IN THE BUTLER COUNTY COMMON PLEAS COURT
CIVIL DIVISION

JULIE SMITH, as guardian of JEFFREY SMITH, 3907 Charfield Lane Hamilton, OH 45011	:	
	:	CASE NO.
Plaintiff,	:	
-vs-	:	
	:	JUDGE:
WEST CHESTER HOSPITAL, LLC DBA WEST CHESTER HOSPITAL C/O GH&R Business Services, Inc. 312 Walnut Street, Suite 1800 Cincinnati, OH 45202	:	
Defendant.	:	

COMPLAINT FOR EMERGENCY MEDICAL DECLARATORY JUDGMENT AND EMERGENCY INJUNCTIVE RELIEF
ORAL ARGUMENT REQUESTED

The Plaintiff, as Guardian of Jeffrey Smith, by and through undersigned counsel, states the following for this Complaint for Emergency Medical Declaratory Judgment and Emergency Injunctive Relief.

I. INTRODUCTION

1. This is a civil action for Emergency Declaratory and Injunctive Relief brought by the Plaintiff, JULIE SMITH, who is the wife and guardian of, JEFFREY SMITH ("Jeffrey"); who is currently a patient in the Intensive Care Unit at West Chester Hospital, LLC, an Ohio nonprofit limited liability company, dba West Chester Hospital, aka UC Health West Chester Hospital; and

who is diagnosed with COVID-19 and intubated.

2. Ms. Smith seeks a declaration that the Defendant honor her decision of treatment as guardian pursuant to Dr. Fred Wagshul's medical order and prescription, requiring the Defendant to administer Ivermectin to Jeffrey, and a declaration that the Defendant comply with Dr. Wagshul's medical orders for further prescriptions for Jeffrey in his battle with Covid-19.

3. Ms. Smith additionally seeks an order for such other, further and different relief as the Court deems just, equitable and proper.

II. JURISDICTION AND VENUE

4. This Court has personal jurisdiction over the Defendant in that Defendant resides and/or transacts or transacted business in the State of Ohio and in Butler County.

5. Venue is proper in this Court pursuant to Ohio Civ.R. 3(C)(3) in that substantially all of the events that give rise to the claims in this action occurred in Butler County.

6. Ms. Smith is not seeking monetary or compensatory damages as her cause of action simply relates to the enforcement of her guardianship decision of a reasonable course of treatment for Jeffrey and the enforcement of his physician's order and prescription; this Court has subject matter jurisdiction over this matter and the parties.

III. PARTIES

7. The Plaintiff, Julie Smith, is a citizen of the Unites States of America, a resident of the State of Ohio, is over the age of 18, and is a resident of Butler County; Ms. Smith is her husband's, Jeffrey Smith's, guardian, and therefore has standing to bring this Complaint.

8. The Defendant is a non-profit limited liability company in good standing and duly registered with the Ohio Secretary of State with an address of 7700 University Drive, West Chester

Township, OH 45069.

9. The Defendant is the physical hospital where Jeffrey is a patient in the Intensive Care Unit, diagnosed with COVID-19, breathing only with the assistance of a ventilator.

IV. STATEMENT OF FACTS

10. On July 9, 2021, Jeffrey tested positive for Covid-19.

11. On July 15, 2021, after excessively coughing and his oxygen saturation dropping dangerously low, Jeffrey was admitted to the Defendant's hospital.

12. That same day, he was moved into the ICU and placed on a nasal cannula during the day and a BiPAP at night.

13. The Defendant treated Jeffrey with its Covid-19 protocol, which consisted of Remdesivir, plasma, and steroids.

14. On July 27, 2021, and after a period of relative stability, Jeffrey's condition began to decline; his oxygen level was dropping and he was unstable.

15. From July 28, 2021 through July 31, 2021, the Defendant proned Jeffrey all night and flipped him to his back during the day.

16. Jeffrey's condition continued to decline.

17. On August 1, 2021, Jeffrey was sedated, intubated, and placed on a ventilator.

18. On August 3, 2021, there was a Code Blue: the Defendant allowed the sedation drug to completely run out, causing Jeffrey to awaken, rip the air tube out of his esophagus, disturbing and/or breaking the feeding tube, which caused food particles and toxins to escape into his lungs; this caused him to aspirate.

19. After the Code Blue, Jeffrey suffered infection after infection and continues to suffer from infections as a result of the aspiration.

20. As of August 19, 2021, the ventilator is at 80%, and he is suffering from another infection.

21. As a 51 year old male, on a ventilator, Jeffrey's chances of survival have dropped to less than 30%.

22. At this point, the Defendant has exhausted its course of treatment and COVID-19 protocol in treating Jeffrey, which is unacceptable to Ms. Smith.

23. Ms. Smith investigated other forms of treatment for COVID-19.

24. Ms. Smith requested that the Defendant administer Ivermectin pursuant to its dosage schedule.

25. The Defendant refused to administer Ivermectin despite its minimal downside and side effects.

26. Ms. Smith offered to sign a release, releasing the Defendant, its agents, assigns, any third parties acting on its behalf, and any doctors acting on its behalf, from any and all liability in administering the Ivermectin to her husband.

27. Despite the aforementioned, the Defendant refused and is unwilling to administer the Ivermectin to Jeffrey.

28. As of August 19, 2021, Jeffrey has been on a ventilator for 19 days; he is on death's doorstep; there is no further COVID-19 treatment protocol for the Defendant to offer to Jeffrey; Ms. Smith does not want to see her husband die, and she is doing everything she can to give him a chance.

29. Ms. Smith sought the medical advice of Dr. Waghsul with regard to her husband's prior medical history, current medical condition, and the usage of Ivermectin in treating Covid-19 and its after effects.

30. Dr. Wagshul is one of the foremost experts on using Ivermectin in treating Covid-19 and a founding member of the Frontline Covid-19 Critical Care Alliance; he supports the use of Ivermectin to treat Jeffrey, and prescribed Ivermectin to him.

31. The Defendant refuses comply with Dr. Wagshul's medical order and prescription to

administer Ivermectin to Jeffrey.

32. Ms. Smith seeks a declaratory judgment declaring that the Defendant follow Dr. Wagshul's order and prescription to administer Ivermectin to their mutual patient, Jeffrey Smith; and a declaration that the Defendant comply with the guardian's reasonable wishes and directives for her husband. Ms. Smith has no other option but to bring the instant declaratory judgment civil action.

V. CAUSE OF ACTION

As and for a Cause of Action Against the Defendant,
Ms. Smith alleges as follows:

33. Repeats and realleges each and every allegation previously made as if restated herein.

34. Ms. Smith is the legal guardian of her husband, Jeffrey Smith.

35. Jeffrey is a patient at the Defendant's hospital with very little chance of survival.

36. Jeffrey has been diagnosed with COVID-19 and is currently in the Intensive Care Unit at the Defendant's hospital; he is only breathing with the assistance of a ventilator.

37. Despite requesting that the Defendant administer Ivermectin to Jeffrey, and despite Dr. Wagshul's order and prescription, the Defendant has refused and is unwilling to do so.

38. Despite Ms. Smith's offer to sign a full release, releasing and relieving the Defendant from any and all liability concerning the administration of Ivermectin to her husband, the Defendant has refused and is unwilling to do so.

39. Despite the Defendant exhausting its Covid-19 protocol with nothing left to treat Jeffrey, the Defendant refuses to administer Ivermectin to Jeffrey based on upon Dr. Wagshul's order and prescription.

40. As a result of the Defendant's refusal to administer Ivermectin to Jeffrey pursuant to Dr. Wagshul's order and prescription, Jeffrey, through Ms. Smith, has been damaged.

41. Ms. Smith does not have an adequate remedy at law to enforce her guardianship wishes for her husband and Dr. Wagshul's order and prescription.

42. Ms. Smith has not made any prior applications for the relief requested herein.

43. It is Ms. Smith's belief that she has made out a cause of action for declaratory judgment.

VI. RELIEF SOUGHT

Based on the facts and the law, Ms. Smith is entitled to a declaratory judgment from this Court (A) declaring and enforcing her guardianship decision for reasonable treatment for her husband; and (B) declaring and enforcing Dr. Wagshul's order and prescription to administer Ivermectin to Jeffrey Smith.

Ms. Smith respectfully requests that this Court enter an order declaring that the Defendant comply with (1) her reasonable requests as Jeffrey's guardian; and (2) Dr. Wagshul's order and prescription to administer Ivermectin to Jeffrey Smith.

WHEREFORE, Ms. Smith respectfully requests that this Court Order the following:

(A) Enter a judgment in favor of Ms. Smith on the Complaint in its entirety and against the Defendant;

(B) Enter a judgment in favor of Ms. Smith, declaring that the Defendant comply with Dr. Wagshul's order and prescription to administer Ivermectin to their Jeffrey Smith;

(C) Award Ms. Smith all relief allowed by law and equity, including, but not limited to, declaratory, preliminary and permanent injunctive relief; and

(D) A judgment granting Ms. Smith such other, further and different relief that the Court deems just, equitable and proper.

Respectfully submitted,

/s/ Jonathan Davidson, Esq.
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2 S. Third St., Suite 301
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/s/ Jeffrey G. Stagnaro, Esq.
Jeffrey G. Stagnaro
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7373 Beechmont Avenue
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jgs@sspfirm.com

and

/s/ Ralph C. Lorigo, Esq.
Ralph C. Lorigo, Esq. (*Pro Hac Vice* Pending)
LAW OFFICE OF RALPH C. LORIGO
101 Slade Avenue
West Seneca, NY 14224
(716) 824-7200
rlorigo@lorigo.com

Counsel for Plaintiff
Julie Smith, Guardian of Jeffrey Smith

CERTIFICATE OF SERVICE

The undersigned hereby certifies that on this _____ day of August, 2021, a copy of the foregoing was filed with the Clerk of Courts by using the ECF System, which will send a notice of electronic filing to all parties indicated on the electronic filing receipt, pursuant to Civ.R. 5(B)(2)(f). All other parties will be served by regular US Mail, postage prepaid pursuant to Civ.R. 5(B)(2)(c):

West Chester Hospital, LLC
dba West Chester Hospital
7700 University Drive
West Chester Township, OH 45069

C/O Registered Agent
GH&R Business Services, Inc.
312 Walnut Street
Suite 1800
Cincinnati, Ohio 45202

/s/ Jonathan Davidson, Esq.
Attorney for Julie Smith
Supreme Court No.: 0090093

and

/s/ Ralph C. Lorigo, Esq.
Ralph C. Lorigo, Esq. (*Pro Hac Vice* Pending)

Counsel for Plaintiff

IN THE BUTLER COUNTY COMMON PLEAS COURT
CIVIL DIVISION

JULIE SMITH, as guardian of JEFFREY SMITH,	:	
	:	CASE NO.
Plaintiff,	:	
-vs-	:	
	:	JUDGE:
WEST CHESTER HOSPITAL, LLC DBA WEST CHESTER HOSPITAL	:	
Defendant.	:	

AFFIDAVIT OF JULIE SMITH IN SUPPORT OF HER MOTION SEEKING EMERGENCY AND INJUCTIVE RELIEF

Julie Smith, having first been duly sworn, deposes and says as follows:

1. I am the guardian of my husband, Jeffrey Smith; this action is brought on his behalf in my capacity as his guardian; attached hereto as Exhibit "A" is the Order, appointing me guardian over my husband, Jeffrey Smith.

