectively). **Other Outcomes:** • Mean values of CRP, LDH, procalcitonin, and ferritin declined in all arms from baseline to Day 7, but there were no between-arm comparisons of the changes. • No between-arm differences in duration of hospitalization ($P = 0.93$). • No SAEs recorded.	**Key Limitations:** • Small sample size • Unclear whether both IVM and DOX placebos were used. • Excluded patients with chronic diseases. • Disease appears to have been mild in all patients; thus, the reason for hospitalization is unclear. • Absolute changes in inflammatory markers were not presented, but were reportedly significant. • PCR results are not a validated surrogate marker for clinical efficacy. **Interpretation:** • A 5-day course of IVM resulted in faster virologic clearance than placebo, but not a faster time to resolution of symptoms (fever, cough, and sore throat). Because time to virologic clearance is not a validated surrogate marker for clinical efficacy, the clinical efficacy of IVM is unknown.

Study Design	Methods	Results	Limitations and Interpretation
Effectiveness and Safety of Adding Ivermectin to Treatment in Patients With Severe COVID-19[19]			
Randomized, single-blind trial of hospitalized adults in Turkey (n = 66)	**Key Inclusion Criteria:** • Hospitalized with PCR-confirmed SARS-CoV-2 infection • ≥1 of the following severity criteria: ◦ Tachypnea (≥30 breaths/min), SpO_2 <90% on RA, or PaO_2/FiO_2 <300 mm Hg in patients who were receiving oxygen ◦ Presence of "specific" radiologic findings ◦ Mechanical ventilation ◦ Acute organ dysfunction **Key Exclusion Criteria:** • Aged <18 years • Pregnant or breast feeding • Autoimmune disease • Chronic liver or kidney disease • Immunosuppression • SNP mutation in MDR1/ABCB1 gene and/or haplotypes and mutations of the CYP3A4 gene (affects IVM metabolism and toxicity) **Interventions:** • IVM 200 µg/kg per day for 5 days plus SOC (HCQ plus favipiravir plus AZM) • SOC alone **Primary Endpoint:** • "Clinical response" at Day 5: extubation (in mechanically ventilated patients), respiratory rate <26 breaths/min, SpO_2 >90% on RA, PaO_2/FiO_2 >300 mm Hg (if patient was receiving oxygen), presence of ≥2 of the 2-point reduction criteria in SOFA **Key Secondary Endpoints:**	**Number of Participants:** • IVM (n = 36) and SOC (n = 30) • 6 participants in IVM arm were excluded after genotyping. **Participant Characteristics:** • Mean age was 58 years in IVM arm and 66 years in SOC arm. • 70% of patients were male in IVM arm and 63% were male in SOC arm. • Comorbidities (IVM vs. SOC): DM (30% vs. 33%), HTN (50% vs. 40%), CAD (17% vs. 27%) **Primary Outcome:** • Clinical improvement at Day 5: 14 of 30 patients (46.7%) in IVM arm, 11 of 30 (36.7%) in SOC arm ($P = 0.43$) **Secondary Outcomes:** *Between-Arm Comparisons at Day 10:* • Clinical improvement: 73.3% in IVM arm, 53.3% in SOC arm ($P = 0.10$) • IVM vs. SOC arm SOFA score at Day 10: $P = 0.50$ • Mean SpO_2: 95.4% in IVM arm, 93.0% in SOC arm ($P = 0.032$) • Mean PaO_2/FiO_2: 236.3 mm Hg in IVM arm, 220.8 mm Hg in SOC arm ($P = 0.39$) • Serum CRP, ferritin, and D-dimer levels were lower in IVM arm than in SOC arm ($P = 0.02$, $P = 0.005$, and $P = 0.03$, respectively). *Within-Group Changes from Baseline:* • Change in SOFA score to Day 10: $P = 0.009$ in IVM arm, $P = 0.88$ in SOC arm • Mean changes in SpO_2 to Day 5: 89.9% to 93.5% ($P = 0.005$) in IVM arm, 89.7% to 93.0% ($P = 0.003$) in SOC arm	**Key Limitations:** • Small sample size • Time from symptom onset to intervention was not reported. • Study used nonstandard severity classification for COVID-19. • Primary endpoint was difficult to characterize; it was presented in the Methods section as a composite endpoint, but each component was analyzed separately. • Power analysis performed for virologic endpoint, not primary endpoint. • Only 57% of patients in IVM arm and 27% in SOC arm were evaluated for VL changes. **Interpretation:** • A 5-day course of IVM in hospitalized patients with severe COVID-19 did not result in clinical improvement at the end of treatment, and no reduction in mortality was observed. • Faster improvement of oxygenation and more pronounced reduction in inflammatory markers were observed in IVM arm.

Study Design	Methods	Results	Limitations and Interpretation
	• Clinical response at Day 10: respiratory rate 22 to 24 breaths/min, SpO_2 >95% on RA, absence of oxygen requirement, and no need for intensive care • Changes in SpO_2, PaO_2/FiO_2, and levels of CRP, ferritin, and D-dimer • Mortality	*Mortality During Follow-Up Period:* • 6 patients (20%) in IVM arm and 9 (30%) in SOC arm (P = 0.37). • Average length of follow-up was 3 months.	
Chloroquine, Hydroxychloroquine, or Ivermectin in Patients With Severe COVID-19[20]			

Randomized, double-blind, Phase 2 trial of hospitalized adults in Brazil (n = 168)	**Key Inclusion Criteria:**
	• Hospitalized with laboratory-confirmed SARS-CoV-2 infection (PCR or IgM positive)
	• ≥1 of the following severity criteria:
	  ◦ Dyspnea
	  ◦ Tachypnea (>30 breaths/min)
	  ◦ SpO_2 <93%
	  ◦ PaO_2/FiO_2 <300 mm Hg
	  ◦ Involvement of >50% of lungs on CXR or CT
	Key Exclusion Criteria:
	• Aged <18 years old
	• Cardiac arrhythmia, including prolonged QT interval
	• Previous use of CQ, HCQ, or IVM for >24 hours
	Interventions:
	• CQ 450 mg twice daily on Day 0, then CQ 450 mg once daily for 4 days
	• HCQ 400 mg twice daily on Day 0, then HCQ 400 mg once daily for 4 days
	• IVM 14 mg once daily for 3 days followed by placebo for 2 days
	Endpoints:
	• Need for supplemental oxygen, invasive mechanical ventilation, or ICU admission
	• Mortality
		Number of Participants:
		• CQ (n = 61), HCQ (n = 54), and IVM (n = 53)
		Participant Characteristics:
		• Mean age was 53.4±15.6 years.
		• 58.2% of patients were male.
		• 78.9% of patients were Hispanic.
		• 37.5% of patients had a BMI >30.
		• Most common comorbidities were HTN (43.4% of patients) and DM (28.1%).
		• On admission, 76.5% of patients had respiratory failure, and 42.5% had "pneumonic syndrome."
		Outcomes:
		• No differences between arms in proportion of patients who required supplemental oxygen (88.5% in CQ arm, 90.2% in HCQ arm, and 88.4% in IVM arm) or mean number of days of supplemental oxygenation (7.9 vs. 7.8 vs. 8.1 days)
		• No differences between arms in proportion of patients admitted to the ICU (22.4% in CQ arm, 21.1% in HCQ arm, and 28.0% in IVM arm) or proportion of patients who received invasive mechanical ventilation (20.6% vs. 21.1% vs. 23.5%)
		• No differences between arms in proportion of patients who were
			Key Limitations:
			• Small sample size
			• No placebo control
			• No clear primary endpoint
			Interpretation:
			• Use of IVM did not reduce risk of oxygen requirement, ICU admission, invasive mechanical ventilation, or death in hospitalized patients with severe COVID-19.

Study Design	Methods	Results	Limitations and Interpretation
		receiving concomitant medications, including steroids and anticoagulants • No differences between arms in death due to COVID-19 complications (21.3% in CQ arm, 22.2% in HCQ arm, and 23.0% in IVM arm) • Baseline characteristics that were associated with mortality included age >60 years (HR 2.44; 95% CI, 1.40–4.30), DM (HR 1.87; 95% CI, 1.02–2.59), BMI >33 (HR 1.95; 95% CI, 1.07–3.09), and SpO_2 <90% (HR 5.79; 95% CI, 2.63–12.7). • No difference in rates of AEs between arms	
Ivermectin Versus Placebo for Outpatients With Mild COVID-19[21]			
Open-label RCT of adult outpatients in Lahore, Pakistan (n = 50)	**Key Inclusion Criteria:** • SARS-CoV-2 PCR positive • Mild disease **Key Exclusion Criteria:** • Severe symptoms likely related to cytokine storm • Malignancy, chronic kidney disease, or cirrhosis • Pregnancy **Interventions:** • IVM 12 mg PO immediately, followed by 12 mg doses at 12 and 24 hours, plus symptomatic treatment • Symptomatic treatment **Primary Endpoint:** • Symptoms reported on Day 7. Patients were stratified as asymptomatic or symptomatic.	**Number of Participants:** • IVM (n = 25) and control (n = 25) **Participant Characteristics:** • Mean age was 40.6 years. • 62% of patients were male. • 40% of patients had diabetes, 30% were smokers, 26% had hypertension, 8% had cardiovascular disease, and 12% had obesity. **Outcomes:** • Proportion of asymptomatic patients at Day 7 was similar in IVM and control arms (64% vs. 60%; $P = 0.500$). • AEs were attributed to IVM in 8 patients (32%).	**Key Limitations:** • Small sample size • Open-label study • Authors reported the proportions of patients with certain symptoms and comorbidities but did not provide objective assessment of disease severity. This precludes the ability to compare outcomes between arms. • Study classified outcomes at Day 7 as "symptomatic" and "asymptomatic," but did not account for symptom worsening or improvement. **Interpretation:** • IVM showed no effect on symptom resolution in patients with mild COVID-19.
Ivermectin in Patients With Mild to Moderate COVID-19[22]			

Study Design	Methods	Results	Limitations and Interpretation
Open-label, single-center, RCT of outpatients with laboratory-confirmed SARS-CoV-2 infection in Bangladesh (n = 62)	**Key Inclusion Criteria:** • Aged ≥18 years • Laboratory-confirmed SARS-CoV-2 infection • ≤7 days of symptoms • Mild or moderate disease **Key Exclusion Criteria:** • Hypersensitivity to IVM • Pregnancy or breastfeeding • Use of HCQ or "other antimicrobials" **Interventions:** • Single dose of IVM 200 µg/kg • SOC **Primary Endpoint:** • Full recovery from all symptoms **Secondary Endpoint:** • Conversion to negative RT-PCR at Day 10	**Number of Participants:** • IVM (n = 32) and SOC (n = 30) **Participant Characteristics:** • 71% of patients were male. • Mean age was 39.2 years (SD 12.1 years). • 81% of patients had mild disease and 19% had moderate disease. • Study provided no information on comorbidities. **Outcomes:** • Mean overall recovery time was 5.3 days (SD 2.5 days) in IVM arm and 6.3 days (SD 4.2 days) in SOC arm. The difference was not statistically significant. Time to resolution of fever, shortness of breath, and fatigue were no shorter in IVM arm. • Negative SARS-CoV-2 PCR result at Day 10: 18 of 20 patients (90%) in IVM arm, 19 of 20 (95%) in SOC arm.	**Key Limitations:** • Open-label study • Small study • Study enrolled young patients with mild disease who were unlikely to progress to severe COVID-19. **Interpretation:** • Compared to SOC, use of IVM did not lead to faster recovery from mild to moderate COVID-19. • The small sample size and large number of comparisons make it difficult to assess the clinical efficacy of IVM in this population.

Ivermectin Plus Doxycycline Versus Hydroxychloroquine Plus Azithromycin for Asymptomatic Patients and Patients With Mild to Moderate COVID-19[23]

Study Design	Methods	Results	Limitations and Interpretation
RCT of outpatients with SARS-CoV-2 infection with or without symptoms in Bangladesh (n = 116) *This is a preliminary report that has not yet been peer reviewed.*	**Key Inclusion Criteria:** • Laboratory-confirmed SARS-CoV-2 infection by RT-PCR • SpO_2 ≥95% • Normal or near-normal CXR • No unstable comorbidities **Interventions** *Group A:* • A single dose of IVM 200 µg/kg plus DOX 100 mg twice daily for 10 days *Group B:* • HCQ 400 mg on Day 1, then HCQ 200 mg twice daily for 9 days plus AZM 500 mg once daily for 5 days **Primary Endpoints:** • Time to negative PCR result. Asymptomatic patients were tested starting on Day 5, then every other day until a negative result occurred. Symptomatic patients were tested on their second symptom-free day, then every other day until a negative result occurred. • Time to resolution of symptoms	**Number of Participants:** • Group A (n = 60) and Group B (n = 56) **Participant Characteristics:** • Mean age was 33.9 years. • 78% of patients were male. • 91 of 116 patients (78.5%) were symptomatic. **Outcomes:** • PCR became negative in 60 of 60 patients (100%) in Group A and in 54 of 56 patients (96.4%) in Group B. • Mean time to negative PCR result: 8.93 days (range 8–13 days) in Group A, 9.33 days (range 5–15 days) in Group B (*P* = 0.2314). • Mean time to symptom recovery: 5.93 days (range 5–10 days) in Group A, 6.99 days (range 4–12 days) in Group B (*P* = 0.071). • In a subgroup analysis of patients who were symptomatic at baseline, the mean time to negative PCR result for Groups A and B were 9.06 days and 9.74 days, respectively (*P* = 0.0714). • Patients who received IVM plus DOX had fewer AEs than those who received HCQ plus AZM (31.7% vs. 46.4%) in the subgroup analysis.	**Key Limitations:** • Small sample size • Open-label study • No SOC alone group • Study enrolled young patients without major risk factors for disease progression. • None of the comparative outcome measures were statistically significant. **Interpretation:** • In this small study with a young population, the authors suggested that IVM plus DOX was superior to HCQ plus AZM despite no statistically significant difference in time from recovery to negative PCR result and symptom recovery between patients who received IVM plus DOX and those who received HCQ plus AZM.
Antiviral Effect of High-Dose Ivermectin in Adults with COVID-19[24]			
Multicenter, randomized, open-label, blinded trial of hospitalized adults with mild to moderate COVID-19 in Argentina (n = 45)	**Key Inclusion Criteria:** • Laboratory-confirmed SARS-CoV-2 infection • Hospitalized • ≤5 days of symptoms **Key Exclusion Criteria:** • Use of immunomodulators or any agent with potential anti-SARS-CoV-2 activity prior to enrollment	**Number of Participants:** • IVM (n = 30) and SOC (n = 15) • After excluding patients with poor sample quality, those without a detectable VL at baseline, and those who withdrew, 32 patients (20 IVM, 12 SOC) were included in the viral efficacy analysis population.	**Key Limitations:** • Small sample size • No clinical response data reported. • The C_{max} level of 160 ng/mL used in the analysis appears to be arbitrary. **Interpretation:** • Concentration-dependent virologic response was seen when using a higher-than-usual dose of IVM (600 µg/kg vs. 200 or 400 µg/kg once

Study Design	Methods	Results	Limitations and Interpretation

	• Poorly controlled comorbidities
	
	Interventions:
	• IVM 600 µg/kg once daily plus SOC for 5 days
	• SOC
	
	Primary Endpoint:
	• VL reduction at Day 5. VL was quantified by NP swab at baseline, then at 24, 48, and 72 hours and Day 5.
	
	PK Sampling:
	• Performed 4 hours after dose on Days 1, 2, 3, 5, and 7 to assess elimination
		Participant Characteristics:
		• Mean age was 42.3±12.8 years in IVM arm and 38.1±11.7 years in SOC arm.
		• 50% of patients were male in IVM arm and 67% were male in SOC arm.
		
		Primary Outcomes:
		• By Day 5, a similar magnitude of VL reduction was seen in both arms.
		
		Other Outcomes:
		• Patients with higher IVM concentrations had greater reductions in VL (r 0.44; $P <$ 0.04).
		• Treated patients were divided into 2 groups based on IVM C_{max}: IVM >160 ng/mL (median of 202 ng/mL) and <160 ng/mL (median of 109 ng/mL).
		  ◦ Median percentage of VL reduction by C_{max} concentration vs. control ($P =$ 0.0096) was 72% (IQR 59% to 77%) in >160 ng/mL group (n = 9), 40% (IQR 21% to 46%) in <160 ng/mL group (n = 11), and 42% (IQR 31% to 73%) in SOC arm.
		  ◦ Median viral decay rate ($P =$ 0.04) was 0.64 day^{-1} in >160 ng/mL group, 0.14 day^{-1} in <160 ng/mL group, and 0.13 day^{-1} in SOC arm.
		• Percentages of AEs were similar between the arms (43% in IVM arm, 33% in SOC arm), and AEs were mostly mild.
			daily), with minimal associated toxicities.
			• The study results showed large interpatient variation of IVM C_{max}. Larger sample sizes are needed to further assess the safety and efficacy of using higher doses of IVM to treat COVID-19.