2. I am fully familiar with all of the facts and circumstances of this Motion; my knowledge is based upon (A) my personal knowledge; (B) my authority as guardian of my husband; and (C) my review of the documents relevant to this Motion.

3. I make this Affidavit in support of my Motion seeking an Order, compelling West Chester Hospital, LLC, dba West Chester Hospital, its agents, assigns, or any third party acting on its behalf to comply with my husband's physician's order and prescription to administer Ivermectin to him.

4. For the reasons set forth herein, it is respectfully submitted that this Motion should

be granted in its entirety.

5. Jeffrey and I have been married for 24 years.

6. He is a 51 year old healthy family man; he is a Verizon Wireless Network Engineer.

7. Jeffrey and I have three children; he loves his children more than anything.

8. He enjoys fishing, hiking, and camping with our family.

9. He participates in Trail Life with our son.

10. He is faithful and loyal to a fault.

11. Family is his everything; attached as Exhibit "B" is a recent picture of Jeffrey before being admitted to the Defendant's hospital.

12. On July 9, 2021, Jeffrey tested positive for Covid-19.

13. On July 15, 2021, after excessively coughing and his oxygen saturation dropping dangerously low, Jeffrey was admitted to the Defendant's hospital.

14. That same day, he was moved into the ICU and placed on a nasal cannula during the day and a BiPAP at night.

15. The Defendant treated Jeffrey with their Covid-19 protocol, which consisted of Remdesivir, plasma, and steroids.

16. On July 27, 2021, and after a period of relative stability, Jeffrey's condition began to decline; his oxygen level was dropping and was unstable.

17. From July 28, 2021 through July 31, 2021, the Defendant proned Jeffrey all night and flipped him to his back during the day.

18. Jeffrey's condition continued to decline.

19. On August 1, 2021, Jeffrey was sedated, intubated, and placed on a ventilator.

20. On August 3, 2021, there was a Code Blue: the Defendant failed to refill the

sedation drug and it completely depleted, causing Jeffrey to awaken, rip the air tube out of his esophagus, disturb and/or break the feeding tube, which caused food particles and toxins to escape into his lungs; this caused him to aspirate.

21. After the Code Blue, Jeffrey suffered infection after infection and continues to suffer from infections as a result of the aspiration.

22. As of August 19, 2021, the ventilator continues to hover at or about 80%, and he continues to suffer from infections.

23. Since August 1, 2021 and now for 19 days, Jeffrey has been on a ventilator in a medically induced coma, aspirated, and suffered from numerous infections; he continues to suffer and decline.

24. The Defendant has exhausted their Covid-19 treatment protocol; in other words, the Defendant has no further treatment options for Jeffrey, and his situation is truly "wait and see".

25. As a 51 year old male placed on a ventilator, Jeffrey's chances of survival have dropped to less than 30%.

26. At this point, there is nothing more the Defendant can do, or will do, for my husband.

27. However, I cannot give up on him, even if the Defendant has. There is no reason why the Defendant cannot approve or authorize other forms of treatment so long as the benefits outweigh the risks.

28. Running out of options, I began researching other Covid-19 treatment options.

29. In my research, I came across an article in the Chicago Tribune about a woman who was 68 years old, Covid-19 positive, in the ICU, and on a ventilator; like my husband, she was on death's doorstep. (Exhibit "C").

30. After being admitted to Elmhurst Hospital for Covid-19, Ms. Nurije's condition rapidly, and consistently deteriorated. (Exhibit "C").

31. Like myself, Ms. Nurije's daughter would not accept her mother's fate by the hospital's refusal to seek other treatment options.

32. Her mother's primary care physician agreed to prescribe Ivermectin, and Ms. Nurije's daughter offered to sign a release and waiver, relinquishing the hospital of any liability. Yet they adamantly refused to administer Ivermectin to Ms. Nurije. (Exhibit "D").

33. Ms. Nurije's daughter then obtained an Order from DuPage County Judge James D. Orel, enforcing Dr. Crevier's order to administer Ivermectin to Ms. Nurije. (Exhibit "E").

34. After Ms. Nurije was administered her first dose of Ivermectin, the ventilator was reduced from 75% to 65%; this was the first sign of improvement in Ms. Nurije's condition since she was admitted over twenty days prior. (Exhibit "F").

35. Ms. Nurije is now out of the hospital and home.

36. Elmhurst Hospital appealed Judge Orel's Order and the Appellate Court recently dismissed the appeal in its entirety, but more importantly, upheld Judge Orel's original order.

37. I also came across an article in the Buffalo News about a woman who was 80 years old, Covid-19 positive, in the ICU, and on a ventilator; like my husband, she was on death's doorstep. (Exhibit "G").

38. Her children convinced the ICU doctor to administer Ivermectin as a Hail Mary attempt to save her life; within 48 hours after the first dosage, she was transferred out of the ICU and taken off the ventilator. (Exhibit "G").

39. However, once on the general Covid-19 floor and with different doctors, they refused to continue with the remaining doses of Ivermectin; the family ended up obtaining a Court

Order from a New York State Supreme Court Justice, enforcing the primary care physician's order to continue the doses of Ivermectin, and within two weeks, she was released from the hospital. (Exhibit "G").

40. New York State Supreme Court Justice Henry Nowak's Order is attached hereto as Exhibit "H".

41. I also discovered the story of Glenna Dickinson. (Exhibit "I").

42. Ms. Dickinson's story is similar to so many suffering from Covid-19; she was placed in the ICU and on a ventilator; she was on death's doorstep. (Exhibit "I").

43. Ms. Dickinson's physician prescribed Ivermectin for her, but Rochester General Hospital refused to administrate it. (Exhibit "I").

44. The family obtained an Order from Supreme Court Justice Frank Caruso, Ordering Rochester General to comply with the physician's order and administer Ivermectin. (Exhibit "J").

45. I continued to research Ivermectin, its use, and effect in treating Covid-19.

46. My research led me to the Front Line Covid-19 Critical Care Alliance ("FLCCC"), which is headed by Doctor Pierre Kory, a lung and ICU specialist.

47. On December 8, 2020, Dr. Kory testified before Congress regarding his findings on the use and success of Ivermectin in treating Covid-19, which can be found at https://vimeo.com/490351508. (Exhibit "K").

48. My research also led me to the latest attached medical articles and studies regarding Ivermectin. (Exhibit "L").

49. The Broward County Study attached in Exhibit "L" is study of more than 200 severe Covid-19 patients, like my husband; in that study, of those who did not receive Ivermectin, 80% died; of those that received Ivermectin, only 30% died. (Exhibit "L").

50. After conducting all of the research, I requested, numerous times, that the Defendant, give my husband a chance and prescribe him Ivermectin.

51. The doctors and administration at the Defendant's hospital refused.

52. I offered to sign a release and waiver, relinquishing the Defendant of any liability if it administered Ivermectin to my husband; however, the doctors and administration refused.

53. My husband's physician, Dr. Fred Wagshul, MD, a pulmonologist, and expert on using Ivermectin in treating Covid-19, prescribed Ivermectin for my husband; the prescription is attached hereto as Exhibit "M"; however, the Defendant will not administer it to my husband.

54. Dr. Wagshul is aware of my husband's past and current medical condition; Dr. Wagshul would not prescribe Ivermectin if he believed it was unsafe.

55. As set forth in the attached Exhibits, Ivermectin has little to no downside.

56. My husband is on death's doorstep; he has no other options.

57. With absolutely nothing to lose, with little to no risk, and with the Defendant likely to begin palliative care, there is no basis for it to refuse Dr. Wagshul's order and prescription to administer Ivermectin to their mutual patient.

58. It is respectfully submitted that this Court give my husband a fighting chance.

59. It is further respectfully submitted that this Court enforce Dr. Wagshul's order and prescription to administer Ivermectin to my husband.

60. It is further respectfully submitted that this Court grant this Motion in its entirety.

61. For all of the foregoing reasons, it is respectfully requested that the Court enter an Order as follows:

A. An order compelling the Defendant and/or its agents to comply Dr. Wagshul's order and prescription to administer Ivermectin to my husband, their mutual patient;

B. An order granting me such other, further and different relief that the Court deems just, equitable and proper.

Julie Smith
JULIE SMITH

Subscribed and sworn to before
me on this 30th day of Aug, 2021

Notary Public

NOTARIAL SEAL * STATE OF OHIO *
JONATHAN E. DAVIDSON, Attorney at Law
In and for the State of Ohio
My Commission has no expiration date.
Section 147.03 O.R.C.

EXHIBIT "A"

FILED

2021 AUG 19 PM 4:30

BUTLER COUNTY
PROBATE COURT
JUDGE JOHN M. HOLCOMB

PROBATE COURT OF BUTLER COUNTY, OHIO

IN THE MATTER OF GUARDIANSHIP OF Jeffrey D. Smith

Case No. PG21-08-0129

EMERGENCY

LETTERS OF GUARDIANSHIP

[R.C. 2111.02]

(guardian 2)

(guardian 2) Julie Smith is appointed Guardian of

Jeffrey D. Smith, an ☒ Incompetent ☐ Minor.

Guardian's powers are:

All powers conferred by the laws of Ohio and rules of this Court over the ward's:

☐ Person and Estate ☒ Person Only ☐ Estate Only

Limited to authorize or approve the provision to the ward of medical, health, or other professional care, counsel , treatment, or services unless the ward or an interested party files objections with the probate court, or the court, by rule or order, provides otherwise.

Those guardianship powers, until revoked, are for an:

☒ Indefinite time period

☐ Definite time period to

The above-named Guardian has the power conferred by law to do and perform all the duties of Guardian as described. No expenditures shall be made without prior Court authorization.

8/19/21
Date

Probate Judge

NOTICE TO FINANCIAL INSTITUTIONS

Funds being held in the name of the within-named Ward shall not be released to Guardian without a Court order directing release of a specific fund and amounts thereof.

CERTIFICATE OF APPOINTMENT AND INCUMBENCY

The above document is a true copy of the original kept by me as custodian of this Court. It constitutes the appointment and letters of authority of the named guardian, who is qualified and acting in such capacity.

Probate Judge

(SEAL)

by Kathy Pope
Deputy Clerk

August 20, 2021
Date

EXHIBIT "B"


FIGHT THE
GOOD FIGHT
OF FAITH

EXHIBIT "C"

After court order, Elmhurst Hospital says it's allowing COVID-19 patient to receive controversial drug ivermectin

By JOHN KEILMAN
CHICAGO TRIBUNE | MAY 04, 2021

An attorney for Elmhurst Hospital said at a court hearing Tuesday that a patient whose daughter sued to procure a controversial treatment for COVID-19 has begun to receive the medication.

The lawyer, Joseph Monahan, said an outside doctor was granted credentials to work at the hospital so he could administer ivermectin to Nurije Fype, a 68-year-old who has been in intensive care for nearly a month and is on a ventilator. She received her first dose Monday night, according to Ralph Lorigo, one of her attorneys.

Nurije Fype is on a ventilator at Elmhurst Hospitel while battling COVID-19. (Fype family photo)

Monahan said the hospital's own doctors did not want to administer the medication, which is normally used to treat patients suffering from diseases caused by parasitic worms. The Food and Drug Administration has cautioned against its use in COVID-19 cases, saying its safety and efficacy for that application has not been established.

But some researchers and physicians say they have seen good results from the drug, and when Fype's daughter Desareta read a news story about an upstate New York woman who recovered from COVID-19 after receiving ivermectin, she went to court to secure its use for her mother.

DuPage County Judge James Orel ordered Elmhurst Hospital not to stand in the way of Fype receiving the medication. When Fype's own doctor was unable to administer it, Lorigo said, the legal team found another physician who had to travel "1½, 2 hours each way" but was willing to do it.

Lorigo asked the judge to order Elmhurst Hospital to pay that doctor's fees, along with Fype's legal expenses and a $25,000 fine, and to allow a nurse to administer the drug instead of the doctor. Orel declined, saying the hospital had met the conditions of his order.

"The medication is being given," he said. "That's why this whole matter is in front of this court. You have resolved that in this court's mind."

Reached after Tuesday's hearing, Desareta Fype said the drug's effects should show up after 24 to 48 hours. The prescription is supposed to last for 10 days, or until her mother's condition improves sufficiently, and Desareta Fype said she hopes nothing will derail that schedule.

"I'm hoping and praying the ivermectin will continue to be used until she gets better," she said.

jkeilman@chicagotribune.com

EXHIBIT "D"

DuPage County judge orders Elmhurst Hospital to allow COVID-19 patient to receive controversial medication

By JOHN KEILMAN
CHICAGO TRIBUNE | MAY 03, 2021

A DuPage County judge on Monday ordered Elmhurst Hospital to allow a comatose woman suffering from COVID-19 to receive a medication the Food and Drug Administration says could be unsafe, but the legal fight appears bound to escalate.

Nurije Fype, 68, of Elmhurst, has been in intensive care at the hospital since early April and is now on a ventilator, according to testimony at the court hearing. Her daughter, Desareta Fype, is pushing for her mother to receive a medication called ivermectin, normally used to treat diseases caused by parasitic worms.

Nurjie Fype is on a ventilator at Elmhurst Hospital while battling COVID-19. (Fype family photo)

Desareta Fype said in an affidavit she learned about the drug in a news article while researching treatment options for her mother. The **story**, published in the Buffalo News, told of an 80-year-old woman in dire shape from COVID-19 who recovered after her family sued to get her ivermectin.

The FDA, however, has **cautioned** against using ivermectin to treat patients suffering from the virus. It says some people have been hospitalized after self-medicating with a form of the drug intended for horses, and that large doses can be fatal.

Another federal agency, the National Institutes of Health, has taken a more measured **stance**, saying that while the drug is well-tolerated when used for its intended purposes, there isn't enough information to allow a recommendation "for or against" using it to treat COVID-19.

Elmhurst Hospital's attorney, Joseph Monahan, said at the hearing none of its doctors would agree to administer ivermectin for COVID-19, and that an internal ethics panel concluded its use couldn't be justified. He argued that judges shouldn't overrule medical decisions.

"(The court) doesn't have the authority to order a medical corporation to use particular medications, particularly when it's an off-label use, particularly when the federal government has said it could be dangerous," he said.

He suggested Desareta Fype could transfer her mother to another facility where doctors would be willing to use the medication, but Judge James Orel seemed astonished at the suggestion.

"Let me get this right: The hospital is willing to transfer a woman in a coma with COVID?" he said. "Is that what you're telling me?"

Orel pointed to an affidavit from Fype's physician, Dr. William Crevier of Orland Park, in which the doctor said he has used the drug successfully for COVID-19 patients since last year. If Elmhurst Hospital's doctors don't want to use ivermectin, Orel said, they should allow Crevier to administer it.

"Why wouldn't this be tried if she's not improving?" Orel said. "Why does the hospital object to providing this medication? If someone has been in the ICU for a month and not improving, why would the hospital not consider another medication?"

It was still not clear, however, whether the hospital would allow Fype to receive the medication. Orel said he expected the case to head to an appellate court, and when he asked Monahan if the hospital was going to follow his order, the attorney replied, "I will talk to my client."

An Elmhurst Hospital spokesman declined to comment. The parties are due to return to court Tuesday.

Like other purported COVID-19 treatments that have not gotten government approval, ivermectin has been embroiled in controversy. One of its leading proponents, Dr. Pierre Kory, a pulmonary and critical care specialist, testified in favor of the drug before a U.S. Senate committee last year, but he said YouTube later took down the video in which he made his statement, calling it medical misinformation.

That brought a charge of **censorship** from Sen. Ron Johnson, a Wisconsin Republican who is on the panel. YouTube did not respond to a request for comment.

A medical journal also rejected a paper Kory co-wrote with fellow members of a group called the Front Line COVID-19 Critical Care Alliance, which advocates for the medication. The journal's chief executive editor **said** the paper contained "a series of strong, unsupported claims based on studies with insufficient statistical significance."

Another journal later **published** the paper, though, and Kory said ivermectin has proven its worth. He has treated upward of 200 COVID-19 patients with the drug and seen "dramatic" results, he said, and colleagues around the world have reported similar findings.

He said government agencies that don't approve the drug's use against COVID-19 "are not keeping up with the data. The data have done nothing but deepen and become more consistent."

The FDA did not respond to the Tribune's request for comment by press time.

Clinical trials involving the medication are underway, and in court papers, the hospital said the judge's decision to order the use of ivermectin was "hurried and unfair" and should have waited for evidence to be presented. But Orel said given Fype's condition, his decision had to be speedy.

"If I wait for an evidentiary hearing, she might not be around," he said.

jkeilman@chicagotribune.com

Twitter @JohnKeilman

EXHIBIT "E"

GUARDIANSHIP ORDER

2021P000542-33

STATE OF ILLINOIS

UNITED STATES OF AMERICA

COUNTY OF DU PAGE

IN THE CIRCUIT COURT OF THE EIGHTEENTH JUDICIAL CIRCUIT

ESTATE OF

NURIJE FYPE

ALLEGED DISABLED PERSON

2021P000542
CASE NUMBER

FILED

21 Apr 30 AM 11: 15

Candice Adams

CLERK OF THE
18TH JUDICIAL CIRCUIT
DUPAGE COUNTY, ILLINOIS

EMERGENCY ORDER

TEMPORARY GUARDIAN FOR DISABLED PERSON

On the verified petition of DESARETA FYPE for an adjudication of disability and the appointment of a guardian for the ☒ person of the above named alleged disabled person, the Court having heard the evidence presented FINDS:

1. The Respondent is:
   - ☒ A disabled person and is totally without understanding or capacity to make or communicate decisions regarding his/her person.
   - ☒ An alleged disabled person and a temporary guardian is necessary for the immediate welfare and protection of the alleged disabled person and his/her state.
2. True factual basis for the finding of the court is as follows per record.
3. No less restrictive means will reasonably protect the assets and/or ensure the safety of the alleged disabled person.

Commentary on Condition. (Optional):
Ward is in a coma and unable to make medical decisions.

ISSUE LETTERS OF OFFICE - IT IS HEREBY ORDERED THAT:

Letters of Office shall issue to: DESARETA FYPE
as ☒ guardian of the person of: NURIJE FYPE

☒ The appointed guardian is exempt from the requirement to complete the guardianship training program under the following good cause: THE GUARDIANSHIP IS TEMPORARY AND FOR MEDICAL DECISION MAKING PURPOSES IN EXIGENT CIRCUMSTANCES.

1. The duration and term of the guardianship shall be:
   ☒ temporary until: further order of court

IT IS ORDERED that this matter is continued to 05/03/2021 at 10:00 AM in court room 2009 for STATUS

Other: Ralph C. Lorigo, licensed attorney in the State of New York is admitted pro hac vice to participate as general counsel in this matter. Appearance to be submitted electronically within 7 days. Elmhurst Hospital and Elmhurst Medical Group are ordered to administer Ivermectin to the ward per prescription of William Crevier, M.D. immediately and as prescribed therafter.

Submitted by: JOHN J PCOLINSKI
DuPage Attorney Number: 313085
Attorney for: DESARETA FYPE
Address: 310 S COUNTY FARM RD, SUITE H
City/State/Zip: WHEATON, IL, 60187
Phone number: 630-665-9033
Email: gkbstaff@gmail.com

Entered: James D Orbel
JUDGE JAMES D ORBL
Validation ID : DP-04302021-1115-0838

Date: 04/30/2021

EXHIBIT "F"

COVID-19 patient shows 'improvement' after receiving ivermectin following legal battle with hospital

By Anthony Ponce | Published May 4 | Coronavirus in Chicago | FOX 32 Chicago

COVID-19 patient shows 'improvement' after receiving ivermectin following court order

After a short but tense legal battle, Edward-Elmhurst Hospital has agreed to allow an outside doctor to administer ivermectin to one of its COVID-19 patients.

ELMHURST - After a short but tense legal battle, Edward-Elmhurst Hospital has agreed to allow an outside doctor to administer ivermectin to one of its COVID-19 patients.

"She looks calm, relaxed, she looks comfortable, so this is all I can tell right now," said Desi Fype, who has been fighting for her mother, 68-year-old Nurije Fype, to receive ivermectin -- an anti-parasitic drug which has not been FDA-approved to treat COVID.

Since Nurije was placed on a ventilator April 28th, and with her condition not improving, Desi has been fighting for Edward-Elmhurst Hospital to allow the drug to be used.

"At the point of me having nothing else to lose, and seeing that no other treatment in the hospital was making her any better, I wanted to try something different. Why not try to save her life instead of seeing her decline?" Desi said.

While ivermectin isn't FDA-approved, some doctors say it's proved to be effective against COVID. Despite a judge's orders, the hospital had been refusing to administer the drug until Monday night, when it agreed to let an outside doctor give Nurije her first dose.

"I was really really excited and hopeful to have this drug administered to my mom as well, because from the day that she was admitted to the hospital, her condition kept only declining," Desi said.

"Today, after her first dose, the ventilator has been reduced from 75 percent to 65 percent," said Fype family attorney Ralph Lorigo. "That's an improvement. Now she will get a dose of ivermectin every day until recovery."

Edward-Elmhurst Hospital has declined to comment on Nurije's treatment, citing privacy regulations.

EXHIBIT "G"

Judith Smentkiewicz, 80, of , was given a 20% chance of surviving Covid-19 when she was on a ventilator at Millard Fillmore Suburban Hospital, according to her children.