Effect of Early Treatment With Ivermectin Versus Placebo on Viral Load, Symptoms, and Humoral Response in Patients With Mild COVID-19[25]			

Study Design	Methods	Results	Limitations and Interpretation
A single-center, randomized, double-blind, placebo-controlled pilot trial in Spain (n = 24)	**Key Inclusion Criteria:** • Laboratory-confirmed SARS-CoV-2 infection • ≤72 hours of symptoms • No risk factors for severe disease or COVID-19 pneumonia **Interventions:** • Single dose of IVM 400 µg/kg • Nonmatching placebo tablet administered by a nurse who did not participate in the patient's care **Primary Endpoint:** • Positive SARS-CoV-2 PCR result from an NP swab at Day 7 post-treatment	**Number of Participants:** • IVM (n = 12) and placebo (n = 12) **Participant Characteristics:** • Mean age was 26 years (range 18–54 years). • 50% of patients were male. • All patients had symptoms at baseline; 70% had headache, 66% had fever, 58% had malaise, and 25% had cough. • Median onset of symptoms was 24 hours in IVM arm and 48 hours in placebo arm. **Outcomes:** • At Day 7, 12 patients (100%) in both groups had a positive PCR (for gene N), and 11 of 12 who received IVM (92%) and 12 of 12 who received placebo (100%) had a positive PCR (for gene E); $P = 1.0$ for both comparisons. • In a post hoc analysis, the authors reported fewer patient-days of cough and anosmia in the IVM-treated patients, but no differences in the patient-days for fever, general malaise, headache, and nasal congestion.	**Key Limitations:** • Small sample size • PCR is not a validated surrogate marker for clinical efficacy. • PCR cycle threshold values were higher for patients who received IVM than those who received placebo at some time points, but these comparisons are not statistically significant. • Symptom results were not a prespecified outcome and are of unclear statistical and clinical significance. **Interpretation:** • Patients who received IVM showed no difference in viral clearance compared to those who received placebo. • The small sample size and large number of comparisons make it difficult to assess the clinical efficacy of IVM in this population.
Ivermectin Plus Doxycycline Plus Standard Therapy Versus Standard Therapy Alone in Patients With Mild to Moderate COVID-19[26]			

Study Design	Methods	Results	Limitations and Interpretation
Randomized, unblinded, single-center study of patients with laboratory-confirmed SARS-CoV-2 infection in Baghdad, Iraq (n = 140) *This is a preliminary report that has not yet been peer reviewed.*	**Key Inclusion Criteria:** • Diagnosis by clinical, radiological, and PCR testing • Outpatients had mild or moderate COVID-19, while inpatients had severe and critical COVID-19. **Interventions:** • IVM 200 µg/kg PO daily for 2 days. If patient required more time to recover, a third dose was given 7 days after the first dose, plus DOX 100 mg twice daily for 5–10 days plus standard therapy (based on clinical condition). • Standard therapy was based on clinical condition and included AZM, acetaminophen, vitamin C, zinc, vitamin D3, dexamethasone 6 mg daily or methylprednisolone 40 mg twice daily if needed, and oxygen or mechanical ventilation if needed. • All critically ill patients were assigned to receive IVM plus DOX.	**Number of Participants:** • IVM plus DOX plus standard therapy (n = 70) and standard therapy alone (n = 70) **Participant Characteristics:** • Median age was 50 years in IVM arm and 47 years in standard therapy arm. • 50% of patients were male in IVM arm and 53% were male in standard therapy arm. • In IVM arm, 48 patients had mild or moderate COVID-19, 11 had severe COVID-19, and 11 had critical COVID-19. • In standard therapy arm, 48 patients had mild or moderate COVID-19, 22 had severe COVID-19, and no patients had critical COVID-19. **Outcomes:** • Mean recovery time in IVM arm was 10.1 days (SD 5.3 days) vs. 17.9 days (SD 6.8 days) for standard therapy arm ($P < 0.0001$). This result was only significant for those with mild to moderate disease. • Disease progression occurred in 3 of 70 patients (4.3%) in IVM arm and 7 of 70 (10.0%) in standard therapy arm ($P = 0.19$) • 2 of 70 patients (2.85%) in IVM arm and 6 of 70 (8.57%) in standard therapy arm died ($P = 0.14$)	**Key Limitations:** • Not blinded • Patient deaths prevent an accurate comparison of mean recovery time between arms in this study, and the authors did not account for competing mortality risks. • Relies heavily on post hoc subgroup comparisons. • Substantial imbalance in disease severity at baseline • Authors noted that critical patients were not assigned to standard therapy arm; thus, the arms were not truly randomized. • Unclear how many patients required corticosteroids. **Interpretation:** • IVM may shorten the time to recovery for patients with mild or moderate disease, but the lack of control for competing mortality causes in the study limits the ability to interpret the results.
Ivermectin in Patients With Mild to Moderate COVID-19[27]			
Double-blind RCT in patients with mild to moderate COVID-19 in India (n = 157)	**Key Inclusion Criteria:** • Aged ≥18 years • Positive SARS-CoV-2 RT-PCR or antigen test • Nonsevere COVID-19 (defined as SpO_2 >90% on RA and no hypotension or need for mechanical ventilation) **Key Exclusion Criteria:**	**Number of Participants:** • ITT analysis (safety): IVM 24 mg (n = 51), IVM 12 mg (n = 49), and placebo (n = 52) • mITT analysis (included only those with positive NP/OP RT-PCR result): IVM 24 mg (n = 40), IVM 12 mg (n = 40), and placebo (n = 45)	**Key Limitations:** • Small sample size **Interpretation:** • Though the rate of negative RT-PCR results was numerically higher in the IVM arms than in the placebo arm on Day 5, the result was not statistically significant.

Study Design	Methods	Results	Limitations and Interpretation
	• CrCl <30 mL/min • Transaminases >5 times ULN • MI or heart failure in previous 90 days • QTc interval >450 ms • Severe comorbidity **Interventions** • Single dose of IVM 24 mg in alcohol-based elixir prepared by pharmacy • Single dose of same elixir with IVM 12 mg • Single dose of same elixir without IVM (placebo) **Primary Endpoint:** • Reduction of SARS-CoV-2 VL as measured by NP and OP swab at Day 5 • Conversion to negative RT-PCR at Day 5 **Key Secondary Endpoints:** • Qualitative and quantitative RT-PCR on Days 3 and 7 • Time to clinical resolution • Frequency of clinical worsening • Clinical status at Day 14 • Number of hospital-free days at Day 28	• 64% of patients had mild disease (including asymptomatic disease) and 36% had moderate disease **Participant Characteristics:** • Mean age was 35.5 years (SD 10.4 years). • 88.8% of patients were male. • Mean BMI was 25. • Median duration of symptoms was similar between the arms (5 days; IQR 3–7 days). • 10% of patients received concurrent antivirals (RDV, favipiravir, or HCQ). No difference in use of antivirals between arms. **Primary Outcomes:** • Proportion of patients with negative RT-PCR result on Day 5: 47.5% in IVM 24 mg arm, 35.0% in IVM 12 mg arm, and 31.1% in placebo arm ($P = 0.30$) • VL at enrollment did not impact conversion to negative RT-PCR on Day 5. • No significant difference in VL decline by Day 5 between the arms • No difference in VL decline in the mild or moderate disease strata at Day 5 **Secondary Outcomes:** • No difference between arms in mean time to symptom resolution or number of hospital-free days at Day 28 • Proportions of patients with clinical worsening were similar across the arms: 7.5% in IVM 24 mg arm, 5.0% in IVM 12 mg arm, and 11.1% in placebo arm ($P = 0.65$) • No difference between arms in frequency of AEs or SAEs	• No difference in clinical outcomes or frequency of AEs.

Efficacy and Safety of Ivermectin and Hydroxychloroquine in Patients With Severe COVID-19[28]

Study Design	Methods	Results	Limitations and Interpretation
Randomized, double-blind trial of hospitalized adults with COVID-19 pneumonia in Mexico (n = 106) *This is a preliminary report that has not yet been peer reviewed.*	**Key Inclusion Criteria:** • Laboratory-confirmed SARS-CoV-2 infection • Pneumonia, diagnosed by CXR or high-resolution chest CT scan • Recently established hypoxemic respiratory failure or deterioration of pre-existing lung or heart disease **Key Exclusion Criteria:** • Receipt of HFNC oxygen or invasive mechanical ventilation • Patients with QT intervals ≥500 ms were not eligible for HCQ but were eligible for IVM. **Interventions:** • HCQ 400 mg twice daily on Day 1, then HCQ 200 mg/kg twice daily for 4 days • Single dose of IVM 12 mg (in patients weighing ≤80 kg) or 18 mg (in those weighing >80 kg) plus calcium citrate for subsequent doses • Calcium citrate placebo **Primary Endpoint:** • Time to discharge due to recovery	**Number of Participants:** • HCQ (n = 33), IVM (n = 36), and placebo (n = 37) **Participant Characteristics:** • Mean age was 53 years (SD 16.9 years). • 62% of patients were male. • 34% of patients had diabetes, 32% had hypertension, and 72% had any comorbidity. • Mean BMI was 29.6 (SD 6.6). **Outcomes:** • Median time to discharge due to recovery was 7 days (IQR 3–9 days) in HCQ arm, 6 days (IQR 4–11 days) in IVM arm, and 5 days (IQR 4–7 days) in placebo arm. The differences between arms were not statistically significant. • Proportion of patients discharged alive: 79% in HCQ arm, 75% in IVM arm, and 73% in placebo arm • Mortality: 6% of patients in HCQ arm, 14% in IVM arm, and 16% in placebo arm	**Key Limitations:** • Small study • Length of follow-up period is unclear. • The study was stopped prior to achieving its target sample size. **Interpretation:** • In hospitalized patients with COVID-19 pneumonia who were not critically ill, neither IVM nor HCQ decreased the number of in-hospital days, rate of respiratory deterioration, or mortality. • The small sample size and large number of comparisons make it difficult to assess the clinical efficacy of IVM in this population.

Ivermectin as Adjunctive Therapy to Hospitalized Patients With COVID-19[29]

Study Design	Methods	Results	Limitations and Interpretation
Randomized, double-blind, placebo-controlled, multicenter, Phase 2 clinical trial of hospitalized adults with mild to severe SARS-CoV-2 infection in 5 facilities in Iran (n = 180) *This is a preliminary report that has not yet been peer reviewed.*	**Key Inclusion Criteria:** • Symptoms suggestive of COVID-19 pneumonia, with chest CT compatible with mild to severe COVID-19 or positive RT-PCR result for SARS-CoV-2 **Key Exclusion Criteria:** • Severe immunosuppression, malignancy, or chronic kidney disease • Pregnancy **Interventions:** • HCQ 200 mg/kg twice daily alone as SOC (standard arm) • SOC plus 1 of the following: ◦ Placebo ◦ Single dose of IVM 200 µg/kg ◦ IVM 200 µg/kg on Days 1, 3, and 5 ◦ Single dose of IVM 400 µg/kg ◦ IVM 400 µg/kg on Day 1, then IVM 200 µg/kg on Days 3 and 5 **Primary Endpoint:** • Clinical recovery within 45 days of enrollment (defined as normal temperature, respiratory rate, and SpO_2 >94% for 24 hours)	**Number of Participants:** • All 6 arms (n = 30 in each arm) **Participant Characteristics:** • Average age was 56 years (range 45–67 years). • 50% of patients were male. • Disease stratification (based on CT findings): negative (1%), mild (14%), moderate (73%), and severe (12%) • Mean SpO_2 at baseline was 89%. **Primary Outcomes:** • Durations of hypoxemia and hospitalization were shorter in IVM arms than placebo arm (P = 0.025 and P = 0.006, respectively), and mortality was lower in the IVM arms (P = 0.001). • There was no difference in number of days of tachypnea (P = 0.584) or return to normal temperature (P = 0.102). • Significant differences in change from baseline to Day 5 in absolute lymphocyte count, platelet count, erythrocyte sedimentation rate, and CRP. • Higher mortality was reported in standard and placebo arms than IVM arms.	**Key Limitations:** • Small study • Power estimation is confusing. • Mortality was not listed as the primary or secondary outcome. • It is unclear whether IVM patients also received HCQ. • It is unclear whether the between-group comparisons are between combined IVM groups and placebo plus SOC. • Patients were stratified by disease severity based on CT findings. These categorizations are unclear and were not taken into account in outcome comparisons. • The post hoc grouping of randomized arms raises risk of false positive findings. **Interpretation:** • IVM appeared to improve laboratory outcomes and some clinical outcomes (shorter duration of hypoxemia and hospitalization) and lowered mortality. • The small size of the study, the unclear treatment arm assignments, and the lack of accounting for disease severity at baseline make it difficult to draw conclusions about the efficacy of using IVM to treat patients with mild COVID-19.

Retrospective Analysis of Ivermectin in Hospitalized Patients With COVID-19[30]

Study Design	Methods	Results	Limitations and Interpretation
Retrospective analysis of consecutive patients with laboratory-confirmed SARS-CoV-2 infection who were admitted to 4 Florida hospitals (n = 276)	**Key Inclusion Criteria:** • Positive NP swab with SARS-CoV-2 RNA **Interventions:** • Single dose of IVM 200 µg/kg, repeated on Day 7 at the doctors' discretion; 90% of patients also received HCQ. • Usual care: 97% of patients received HCQ and most also received AZM. **Primary Endpoint:** • All-cause, in-hospital mortality	**Number of Participants:** • IVM (n = 173; 160 patients received a single dose, 13 patients received a second dose) and usual care (n = 103) **Participant Characteristics:** • Mean age was 60.2 years in IVM arm and 58.6 years in usual care arm. • 51.4% of patients were male in IVM arm and 58.8% were male in usual care arm. • 56.6% of patients were Black in IVM arm and 51.4% were Black in usual care arm. **Outcomes:** • All-cause mortality was lower in IVM arm than in usual care arm (OR 0.27; 95% CI, 0.09–0.80; *P* = 0.03); the benefit appeared to be limited to the subgroup of patients with severe disease. • No difference in median length of hospital stay between arms (7 days for both) or proportion of mechanically ventilated patients who were successfully extubated (36% in IVM arm vs. 15% in usual care arm; *P* = 0.07).	**Key Limitations:** • Not randomized • Little to no information on SpO_2 or radiographic findings • Timing of therapeutic interventions was not standardized. • Ventilation and hospitalization duration analyses do not appear to account for death as a competing risk. • No virologic assessments were performed. **Interpretation:** • IVM use was associated with lower mortality than usual care. However, the limitations of this retrospective analysis make it difficult to draw conclusions about the efficacy of using IVM to treat patients with COVID-19.

Observational Study on the Effectiveness of Hydroxychloroquine, Azithromycin, and Ivermectin Among Hospitalized Patients With COVID-19[31]

Study Design	Methods	Results	Limitations and Interpretation

Retrospective cohort study of hospitalized adults with COVID-19 in Peru (n = 5,683)
This is a preliminary report that has not yet been peer reviewed.
	Key Inclusion Criteria:
	• Aged ≥18 years
	• Symptomatic
	• Laboratory-confirmed SARS-CoV-2 infection
	• No life-threatening illness at admission
	Key Exclusion Criteria:
	• Required oxygen at admission
	• Use of tocilizumab, LPV/RTV, or RDV
	Interventions:
	• One of the following interventions administered within 48 hours of admission:
	  ◦ HCQ or CQ alone
	  ◦ IVM alone
	  ◦ AZM alone
	  ◦ HCQ or CQ plus AZM
	  ◦ IVM plus AZM
	  ◦ SOC (e.g., supportive care, antipyretics, hydration)
	Primary Endpoint:
	• All-cause mortality
	Secondary Endpoint:
	• All-cause mortality and/or transfer to ICU
		Number of Participants:
		• HCQ or CQ alone (n = 200), IVM alone (n = 203), AZM alone (n = 1,600), HCQ or CQ plus AZM (n = 692), IVM plus AZM (n = 358), and SOC (n = 2,630)
		Participant Characteristics:
		• 63% of patients were male.
		• Mean age was 59.4 years (range 18–104 years).
		• All patients had mild or moderate disease.
		Outcomes:
		• Median follow-up time was 7 days. Mortality rate was 18.9% at the end of follow-up.
		• IVM alone was associated with increased risk of death and/or ICU transfer compared to SOC (wHR 1.58; 95% CI, 1.11–2.25).
		• IVM plus AZM did not have an effect on deaths or any secondary outcomes (all-cause death and/or ICU transfer, all-cause death and/or oxygen prescription) compared to SOC.
		• HCQ or CQ plus AZM was associated with a higher risk of death (wHR 1.84; 95% CI, 1.12–3.02), death and/or ICU transfer (wHR 1.49; 95% CI, 1.01–2.19), and death and/or oxygen prescription (wHR 1.70; 95% CI, 1.07–2.69) compared to SOC.
			Key Limitations:
			• Not randomized
			• Unclear whether all patients received IVM or other medications according to Peruvian guidelines referred to in the manuscript.
			• Dosing and timing of administration are unclear.
			Interpretation:
			• Compared to SOC, IVM alone was associated with increased risk of death and/or ICU admission. Using IVM in combination with AZM was not associated with effects on mortality, ICU transfer, or oxygen prescription compared to SOC.