Provided by Judith Smentkiewicz's family

Dan Herbeck

judge ordered Millard Fillmore

A Suburban Hospital last week to give a Covid-19 patient an experimental treatment, and her family and attorneys say they believe that saved 80-year-old Judith Smentkiewicz's life.

The drug Ivermectin – a pill sometimes used to treat children with head lice or to rid dogs and cats of worms – is **not yet approved by the federal government for use against Covid-19.** But Smentkiewicz's son and daughter call it "a miracle drug" in their court papers.

So do her attorneys, Ralph C. Lorigo and Jon F. Minear.

"This lady was on a ventilator, literally on her deathbed, before she was given this drug," Lorigo told The Buffalo News about Smentkiewicz, a Cheektowaga resident. "As far as we're concerned, the judge's order saved this woman's life."

Lorigo said one doctor at the hospital allowed the patient to be given the drug, but after she had been given one dose, another doctor at the hospital refused to allow further doses. He said family

members went to court to force the hospital to resume treatment with Ivermectin. State Supreme Court Judge Henry A. Nowak sided with them.

Dr. Thomas A. Russo, one of the region's leading experts on infectious diseases, said he was glad to hear that Smentkiewicz is doing better, but he said people should never jump to conclusions about Ivermectin or any other drug based on one patient's outcome.

"There are some indications that this drug may have some merit in treating Covid-19 ... Yes, it is possible that it helped this woman," Russo said. "But the trials and testing are ongoing. We don't have definitive data yet to show it does help. Presently, it is not recommended as a treatment for Covid-19."

Russo is the chief of infectious diseases at the University at Buffalo's Jacobs School of Medicine and Biomedical Sciences. He has no involvement in the Smentkiewicz case.

The patient's son, Michael Smentkiewicz, said hospital officials had told him and his sister, Michelle Kulbacki, on Dec. 31 that their mother's chance of survival – as an 80-year-old Covid-19 patient on a ventilator – was about 20%.

He said doctors at the hospital also told the family that Smentkiewicz would probably be on a ventilator in the Intensive Care Unit for at least a month.

"We did a lot of our own research, we read about Ivermectin ... The results sounded very promising, and we

decided we had to try something different," Michael Smentkiewicz said. "We pressured the doctor in the ICU to give it to her. He finally agreed."

On Jan. 2, Smentkiewicz was given her first dose of Ivermectin, and according to court papers filed by her family, she made "a complete turnaround."

"In less than 48 hours, my mother was taken off the ventilator, transferred out of the Intensive Care Unit, sitting up on her own and communicating," Kulbacki said in a court affidavit.

But after her mother was transferred to another hospital wing away from the ICU, doctors in that unit refused to give her any more doses of the drug, and her condition quickly declined, the family said in court papers.

"We were astounded when they refused to give her any more doses," Michael Smentkiewicz said. "That's why I called Ralph Lorigo and we took the hospital to court."

Kaleida Health, which operates the hospital, opposed the family's request in court. Lorigo said Kaleida attorney Michael J. Roach argued to Judge Nowak that doctors – and not the courts – should be making decisions about medical care.

On Jan. 8, Nowak ordered the hospital to "immediately administer the drug Ivermectin" to Smentkiewicz, court papers show.

"But the judge also told us verbally that Judith's family doctor would have to write a prescription for Ivermectin, which he did," Lorigo said. "In 46 years as an attorney, I've never seen another case where a family had to get a court order to continue a treatment that had already been started by a hospital."

Michael P. Hughes, spokesman and chief of staff for Kaleida Health, said the health care company is "aware of this family's position," but he declined to discuss details because of federal privacy laws and because the case has become "a legal matter."

Roach, the hospital attorney, declined to comment, telling a reporter to call Hughes.

Michael Smentkiewicz said Thursday that his mother's condition has improved again since the Ivermectin treatments resumed.

"She called me (Wednesday) night. Her voice was raspy, but it was so exciting to hear her voice," he said. "She is sitting up in bed. She's off the ventilator, but she has a canula in her nose, providing supplemental oxygen."

He added that a doctor from the hospital told him Thursday that his mother appears to have "turned the corner" in her fight against the virus.

Michael Smentkiewicz said he also believes the power of prayer helped his mother.

"We have not been able to see her since she was taken to the hospital by ambulance on December 29, and that has been hard on all of us," he said. "Family flew in from all over the country to be here. On New Year's Eve, about eight of us held a little prayer

service for her, out in the hospital parking lot. Even though we couldn't be with her, we felt that it was important to be on that property, praying for her."

Ivermectin has some passionate supporters in the medical field, but the U.S. Food & Drug Administration says the drug has not yet been approved for use in this country as a Covid-19 treatment.

"While there are approved uses for Ivermectin in people and animals, it is not approved for the prevention or treatment of Covid-19," the federal

agency says on its website. "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 ... Additional testing is needed to determine whether Ivermectin might be appropriate to prevent or treat coronavirus or Covid-19."

Some doctors feel the government should move much more quickly to approve Ivermectin as a treatment for the virus that has killed nearly 400,000 Americans.

Dr. Pierre Kory, who heads an association of critical care doctors, testified before Congress in December, asking federal agencies to prevent "needless deaths" by speeding up its testing and research on Ivermectin.

Smentkiewicz's family describes her as an "amazing woman," a retired secretary who raised two children as a single mother. They said she still works five days a week, cleaning houses.

Russo, who urges caution until the government gets more data about Ivermectin, said he "absolutely"

understands why Smentkiewicz's family was so insistent that Kaleida doctors give her the drug.

"I think we all can understand where this family was coming from," Russo said. "From their point of view, desperate times call for desperate measures."

Dan Herbeck
News reporter, Watchdog Team

EXHIBIT "H"

FILED: ERIE COUNTY CLERK 01/08/2021 12:49 PM INDEX NO. 800259/2021
NYSCEF DOC. NO. 11 RECEIVED NYSCEF: 01/08/2021

At an Special Term of the Supreme Court, held in and for the County of Erie Erie in the City of Buffalo, New York, on the 8th day of January 2021.

PRESENT: HON. HENRY J. NOWAK, J.S.C.
Presiding Justice

STATE OF NEW YORK : COUNTY OF ERIE
SUPREME COURT

MICHELLE KULBACKI,

Plaintiff,

v.

KALEIDA HEALTH
KALEIDA HEALTH FOUNDATION,
MILLARD FILLMORE SUBURBAN HOSPITAL,

Defendants.

ORDER TO SHOW CAUSE

Index No.: 800259/2021

Upon reviewing and filing the annexed Affidavit of Michelle Kulbacki and the Exhibits attached thereto, the Plaintiff, Michelle Kulbacki, seeks an Order granting her immediate and emergency relief (A) compelling the Defendants and/or their agents to administer Ivermectin to their patient, Judith Smentkiewicz according to its dosage chart for Covid-19, and (B) such other, further and different relief as this Court may deem just, equitable and proper.

NOW, upon the motion of the Michelle Kulbacki, it is hereby

ORDERED, that the Defendants show cause, at a special term of the Supreme Court, before the Honorable HENRY J. NOWAK, at the Courthouse located at 50 Delaware Avenue, Part 81, in the City of Buffalo, County of Erie and State of New York, on the 8th 11th day of January, 2021, ~~by 4:00~~ at 2:00 P.M., or as soon thereafter as counsel can be heard, why this Court should not issue via Microsoft Teams

an order as follows:

A. An Order compelling the Defendants, agents, and assigns to administer the drug Ivermectin according to its dosage chart for Covid-19 to their patient, Judith Smentkiewicz; and

B. An Order granting the Michelle Kulbacki such other, further and different relief as this Court may deem just, equitable and proper; and it is further

ORDERED, that pending further order of this Court, the Defendants, agents, and assigns, and any third parties acting on their behalf, shall upon receipt of this Order to Show Cause and its supporting papers immediately administer the drug Invermectin according to its dosage chart for Covid-19 to their patient, Judith Smentkiewicz.

ORDERED, that the service of this Order to Show Cause and supporting papers, as follows, before 4:00 P.M. on January 8, 2021, shall be deemed good and sufficient service to the following:

Kaleida Health and Kaleida Health Foundation
726 Exchange Street
Buffalo, NY 14210

Millard Fillmore Suburban Hospital
1540 Maple Road
Williamsville, NY 14221

HON. HENRY J. NOWAK, J.S.C.

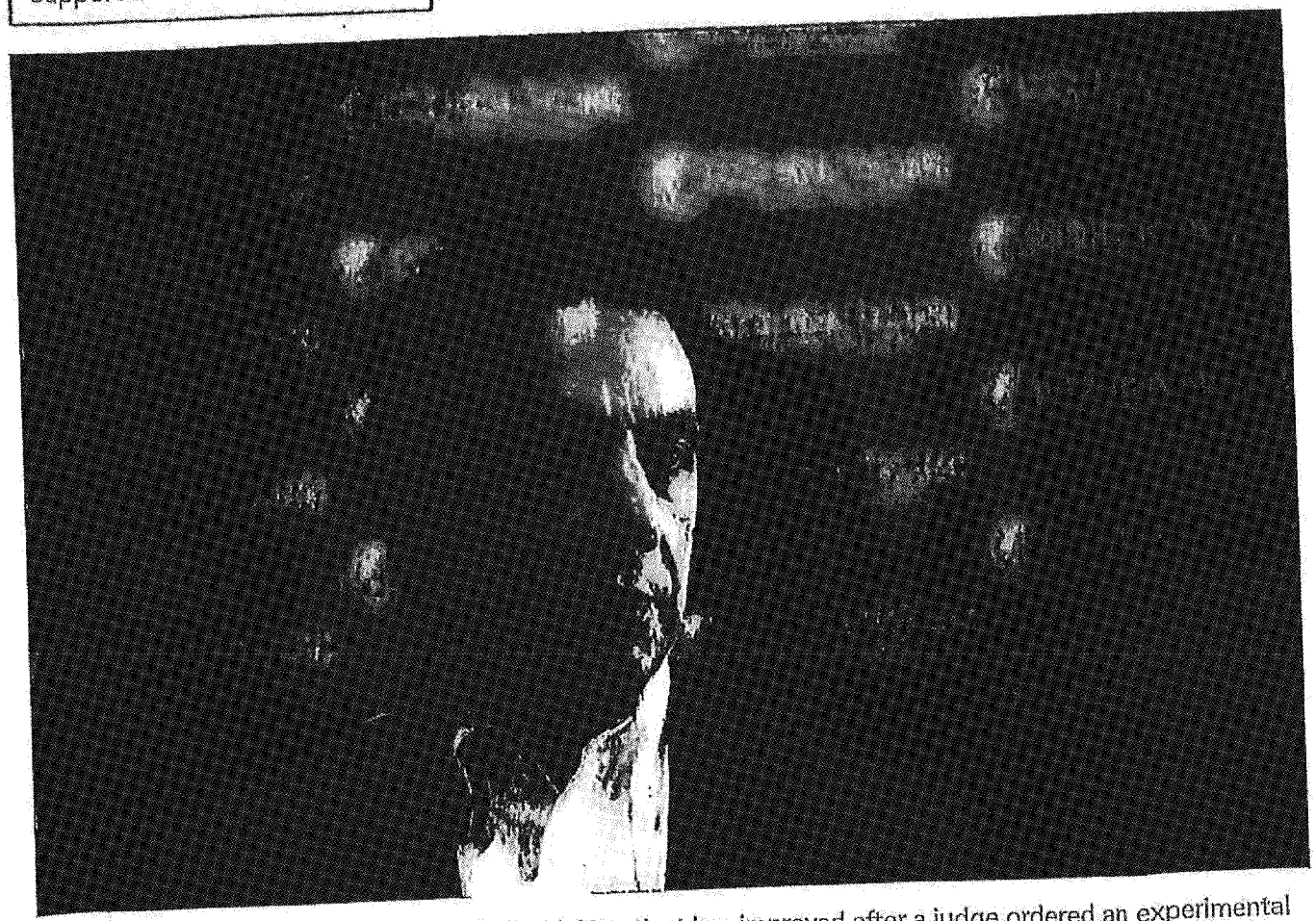
DATED: January 8, 2021

EXHIBIT "I"

https://buffalonews.com/news/local/2nd-wny-hospital-ordered-to-treat-covid-19-patient-with-experimental-drug/article_f32339f0-5d01-11eb-b752-4f8966804581.html

2nd WNY hospital ordered to treat Covid-19 patient with experimental drug

Dan Herbeck , Deidre Williams
Jan 24, 2021



Attorney Ralph C. Lorigo says a second Covid-19 patient has improved after a judge ordered an experimental treatment that has yet to be authorized by the Food and Drug Administration. (Derek Gee/Buffalo News file photo)

By BN

Dan Herbeck , Deidre Williams

For the second time in recent weeks, a state judge has ordered a Western New York hospital to use the drug Ivermectin as an experimental treatment for a patient suffering from Covid-19.

State Supreme Court Justice Frank Caruso on Friday ordered a Rochester hospital to continue Ivermectin treatments to Glenna Dickinson, 65, of Albion.

The Orleans County woman had been in Rochester General Hospital since Jan. 12 with Covid-19, had been put on a ventilator Jan. 17 and had shown "no improvement" until Jan. 20, when her family convinced an intensive care unit doctor to treat her with Ivermectin, said Dickinson's attorneys Ralph C. Lorigo and Jon F. Minear.

"Within 12 hours, she had made a strong improvement, but the hospital was reluctant to continue giving her Ivermectin," Lorigo said late Friday. "We got an order from Judge Caruso, and he may have saved this woman's life."

Although it has reportedly been used successfully in Australia and several other countries to treat Covid-19, Ivermectin is not approved by the United States government as a Covid-19 treatment. The U.S. Food & Drug Administration has said it is testing Ivermectin for that use.

In court papers obtained by The Buffalo News on Friday, Caruso said he was influenced by an affidavit from Dickinson's personal physician, Dr. Thomas Madejski.

Madejski said Dickinson tested positive for Covid-19 on Jan. 7 and continued to get worse until the ICU staff – with a prescription from Madejski and at the family's insistence – gave Ivermectin to the patient.

In court papers, family members said they were told that Dickinson's estimated chances of survival, as a 65-year-old Covid patient on a ventilator, were about 40%.

Caruso's order directed Rochester General Hospital to "comply" with Madejski's prescription for Ivermectin, which is now given to Dickinson every two days. Caruso's order will be in effect until at least Wednesday, when further arguments will be heard,

Saturday afternoon, things were not going as smoothly as the family had hoped, said Dickinson's daughter Natalie Kingdollar. The family's attorneys were in the process Saturday of filing another request for a court order to make sure the hospital is required to obtain and keep Ivermectin on hand while Dickinson is in the hospital, Kingdollar said.

The hospital pharmacy did not have Ivermectin on hand when it agreed to administer the drug, Kingdollar explained.

Madejski had secured enough of the medication from an outside pharmacy for two doses over two days, and the family delivered it to the hospital last Tuesday, Kingdollar said.

The family delivered a third dose to the hospital on Wednesday, but Thursday a hospital nurse called Kingdollar, saying she could not find the third dose and didn't know what happened to it, Kingdollar said.

A nurse called Kingdollar Friday night, again saying the hospital pharmacy could not find Dickinson's medication, said Kingdollar, who then called the family's attorneys.

"We are feeling a bit unsettled about the fact that they misplaced her medication, and she was making progress," Kingdollar said.

After receiving the first two doses, Dickinson's condition improved. Her ventilator was turned down, and doctors were starting the process of trying to bring her out of a medically induced coma, Kingdollar said.

Madejski ultimately secured three additional doses, which were delivered to the hospital Saturday at 12:30 p.m. But Kingdollar now is concerned that her mother's progress is impacted because she was not administered the third dose last Thursday.

But Madejski is reassuring Kingdollar that if her mother did not receive a third dose before Saturday, it shouldn't make too much of a difference as some doctors prescribe the medicine to be taken every other day, Kingdollar said.

Dickinson, who has four grandchildren, turned 65 last December and had just retired. She contracted Covid-19 after her husband had been exposed to a business partner who was unaware at the time that he had been exposed to the virus, Kingdollar said.

"I'm just generally worried. All I want out of this I want my mother to get better and I want to be able to help other families," Kingdollar said.

Dickinson's family has set up **a GoFundMe page** to help with her legal and medical expenses.

Lorigo said Dickinson's case is "very similar" to the case of **Judith Smentkiewicz,** 80, of Cheektowaga. Another State Supreme Court judge, Henry J. Nowak, ordered officials of Millard Fillmore Suburban Hospital on Jan. 8 to treat her Covid-19 with Ivermectin.

Smentkiewicz, who was "on a ventilator and in real distress," has since improved to the point that she has been released from the hospital and is recuperating in a rehabilitation facility, Lorigo said.

Dr. Thomas A. Russo, chief of infectious disease studies at the University at Buffalo's Jacobs School of Medicine and Biomedical Sciences, said Ivermectin is still under study as a potential Covid-19 treatment.

"We don't have definitive data yet to show it does help," Russo cautioned last week. "Presently, it is not recommended as a treatment for Covid-19."

According to Lorigo and other attorneys, it is highly unusual for a judge to order a hospital or doctor to give a certain medication to a patient.

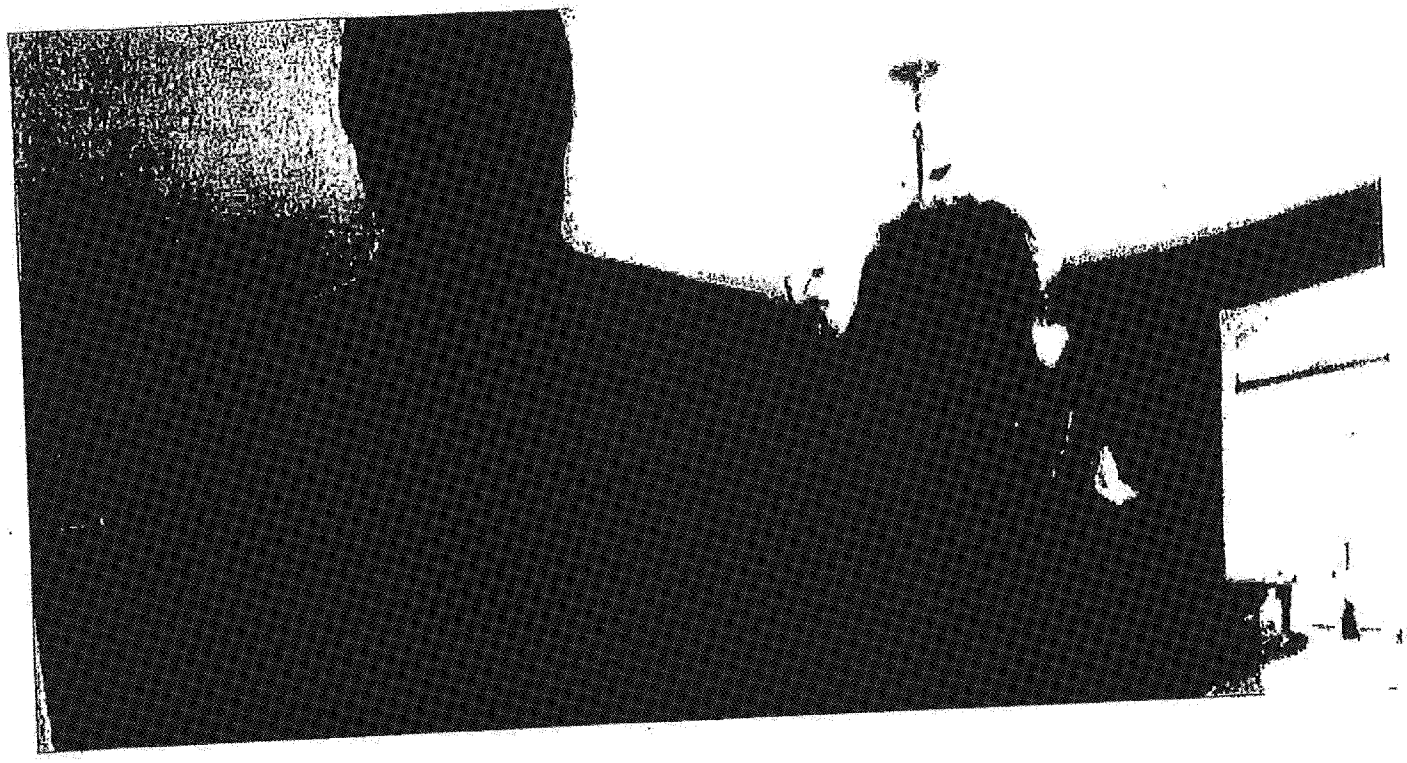
But the Covid-19 pandemic has put some patients in dire situations, Lorigo said. "We did not take it lightly to go to the courts in these two cases, but the families of these two women felt something had to be done," the attorney said.

https://www.thedailynewsonline.com/news/local/albion-woman-gets-experimental-covid-treatment/article_c190de80-3913-5cd6-abfb-070085bf306d.html

Albion woman gets experimental COVID treatment

COURT ORDER: Family members say Dickinson's condition has improved

By SCOTT DESMIT
sdesmit@batavianews.com
Jan 28, 2021



Bob and Glenna Dickinson

eyJpdiI6Imt0dWg0TUlXb0lIUWFMaVVP

ALBION — A fundraiser has been established for an Albion woman who last week became the second person in Western New York to have a court-ordered treatment for COVID-19.

Glenna Dickinson, 65, was hospitalized in Rochester Jan. 12 and was on a ventilator since Jan. 17.

According to family posts on a gofundme account and on Facebook, Dickinson's condition deteriorated.

Doctors began treating her with Ivermectin, a drug used to treat children and animals for lice.

Friday, a state Supreme Court judge ordered those treatments to continue.