Retrospective Study of Ivermectin Versus Standard of Care in Patients With COVID-19[32]

Study Design	Methods	Results	Limitations and Interpretation
Retrospective study of consecutive adult patients hospitalized in Bangladesh with laboratory-confirmed SARS-CoV-2 infection (n = 248) *This is a preliminary report that has not yet been peer-reviewed.*	**Key Inclusion Criteria:** • Aged ≥18 years • Positive NP swab with SARS-CoV-2 RNA • "Free from any other serious pathological conditions" **Interventions:** • Single dose of IVM 12 mg within 24 hours of hospital admission • SOC **Primary Endpoint:** • Not specified	**Number of Participants:** • IVM (n = 115) and SOC (n = 133) **Participant Characteristics:** • Median age in IVM arm was 34 years; 70% of patients were male. • Median age in SOC arm was 35 years; 52% of patients were male. • All patients had mild or moderate disease. • 12% of patients had hypertension in both arms. • 17% of patients in IVM arm and 12% in SOC arm had DM. **Outcomes:** • Fewer patients in IVM arm had evidence of disease progression compared to SOC arm ($P < 0.001$): moderate respiratory distress (2.6% vs. 15.8%), pneumonia (0% vs. 9.8%), ischemic stroke (0% vs. 1.5%). • Fewer patients in IVM arm required intensive care management compared to SOC arm (0.9% vs. 8.8%; $P < 0.001$). • Fewer patients in IVM arm required antibiotic therapy (15.7% vs. 60.2%; $P < 0.001$) or supplemental oxygen (9.6% vs. 45.9%; $P < 0.001$) compared to SOC arm. • Shorter median duration of viral clearance in IVM arm compared to SOC arm (4 vs. 15 days; $P < 0.001$). • Shorter median duration of hospital stay in IVM arm compared to SOC arm (9 vs. 15 days; $P < 0.001$) • Lower mortality in IVM arm compared to SOC arm (0.9% vs. 6.8%; $P < 0.05$)	**Key Limitations:** • Not randomized • Disease severity at admission was reported as mild or moderate, but 12% of patients in IVM arm and 9% in SOC arm had SpO_2 <94% • Even though only 10% of patients developed pneumonia, 60% received antibiotics. • Possibility of harm from concomitant medications **Interpretation:** • Compared to SOC, IVM use was associated with faster rates of viral clearance and better clinical outcomes, including shorter hospital stay and lower mortality.

Study Design	Methods	Results	Limitations and Interpretation

Key: AE = adverse event; AZM = azithromycin; BMI = body mass index; CAD = coronary artery disease; C_{max} = maximum concentration; CQ = chloroquine; CrCl = creatinine clearance; CRP = C-reactive protein; CT = computed tomography; CXR = chest X-ray; CYP = cytochrome P450; DM = diabetes mellitus; DOX = doxycycline; HCQ = hydroxychloroquine; HFNC = high-flow nasal cannula; HTN = hypertension; ICU = intensive care unit; Ig = immunoglobulin; ITT = intention-to-treat; IVM = ivermectin; LDH = lactose dehydrogenase; LPV/RTV = lopinavir/ritonavir; MDR1 = multidrug resistance mutation 1; MI = myocardial infarction; mITT = modified intention-to-treat; NP = nasopharyngeal; OP = oropharyngeal; the Panel = the COVID-19 Treatment Guidelines Panel; PaO_2/FiO_2 = ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; PCR = polymerase chain reaction; PK = pharmacokinetic; PO = orally; r = correlation coefficient; RA = room air; RCT = randomized controlled trial; RDV = remdesivir; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = severe adverse event; SNP = single-nucleotide polymorphism; SOC = standard of care; SOFA = sequential organ failure assessment; SpO_2 = oxygen saturation; ULN = upper limit of normal; VL = viral load

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Ivermectin for preventing and treating COVID-19

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Is ivermectin effective for COVID-19?

Key messages

We found no evidence to support the use of ivermectin for treating or preventing COVID-19 infection, but the evidence base is limited.

Evaluation of ivermectin is continuing in 31 ongoing studies, and we will update this review with their results when they become available.

What is ivermectin?

Ivermectin is a medicine used to treat parasites such as intestinal parasites in animals and scabies in humans. It is cheap and is widely used in regions of the world where parasitic infestations are common. It has few unwanted effects.

Tests in the laboratory show ivermectin can slow the reproduction of the COVID-19 (SARS-CoV-2) virus but such effects would need major doses in humans. Medical regulators have not approved ivermectin for COVID-19. It should only be used as part of well-designed studies (called randomized controlled trials) evaluating potential effects.

What did we want to find out?

We wanted to know if ivermectin reduces death, illness, and length of infection in people with COVID-19, or is useful in prevention of the disease. We included studies comparing the medicine to placebo (dummy treatment), no treatment, usual care, or treatments for COVID-19 that are known to work to some extent, such as remdesivir

or dexamethasone. We excluded studies that compared ivermectin to other drugs that do not work, such as hydroxychloroquine, or that are not known to be effective against COVID-19.

We evaluated the effects of ivermectin in infected people on:

– people dying;
– whether people's COVID-19 symptoms got better or worse;
– unwanted effects;
– hospital admission or time in hospital;
– viral clearance.

For prevention, we sought the effect on preventing COVID-19 and SARS-CoV-2 infection.

What did we do?

We searched for randomized controlled trials that investigated ivermectin to prevent or treat COVID-19 in humans. People being treated with ivermectin had to have laboratory-test confirmed COVID-19 and be receiving treatment in hospital or as outpatients.

We compared and summarized the results of the studies and rated our confidence in the evidence, based on common criteria as to how reliable the evidence is.

What did we find?

We found 14 studies with 1678 participants that investigated ivermectin compared to no treatment, placebo, or usual care.

For treatment, there were nine studies of people with moderate COVID-19 in hospital and four of outpatients with mild COVID-19. The studies used different doses of ivermectin and different durations of treatment.

One study investigated ivermectin to prevent COVID-19.

We also found 31 ongoing studies, and there are 18 studies still requiring clarification from the authors or not yet published.

Main results

Treating people in hospital with COVID-19

We don't know whether ivermectin compared with placebo or usual care, 28 days after treatment:

– leads to more or fewer deaths (2 studies, 185 people);
– worsens or improves patients' condition assessed by need for ventilation (2 studies, 185 people) or oxygen (1 study, 45 people);
– increases or reduces unwanted events (1 study, 152 people).

Seven days after treatment, we don't know if ivermectin:

– increases or reduces negative COVID-19 tests (2 studies, 159 people).

Ivermectin compared to placebo or usual care may make little or no difference to improving patients' condition 28 days after treatment (1 study, 73 people) or to length of hospital stay (1 study, 45 people).

Treating outpatients with COVID-19

We don't know whether ivermectin compared with placebo or usual care:

– leads to more or fewer deaths 28 days after treatment (2 studies, 422 people);
– worsens or improves patients' condition 14 days after treatment assessed by need for ventilation (1 study, 398 people);
– increases or reduces negative COVID-19 tests seven days after treatment (1 study, 24 people).

Ivermectin compared to placebo or usual care may make little or no difference to improving outpatients' condition 14 days after treatment (1 study, 398 people) or to the number of unwanted events 28 days after treatment (2 studies, 422 people).

No studies looked at hospital admissions in outpatients.

Preventing COVID-19

We don't know whether ivermectin leads to more or fewer deaths compared with no drug (1 study, 304 people); no participant died 28 days after the drug. This study reported results for development of COVID-19 symptoms (but not confirmed SARS-CoV-2 infection) and unwanted events, but in a way that we could not include in our analyses. This study did not look at hospital admissions.

What are the limitations of the evidence?

Our confidence in the evidence is very low because we could only include 14 studies with few participants and few events, such as deaths or need for ventilation. The methods differed between studies, and they did not report everything we were interested in, such as quality of life.

How up to date is this evidence?

The evidence is up to date to 26 May 2021.

Authors' conclusions:

Based on the current very low- to low-certainty evidence, we are uncertain about the efficacy and safety of ivermectin used to treat or prevent COVID-19. The completed studies are small and few are considered high

quality. Several studies are underway that may produce clearer answers in review updates. Overall, the reliable evidence available does not support the use of ivermectin for treatment or prevention of COVID-19 outside of well-designed randomized trials.

Read the full abstract...

Background:

Ivermectin, an antiparasitic agent used to treat parasitic infestations, inhibits the replication of viruses in vitro. The molecular hypothesis of ivermectin's antiviral mode of action suggests an inhibitory effect on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication in the early stages of infection. Currently, evidence on efficacy and safety of ivermectin for prevention of SARS-CoV-2 infection and COVID-19 treatment is conflicting.

Objectives:

To assess the efficacy and safety of ivermectin compared to no treatment, standard of care, placebo, or any other proven intervention for people with COVID-19 receiving treatment as inpatients or outpatients, and for prevention of an infection with SARS-CoV-2 (postexposure prophylaxis).

Search strategy:

We searched the Cochrane COVID-19 Study Register, Web of Science (Emerging Citation Index and Science Citation Index), medRxiv, and Research Square, identifying completed and ongoing studies without language restrictions to 26 May 2021.

Selection criteria:

We included randomized controlled trials (RCTs) comparing ivermectin to no treatment, standard of care, placebo, or another proven intervention for treatment of people with confirmed COVID-19 diagnosis, irrespective of disease severity, treated in inpatient or outpatient settings, and for prevention of SARS-CoV-2 infection.

Co-interventions had to be the same in both study arms.

We excluded studies comparing ivermectin to other pharmacological interventions with unproven efficacy.

Data collection and analysis:

We assessed RCTs for bias, using the Cochrane risk of bias 2 tool. The primary analysis excluded studies with high risk of bias. We used GRADE to rate the certainty of evidence for the following outcomes 1. to treat inpatients with moderate-to-severe COVID-19: mortality, clinical worsening or improvement, adverse events, quality of life, duration of hospitalization, and viral clearance; 2. to treat outpatients with mild COVID-19: mortality, clinical worsening or improvement, admission to hospital, adverse events, quality of life, and viral clearance; (3) to prevent SARS-CoV-2 infection: SARS-CoV-2 infection, development of COVID-19 symptoms, adverse events, mortality, admission to hospital, and quality of life.

Main results:

We found 14 studies with 1678 participants investigating ivermectin compared to no treatment, placebo, or standard of care. No study compared ivermectin to an intervention with proven efficacy. There were nine studies treating participants with moderate COVID-19 in inpatient settings and four treating mild COVID-19 cases in outpatient settings. One study investigated ivermectin for prevention of SARS-CoV-2 infection. Eight studies had an open-label design, six were double-blind and placebo-controlled. Of the 41 study results contributed by included studies, about one third were at overall high risk of bias.

Ivermectin doses and treatment duration varied among included studies.

We identified 31 ongoing and 18 studies awaiting classification until publication of results or clarification of inconsistencies.

Ivermectin compared to placebo or standard of care for inpatient COVID-19 treatment

We are uncertain whether ivermectin compared to placebo or standard of care reduces or increases mortality (risk ratio (RR) 0.60, 95% confidence interval (CI) 0.14 to 2.51; 2 studies, 185 participants; very low-certainty evidence) and clinical worsening up to day 28 assessed as need for invasive mechanical ventilation (IMV) (RR 0.55, 95% CI 0.11 to 2.59; 2 studies, 185 participants; very low-certainty evidence) or need for supplemental oxygen (0 participants required supplemental oxygen; 1 study, 45 participants; very low-certainty evidence), adverse events within 28 days (RR 1.21, 95% CI 0.50 to 2.97; 1 study, 152 participants; very low-certainty evidence), and viral clearance at day seven (RR 1.82, 95% CI 0.51 to 6.48; 2 studies, 159 participants; very low-certainty evidence). Ivermectin may have little or no effect compared to placebo or standard of care on clinical improvement up to 28 days (RR 1.03, 95% CI 0.78 to 1.35; 1 study; 73 participants; low-certainty evidence) and duration of hospitalization (mean difference (MD) −0.10 days, 95% CI −2.43 to 2.23; 1 study; 45 participants; low-certainty evidence). No study reported quality of life up to 28 days.

Ivermectin compared to placebo or standard of care for outpatient COVID-19 treatment

We are uncertain whether ivermectin compared to placebo or standard of care reduces or increases mortality up to 28 days (RR 0.33, 95% CI 0.01 to 8.05; 2 studies, 422 participants; very low-certainty evidence)

and clinical worsening up to 14 days assessed as need for IMV (RR 2.97, 95% CI 0.12 to 72.47; 1 study, 398 participants; very low-certainty evidence) or non-IMV or high flow oxygen requirement (0 participants required non-IMV or high flow; 1 study, 398 participants; very low-certainty evidence). We are uncertain whether ivermectin compared to placebo reduces or increases viral clearance at seven days (RR 3.00, 95% CI 0.13 to 67.06; 1 study, 24 participants; low-certainty evidence). Ivermectin may have little or no effect compared to placebo or standard of care on the number of participants with symptoms resolved up to 14 days (RR 1.04, 95% CI 0.89 to 1.21; 1 study, 398 participants; low-certainty evidence) and adverse events within 28 days (RR 0.95, 95% CI 0.86 to 1.05; 2 studies, 422 participants; low-certainty evidence). None of the studies reporting duration of symptoms were eligible for primary analysis. No study reported hospital admission or quality of life up to 14 days.

Ivermectin compared to no treatment for prevention of SARS-CoV-2 infection

We found one study. Mortality up to 28 days was the only outcome eligible for primary analysis. We are uncertain whether ivermectin reduces or increases mortality compared to no treatment (0 participants died; 1 study, 304 participants; very low-certainty evidence). The study reported results for development of COVID-19 symptoms and adverse events up to 14 days that were included in a secondary analysis due to high risk of bias. No study reported SARS-CoV-2 infection, hospital admission, and quality of life up to 14 days.

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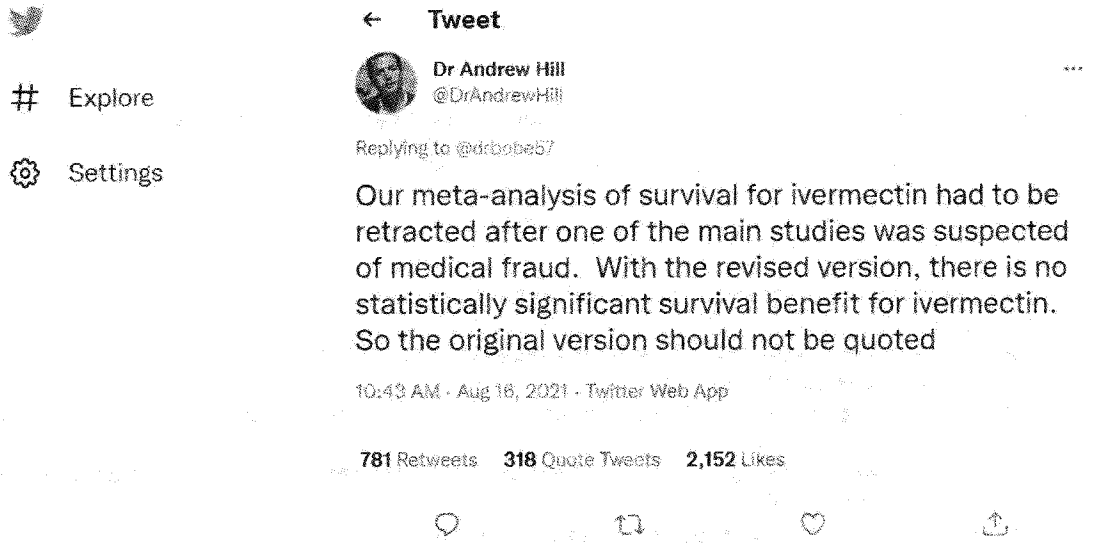
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Our meta-analysis of survival for ivermectin had to be retracted after one of the main studies was suspected of medical fraud. With the revised version, there is no statistically significant survival benefit for ivermectin. So the original version should not be quoted
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EXHIBIT L

Meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection

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Abstract

Ivermectin is an antiparasitic drug being investigated for repurposing against SARS-CoV-2. Ivermectin showed in-vitro activity against SARS-COV-2 at high concentrations. This meta-analysis investigated ivermectin in 24 randomized clinical trials (3328 patients) identified through systematic searches of PUBMED, EMBASE, MedRxiv and trial registries. Ivermectin was associated with reduced inflammatory markers (C-Reactive Protein, d-dimer and ferritin) and faster viral clearance by PCR. Viral clearance was treatment dose- and duration-dependent. In 11 randomized trials of moderate/severe infection, there was a 56% reduction in mortality (Relative Risk 0.44 [95%CI 0.25-0.77]; p=0.004; 35/1064 (3%) deaths on ivermectin; 93/1063 (9%) deaths in controls) with favorable clinical recovery and reduced hospitalization. Many studies included were not peer reviewed and a wide range of doses were evaluated. Currently, WHO recommends the use of ivermectin only inside clinical trials. A network of large clinical trials is in progress to validate the results seen to date.

Keywords: SARS-CoV2, COVID-19, Ivermectin, Repurposed

Introduction

The SARS-CoV-2 pandemic continues to grow, with over 350,000 new infections and over 7,000 deaths recorded worldwide daily in May 2021 [1]. Protective vaccines have been developed, but current supplies are too low to cover worldwide demand in the coming months [2]. Researchers worldwide are urgently looking for interventions to prevent new infections, or prevent disease progression, and lessen disease severity for those already infected.

While research on new therapeutic agents for COVID-19 is key, there is also great interest in evaluating the potential of already existing medicines against COVID-19, and many clinical trials are in progress to 're-purpose' drugs normally indicated for other diseases. The known safety profiles, shortened development timelines, and well-established markets (with low price points and higher capacity to deliver at scale) for most of the already existing compounds proposed for COVID-19 are particularly advantageous compared to new drug discovery in a pandemic situation. Three re-purposed anti-inflammatory drugs have shown significant survival benefits to date: the corticosteroid dexamethasone in the UK RECOVERY trial [3], and the Interleukin-6 (IL-6) receptor antagonist drugs, tocilizumab and sarilumab, in the REMAP-CAP trial and RECOVERY trial [4,5]. Other re-purposed antimicrobials such as, hydroxychloroquine, lopinavir/ritonavir, remdesivir and interferon-beta, have shown no significant survival benefit in two large, randomized trials [3, 6] despite initial reports of efficacy, underscoring the need for caution when interpreting early clinical trial data.

Dexamethasone is recommended for use by the WHO and has proven survival benefits for oxygen-dependent patients with COVID-19, while tocilizumab and sarilumab improve survival for patients in intensive care [3, 4]. Preliminary data suggest that nitazoxanide and budesonide may have a role in mild infection [7,8]. However, there are no approved treatments for patients with mild SARS-CoV-2 infection, either to prevent disease progression or reduce viral transmission. Treatments increasing viral clearance rate may reduce the risk of onward transmission but this requires empirical demonstration.

Ivermectin is a well-established anti-parasitic drug used worldwide for a broad number of parasites and also for topical use against rosacea. Antiviral activity of ivermectin has been demonstrated recently for SARS-CoV-2 in Vero/hSLAM cells [9]. However, concentrations required to inhibit viral replication in-vitro (EC_{50}=2.2 - 2.8μM; EC_{90}=4.4μM) are not achieved systemically after oral administration of the drug to humans [9, 10].

The drug is estimated to accumulate in lung tissues (2.67 times that of plasma) [11], but this is also unlikely to be sufficient to maintain target concentrations for pulmonary antiviral activity [10, 12]. Notwithstanding, ivermectin is usually present as a mixture of two agents and although mainly excreted unchanged in humans, has two major metabolites [13]. Current data are insufficient to determine whether the minor form or a circulating metabolite has higher direct potency against SARS-CoV-2, but it seems likely that it would need to be profoundly more potent than the reported values.

Ivermectin has also demonstrated immunomodulatory and anti-inflammatory mechanisms of action in preclinical models of several other indications. *In-vitro* studies have demonstrated that ivermectin suppresses production of the inflammatory mediators nitric oxide and prostaglandin E2 [14]. Furthermore, avermectin (from which ivermectin is derived) significantly impairs pro-inflammatory cytokine secretion (IL-1β and TNF-α) and increases secretion of the immunoregulatory cytokine IL-10 [15]. Ivermectin also reduced TNF-α, IL-1, and IL-6, and improved survival in mice given a lethal dose of lipopolysaccharide [16]. Preclinical evidence to support these immunomodulatory and anti-inflammatory mechanisms of action have also been generated in murine models [17, 18]. Finally, in Syrian golden hamsters infected with SARS-CoV-2, subcutaneous ivermectin demonstrated a reduction in the IL-6/IL-10 ratio in lung tissues. In this study, ivermectin also prevented pathological deterioration [19]. Ultimately, various potential mechanisms of action for ivermectin against COVID19 exist and are undergoing further investigation, as recently summarised in a review article [20].

At standard doses, of 0.2-0.4mg/kg for 1-2 days, ivermectin has a good safety profile and has been distributed to billions of patients worldwide in mass drug administration programs. A recent meta-analysis found no significant difference in adverse events in those given

higher doses of ivermectin, of up to 2mg/kg, and those receiving longer courses, of up to 4 days, compared to those receiving standard doses [21]. Ivermectin is not licensed for pregnant or breast-feeding women, or children <15kg. The WHO Guidelines Group found that in 16 RCTs with 2407 participants ivermectin improved mortality outcomes compared with control but rated the quality of available evidence as low or very low [22]. Currently, the WHO does not recommend the use of ivermectin outside clinical trials.

The objective of this systematic review and meta-analysis was to combine available results from new published or unpublished randomized trials of ivermectin in SARS-CoV-2 infection to inform current guidelines.

Methods

The systematic review and meta-analysis was conducted according to PRISMA guidelines. A systematic search of PUBMED and EMBASE was conducted to identify randomized control trials (RCTs) evaluating treatment with ivermectin for SARS-CoV-2 infected patients. Clinical trials with no control arm, or those evaluating prevention of infection were excluded alongside non-randomized trials and case-control studies. Key data extracted included baseline characteristics (age, sex, weight, oxygen saturation, stage of infection), changes in inflammatory markers, viral suppression after treatment, clinical recovery, hospitalization and survival. Data were extracted and cross-checked by two independent reviewers (HW and LE).

Search strategy and selection criteria

RCTs were eligible for inclusion if they compared an ivermectin-based regimen with a comparator or standard of care (SOC) for the treatment of SARS-CoV-2 infection. PRISMA checklist, PRISMA flow diagram, the search terms, and inclusion/exclusion criteria used are detailed in Supplementary Figure 1, Supplementary Tables 1, 2 and 3.

Registry databases were searched up until the 12th of May 2021. Clinicaltrials.gov [23] was searched using key words COVID, SARS-CoV-2 and ivermectin to identify studies. The WHO International Clinical Trials Registry Platform (ICTRP) was accessed via the COVID-NMA Initiative's mapping tool [24] and Stanford University's Coronavirus Antiviral Research

Database (CoV-RDB) [25] to identify additional trials listed on other national, and international registries. Literature searches via PubMed, Embase, and the preprint servers MedRxiv and Researchsquare were conducted to identify published studies. Duplicate registrations, non-randomised studies and prevention studies were excluded following discussion between the authors.

Additionally, the research teams conducting unpublished clinical trials were contacted and requested to join regular international team meetings from December 2020 to May 2021. All results available from eligible unpublished studies were also included in this systematic review.

All of the clinical trials included in this meta-analysis were approved by local ethics committees and all patients gave informed consent.

The primary outcome was all-cause mortality from randomization to the end of follow-up. Secondary outcomes included time to viral clearance, PCR negativity at day 7, clinical recovery, time to clinical recovery, mechanical ventilation, duration of hospitalization and number of hospitalizations. Changes in inflammatory markers, viral suppression, clinical recovery and hospitalization were also summarized for individual trials where endpoints could not be combined.

Data analysis

Statistical analyses for all-cause mortality, time to viral clearance and clinical recovery were conducted using published data summaries. For the mortality outcome, clinical trials with at least one death reported were included in this analysis. Furthermore, any hospitalization within 12 hours of randomization was excluded. Treatment effects were expressed as risk ratios (RR) for binary outcomes and mean difference (MD) for continuous outcomes. For each outcome, we pooled the individual trial statistics using the random-effects inverse-variance model; a continuity correction of 0.5 was applied to treatment arms with no deaths. Heterogeneity was evaluated by I^2. The significance threshold was set at 5% (two-sided) and all analyses were conducted using Revman 5.3. A funnel plot for the mortality outcome was

created to assess publication bias and small study effects; the p-value was estimated from the regression-based Harbord test for small study effects.

All studies included in this analysis were assessed for risk of bias using the Cochrane Collaboration risk of bias standardized assessment tool [26]. The outcome of this assessment is given in Supplementary Table 3. Each study was assessed for risk of bias for the primary endpoint, viral load, and survival outcomes. The primary endpoint in the trials tended to be clinical recovery which is more subjective and likely to be influenced by knowledge of treatment arms. An assessment was also carried out on more objective endpoints including survival and viral load which are less likely to be influenced by this bias. Where information was not available in published papers, clinical trial investigators were proactively contacted to inform the risk bias analysis.

Results

24 RCTs involving a total of 3328 participants were included in this meta-analysis. The sample sizes of each trial ranged from 24 to 400 participants. Of the 24 included studies, eight were published papers, nine were available as pre-prints, six were unpublished results shared for this analysis, and one reported results via a trial registry website.

Overall, nine trials investigated ivermectin as a single dose (Table 1A) [27-35], 15 trials investigated multi-day dosing up to seven days (Table 1B) [36-50] , of which four trials were dose-ranging [28,39, 46, 48]. In the included trials, ivermectin was largely investigated in mild/moderate participants (15 trials). Overall, 18 trials were either single or double-blinded and six were open-label.

Evaluation of Studies.

An evaluation of the quality of the studies included in this meta-analysis was conducted according to the Cochrane Collaboration tool to assess the risk of bias across the following outcomes: primary endpoints, viral load, and survival. For the primary outcome assessment, 6/24 (25%) studies were assessed as high risk of bias [Supplementary table 3A]. However, in assessments of more objective outcomes, including viral load and mortality, the number of

high risk studies was lower. In the PCR assessment, 3/15 (20%) of the studies were assessed as high risk [Supplementary Table 3B]. In the survival assessment, 1/11 (9%) of the studies were assessed as high risk of. [Supplementary Table 3C].

Effects on Inflammatory Markers

Five trials provided results of the effect of ivermectin on inflammatory markers including C-reactive protein (CRP), ferritin and d-dimer (Table 2). Four of these trials demonstrated significant reductions in CRP compared to control. Furthermore, in the Elgazzar trial [36], ivermectin significantly reduced ferritin levels compared to control in the severe patient population while no significant difference was demonstrated in the mild/moderate population. The Okumus trial [47] showed significantly greater reductions in ferritin on day 10 of follow-up for ivermectin versus control. The Chaccour [35] and Ahmed [46] trials showed no significant difference in ferritin count between ivermectin and control. Elgazzar [36] showed significant differences in d-dimer between ivermectin and control in both the mild/moderate and severe populations. Okumus [47] showed significant differences in d-dimer on day 5 whilst Chaccour [35] found no significant differences in d-dimer between ivermectin and control, but with a smaller sample size.

Effects on Viral Clearance

Three different endpoints were used to analyze viral clearance: the percentage of patients undetectable on a set day (Table 3A), the number of days from randomization to negativity (Table 3B), and other measures such as cycle time (Ct) values and dose-response correlations (Table 3C). The Kirti [43] and Okumus [47] trials included viral load analysis only in a subset of patients. The effects of ivermectin on viral clearance were generally smaller when dosed on only one day. Several studies showed no statistically significant effect of ivermectin on viral clearance [28, 29, 34].

The three studies randomizing patients to different doses or durations of ivermectin showed apparent dose-dependent effects on viral clearance. First, in the Babalola trial (n=60) [48], the 0.4mg/kg dose showed trends for faster viral clearance than the 0.2mg/kg dose. Second, in the Mohan trial (n=125) [28], the 0.4 mg/kg dose of ivermectin led to a numerically higher

percentage of patients with viral clearance by day five than the 0.2mg/kg dose. Third, in the Ahmed trial (n=72) [46], ivermectin treatment for five days led to a higher percentage of patients with viral clearance at day 13 compared with one day of treatment. Finally, in Krolewiecki (n=45) [50], PK/PD correlations showed significantly faster viral clearance for patients with PK exposures above 160ng/mL.

The effect of ivermectin on viral clearance was most pronounced in the randomized trials evaluating doses of up to five days of ivermectin using doses of 0.4mg/kg. At these doses, there were statistically significant effects on viral clearance in all four randomized trials. In a meta-analysis of viral clearance with subgroups of dose duration, there were significant differences in time to viral clearance in favour of ivermectin (Mean Difference -3.00 days [95%CI -4.96, -1.03]; p=0.003, Figure 1A]. In a sensitivity analysis excluding high risk of bias studies, similar effects of ivermectin on time to viral clearance were seen [Supplementary Figure 2]. Furthermore, in another analysis, ivermectin showed improved viral clearance at day 7 (Relative Risk 1.35 [95%CI 1.05-1.75]; p=0.02, Figure 1B].

Effects on Clinical Recovery and Duration of Hospitalization

Definitions of clinical recovery varied across trials, as shown in Table 4. In Table 4A, three of the six trials showed significantly faster time to clinical recovery on ivermectin compared to control. In four trials, ivermectin showed significantly shorter duration of hospitalization compared to control (Table 4B).

In a meta-analysis of clinical recovery with subgroups of dose duration, there were significant differences in time to clinical recovery in favour of ivermectin (Mean Difference -1.58 days [95%CI -2.80, -0.35]; p=0.01, Figure 1C]. Additionally, ivermectin showed a 29% improvement in clinical recovery in an analysis with subgroups of dose duration (RR 1.29 [95%CI 1.12-1.47]; p=0.0003, Figure 1D].

Ivermectin demonstrated a shorter duration of hospitalization compared to control (Mean Difference -4.27 days [95%CI -8.60-0.06]; p=0.05, Figure 1E). Ivermectin was not associated with a lower risk of hospitalization compared to control (RR 0.40 [95%CI 0.14-1.08]; p=0.07, Figure 1F). However, this analysis involved only four trials in 704 participants. In a sensitivity

analysis including any hospitalization within 12 hours of randomization, there were significantly fewer hospitalisations compared to control (RR 0.32 [95%CI 0.13-0.80]; p=0.01, Supplementary Figure 3).

Effects on Survival

11 randomized trials reported that at least one person had died post-randomization and were included in the analysis (Table 5). Across these 11 trials in 2127 patients, there were 35/1064 (3%) deaths in the ivermectin arms, versus 93/1063 (9%) deaths in the control arms. In a combined analysis using inverse variance weighting, ivermectin showed a 56% reduction in mortality (RR 0.44 [95%CI 0.25-0.77]; p=0.004, Figure 1G). Heterogeneity was moderate, I^2 = 43%. There was a 70% improvement in survival in the subgroup of mild/moderate participants (RR 0.30 [95%CI 0.15-0.58]; p=0.0004). The total number of deaths was small, the analysis was based on 128 deaths and there was no significant difference between ivermectin and control in the severe subgroup (0.58 [95%CI 0.25-1.32]; p=0.19).

Consistent results were observed in an analysis excluding high risk of bias studies (RR 0.45 (95%CI 0.24-0.82); p=0.01, Supplementary Figure 4). When only low risk of bias studies were included this result was also maintained (RR 0.31 [95%CI 0.10-0.90]; p=0.03, Supplementary Figure 5).

Additional subgroup analysis of the mortality outcome with trials separated by dose-duration, blinding and control group showed consistent survival benefit and no significant subgroup differences were found (Supplementary Figures 6, 7 and 8).

A leave-one-out sensitivity analysis was performed and no single study had a substantial effect on the overall effect size (Supplementary Table 4).

A funnel plot for the mortality outcome showed no significant effects of publication bias: the treatment effects were similar in studies of different sizes, p= 0.618 (Supplementary Figure 9).

Ivermectin was not associated with lower risk of mechanical ventilation (RR 0.97 [95%CI 0.57-1.67]; p=0.92, Figure 1H]. However, this estimate was based on five studies in 641 participants including only 49 events.

Discussion

This systematic review and meta-analysis of 24 RCTs (n = 3328) showed ivermectin treatment reduces inflammatory markers, achieves viral clearance more quickly and improves survival compared with SOC. The effects of ivermectin on viral clearance were stronger for higher doses and longer durations of treatment. These effects were seen across a wide range of RCTs conducted in several different countries.

The results from this analysis have emerged from the International Ivermectin Project Team meetings between December 2020 and May 2021. Independent research teams were conducting the trials across 16 countries and agreed to share their data, which was often unpublished, to accelerate the speed of reporting and to ensure their fragmented research, widespread across the world, could contribute to global learning. Viral clearance was evaluated by Polymerase Chain Reaction (PCR) assays in all the studies. We have only included randomized clinical trials in this meta-analysis. The 24 RCTs included were designed and conducted independently, with results combined in May 2021. However each individual trial was small and a wide range of population types included. Clinical recovery definitions differed between trials and there were no significant differences on survival in severe participants.

Secondary Endpoints

Secondary endpoints for some RCTs included biomarkers of disease severity. Some of these provide evidence for an anti-inflammatory mechanism of action of ivermectin in SARS-CoV-2 infected patients. Previous meta-analyses have demonstrated that high levels of CRP, ferritin, d-dimer and lymphocytopenia are related to COVID-19 severity and hyper-inflammation [51, 52]. Studies of IL-6 receptor antagonists have been shown to reduce CRP and d-dimer levels in patients with COVID-19 [5].

Ivermectin may also have a role in short-term prevention of SARS-CoV-2 infection, suggested by pilot studies [53, 54]. This potential benefit also needs to be validated in larger randomized trials.

Mechanism of action

At the time of writing, knowledge gaps prevent a robust conclusion about the mechanism of action of ivermectin. Ivermectin's broad-spectrum anti-viral effects have been proposed to be related to its impact on the NF-κB pathway and via binding to the host cell importin α/β1 heterodimer, nuclear transport proteins responsible for nuclear entry of cargoes, and these effects in turn also prevent viral replication.

As discussed in the introduction, the current *in-vitro* EC_{50} estimates (2.2μ, 2.4μM and 2.8μM depending on gene assay analyzed by RT-qPCR) are still 35 times higher than plasma concentrations following normal oral dosing. Even doses 8.5x fold the FDA recommended 200μg/kg of 1.7mg/kg only reach plasma concentrations of 0.28μM [55]. The increased bioavailability in the fed state and higher concentrations seen in lung tissue compared to plasma is still below the current published EC_{50} results.

However, EC_{50} results can vary greatly depending on lab methodology; cell lineage, viral quantification methods, the strain of the virus cultured and the Multiplicity of infection used. This is an established phenomenon: viral polymorphisms of influenza demonstrated a 5-fold variation in EC_{50} of different neuraminidase assays that looked at the susceptibility of field isolates of influenza virus against oseltamivir [56]. Specifically in SARS-CoV-2, EC_{50}s for previously repurposed drugs have varied significantly. Remdesivir, now licensed for SARS-CoV-2, performed >10 fold better in hACE2 augmented A549 cells (0.115 μM) than Vero E6 (1.28μM) [57]. whereas other examples of repurposed drugs like sofosbuvir demonstrated over 10-fold variation in EC_{50} when used in Vero E6 cells versus HUH7 [58]. Consequently, the EC_{50} so far demonstrated for ivermectin against SARS-CoV-2 should be interpreted with caution as it is unlikely to be one set value and liable to change depending on the lab

methodology used. In vitro assays for ivermectin should be repeated for different cell types using different measures of activity.