[illegible] family members say

"She has been able to make this miraculous progress thanks to legal intervention and an experimental medicine being administered as a result of a court order," her niece, Nicole Mitchell wrote on a gofundme account she established. "As you can imagine, the medical costs and legal expenses are adding up. The family needs to retain a lawyer to ensure she receives the doses that are keeping her alive. Any donation is greatly appreciated. If you are not able to donate please help by sharing her story to spread awareness and say a prayer for her. Thank you."

Ivermectin has been used in numerous cases across the county but has not been FDA-approved for treatment of COVID.

Earlier this month, a judge in Erie County ordered doctors at Millard Fillmore Suburban Hospital to treat an 80-year old woman with Ivermectin. The patient has since been removed from a ventilator and discharged to a rehabilitation facility, according to The Buffalo News.

The fundraiser for Dickinson has raised about $3,200 of its $7,000 goal.

To visit the page, go to https://www.gofundme.com/f/a4udz2?utm_medium=copy_link&utm_source=customer&utm_campaign=p_lico+share-sheet

Scott

EXHIBIT "J"

PAID

At an Special Term of the Supreme Court, held in and for the County of Orleans in the Town of Albion, New York, on the 21st day of January 2021.

PRESENT: HON. FRANK CARUSO, J.S.C.
Presiding Justice

STATE OF NEW YORK : COUNTY OF ORLEANS
SUPREME COURT

ROBERT DICKINSON,

Plaintiff,

v.

ROCHESTER GENERAL HOSPITAL, ROCHESTER REGIONAL HEALTH,

Defendants.

ORDER TO SHOW CAUSE

Index No.: 21-47013

Upon reviewing and filing the annexed Affidavit of Robert Dickinson and the Affirmation Dr. Thomas Madejski, and the Exhibits attached thereto, the Plaintiff, Robert Dickinson, seeks an Order granting him immediate and emergency relief (A) compelling the Defendants and/or their agents to comply with primary care physician, Dr. Thomas Madejski's, order prescribing Ivermectin to their mutual patient, Glenna Dickinson, according to its dosage for Covid-19, namely 12 milligrams on day 1, day 3, day 5, and every other day thereafter as ordered by Dr. Madejski, and (B) such other, further, and different relief as this Court may deem just, equitable, and proper.

NOW, upon the Motion of Mr. Dickinson, it is hereby

ORDERED, that the Defendants show cause, at a special term of the Supreme Court, before the Honorable Frank Caruso at the Courthouse located at 1 South Main Street, Suite 3,

or virtually by Microsoft Teams

located in Albion, the County of Orleans, and State of New York on the 27 day of January, 2021, at 1:30pm or as soon thereafter as counsel can be heard, why this Court should not issue an order as follows:

A. Compelling the Defendants and/or their agents to comply with primary care physician, Dr. Thomas Madejski's, order prescribing Ivermectin to their mutual patient, Glenna Dickinson, according to its dosage for Covid-19, namely 12 milligrams on day 1, day 3, day 5, and every other day thereafter as ordered by Dr. Madejski; and

B. An Order granting Mr. Dickinson such other, further and different relief as this Court may deem just, equitable and proper; and it is further

ORDERED, that pending further order of this Court, the Defendants, its agents, and assigns, and any third parties acting on their behalf, upon receipt of this Order to Show Cause and its supporting papers, shall immediately enforce primary care physician, Dr. Thomas Madejski's, order and prescription to administer the drug Invermectin to their mutual patient, Glenna Dickinson, according to its dosage for Covid-19, namely 12 milligrams on day 1, day 3, day 5, and every other day thereafter as further ordered by Dr. Madejski.

ORDERED, that the service of this Order to Show Cause and supporting papers, shall occur on or before January 23, 2021 and shall be deemed good and sufficient service to the following:

Rochester General Hospital
1425 Portland Avenue
Rochester, NY 14621

Rochester Regional Health
Attn: General Counsel
100 Kings Highway S.
Rochester, NY 14617

HON. FRANK CARUSO, J.S.C.

DATED: 1/21/21

GRANTED
January 21, 2021

Rec'd & filed
ORLEANS CO CLERK NY
2021 JAN 21 PM 1:43

EXHIBIT "K"

Dr. Pierre Kory (FLCCC Alliance) testifies to senate committee about I-MASK+ (incl. the following Q&A part)

2 months ago | More

FLCCC Alliance PREMIUM Follow

This is an updated version of Dr. Kory's testimony on December 8, 2020, including the Q & A part and in better quality (old version: youtube.com/video/CuHq12B_TvK).

Appearing as a witness Tuesday morning before the Senate Committee on Homeland Security and Governmental Affairs—which held a hearing on "Early Outpatient Treatment: An Essential Part of a COVID-19 Solution"— Dr. Pierre Kory, President of the Frontline COVID-19 Critical Care Alliance (FLCCC), called for the government to swiftly review the already expansive and still rapidly emerging medical evidence on Ivermectin.

The data shows the ability of the drug Ivermectin to prevent COVID-19, to keep those with early symptoms from progressing to the hyper-inflammatory phase of the disease, and even to help critically ill patients recover.

Dr. Kory testified that Ivermectin is effectively a "miracle drug" against COVID-19 and called upon the government's medical authorities — the NIH, CDC, and FDA—to urgently review the latest data and then issue guidelines for physicians, nurse-practitioners, and physician assistants to prescribe Ivermectin for COVID-19.

Get all relevant information on the FLCCC Alliance's prophylaxis and treatment protocols for COVID-19 on flccc.net

EXHIBIT "L"

One Page Summary of the Clinical Trials Evidence for Ivermectin in COVID-19

Ivermectin, an anti-parasitic medicine whose discovery won the Nobel Prize in 2015, has proven, highly potent, anti-viral and anti-inflammatory properties in laboratory studies. In the past 4 months, numerous, controlled clinical trials from multiple centers and countries worldwide are reporting consistent, large improvements in COVID-19 patient outcomes when treated with ivermectin. Our comprehensive scientific review of these referenced trials can be found on the Open Science Foundation pre-print server here: https://osf.io/wx3zn/.

Properties of Ivermectin

1) Ivermectin inhibits the replication of many viruses, including SARS-CoV-2, influenza, and others;
2) Ivermectin has potent anti-inflammatory properties with multiple mechanisms of inhibition;
3) Ivermectin diminishes viral load and protects against organ damage in animal models;
4) Ivermectin prevents transmission of COVID-19 when taken either pre- or post-exposure;
5) Ivermectin hastens recovery and decreases hospitalization and mortality in patients with COVID-19;
6) Ivermectin leads to far lower case-fatality rates in regions with widespread use.

Evidence Base Supporting the Efficacy of Ivermectin in COVID-19

as of January 11, 2021

(RCT's = randomized controlled trials, OCT's = observational controlled trials). Every clinical trial shows a benefit, with RCT's and OCT's reporting the same direction and magnitude; nearly all are statistically significant.

Controlled trials studying the prevention of COVID-19 (8 trials completed)

- 3 RCT's with large statistically significant reductions in transmission rates, a total of 774 patients
- 5 OCT's with large statistically significant reductions in transmission rates, a total of 2,052 patients

Controlled trials in the treatment of both early and hospitalized COVID-19 patients (19 trials completed)

- 5 RCT's with large, significant reductions in time to recovery or hospital length of stay, a total of 774 patients
- 1 RCT with a large, statistically significant reduction in rate of deterioration/hospitalization, total of 363 patients
- 1 RCT with a large, statistically significant reduction in rate of deterioration/hospitalization, total of 363 patients
- 2 RCT's with significant decreases in viral load, days of anosmia, cough, or time to recovery, a total of 85 patients
- 3 RCT's with large, significant reductions in mortality, a total of 695 patients
- 3 RCT's with large, statistically significant reductions in mortality, a total of 1,688 patients
- 3 OCT's with large, statistically significant reductions in mortality, a total of 1,688 patients

Number of Studies and Patients Among the Existing Clinical Trials of Ivermectin in COVID-19

- 27 controlled trials, including a total of 6,612 patients have been completed using well-matched control groups
- 16 trials, including over 2,500 patients, are prospective, randomized, controlled studies
- 11 of the 27 trials have been published in peer-reviewed journals, 3,500 patients, remainder are in pre-print

Front Line COVID-19 Critical Care Alliance – Recommendation on Ivermectin in COVID-19

Even restricting analysis to just the 16 randomized controlled trials (totaling over 2,500 patients), the majority report a statistically significant reduction in transmission or disease progression or mortality. Further, a meta-analysis recently performed by an independent research consortium calculated the chances that ivermectin is ineffective in COVID-19 to be 1 in 67 million.[1]

The FLCCC Alliance, based on the totality of the existing evidence, supports an A-I recommendation (NIH rating scheme; strong level, high quality evidence) for the use of ivermectin in both the prophylaxis and treatment of all phases of COVID-19.

Furthermore, we encourage all regulatory agencies to review our manuscript detailing these studies above as well as the multiple population-wide "natural experiments" that occurred in numerous cities and regions after the initiation of ivermectin distribution programs.[2] The widespread use of ivermectin resulted in a significant reduction in cases and mortality rates that approached pre-pandemic levels in these areas. As evidenced by what occurred in these regions, ivermectin is clearly an essential and vital treatment component in achieving control of the pandemic.

1 ivmmeta.com
2 Kory P, Meduri GU, Iglesias J, Varon J et al. Review of the Emerging Evidence Demonstrating the Efficacy of Ivermectin in the Prophylaxis and Treatment of COVID-19. *Open Science Foundation*. https://osf.io/wx3zn/

American Journal of Therapeutics 28, e299–e318 (2021)

OPEN

Review of the Emerging Evidence Demonstrating the Efficacy of Ivermectin in the Prophylaxis and Treatment of COVID-19

Pierre Kory, MD,[1*] Gianfranco Umberto Meduri, MD,[2] Joseph Varon, MD,[3]
Jose Iglesias, DO,[4] and Paul E. Marik, MD[5]

Background: After COVID-19 emerged on U.S shores, providers began reviewing the emerging basic science, translational, and clinical data to identify potentially effective treatment options. In addition, a multitude of both novel and repurposed therapeutic agents were used empirically and studied within clinical trials.

Areas of Uncertainty: The majority of trialed agents have failed to provide reproducible, definitive proof of efficacy in reducing the mortality of COVID-19 with the exception of corticosteroids in moderate to severe disease. Recently, evidence has emerged that the oral antiparasitic agent ivermectin exhibits numerous antiviral and anti-inflammatory mechanisms with trial results reporting significant outcome benefits. Given some have not passed peer review, several expert groups including Unitaid/World Health Organization have undertaken a systematic global effort to contact all active trial investigators to rapidly gather the data needed to grade and perform meta-analyses.

Data Sources: Data were sourced from published peer-reviewed studies, manuscripts posted to preprint servers, expert meta-analyses, and numerous epidemiological analyses of regions with ivermectin distribution campaigns.

Therapeutic Advances: A large majority of randomized and observational controlled trials of ivermectin are reporting repeated, large magnitude improvements in clinical outcomes. Numerous prophylaxis trials demonstrate that regular ivermectin use leads to large reductions in transmission. Multiple, large "natural experiments" occurred in regions that initiated "ivermectin distribution" campaigns followed by tight, reproducible, temporally associated decreases in case counts and case fatality rates compared with nearby regions without such campaigns.