Limitations

A key limitation to this meta-analysis is the comparability of the data, with studies differing in dosage, treatment duration, and inclusion criteria. Furthermore, the standard of care used in the control arm differed between trials. In this meta-analysis, trials that used active controls such as hydroxychloroquine or lopinavir/ritonavir were combined together with those that used placebo or standard care. However, lopinavir/ritonavir and hydroxychloroquine have shown no overall benefit or harm in large randomized trials and meta-analyses. [7, 59-61] Furthermore, additional analyses in this paper separating trials by subgroups of standard care/ placebo and active control showed no significant difference between groups.

Another limitation is that ivermectin was given in combination with doxycycline in three trials. Individual trials may not have power to detect treatment effects on rare endpoints such as survival. Outcome measures were not standardized; viral clearance was measured in most trials, but at different time points and with different PCR cycle thresholds. The reliability of PCR tests for quantification purposes has been the subject of substantive debate. Most studies were conducted in populations with only mild/moderate infection and some trials excluded patients with multiple comorbidities.

For open label studies, there is a risk of bias in the evaluation of subjective endpoints such as clinical recovery and hospital discharge. However, the risk is lower for objective endpoints such as viral clearance and survival. We have attempted to control for publication bias by contacting each research team conducting the trials directly. This has generated more results than would be apparent from a survey of published clinical trials only but means that many of the included trials have not been peer-reviewed. Review and publication of RCTs generally takes three to six months. It has become common practice for clinical trials of key COVID-19 treatments to be evaluated from pre-prints, such as for the WHO SOLIDARITY, RECOVERY and REMAP-CAP trials [4,5,7].

These RCTs have been conducted in a wide range of countries, often in low-resource conditions and overburdened healthcare systems. Larger RCTs are currently underway in Spain, South America, Africa and North America, with results from an additional 5000 participants expected in Summer 2021 (Supplementary Table 5).

Despite limitations, this analysis suggests a dose and duration-dependent impact of ivermectin on rate of viral clearance. These trials evaluated a wide range of ivermectin dosing, from 0.2mg/kg for 1 day to 0.6mg/kg for 5 days. This wide range of doses allowed an estimation of dose-dependency on viral clearance but reduces the number of patients included that were consistently administered the same dose for the same duration. The maximum effective dose of ivermectin is not yet clear and new clinical trials are evaluating higher doses, up to 1.2mg/kg for 5 days.

The 56% survival benefit seen in this meta-analysis is based on 128 deaths, in 11 different clinical trials. This is a smaller total number of deaths than the RECOVERY trial, which led to the approval of dexamethasone and is based on 1592 deaths. However, the observed survival benefit of 56% in ivermectin is stronger than for other repurposed drugs, requiring a smaller sample size to be demonstrated. Emerging mortality results from larger studies of ivermectin will require careful evaluation and may change the conclusions from the current analysis.

Several other repurposed medications have shown promise in early smaller trials for example sofosbuvir/daclatasvir, colchicine and remdesivir but the benefit was not seen later in larger trials. This meta-analysis of 24 RCTs in 3328 patients showed a 56% improvement in survival, faster time to clinical recovery and signs of a dose-dependent effect of viral clearance for patients given ivermectin versus control treatment. This benefit needs to be validated in larger confirmatory trials.

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Potential Conflicts of Interest: None of the authors has declared a conflict of interest.

Patient Consent Statement: All of the clinical trials included in this meta-analysis were approved by local ethics committees and all patients signed informed consent.

References

1. WHO. WHO Coronavirus Disease (COVID-19) Dashboard [Internet]. 2020 [cited 2021 March 9]. Available from: https://covid19.who.int/

2. Stolberg SG, LaFraniere S. Warning of Shortages, Researchers Look to Stretch Vaccine Supply. New York Times [Internet]. 2020; Available from: https://www.nytimes.com/2021/01/05/us/politics/coronavirus-vaccine-supply.html

3. RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19—preliminary report. New England Journal of Medicine. 2020. DOI: 10.1056/NEJMoa2021436

4. The REMAP-CAP Investigators. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19 - Preliminary report. medrXiv [preprint] 2020; Available at: https://doi.org/10.1101/2021.01.07.21249390

5. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet (London, England). 2021 May 1;397(10285):1637–45.

6. WHO Solidarity Trial Consortium. 2021. "Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results." *The New England Journal of Medicine* 384 (6): 497–511. https://doi.org/10.1056/NEJMoa2023184.

7. Mahase E. Covid-19: Budesonide shortens recovery time in patients not admitted to hospital, study finds *BMJ* 2021; 373:n957 doi:10.1136/bmj.n957

8. Romark. ROMARK ANNOUNCES INITIAL RESULTS OF PHASE 3 CLINICAL TRIAL OF NT-300 TABLETS FOR THE TREATMENT OF COVID-19 [Internet]. 2020 [cited 2021 Apr 22]. Available from: https://www.romark.com/romark-announces-initial-results-of-phase-3-clinical-trial-of-nt-300-tablets-for-the-treatment-of-covid-19/

9. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res. 2020 Jun;178:104787. doi: 10.1016/j.antiviral.2020.104787.

10. Arshad U, Pertinez H, Box H, et al. Prioritization of Anti-SARS-Cov-2 Drug Repurposing Opportunities Based on Plasma and Target Site Concentrations Derived from their Established Human Pharmacokinetics. Clin Pharmacol Ther. 2020 Oct;108(4):775-790. doi: 10.1002/cpt.1909.

11. Schmith, V., Zhou, J. Lohmer, 2020. The Approved Dose of Ivermectin Alone is not the Ideal Dose for the Treatment of COVID-19. *Clinical Pharmacology & Therapeutics*, 108(4), pp.762-765.

12. Jermain B, Hanafin PO, Cao Y, Lifschitz A, Lanusse C, Rao GG. Development of a Minimal Physiologically-Based Pharmacokinetic Model to Simulate Lung Exposure in Humans Following Oral Administration of Ivermectin for COVID-19 Drug Repurposing. J Pharm Sci. 2020;109(12):3574-3578. doi:10.1016/j.xphs.2020.08.024

13. González Canga A, Sahagún Prieto AM, Diez Liébana MJ, et al. The pharmacokinetics and interactions of ivermectin in humans--a mini-review. AAPS J. 2008;10(1):42-46. doi:10.1208/s12248-007-9000-9

14. Zhang X, Song Y, Xiong H, et al. Inhibitory effects of ivermectin on nitric oxide and prostaglandin E2 production in LPS-stimulated RAW 264.7 macrophages. Int Immunopharmacol. 2009 Mar;9(3):354-9. doi: 10.1016/j.intimp.2008.12.016.

15. Ci X, Li H, Yu Q, et al. Avermectin exerts anti-inflammatory effect by downregulating the nuclear transcription factor kappa-B and mitogen-activated protein kinase activation pathway. Fundam Clin Pharmacol. 2009 Aug;23(4):449-55. doi: 10.1111/j.1472-8206.2009.00684.x.

16. Zhang X, Song Y, Ci X, et al. Ivermectin inhibits LPS-induced production of inflammatory cytokines and improves LPS-induced survival in mice. Inflamm Res. 2008 Nov;57(11):524-9. doi: 10.1007/s00011-008-8007-8

17. Ventre E, Rozières A, Lenief V, et al. Topical ivermectin improves allergic skin inflammation. Allergy. 2017 Aug;72(8):1212-1221. doi: 10.1111/all.13118.

18. Yan S, Ci X, Chen N, Chen C, et al. Anti-inflammatory effects of ivermectin in mouse model of allergic asthma. Inflamm Res. 2011 Jun;60(6):589-96. doi: 10.1007/s00011-011-0307-8.

19. de Melo GD, Lazarini F, Larrous F, et al. Anti-COVID-19 efficacy of ivermectin in the golden hamster. bioRxiv 2020.11.21.392639; doi: https://doi.org/10.1101/2020.11.21.392639

20. Navarro, M., Camprubí, D., Requena-Méndez, A., et al. 2020. Safety of high-dose ivermectin: a systematic review and meta-analysis. *Journal of Antimicrobial Chemotherapy*, 75(4), pp.827-834.

21. Zaidi AK, Dehgani-Mobaraki P. The mechanisms of action of Ivermectin against SARS-CoV-2: An evidence-based clinical review article. The Journal of Antibiotics. 2021 Jun 15:1-3.

22. WHO. Therapeutics and COVID-19: living guideline [Internet]. 2020. [cited 2021 Apr 22]. Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021.1

23. NIH ClinicalTrials.gov. [Accessed 14th December]

24. Thu Van Nguyen, Gabriel Ferrand, Sarah Cohen-Boulakia, Ruben Martinez, Philipp Kapp, Emmanuel Coquery, for the COVID-NMA consortium. (2020). RCT studies on preventive measures and treatments for COVID-19 [Data set]. Zenodo. http://doi.org/10.5281/zenodo.4266528

25. Tzou PL, Tao K, Nouhin J, et al. Coronavirus Antiviral Research Database (CoV-RDB): An Online Database Designed to Facilitate Comparisons between Candidate Anti-Coronavirus Compounds. Viruses. 2020;12(9):1006. Published 2020 Sep 9. doi:10.3390/v12091006

26. Higgins JPT, Thomas J, Chandler J, et al. *Cochrane Handbook for Systematic Reviews of Interventions* version 6.1 (updated September 2020). Cochrane, 2020. Available from www.training.cochrane.org/handbook.

27. Mahmud et al. ClinicalTrials.gov. National Library of Medicine. NCT04523831. Clinical trial of ivermectin plus doxycycline for the treatment of confirmed COVID-19 infection. Available at: https://clinicaltrials.gov/ct2/show/study/NCT04523831 [Accessed 15/12/2020]

28. Mohan A, Tiwari P, Suri T et al. Ivermectin in mild and moderate COVID-19 (RIVET-COV): a randomized, placebo-controlled trial. Research Square. 2021. https://doi.org/10.21203/rs.3.rs-191648/v1 [preprint]

29. Chowdhury et al. A randomised trial of Ivermectin-Doxycycline and Hydroxychloroquine-Azithromycin therapy on COVID19 patients. 2020 [Internet] Available at: https://doi.org/10.21203/rs.3.rs-38896/v1

30. Gonzalez et al. Efficacy and safety of Ivermectin and Hydroxychloroquine in patients with severe COVID-19. A randomized controlled trial. medRxiv. Available at: https://www.medrxiv.org/content/10.1101/2021.02.18.21252037v1. [preprint]

31. Raad et al. 2020. In vivo use of ivermectin (IVR) for treatment for corona virus infected patients (COVID-19): a randomized controlled trial. 2020
Avaiable at: http://www.chictr.org.cn/showproj.aspx?proj=54707 [unpublished]

32. Bukhari, Asghar, Perveen et al. Efficacy of Ivermectin in COVID-19 Patients with Mild to Moderate Disease. medRXiv. 2020. https://doi.org/10.1101/2021.02.02.21250840 [preprint]

33. Rezai et al. Effect of Ivermectin on COVID-19: A multicenter double-blind randomized clinical trial. 2020. Available at: https://en.irct.ir/trial/49174 [unpublished]

34. Podder S, Chowdhury N, Sina M, Ul Haque W. Outcome of ivermectin treated mild to moderate COVID-19 cases: a single-centre, open-label, randomized controlled study. IMC J Med Sci 2020; 14 (2): 002

35. Chaccour C, Casellas A, Blanco-Di Matteo A, Pineda I, Fernandez-Montero A, Ruiz-Castillo P, Richardson MA, Rodríguez-Mateos M, Jordán-Iborra C, Brew J, Carmona-Torre F. The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with non-severe COVID-19: A pilot, double-blind, placebo-controlled, randomized clinical trial. EClinicalMedicine. 2021 Jan 19:100720.

36. Elgazzar A, Hany B, Youssef S, Hafez M, Moussa H, Eltaweel A. Efficacy and safety of ivermectin for treatment and prophylaxis of COVID-19 pandemic. [Pre-print]. 28th December 2020. Research Square. https://www.researchsquare.com/article/rs-100956/v3

37. López-Medina E, López P, Hurtado IC, et al. Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19: A Randomized Clinical Trial. *JAMA*. Published online March 04, 2021. doi:10.1001/jama.2021.3071

38. Chahla R, Ruiz L, Mena T et al. Cluster Randomised Trials - Ivermectin Repurposing For COVID-19 Treatment Of Outpatients With Mild Disease In Primary Health Care Centers. Researchsquare. 2021. Available at: https://doi.org/10.21203/rs.3.rs-495945/v1 [preprint]

39. Niaee M, Gheibi N, Namdar P, et al. Invermectin as an adjunct treatment for hospitalized adult COVID-19 patients: a randomized, multi-center clinical trial. [Preprint]. 24th November 2020. Research Square. Available at: https://doi.org/10.21203/rs.3.rs-109670/v1

40. Galan et al (2021) Phase 2 randomized study on chloroquine, hydroxychloroquine or ivermectin in hospitalized patients with severe manifestations of SARS-CoV-2 infection, Pathogens and Global Health, DOI: 10.1080/20477724.2021.1890887

41. Abd-Elsalam et al. Ivermectin as a Novel Therapy for COVID-19 Treatements. Available at: https://clinicaltrials.gov/ct2/show/NCT04403555 [unpublished]

42. Hashim H, Maulood M, Rasheed A, Fatak D, Kabah K, Abdulamir A. Controlled randomized clinical trial on using Ivermectin with doxycycline for treating COVID-19 patients in Baghdad, Iraq. [Preprint]. 27th October 2020. medRxiv. Available at: https://doi.org/10.1101/2020.10.26.20219345

43. Kirti R, Roy R, Pattadar C, et al. Ivermectin as a potential treatment for mild to moderate COVID-19: A double blind randomized placebo-controlled trial. [Preprint]. 9th January 2021. Medrxiv. doi: https://doi.org/10.1101/2021.01.05.21249310

44. Petkov S. Multicenter, randomized, double-blind, placebo-controlled study investigating efficacy, safety and tolerability of ivermectin HUVE-19 in patients with proven SARS-CoV-2 infection (covid-19) and manifested clinical symptoms. 2021. https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-002091-12/BG (accessed January 2021) [unpublished]

45. Schwartz E. Ivermectin vs. Placebo for the Treatment of Patients With Mild to Moderate covid-19. 2020. Available at: https://clinicaltrials.gov/ct2/show/NCT04429711 [unpublished]

46. Ahmed S, Karim M, Ross A, et al. A five day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. Int J Infect Dis. 2020 Dec 2:S1201-9712(20)32506-6. doi: 10.1016/j.ijid.2020.11.191.

47. Okumuş, N., Demirtürk, N., Çetinkaya, R.A. *et al.* Evaluation of the effectiveness and safety of adding ivermectin to treatment in severe COVID-19 patients. *BMC Infect Dis* **21**, 411 (2021). https://doi.org/10.1186/s12879-021-06104-9

48. O E Babalola, C O Bode, A A Ajayi, et al. Ivermectin shows clinical benefits in mild to moderate COVID19: A randomised controlled double-blind, dose-response study in

Lagos, *QJM: An International Journal of Medicine*, 2021; https://doi.org/10.1093/qjmed/hcab035

49. Chachar A, Khan K, Asif M, Khaqan A, Basri R. Effectiveness of ivermectin in SARS-CoV-2 / COVID-19 patients. International Journal of Sciences 09(2020):31-35 DOI: 10.18483/ijSci.2378

50. Krolewiecki A, Lifschitz A, Moragas M, et al. Antiviral Effect of High-Dose Ivermectin in Adults with COVID-19: A Pilot Randomised, Controlled, Open Label, Multicentre Trial. [Preprint]. 11th November 2020. SSRN. Available at: http://dx.doi.org/10.2139/ssrn.3714649

51. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. *Clin Chem Lab Med*. 2020;58(7):1021-1028. https://doi.org/10.1515/cclm-2020-0369

52. Singh K, Mittal S, Gollapudi S, Butzmann A, Kumar J, Ohgami RS. A meta-analysis of SARS-CoV-2 patients identifies the combinatorial significance of D-dimer, C-reactive protein, lymphocyte, and neutrophil values as a predictor of disease severity. International journal of laboratory hematology. 2020 Oct 3.

53. Clinicaltrials.gov. NCT04701710. Prophylaxis Covid-19 In Healthcare Agents By Intensive Treatment With Ivermectin And Iota-Carrageenan. Available at: https://clinicaltrials.gov/ct2/show/NCT0470171019 [Accessed 12/01/2021].

54. Clinicaltrials.gov. NCT04422561. Prophylactic Ivermectin In COVID-19 Contacts - Study Results. Available at: https://clinicaltrials.gov/ct2/show/results/NCT04422561. [Accessed 12/01/2021].

55. Wang K, Gao W, Dou Q, et al. Ivermectin induces PAK1-mediated cytostatic autophagy in breast cancer. Autophagy. 2016 Dec;12(12):2498-2499. doi: 10.1080/15548627.2016.1231494.

56. Abed Y, Baz M, Boivin G. et al. Impact of neuraminidase mutations conferring influenza resistance to neuraminidase inhibitors in the N1 and N2 genetic backgrounds. Antiviral therapy. 2006 Jan 1;11(8):971.

57. Shi PY, Xie X, Muruato et al. nanoluciferase SARS-CoV-2 for rapid neutralization testing and screening of anti-infective drugs for COVID-19. bioRxiv. 2020 Jan 1. https://www.biorxiv.org/content/biorxiv/early/2020/06/23/2020.06.22.165712.full.pdf

58. 54.Levi et al Interpreting in-vitro data for sofosbuvir against SARS-CoV-2: cell lineage is key. Oral abstract. ISIRV conference. 6-8 October 2020.

59. Ghazy R, Almaghraby A, Shaaban R, Kamal A, Beshir H, Moursi A et al. A systematic review and meta-analysis on chloroquine and hydroxychloroquine as monotherapy or combined with

azithromycin in COVID-19 treatment. Scientific Reports [Internet]. 2020;10(1). Available from: https://www.nature.com/articles/s41598-020-77748-x

60. Alhumaid, Saad, Abbas Al Mutair, Zainab Al Alawi, Naif Alhmeed, Abdul Rehman Zia Zaidi, and Mansour Tobaiqy. 2020. "Efficacy and Safety of Lopinavir/Ritonavir for Treatment of COVID-19: A Systematic Review and Meta-Analysis." *Tropical Medicine and Infectious Disease* 5 (4). https://doi.org/10.3390/tropicalmed5040180.

61. RECOVERY Collaborative Group. 2020. "Lopinavir-Ritonavir in Patients Admitted to Hospital with COVID-19 (RECOVERY): A Randomised, Controlled, Open-Label, Platform Trial." *Lancet (London, England)* 396 (10259): 1345–52. https://doi.org/10.1016/S0140-6736(20)32013-4.

62. Mills et al. Hydroxychloroquine and Lopinavir/ Ritonavir to Improve the Health of People With COVID-19: "The Hope Coalition - 1". ClinicalTrials.gov [Internet]. 2020. https://www.clinicaltrials.gov/ct2/show/NCT04403100?term=NCT04403100&draw=2&rank=1

63. DNDi. ANTICOV Clinical Trial. 2020 [Internet] Available at: https://dndi.org/research-development/portfolio/anticov/

64. Rezai et al. Double-blind placebo-controlled clinical trial of evaluating the effectiveness of Ivermectin in treatment of outpatients with COVID-19 in 2021. IRCT [Internet]. 2020. https://www.irct.ir/trial/53949

65. Rezai et al. Double-blind placebo-controlled clinical trial of evaluating the effectiveness of Ivermectin in treatment of admitted with COVID-19 in 2021. IRCT [Internet]. 2020. Available at: https://www.irct.ir/trial/54402

66. Munoz et al. Multicenter, phase III, double-blind, randomized, parallel, placebo-controlled trial to evaluate the efficacy and safety of an early administration of Ivermectin for three consecutive days to prevent hospitalization related to SARS-Cov-2 (COVID-19) in adults over 50 years old with less than 5 days of symptoms. *Exeltis* [personal communication]

67. Mukonzo et al. Safety and Efficacy of low dose aspirin/ ivermectin combination therapy for treatment of covid-19 patients (IVCOM). Clinicaltrials.gov [Internet]. Available at: https://clinicaltrials.gov/ct2/show/NCT04768179?cond=COVID-19&intr=Ivermectin&sfpd_s=01%2F02%2F2021&sfpd_e=12%2F03%2F2021&draw=2

68. Avila et al Efficacy of ivermectin in outpatients with non-severe Covid-19. Clinicaltrials.gov [Internet]. Available at: https://clinicaltrials.gov/ct2/show/NCT04834115?term=ivermectin&draw=2

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Table 1: Trial Summaries

Table 1A: Ivermectin trials with Dosing on day 1 only

Study	Country	Sample Size	Daily dose	Duration	Patients	Ivermectin Arm	Comparator Arm
Mahmud et a l [25] †	Bangladesh	363	12 mg	1 day (DB)	Mild/ moderate	Ivermectin + Doxycycline + SOC	SOC
Mohan et al [26] †	India	125	0.2-0.4 mg/kg (elixir)	1 day (DB)	Mild / moderate	Ivermectin + SOC	Placebo + SOC
Chowdhury [27] †	Bangladesh	116	0.2 mg/kg	1 day (DB)	PCR positive	Ivermectin + Doxycycline	HCQ + Azithromycin
Gonzalez [28] †	Mexico	106	12 mg	1 day (DB)	Severe	Ivermectin	Placebo
Raad et al [29] †	Lebanon	100	0.2 mg/kg	1 day (SB)	Mild	Ivermectin + SOC	SOC

Asghar et al [32] †	Pakistan	86	0.2 mg/kg	1 day (OL)	Mild / moderate	Ivermectin + SOC	SOC
Rezai et al [31] *	Iran	69	0.2 mg/kg	1 day (DB)	Moderate / severe	Ivermectin + SOC	SOC
Podder et al [32] †	Bangladesh	62	0.2 mg/kg	1 day (OL)	Mild	Ivermectin + SOC	SOC
SAINT [33] *	Spain	24	0.4 mg/kg	1 day (DB)	Moderate	Ivermectin	Placebo

SOC = Standard of care; OL= open label; SB= single-blind; DB= double-blind

Table 1B: Ivermectin trials with multi-day dosing

Study	Country	Sample Size	Daily dose	Duration	Patients	Ivermectin Arm	Comparator Arm
Elgazzar et al [36] †	Egypt	400	0.4 mg/kg	5 days (DB)	Mild to severe	Ivermectin + SOC	HCQ + SOC
Lopez-Medina et al [37]*	Colombia	398	0.3 mg/kg	5 days (DB)	Mild	Ivermectin	Placebo
Chahla et al [38] †	Argentina	254	24mg	1 / week for 4 weeks (OL)	Mild	Ivermectin + SOC	SOC
Niaee et al [39] *	Iran	180	0.2 - 0.4 mg/kg	1-3 days (DB)	Mild / moderate	Ivermectin + SOC	SOC + Placebo
Fonseca et al [40]*	Brazil	168	14mg	3 days (DB)	Severe	Ivermectin	Hydroxychloroquine or Chloroquine
Abd-Elsalam et al [41] †	Egypt	164	12 mg	3 days (OL)	PCR Positive	Ivermectin +SOC	SOC
Hashim et al [42] †	Iraq	140	0.2 mg/kg	2-3 days (SB)	Symptomatic	Ivermectin + Doxycycline + SOC	SOC

Kirti et al [43] *	India	112	12 mg	2 days (DB)	Mild / moderate	Ivermectin + SOC	SOC + Placebo
Petkov et al [44] *	Bulgaria	100	0.4 mg/kg	3 days (DB)	Mild/ moderate	Ivermectin	Placebo
Schwartz et al [45] †	Israel	94	12-15mg	3 days (DB)	Mild/moderate	Ivermectin	Placebo
Ahmed et al [46] *	Bangladesh	72	0.2 mg/kg	5 days (DB)	Mild	Ivermectin + SOC	SOC + Placebo
Okumus et al [47] †	Turkey	60	0.2 mg/kg	5 days (DB)	Severe	Ivermectin + SOC	FAVI/HQ/AZI (SOC)
Babalola et al [48] *	Nigeria	60	0.1-0.2 mg/kg	2 / week (DB)	Mild	Ivermectin + SOC	Placebo + LPV/r (SOC)
Chachar et al [49] †	Pakistan	50	0.2 mg/kg	2 days (OL)	Mild	Ivermectin + SOC	SOC
Krolewiecki et al [50] †	Argentina	45	0.6 mg/kg	5 days (OL)	Mild to moderate	Ivermectin + SOC	SOC

* Denoted studies were evaluated as having fair or good overall quality of evidence using the Cochrane Risk of Bias Tool. See Supplementary Table 3 for further details.

† Denoted studies were evaluated as having limited overall quality of evidence using the Cochrane Risk of Bias Tool. See Supplementary Table 3 for further details.

SOC = Standard of care

Table 2: Changes in inflammatory Markers

	CRP (mg/L)			Ferritin (µg/L)			D-dimer (mg/L)		
	Ivermectin	Control	p value	Ivermectin	Control	p value	Ivermectin	Control	p value
Elgazzar, Egypt (n=200, mild/moderate COVID-19)									
Baseline	48.4	50.6		168	172		4.8	5.4	
Day 7	4.8	8.3	p<0.001	95	98	0.62	0.5	0.7	p<0.001
Elgazzar, Egypt (n=200, severe COVID-19)									
Baseline	64.8	68.2		420	334		8.2	8.6	
Day 7	28.6	58.6	p<0.001	104	294	p<0.001	0.7	1.9	p<0.001
Okumus, Turkey (n=60)									
Baseline	340.3	215.0		683	747		1.3	1.3	
Day 5	51.8	194.3	p<0.01	875	1028	0.12	5.9	3.6	0.22
Day 10	36.1	92.4	p<0.05	495	1207	p<0.01	0.7	1.5	p<0.05
Chaccour, Spain (n=24)*									

Baseline	3.5	3.0		165	156		0.3	0.3	
Day 7	1.0	1.1	n.s**	125	199	n.s**	0.3	0.3	n.s**
Day 14	0.8	0.6	n.s**	152	145	n.s**	0.3	0.3	n.s**
Ahmed, Bangladesh (n=45, Ivermectin 5 days)									
Baseline	22.0	29.0		269	222		-	-	
Day 7	3.0	14.0	**p<0.05+**	211	218	0.06+	-	-	
Ahmed, Bangladesh (n= 46, Ivermectin 1 day)									
Baseline	26.0	29.0		259	222		-	-	
Day 7	11.0	14.0	0.07+	213	218	0.17+	-	-	
Iran Niaee (n=60, Ivermectin- 0.2 mg)*									
Baseline	200.0	270.0		-	-		-	-	
Day 5	85.0	245.0	p<0.001++	-	-		-	-	
Iran Niaee (n=60, Ivermectin- 0.2, 0.2, 0.2 mg)*									
Baseline	390.0	270.0		-	-		-	-	
Day 5	200.0	245.0	p<0.001++	-	-		-	-	
Iran Niaee (n=60, Ivermectin- 0.4 mg)*									
Baseline	250.0	270.0		-	-		-	-	

Day 5	80.0	245.0	p<0.001++	-	-	-	-
Iran Niaee (n=60, Ivermectin- 0.4, 0.2, 0.2 mg)*							
Baseline	340.0	270.0		-	-	-	-
Day 5	170.0	245.0	p<0.001++	-	-	-	-

*Median presented, all other data mean.

** 'n.s.' was used when no statistically significant difference was found, but the actual p-value was ot reported by the individual authors and could not be calculated by current authors

+p value compares within group changes from baseline to end point of ivermectin group. ++p value shows significance of total changes from baseline. All other p values compare ivermectin vs. control

*Normal ranges: CRP(<10mg/L), Ferritin(***11-336µg/L***) D-dimer(<0.5mg/L).*

Table 3: Effects of ivermectin on viral clearance

Table 3A:

Study	Country (n)	Daily dose	Duration	Viral load endpoint	Result IVM vs Control	P value
Number Detectable or Undetectable (%)						
Mahmud et al	Bangladesh, n=363	12 mg	1 day (DB)	Undetectable Day 14	92% vs 80%	p < 0.001
Asghar et al	Pakistan, n=86	0.2 mg/kg	1 day	Undetectable Day 7	90% vs 44%	p < 0.001
Mohan et al	India, n=125	0.2mg/kg Elixir	1 day	Undetectable Day 5	35% vs 31%	p = 0.3
Mohan et al	India, n=125	0.4mg/kg Elixir	1 day	Undetectable Day 5	48% vs 31%	p = 0.3
Kirti et al	India, n=112	12 mg	2 days	Undetectable Day 6	24% vs. 32%	p = 0.35

Podder et al	Bangladesh, n=62	0.2 mg/kg	1 day (OL)	Day 10 PCR neg	90% vs 95%	p > 0.05
Okumus et al	Turkey, n=60	0.2 mg/kg	5 days (DB)	Day 10 PCR Neg	88% vs 38%	p = 0.01
Schwartz et al	Israel n=100	12-15mg	3 days (DB)	Day 10 PCR Neg Ct>30	81% vs 60%	p=0.02

Table 3B: Effects of Ivermectin on Time to Viral Clearance

Study	Country (n)	Daily dose	Duration	Viral load endpoint	Result IVM vs Control	P value
Time to Viral Clearance (Days)						
Chowdhury	Bangladesh, n=112	0.2 mg/kg	1 day (DB)	Time to PCR neg	9 vs 9.3 days	p = 0.23
Elgazzar et al Mild/Moderate	Egypt, n=200	0.4 mg/kg	5 days (OL)	Days detectable	5 vs 10 days	p < 0.001
Elgazzar et al Severe	Egypt, n=200	0.4 mg/kg	5 days (OL)	Days detectable	6 vs 12 days	p < 0.001
Babaloa et al *	Nigeria, n=60	0.1 mg/kg	2 / week (DB)	Time to PCR neg	6 vs 9 days	p = 0.003
Babaloa et al *	Nigeria, n=60	0.2 mg/kg	2 / week (DB)	Time to PCR neg	4.7 vs 9 days	p = 0.003

Ahmed et al *	Bangladesh, n=72	0.2 mg/kg	5 days (DB)	Time to PCR neg	10 vs 13 days	p = 0.02
Ahmed et al *	Bangladesh, n=72	0.2 mg/kg	1 days (DB)	Time to PCR neg	11.5 vs 13 days	p = 0.27
Petkov et al	Bulgaria n=100	0.4 mg/kg	3 days (DB)	Time to PCR neg	4.52 vs 5.06	p=0.341

Table 3C: Effect of ivermectin on other measures of viral clearance.

Study	Country (n)	Daily dose	Duration	Viral load endpoint	Result IVM vs Control	P value
Other Measures of Viral clearance						
Raad et al	Lebanon, n=100	0.2 mg/kg	1 day	Day 3	Ct values 30.1 ± 6.22 vs. 18.96 ± 3.26	p = 0.01
Krolewiecki et al*	Argentina, n=45	0.6 mg/kg	5 days	PK/PD	Dose-related	p = 0.02

*Dose-response effect seen

Table 4: Effects on of ivermectin on clinical recovery and hospitalization

Table 4A: Time to clinical recovery

Study	Country	Daily dose	Duration	Endpoint	Results IVM vs control	P value
Time to clinical recovery						
Mohan et al	India n=125	0.2 mg/kg Elixir	1 day (SB)	Time to clinical recovery	4.8 vs 4.6 days	p = 0.77
Mohan et al	India n=125	0.4 mg/kg Elixir	1 day (SB)	Time to clinical recovery	4.3 vs 4.6 days	p = 0.77
Hashim et al	Iraq n=140	0.2 mg/kg	2-3 days (SB)	Time to clinical recovery	10.6 vs 17.9 days	p < 0.001
Chowdhury et al	Bangladesh n=116	0.2 mg/kg	1 day (DB)	Time to clinical recovery	5.9 vs 6.9 days	p = 0.071

Podder et al	Bangladesh n=62	0.2 mg/kg	1 day (OL)	Time to clinical recovery	5.3 vs 6.3 days	p > 0.05
Rezai et al	Iran n=69	0.2 mg/kg	1 days (OL)	Time to clinical recovery	4.1 vs 5.2 days	p = 0.018
Lopez-Medina et al	Colombia n=398	0.3 mg/kg	5 days (DB)	Time to clinical recovery	10 vs 12 days	p=0.53

Table 4B: Effect of Ivermectin on duration of hospitalization

Study	Country	Daily dose	Duration	Endpoint	Results IVM vs control	P value
Duration of hospitalization						
Rezai et al	Iran n=69	0.2 mg/kg	1 days (OL)	Days in hospital	6.9 vs 8.4 days	p = 0.01
Raad et al	Lebanon n=100	0.2 mg/kg	1 day (OL)	Hospitalization	0% vs 6%	p = 0.00
Niaee et al	Iran n=165	0.2 - 0.4 mg/kg	1-3 days (DB)	Days in hospital	6.5 vs 7.5 days	p = 0.006
Elgazzar et al Mild/moderate	Egypt n=200	0.4 mg/kg	5 days (OL)	Days in hospital	5 vs 15 days	p < 0.001
Elgazzar et al	Egypt	0.4 mg/kg	5 days (OL)	Days in hospital	6 vs 18 days	p < 0.001

Severe	n=200					
Ahmed et al	Bangladesh, n=72	0.2 mg/kg	5 days (DB)	Days in hospital	9.6 vs 9.7	p=0.93
Ahmed et al	Bangladesh, n=72	0.2 mg/kg	1 days (DB)	Days in hospital	10.1 vs 9.7	p=0.93
Abd El-Salam et al	Egypt n=164	12 mg	3 days	Days in hospital	8.82 vs. 10.97	p=0.09
Gonzalez et al	Mexico n=106	12 mg	1 day	Days in hospital	6 vs 5	p=0.45

Table 4C: Number of Participants with clinical recovery by Day 7 to 10 post-randomization

Study	Country	Daily dose	Duration	Endpoint	Results IVM vs control	P value
Number of Participants Recovered (%)						
Chachar et al	Pakistan n=50	0.2 mg/kg	2 days (OL)	Day 7 Clinical recovery	64% vs 60%	p = 0.5
Okumus et al	Turkey n=60	0.2 mg/kg	5 days (DB)	Day 10 Clinical improvement	73% vs 53%	p = 0.10
Mahmud et al	Bangladesh n=363	12 mg	1 day (DB)	Day 7 Clinical recovery	61% vs 44%	p <0.03
Petkov et al	Bulgaria n=100	0.4 mg/kg	3 days (DB)	Day 7 Clinical recovery	20% vs 14%	n/a
Elgazzar et al Mild/Moderate	Egypt, n=200	0.4 mg/kg	5 days (OL)	Clinical improvement	99% vs 74%	p<0.001

Elgazzar et al Severe	Egypt, n=200	0.4 mg/kg	5 days (OL)	Clinical improvement	94% vs 50%	p<0.001
Chahla et al	Argentina n=254	24 mg	1/ week for 4 weeks (OL)	Clinical improvement	98% vs 87%	p=0.0007