Conclusions: Meta-analyses based on 18 randomized controlled treatment trials of ivermectin in COVID-19 have found large, statistically significant reductions in mortality, time to clinical recovery, and time to viral clearance. Furthermore, results from numerous controlled prophylaxis trials report significantly

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Off-Label Use: This manuscript includes discussion of off-label use in COVID-19 of the FDA-approved medication ivermectin.

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reduced risks of contracting COVID-19 with the regular use of ivermectin. Finally, the many examples of ivermectin distribution campaigns leading to rapid population-wide decreases in morbidity and mortality indicate that an oral agent effective in all phases of COVID-19 has been identified.

Keywords: ivermectin, COVID-19, infectious disease, pulmonary infection, respiratory failure

INTRODUCTION

In early 2020, on the onset of the spreading pandemic, many providers and institutions began to continuously review the rapidly emerging basic science, translational, and clinical data to identify potentially effective treatment options for COVID-19. Although there is now a small and increasing number of therapeutics showing some efficacy in important clinical outcomes, chief of which are corticosteroids in moderate to severe illness, the world continues to suffer from a worsening crisis with the potential of again overwhelming hospitals and intensive care units (ICU). As of February 21, 2020, the number of deaths attributed to COVID-19 in the United States reached 510,248 with more than 9.3 million active cases, the highest number to date. In addition, multiple European countries have imposed new rounds of restrictions and lockdowns.

Further compounding these alarming developments was a wave of recently published results from therapeutic randomized controlled trials conducted on medicines believed effective for COVID-19 that found a lack of impact on mortality in hospitalized patients with the use of remdesivir, hydroxychloroquine, lopinavir/ritonavir, interferon, convalescent plasma, and monoclonal antibody therapy.[1–4] One year into the pandemic, the only therapy considered "proven" as a life-saving treatment in COVID-19 is the use of corticosteroids in patients with moderate to severe illness.[5,6] Similarly, most concerning is the fact that no agent has yet proven effective in outpatients to prevent disease progression to prevent hospitalization.

More recently, trial results of ivermectin, a widely used antiparasitic medicine with known antiviral and anti-inflammatory properties, have been showing benefits in multiple important clinical and virologic outcomes, including mortality. Although growing numbers of the studies supporting this conclusion have passed through peer review, approximately half of the remaining trials data are from manuscripts uploaded to medical preprint servers, a now standard practice for both rapid dissemination and adoption of new therapeutics throughout the pandemic. Following is a comprehensive review of the available efficacy data as of December 12, 2020, taken from in vitro, animal, clinical, and real-world studies all showing the above impacts of ivermectin in COVID-19.

History of ivermectin

In 1975, Professor Satoshi Omura at the Kitsato institute in Japan isolated an unusual *Streptomyces* bacterium from the soil near a golf course along the southeast coast of Honshu, Japan. Omura, along with William Campbell, found that the bacterial culture could cure mice infected with the roundworm *Heligmosomoides polygyrus*. Campbell isolated the active compounds from the bacterial culture, naming them "avermectins" and the bacterium *S. avermitilis* for the compounds' ability to clear mice of worms.[7] Despite decades of searching around the world, the Japanese microorganism remains the only source of avermectin ever found. Ivermectin, a derivative of avermectin, then proved revolutionary. Originally introduced as a veterinary drug, it soon made historic impacts in human health, improving the nutrition, general health, and well-being of billions of people worldwide ever since it was first used to treat onchocerciasis (river blindness) in humans in 1988. It proved ideal in many ways, given that it was highly effective, broad-spectrum, safe, well tolerated, and could be easily administered.[7] Although it was used to treat a variety of internal nematode infections, it was most known as the essential mainstay of 2 global disease elimination campaigns that has nearly eliminated the world of two of its most disfiguring and devastating diseases. The unprecedented partnership between Merck & Co. Inc, and the Kitasato Institute combined with the aid of international health care organizations has been recognized by many experts as one of the greatest medical accomplishments of the 20th century. One example was the decision by Merck & Co to donate ivermectin doses to support the Mectizan Donation Program that then provided more than 570 million treatments in its first 20 years alone.[8] Ivermectin's impacts in controlling onchocerciasis and lymphatic filariasis, diseases which blighted the lives of billions of the poor and disadvantaged throughout the tropics, is why its discoverers were awarded the Nobel Prize in Medicine in 2015 and the reason for its inclusion on the World Health Organization's (WHO) "List of Essential Medicines." Furthermore, it has also been used to successfully overcome several other human diseases and new uses for it are continually being found.[7]

Preclinical studies of Ivermectin's activity against SARS-CoV-2

Since 2012, a growing number of cellular studies have demonstrated that ivermectin has antiviral properties against an increasing number of RNA viruses, including influenza, *Zika*, HIV, *Dengue*, and most importantly, SARS-CoV-2.[9–17] Insights into the mechanisms of action by which ivermectin both interferes with the entrance and replication of SARS-CoV-2 within human cells are mounting. Caly et al[18] first reported that ivermectin significantly inhibits SARS-CoV-2 replication in a cell culture model, observing the near absence of all viral material 48 hours after exposure to ivermectin. However, some questioned whether this observation is generalizable clinically given the inability to achieve similar tissue concentrations used in their experimental model using standard or even massive doses of ivermectin.[19,20] It should be noted that the concentrations required for an effect in cell culture models bear little resemblance to human physiology given the absence of an active immune system working synergistically with a therapeutic agent, such as ivermectin. Furthermore, prolonged durations of exposure to a drug likely would require a fraction of the dosing in short-term cell model exposure. Furthermore, multiple coexisting or alternate mechanisms of action likely explain the clinical effects observed, such as the competitive binding of ivermectin with the host receptor-binding region of SARS-CoV-2 spike protein, as proposed in 6 molecular modeling studies.[21–26] In 4 of the studies, ivermectin was identified as having the highest or among the highest of binding affinities to spike protein S1 binding domains of SARS-CoV-2 among hundreds of molecules collectively examined, with ivermectin not being the particular focus of study in 4 of these studies.[27] This is the same mechanism by which viral antibodies, in particular, those generated by the Pfizer and Moderna vaccines contain the SARS-CoV-2 virus. The high binding activity of ivermectin to the SARS-CoV-2 spike protein could limit binding to either the ACE-2 receptor or sialic acid receptors, respectively, either preventing cellular entry of the virus or preventing hemagglutination, a recently proposed pathologic mechanism in COVID-19.[21,22,26–28] Ivermectin has also been shown to bind to or interfere with multiple essential structural and nonstructural proteins required by the virus to replicate.[26,29] Finally, ivermectin also binds to the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), thereby inhibiting viral replication.[30]

Arevalo et al investigated in a murine model infected with a type 2 family RNA coronavirus similar to SARS-CoV-2, (mouse hepatitis virus), the response to 500 μg/kg of ivermectin versus placebo.[31] The study included 40 infected mice, with 20 treated with ivermectin, 20 with phosphate-buffered saline, and then 16 uninfected control mice that were also given phosphate-buffered saline. At day 5, all the mice were killed to obtain tissues for examination and viral load assessment. The 20 nonivermectin-treated infected mice all showed severe hepatocellular necrosis surrounded by a severe lymphoplasmacytic inflammatory infiltration associated with a high hepatic viral load (52,158), whereas in the ivermectin-treated mice a much lower viral load was measured (23,192; $P < 0.05$), with only few livers in the ivermectin-treated mice showing histopathological damage such that the differences between the livers from the uninfected control mice were not statistically significant.

Dias De Melo et al[32] recently posted the results of a study they did with golden hamsters that were intranasally inoculated with SARS-CoV-2 virus, and at the time of the infection, the animals also received a single subcutaneous injection of ivermectin at a dose of 0.4 mg/kg on day 1. Control animals received only the physiologic solution. They found the following among the ivermectin-treated hamsters: a dramatic reduction in anosmia (33.3% vs. 83.3%, $P = 0.03$), which was also sex dependent in that the male hamsters exhibited a reduction in clinical score while the treated female hamsters failed to show any sign of anosmia. They also found significant reductions in cytokine concentrations in the nasal turbinates and lungs of the treated animals, despite the lack of apparent differences in viral titers.

Despite these mounting insights into the existing and potential mechanisms of action of ivermectin both as a prophylactic and treatment agent, it must be emphasized that significant research gaps remain and that many further in vitro and animal studies should be undertaken to better define not only these mechanisms but also to further support ivermectin's role as a prophylactic agent, especially in the optimal dose and frequency required.

Preclinical studies of ivermectin's anti-inflammatory properties

Given that little viral replication occurs in the later phases of COVID-19, nor can virus be cultured, and only in a minority of autopsies can viral cytopathic changes be found,[33–35] the most likely pathophysiologic mechanism is that identified by Li et al[36] where they showed that the nonviable RNA fragments of SARS-CoV-2 lead to a high mortality and morbidity in COVID-19 through the provocation of an overwhelming and injurious inflammatory response. Based on these insights and the clinical benefits of ivermectin in the late phase of disease to be reviewed below, it seems that the increasingly well-described in vitro properties of ivermectin as an inhibitor of inflammation are far more clinically potent than previously recognized. The growing list of studies demonstrating the anti-inflammatory properties of ivermectin include its

ability to inhibit cytokine production after lipopolysaccharide exposure, downregulate transcription of NF-kB, and limit the production of both nitric oxide and prostaglandin E_2.[37-39]

Exposure prophylaxis studies of ivermectin's ability to prevent transmission of COVID-19

Data are also now available showing large and statistically significant decreases in the transmission of COVID-19 among human subjects based on data from 3 randomized controlled trials (RCTs) and 5 observational controlled trials (OCTs) with 4 of the 8 (2 of them RCTs) published in peer-reviewed journals.[40-46]

Elgazzar and colleagues[45] at Benha University in Egypt randomized 200 health care and household contacts of patients with COVID-19 where the intervention group consisted of 100 patients given a high dose of 0.4 mg/kg on day 1 and a second dose on day 7 in addition to wearing personal protective equipment, whereas the control group of 100 contacts wore personal protective equipment alone. They reported a large and statistically significant reduction in contacts testing positive by Reverse Transcriptase Polymerase Chain Reaction (PCR) when treated with ivermectin versus controls, 2% versus 10%, $P < 0.05$.

Shouman conducted an RCT at Zagazig University in Egypt, including 340 (228 treated and 112 control) family members of patients positive for SARS-CoV-2 through PCR.[44] Ivermectin (approximately 0.25 mg/kg) was administered twice, on the day of the positive test and 72 hours later. After a two-week follow-up, a large and statistically significant decrease in COVID-19 symptoms among household members treated with ivermectin was found, 7.4% versus 58.4%, $P < 0.001$.