Table 5: Effects of ivermectin on survival

Trial	Country	Dosing	Ivermectin	Control
Mahmud et al	Bangladesh	0.2 mg/kg, 1 day	0/183	3/180
Niaee et al	Iran	0.2 mg/kg 1-3 days	4/120	11/60
Hashim et al	Iraq	0.2-0.4 mg/kg 2-3 days	2/70	6/70
Elgazzar et al	Egypt	0.4 mg/kg 5 days	2/200	24/200
Okumus et al	Turkey	0.2 mg/kg, 5 days	6/30	9/30
Kirti et al	India	12 mg, 5 days	0/55	4/57
Rezai et al	Iran	0.2 mg/kg, 1 day	1/35	0/34
Abd-Elsalam	Egypt	0.2 mg/kg, 3 days	3/82	4/82
Gonzalez	Mexico	0.2 mg/kg, 1 day	5/36	6/37

Lopez-Medina	Colombia	0.3 mg/kg 5 days	0/200	1/198
Fonseca	Brazil	14mg 3 days	12/53	25/115
Total			**35/1064 (3%)**	**93/1063 (8.7%)**

Figure1A

1A)

Study or Subgroup	Ivermectin Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
5.2.1 Single-day dosing								
Ahmed et al IVM+Doxy	11.5	4.2	24	12.7	3.6	24	12.2%	-1.20 [-3.41, 1.01]
Bangladesh Chowdhury et al	9	1.5	60	9.7	2.2	56	14.2%	-0.70 [-1.39, -0.01]
Subtotal (95% CI)			**84**			**80**	**26.4%**	**-0.74 [-1.40, -0.09]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.18$, df = 1 (P = 0.67); $I^2 = 0\%$								
Test for overall effect: Z = 2.21 (P = 0.03)								
5.2.2 Multi-day dosing								
Ahmed et al IVM 5days	9.7	5	24	12.7	3.6	24	11.8%	-3.00 [-5.46, -0.54]
Babalola et al 12mg	4.7	3.2	20	9.2	7.4	20	9.8%	-4.50 [-8.03, -0.97]
Babalola et al 6mg	6	3	20	9.2	7.4	20	9.9%	-3.20 [-6.70, 0.30]
Bulgaria Petkov et al	4.5	2.8	50	5.1	2.9	50	13.8%	-0.60 [-1.72, 0.52]
Egypt Elgazzar Moderate	5	1	100	10	4	100	14.1%	-5.00 [-5.81, -4.19]
Egypt Elgazzar Severe	6	1	100	12	4	100	14.1%	-6.00 [-6.81, -5.19]
Subtotal (95% CI)			**314**			**314**	**73.6%**	**-3.74 [-5.77, -1.72]**
Heterogeneity: $Tau^2 = 5.22$; $Chi^2 = 63.30$, df = 5 (P < 0.00001); $I^2 = 92\%$								
Test for overall effect: Z = 3.62 (P = 0.0003)								
Total (95% CI)			**398**			**394**	**100.0%**	**-3.00 [-4.96, -1.03]**
Heterogeneity: $Tau^2 = 6.94$; $Chi^2 = 139.86$, df = 7 (P < 0.00001); $I^2 = 95\%$								
Test for overall effect: Z = 2.99 (P = 0.003)								
Test for subgroup differences: $Chi^2 = 7.61$, df = 1 (P = 0.006), $I^2 = 86.9\%$								

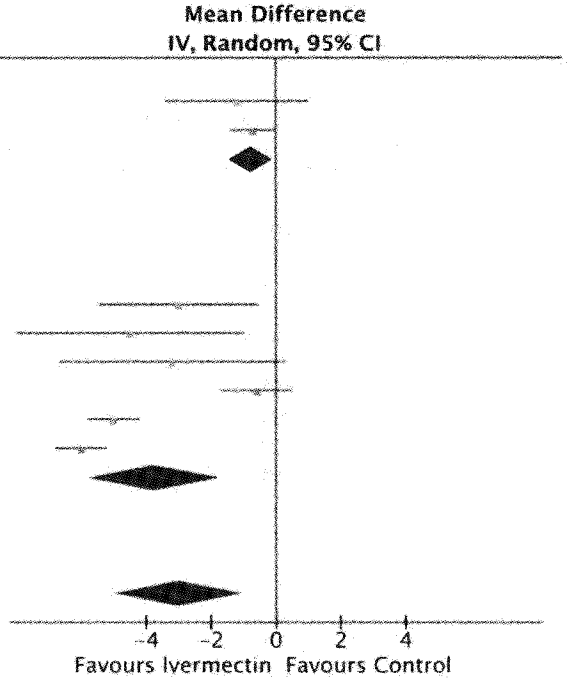


Figure 1B

1B)

Study or Subgroup	Ivermectin Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
3.7.1 Single-day dosing						
Ahmed et al IVM+Doxy	7	24	3	24	3.7%	2.33 [0.68, 7.97]
India Mohan et al 0.2mg/kg	13	36	16	42	11.1%	0.95 [0.53, 1.69]
India Mohan et al 0.4mg/kg	16	36	16	42	12.3%	1.17 [0.69, 1.98]
Pakistan Asghar et al	37	41	20	45	17.8%	2.03 [1.44, 2.86]
Subtotal (95% CI)		**137**		**153**	**44.9%**	**1.45 [0.95, 2.23]**
Total events	73		55			
Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 6.67$, df = 3 (P = 0.08); $I^2 = 55\%$						
Test for overall effect: Z = 1.71 (P = 0.09)						
3.7.2 Multi-day dosing						
Ahmed et al IVM 5days	11	24	3	24	4.2%	3.67 [1.17, 11.52]
Bulgaria Petkov et al	40	50	37	50	22.1%	1.08 [0.87, 1.34]
India Kirti et al	13	32	18	44	11.8%	0.99 [0.57, 1.72]
Israel Schwartz et al	33	49	21	45	17.0%	1.44 [1.00, 2.09]
Subtotal (95% CI)		**155**		**163**	**55.1%**	**1.26 [0.92, 1.71]**
Total events	97		79			
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 5.93$, df = 3 (P = 0.11); $I^2 = 49\%$						
Test for overall effect: Z = 1.45 (P = 0.15)						
Total (95% CI)		**292**		**316**	**100.0%**	**1.35 [1.05, 1.75]**
Total events	170		134			
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 15.90$, df = 7 (P = 0.03); $I^2 = 56\%$						
Test for overall effect: Z = 2.33 (P = 0.02)						
Test for subgroup differences: $Chi^2 = 0.29$, df = 1 (P = 0.59), $I^2 = 0\%$						

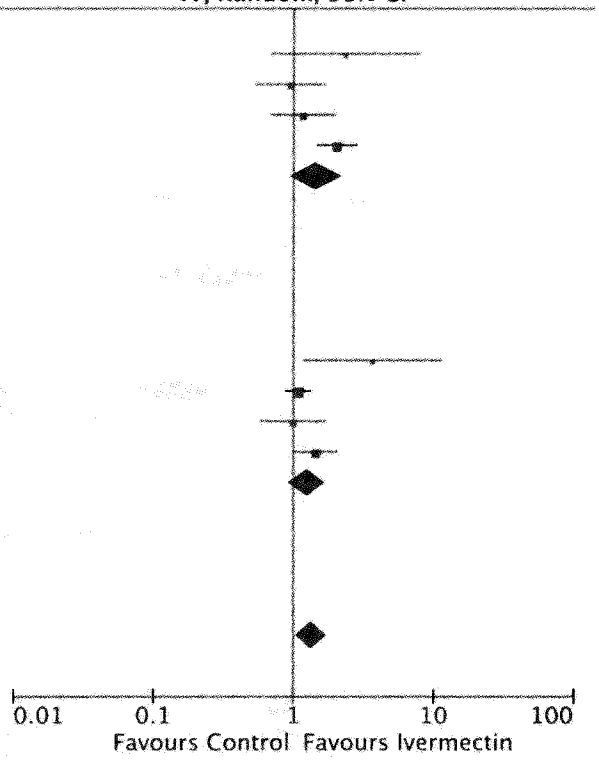


Figure 1C

1C)

Study or Subgroup	Mean Difference	SE	Ivermectin Total	Control Total	Weight	Mean Difference IV, Random, 95% CI
2.4.1 Single-day dosing						
Bangladesh Chowdhury et al	-1	0.31	60	56	17.5%	-1.00 [-1.61, -0.39]
Bangladesh Podder et al	-1	0.88	30	32	13.4%	-1.00 [-2.72, 0.72]
India Mohan et al 0.2mg/kg	0.2	0.58	40	45	15.8%	0.20 [-0.94, 1.34]
India Mohan et al 0.4mg/kg	-0.3	0.61	40	45	15.6%	-0.30 [-1.50, 0.90]
Iran Rezai et al	-1.1	0.44	35	34	16.8%	-1.10 [-1.96, -0.24]
Subtotal (95% CI)			**205**	**212**	**79.0%**	**-0.75 [-1.21, -0.30]**
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 4.57$, df = 4 (P = 0.33); $I^2 = 12\%$						
Test for overall effect: Z = 3.22 (P = 0.001)						
2.4.2 Multi-day dosing						
Colombia Lopez-Medina et al	-2	1.53	200	198	8.7%	-2.00 [-5.00, 1.00]
Iraq Hashim et al	-7.3	1.03	70	70	12.2%	-7.30 [-9.32, -5.28]
Subtotal (95% CI)			**270**	**268**	**21.0%**	**-4.77 [-9.96, 0.42]**
Heterogeneity: $Tau^2 = 12.34$; $Chi^2 = 8.26$, df = 1 (P = 0.004); $I^2 = 88\%$						
Test for overall effect: Z = 1.80 (P = 0.07)						
Total (95% CI)			**475**	**480**	**100.0%**	**-1.58 [-2.80, -0.35]**
Heterogeneity: $Tau^2 = 2.14$; $Chi^2 = 43.40$, df = 6 (P < 0.00001); $I^2 = 86\%$						
Test for overall effect: Z = 2.52 (P = 0.01)						
Test for subgroup differences: $Chi^2 = 2.28$, df = 1 (P = 0.13), $I^2 = 56.2\%$						

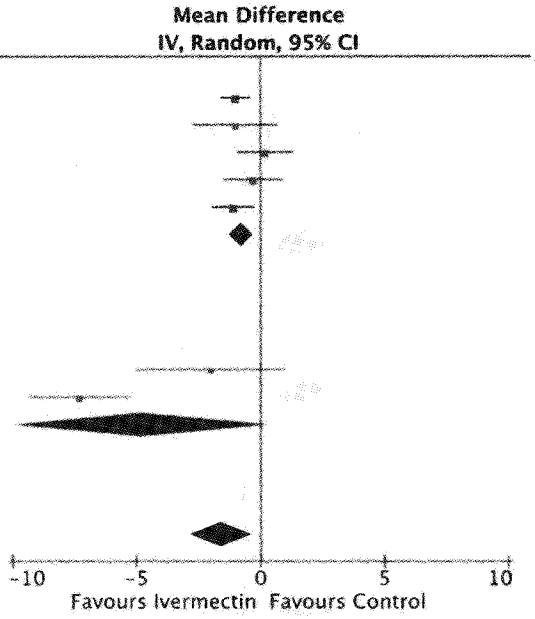


Figure 1D

1D)

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
2.1.1 Multi-day Dosing						
Argentina Chahla et al	108	110	124	144	19.4%	1.14 [1.06, 1.22]
Bangladesh Chachar et al	16	25	15	25	6.6%	1.07 [0.69, 1.65]
Bulgaria Petkov et al	10	50	7	50	2.1%	1.43 [0.59, 3.45]
Colombia Lopez-Medina et al	164	200	156	198	18.5%	1.04 [0.94, 1.15]
Egypt Elgazzar Moderate	99	100	74	100	17.7%	1.34 [1.19, 1.51]
Egypt Elgazzar Severe	94	100	50	100	14.1%	1.88 [1.54, 2.30]
Turkey Okumus et al	22	30	16	30	7.4%	1.38 [0.92, 2.05]
Subtotal (95% CI)		**615**		**647**	**85.9%**	**1.28 [1.10, 1.48]**
Total events	513		442			
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 33.03$, df = 6 ($P < 0.0001$); $I^2 = 82\%$						
Test for overall effect: Z = 3.17 (P = 0.002)						
2.1.2 Single-day dosing						
Bangladesh Mahmud et al	111	183	80	180	14.1%	1.36 [1.12, 1.67]
Subtotal (95% CI)		**183**		**180**	**14.1%**	**1.36 [1.12, 1.67]**
Total events	111		80			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.04 (P = 0.002)						
Total (95% CI)		**798**		**827**	**100.0%**	**1.29 [1.12, 1.47]**
Total events	624		522			
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 34.88$, df = 7 ($P < 0.0001$); $I^2 = 80\%$						
Test for overall effect: Z = 3.65 (P = 0.0003)						
Test for subgroup differences: $Chi^2 = 0.27$, df = 1 ($P = 0.60$), $I^2 = 0\%$						

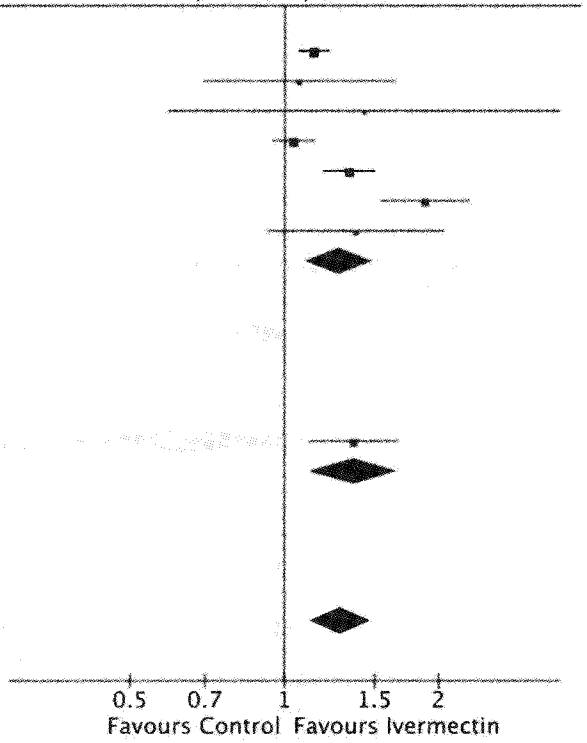


Figure 1E

1E)

Study or Subgroup	Ivermectin Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
6.2.1 Multi-day dosing								
Ahmed et al IVM 5days	9.6	5	24	9.7	4	24	16.2%	-0.10 [-2.66, 2.46]
Egypt Abd-Elsalam et al	8.8	4.9	82	10.97	5.2	82	16.8%	-2.17 [-3.72, -0.62]
Egypt Elgazzar Moderate	5	1	100	15	8	100	16.8%	-10.00 [-11.58, -8.42]
Egypt Elgazzar Severe	6	1	100	18	8	100	16.8%	-12.00 [-13.58, -10.42]
Subtotal (95% CI)			**306**			**306**	**66.7%**	**-6.12 [-11.57, -0.67]**
Heterogeneity: Tau^2 = 30.04; Chi^2 = 117.60, df = 3 (P < 0.00001); I^2 = 97%								
Test for overall effect: Z = 2.20 (P = 0.03)								
6.2.2 Single-day dosing								
Ahmed et al IVM+Doxy	10.1	4	24	9.7	4	24	16.4%	0.40 [-1.86, 2.66]
Iran Rezai et al	6.9	3.1	34	8.4	3.3	35	16.9%	-1.50 [-3.01, 0.01]
Subtotal (95% CI)			**58**			**59**	**33.3%**	**-0.74 [-2.57, 1.08]**
Heterogeneity: Tau^2 = 0.84; Chi^2 = 1.87, df = 1 (P = 0.17); I^2 = 47%								
Test for overall effect: Z = 0.80 (P = 0.42)								
Total (95% CI)			**364**			**365**	**100.0%**	**-4.27 [-8.60, 0.06]**
Heterogeneity: Tau^2 = 28.42; Chi^2 = 183.11, df = 5 (P < 0.00001); I^2 = 97%								
Test for overall effect: Z = 1.93 (P = 0.05)								
Test for subgroup differences: Chi^2 = 3.36, df = 1 (P = 0.07), I^2 = 70.2%								

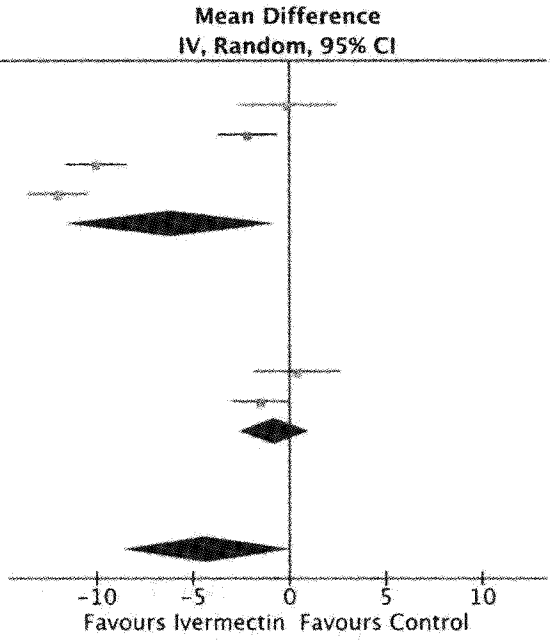


Figure 1F

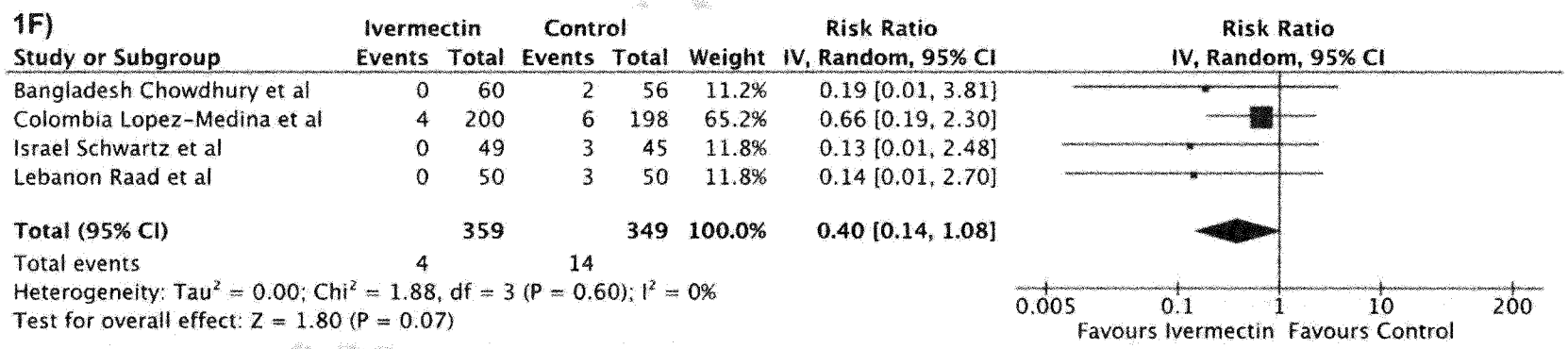


Figure 1G

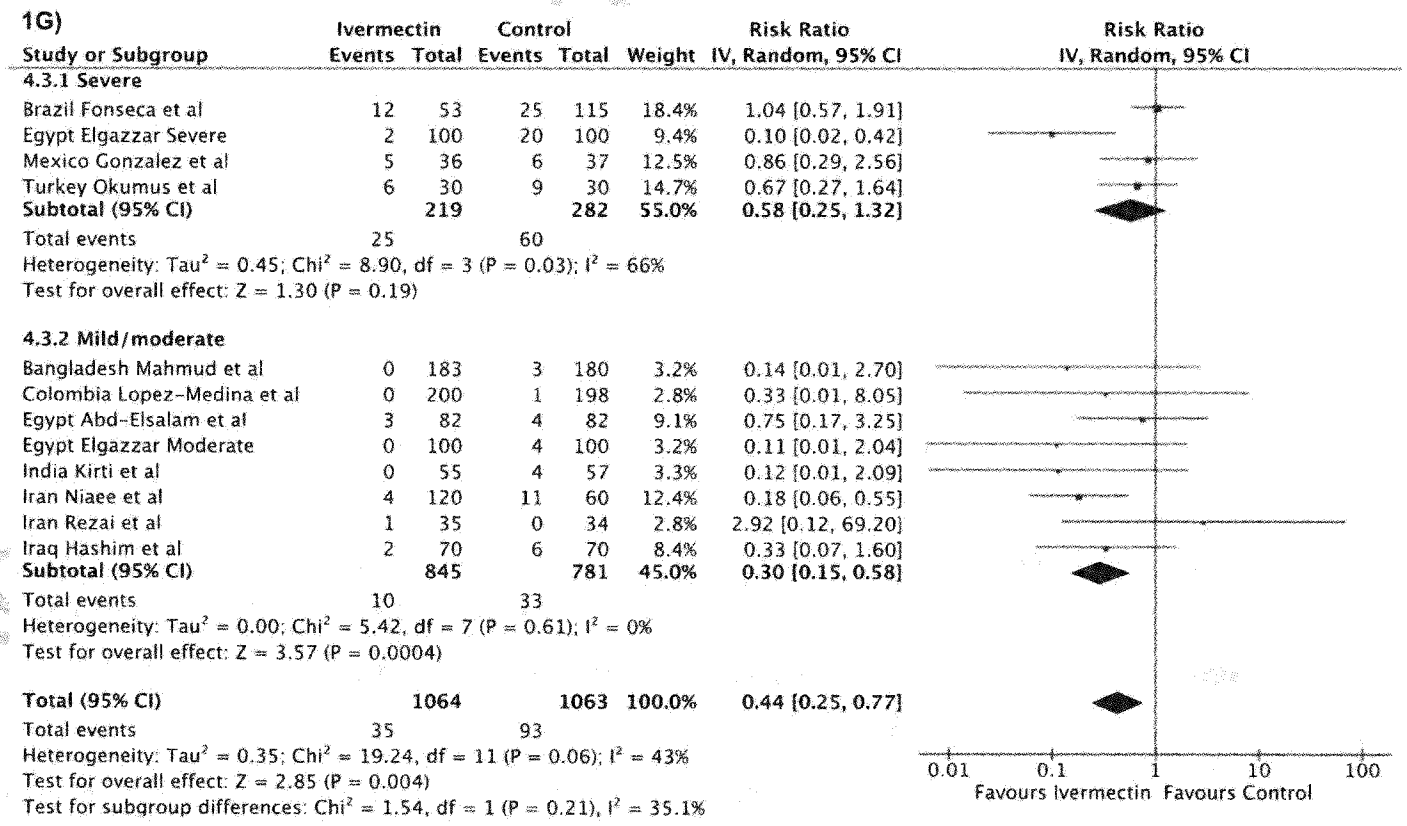


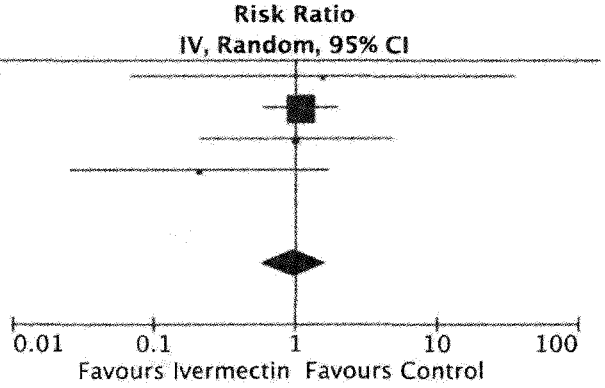
Figure 1H

1H)

Study or Subgroup	Ivermectin Events	Ivermectin Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Argentina Krolewiecki et al	1	30	0	15	3.0%	1.55 [0.07, 35.89]
Brazil Fonseca et al	12	53	24	115	78.5%	1.08 [0.59, 2.00]
Egypt Abd-Elsalam et al	3	82	3	82	11.9%	1.00 [0.21, 4.81]
India Kirti et al	1	55	5	57	6.6%	0.21 [0.03, 1.72]
India Mohan et al	0	100	0	52		Not estimable
Total (95% CI)		**320**		**321**	**100.0%**	**0.97 [0.57, 1.67]**
Total events	17		32			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.26$, df = 3 ($P = 0.52$); $I^2 = 0\%$

Test for overall effect: $Z = 0.10$ ($P = 0.92$)



RODRIGO URZAGASTI/REUTERS/ALAMY

People in Bolivia and elsewhere have been buying ivermectin as protection against COVID-19.

FLAWED PREPRINT HIGHLIGHTS CHALLENGES OF COVID DRUG STUDIES

Paper's withdrawal from online platform deals blow to an anti-parasite drug's promise to treat COVID-19.

By Sara Reardon

Throughout the pandemic, the anti-parasite drug ivermectin has attracted much attention, particularly in Latin America, as a potential way to treat COVID-19. But scientists say that recent, shocking revelations of widespread flaws in the data of a preprint study reporting that the medication greatly reduces COVID-19 deaths have dampened ivermectin's promise – and highlight the challenges of investigating drug efficacy during a pandemic.

"I was shocked, as everyone in the scientific community probably were," says Eduardo López-Medina, a paediatrician at the Centre for the Study of Paediatric Infections in Cali, Colombia, who was not involved with the study and who has investigated whether ivermectin can improve COVID-19 symptoms. "It was one of the first papers that led everyone to get into the idea ivermectin worked" in a clinical-trial setting, he adds.

The paper summarized the results of a clinical trial seeming to show that ivermectin can reduce COVID-19 death rates by more than 90% (ref. 1) – among the largest studies of the drug's ability to treat COVID-19 so far. But on 14 July, after Internet sleuths raised concerns about plagiarism and data manipulation, the preprint server Research Square withdrew the paper because of "ethical concerns".

Ahmed Elgazzar at Benha University in Egypt, who is one of the authors of the paper, told *Nature* he was not given a chance to defend his work before it was removed.

Early in the pandemic, scientists showed that ivermectin could inhibit the coronavirus SARS-CoV-2 in cells in laboratory studies[2]. But data on ivermectin's efficacy against COVID-19 in people are still scarce, and study conclusions conflict greatly, making the withdrawal of a major trial particularly noteworthy.

Although the World Health Organization advises against taking ivermectin as a COVID-19 treatment outside clinical trials, the over-the-counter drug has become popular in some regions of the world. Some view it as a stop-gap until vaccines become available in their areas, even though it has not yet been proved effective. Scientists worry that it will also be seen as an alternative to vaccines, which are highly effective.

The paper's irregularities came to light when Jack Lawrence, a master's student at the University of London, was reading it for a class assignment and noticed that some phrases were identical to those in other published work. When he contacted researchers who specialize in detecting fraud in scientific publications, the group found other causes for concern, including dozens of patient records that seemed to be duplicates, inconsistencies between the raw data and the information in the paper, patients whose records indicate they died before the study's start date, and numbers that seemed to be too consistent to have occurred by chance.

In an editorial note, Research Square said that it has launched a formal investigation into the concerns raised by Lawrence and his colleagues. According to the Egyptian newspaper *Al-Shorouk*, Egypt's minister of higher education and scientific research is also examining the allegations.

The paper was "withdrawn from the Research Square platform without informing or asking me", Elgazzar wrote in an e-mail to *Nature*. He defended the paper, and said of the plagiarism allegations that "often phrases or sentences are commonly used and referenced" when researchers read one another's papers.

Ripple effects

Although dozens of ivermectin clinical trials have been launched over the past year[3], the Elgazzar paper was notable for announcing one of the first positive results, as well as for its size – it included 400 people with symptoms of COVID-19 – and the magnitude of the drug's effect. Few therapies can claim such an impressive reduction in death rates. "It was a significant difference, and that stood out," says Andrew Hill, who studies repurposed drugs at the University of Liverpool, UK. "It should have raised red flags even then."

Before its withdrawal, the paper was viewed more than 150,000 times, cited more than 30 times and included in a number of meta-analyses that collect trial findings into a single, statistically weighted result. In one meta-analysis in the *American Journal of Therapeutics* that found ivermectin greatly reduced COVID-19 deaths[4], the Elgazzar paper accounted for 15.5% of the effect.

One of the authors of the meta-analysis, statistician Andrew Bryant at Newcastle University, UK, says that his team corresponded with Elgazzar before publishing the work to clarify some data. "We had no reason to doubt the integrity of Elgazzar," he said in an e-mail. He added that in a pandemic setting, no one can reanalyse all of the raw data from patient records when writing a review. Bryant went on to say that his group will revise the conclusion if investigations find the study to be unreliable. However, even if the study is removed, the meta-analysis would still show that ivermectin causes a major reduction in deaths from COVID-19, he says.

The paper's withdrawal is not the first scandal to dog studies of ivermectin and COVID-19. Hill thinks many of the other ivermectin trial

papers that he has scanned are likely to be flawed or statistically biased. Many rely on small sample sizes or were not randomized or well controlled, he says. And in 2020, an observational study of the drug was withdrawn after scientists raised concerns about it and a few other papers using data by the company Surgisphere in Chicago, Illinois, that investigated a range of repurposed drugs against COVID-19. "We've seen a pattern of people releasing information that's not reliable," says Hill. "It's hard enough to do work on COVID and treatment without people distorting databases."

Carlos Chaccour, a global-health researcher at the Barcelona Institute for Global Health in Spain, says it has been difficult to conduct rigorous studies on ivermectin. That's partly because funders and academics in wealthy countries haven't supported them, and, he suspects, have often dismissed trials of ivermectin because most of them have been done in lower-income countries. Furthermore, says Rodrigo Zoni, a cardiologist at the Corrientes Cardiology Institute in Argentina, it is difficult to recruit participants because many people — particularly in Latin America — are already taking the widely available drug in an attempt to prevent COVID-19.

Adding to the difficulty are conspiracy theories holding that ivermectin has been proved to work and that drug companies are depriving the public of a cheap cure. Chaccour says he has been called 'genocidal' for doing research on the drug rather than just endorsing it.

Although the jury is still out on ivermectin, many say the retraction speaks to the difficulty of assessing research during a pandemic. "I personally have lost all faith in the results of [ivermectin] trials published to date," says Gideon Meyerowitz-Katz, an epidemiologist at the University of Wollongong in Australia who helped Lawrence to analyse the Elgazzar paper. It's not yet possible to assess whether ivermectin works against COVID-19, because the data currently available are not of sufficiently high quality, he says.

Chaccour and others studying ivermectin say that proof of whether the drug is effective against COVID-19 rests on a handful of large, ongoing studies, including a trial in Brazil with more than 3,500 participants. By the end of 2021, says Zoni, around 33,000 people will have participated in some kind of ivermectin trial.

"I think it is our duty to exhaust all potential benefits," says Chaccour, particularly given that most countries still do not have widespread access to vaccines. "Ultimately if you do a trial and it fails, fine, but at least we tried."

1. Elgazzar, A. *et al.* Preprint at Research Square https://doi.org/10.21203/rs.3.rs-100956/v3 (2020).
2. Caly, L., Druce, J. D., Catton, M. G., Jans, D. A. & Wagstaff, K. M. *Antiviral Res.* **178**, 104787 (2020).
3. Popp, M. *et al. Cochrane Data. System. Rev.* https://doi.org/10.1002/14651858.CD015017.pub2 (2021).
4. Bryant, A. *et al. Am. J. Ther.* **28**, e434–e460 (2021).

BIDEN URGED TO BLOCK POLITICAL MEDDLING IN US SCIENCE

White House science office expected to deliver a review of scientific-integrity policies next month.

By Nidhi Subbaraman

US researchers and science groups appealed to President Joe Biden's administration last month to protect government science from political interference and to empower federal scientists to speak to the media and public. They made this request during public listening sessions hosted by the White House Office of Science and Technology Policy (OSTP) — the first such sessions held since the science office kicked off a massive project to bolster scientific integrity in the federal government.

After four years in which former president Donald Trump's administration sidelined science and scientists in government decisions, researchers were hopeful that Biden would safeguard independent scientific work and communication. In January, he made moves in this direction when he instructed the OSTP to review rules at all US agencies, with the goal of ensuring the existence of policies that "ban improper political interference in the conduct of scientific research". The OSTP convened a task force in May, comprising nearly 50 representatives from several US agencies, to tackle the issue. The group has so far met in closed-door sessions and with scientific-integrity experts.

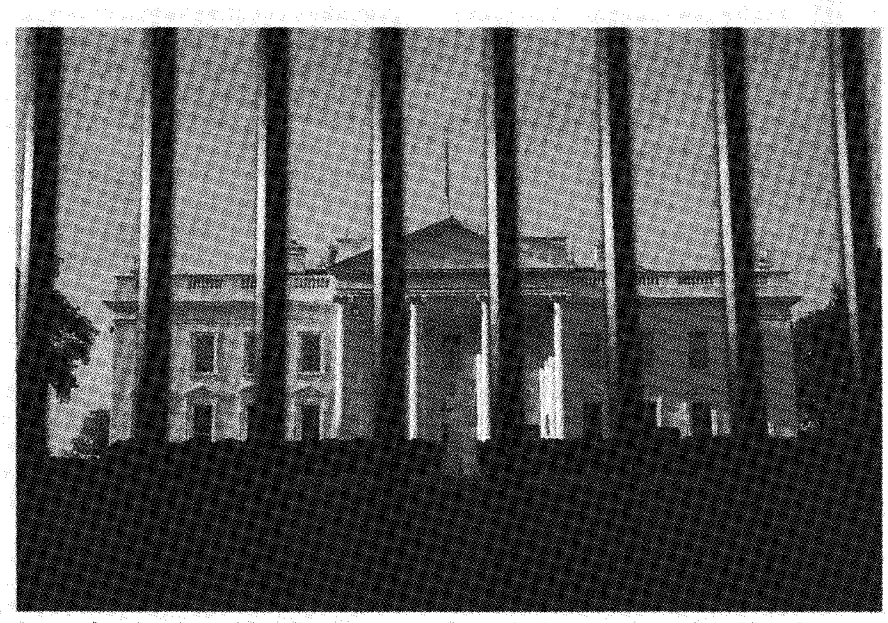
"This level of engagement has not really happened before in the federal government around the issue of scientific integrity," says Alondra Nelson, the OSTP's deputy director for science and society, who co-chairs the task force.

The current effort expands on a push to protect scientific integrity that former president Barack Obama began a decade ago. Policies at US science agencies were the focus of that OSTP-led drive, Nelson tells *Nature*, but Biden's project further aims to guide the use of evidence at all government agencies.

Speaking up

During three public listening sessions in July, attendees urged government agencies to be transparent about how science is used in policy and regulation, and recommended that scientists be enabled to pursue their work without political interference — and be free to speak about it.

Andrew Rosenberg, director of the Center for Science and Democracy at the Union of



STEFANI REYNOLDS/BLOOMBERG VIA GETTY

Researchers have urged the White House to safeguard science against political interference.