Recently, Alam et al from Bangladesh performed a prospective observational study of 118 patients who were evenly split into those who volunteered for either the treatment or control arms, described as a persuasive approach. Although this method, along with the study being unblinded, likely led to confounders, the difference between the 2 groups was so large (6.7% vs. 73.3%, $P < 0.001$) and similar to the other prophylaxis trial results that confounders alone are unlikely to explain such a result.[47] Carvallo et al also performed a prospective observational trial where they gave healthy volunteers ivermectin and carrageenan daily for 28 days and matched them to similarly healthy controls who did not take the medicines.[40] Of the 229 study subjects, 131 were treated with 0.2 mg of ivermectin drops taken by mouth 5 times per day. After 28 days, none of those receiving ivermectin in the prophylaxis group had tested positive for SARS-COV-2 versus 11.2% of patients in the control arm ($P < 0.001$). In a much larger follow-up prospective, observational controlled trial by the same group that included 1195 health care workers, they found that over a 3-month period there were no infections recorded among the 788 workers who took weekly ivermectin prophylaxis, whereas 58% of the 407 controls had become ill with COVID-19. This study demonstrates that remarkable protection against transmission can be achieved among high-risk health care workers by taking 12 mg once weekly.[40] The Carvallo IVERCAR protocol was also separately tested in a prospective RCT by the Health Ministry of Tucuman, Argentina, where they found that among 234 health care workers, the intervention group that took 12 mg once weekly, only 3.4% contracted COVID-19 versus 21.4% of controls, $P < .0001$.[46]

The need for weekly dosing in the Carvallo study over a 4-month period may not have been necessary given that, in a recent RCT from Dhaka, Bangladesh, the intervention group (n = 58) took 12 mg once monthly for a similar 4-month period and also reported a large and statistically significant decrease in infections compared with controls, 6.9% versus 73.3%, $P < 0.05$.[47] Then, in a large retrospective observational case-control study from India, Behera et al[41] reported that among 186 case–control pairs (n = 372) of health care workers, they identified 169 participants who had taken some form of prophylaxis, with 115 participants that had taken ivermectin. After matched pair analysis, they reported that in the workers who had taken 2 dose ivermectin prophylaxis, the odds ratio for contracting COVID-19 was markedly decreased (0.27, 95% confidence interval (CI) 0.15–0.51). Notably, one dose prophylaxis was not found to be protective in this study. Based on both their study finding and the Egyptian prophylaxis study, the All India Institute of Medical Sciences instituted a prophylaxis protocol for their health care workers where they now take two 0.3 mg/kg doses of ivermectin 72 hours apart and repeat the dose monthly.

Data that further illuminates the potential protective role of ivermectin against COVID-19 come from a study of nursing home residents in France which reported that in a facility that suffered a scabies outbreak where all 69 residents and 52 staff were treated with ivermectin,[41] they found that during the period surrounding this event, 7 of the 69 residents fell ill with COVID-19 (10.1%). In this group with an average age of 90 years, only one resident required oxygen support and no resident died. In a matched control group of residents from surrounding facilities, they found 22.6% of residents fell ill and 4.9% died.

Further evidence supporting the efficacy of ivermectin as a prophylaxis agent was published recently in the *International Journal of Antimicrobial agents* where a group of researchers analyzed data using the prophylactic chemotherapy databank administered by the WHO along with case counts obtained by Worldometers, a public data

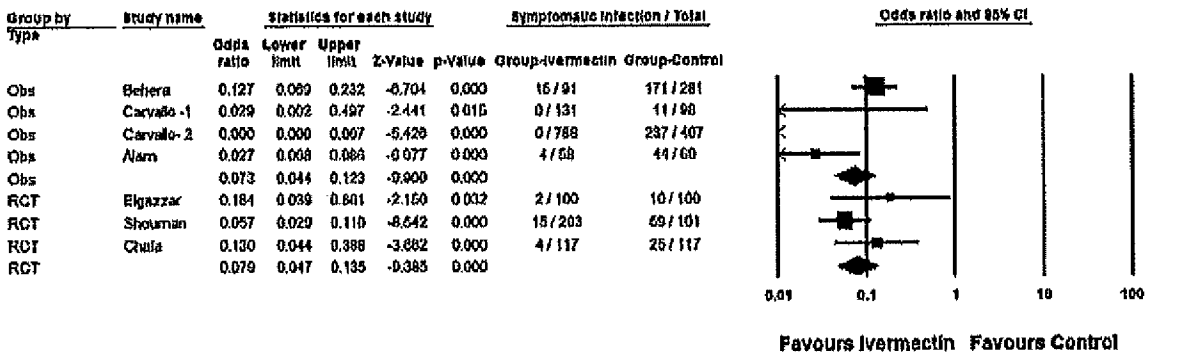

FIGURE 1. Meta-analysis of ivermectin prophylaxis trials in COVID-19. OBS, observational study; RCT, randomized controlled trial. Symbols: Squares: Indicate treatment effect of an individual study. Large diamond: Reflect summary of study design immediately above. Size of each symbol correlates with the size of the confidence interval around the point estimate of treatment effect with larger sizes indicating a more precise confidence interval.

aggregation site used by among others, the Johns Hopkins University.[42] When they compared the data from countries with active ivermectin mass drug administration programs for the prevention of parasite infections, they discovered that the COVID-19 case counts were significantly lower in the countries with recently active programs, to a high degree of statistical significance, $P < 0.001$.

Figure 1 presents a meta-analysis performed by the study authors of the controlled ivermectin prophylaxis trials in COVID-19.

Further data supporting a role of ivermectin in decreasing transmission rates can be found from South American countries where, in retrospect, large "natural experiments" seem to have occurred. For instance, beginning as early as May, various regional health ministries and governmental authorities within Peru, Brazil, and Paraguay initiated "ivermectin distribution" campaigns to their citizen populations.[48] In one such example from Brazil, the cities of Itajai, Macapa, and Natal distributed massive amounts of ivermectin doses to their city's population, where in the case of Natal, 1 million doses were distributed. The distribution campaign of Itajai began in mid-July, in Natal they began on June 30th, and in Macapa, the capital city of Amapa and others nearby, they incorporated ivermectin into their treatment protocols in late May after they were particularly hard hit in April. The data in Table 1 were obtained from the official Brazilian government site and the national press consortium and show large decreases in case counts in the 3 cities soon after distribution began compared with their neighboring cities without such campaigns.

The decreases in case counts among the 3 Brazilian cities given in Table 1 were also associated with reduced mortality rates as summarized in Table 2.

Clinical studies on the efficacy of ivermectin in treating mildly ill outpatients

Currently, 7 trials that include a total of more than 3000 patients with mild outpatient illness have been completed, a set composed of 7 RCTs and 4 case series.[49–60]

Table 1. Comparison of case count decreases among Brazilian cities with and without ivermectin distribution campaigns.

Region	New cases	June	July	August	Population 2020 (1000)	% Decline in new cases between June and August 2020
South	**Itajaí**	**2123**	**2854**	**998**	**223**	**−53%**
	Chapecó	1760	1754	1405	224	−20%
North	**Macapá**	**7966**	**2481**	**2370**	**503**	**−70%**
	Ananindeua	1520	1521	1014	535	−30%
North East	**Natal**	**9009**	**7554**	**1590**	**890**	**−82%**
	João Pessoa	9437	7963	5384	817	−43%

Bolded cities distributed ivermectin, neighboring regional city below did not.

Table 2. Change in death rates among neighboring regions in Brazil.

Region	State	% Change in average deaths/week compared with 2 weeks before
South	**Santa Catarina**	**–36%**
	PARANÁ	–3%
	Rio Grande do Sul	–5%
North	**Amapá**	**–75%**
	AMAZONAS	–42%
	Pará	+13%
North East	**Rio Grande do Norte**	**–65%**
	CEARÁ	+62%
	Paraíba	–30%

Bolded regions contained a major city that distributed ivermectin to its citizens, the other regions did not.

The largest, a double-blinded RCT by Mahmud[49] was conducted in Dhaka, Bangladesh, and targeted 400 patients with 363 patients completing the study. In this study, as in many other of the clinical studies to be reviewed, either a tetracycline (doxycycline) or macrolide antibiotic (azithromycin) was included as part of the treatment. The importance of including antibiotics such as doxycycline or azithromycin is unclear; however, both tetracycline and macrolide antibiotics have recognized anti-inflammatory, immunomodulatory, and even antiviral effects (58–61). Although the posted data from this study does not specify the amount of mildly ill outpatients versus hospitalized patients treated, important clinical outcomes were profoundly affected, with increased rates of early improvement (60.7% vs. 44.4% $P < 0.03$) and decreased rates of clinical deterioration (8.7% vs. 17.8%, $P < 0.02$). Given that mildly ill outpatients mainly comprised the study cohort, only 2 deaths were observed (both in the control group).

Ravikirti performed a double-blinded RCT of 115 patients, and although the primary outcome of PCR positivity on day 6 was no different, the secondary outcome of mortality was 0% versus 6.9%, $P = .019$.[60] Babalola in Nigeria also performed a double-blinded RCT of 62 patients, and in contrast to Ravikirti, they found a significant difference in viral clearance between both the low-dose and high-dose treatment groups and controls in a dose dependent fashion, $P = .006$.[59]

Another RCT by Hashim et al[53] in Baghdad, Iraq, included 140 patients equally divided; the control group received standard care, and the treated group included a combination of both outpatient and hospitalized patients. In the 96 patients with mild-to-moderate outpatient illness, they treated 48 patients with a combination of ivermectin/doxycycline and standard of care and compared outcomes with the 48 patients treated with standard of care alone. The standard of care in this trial included medicines such as dexamethasone 6 mg/d or methylprednisolone 40 mg twice per day if needed, vitamin C 1000 mg twice/day, zinc 75–125 mg/d, vitamin D3 5000 IU/day, azithromycin 250 mg/d for 5 days, and acetaminophen 500 mg as needed. Although no patients in either group progressed or died, the time to recovery was significantly shorter in the ivermectin-treated group (6.3 days vs. 13.7 days, $P < 0.0001$).

Chaccour et al conducted a small, double-blinded RCT in Spain where they randomized 24 patients to ivermectin versus placebo, and although they found no difference in PCR positivity at day 7, they did find statistically significant decreases in viral loads, patient days of anosmia (76 vs. 158, $P < 0.05$), and patient days with cough (68 vs. 98, $P < 0.05$).[57]

Another RCT of ivermectin treatment in 116 outpatients was performed by Chowdhury et al in Bangladesh where they compared a group of 60 patients treated with the combination of ivermectin/doxycycline to a group of 60 patients treated with hydroxychloroquine/doxycycline with a primary outcome of time to negative PCR.[54] Although they found no difference in this outcome, in the treatment group, the time to symptomatic recovery approached statistical significance (5.9 days vs. 7.0 days, $P = 0.07$). In another smaller RCT of 62 patients by Podder et al, they also found a shorter time to symptomatic recovery that approached statistical significance (10.1 days vs. 11.5 days, $P > 0.05$, 95% CI, 0.86–3.67).[55]

A medical group in the Dominican Republic reported a case series of 2688 consecutive symptomatic outpatients seeking treatment in the emergency department, most whom were diagnosed using a clinical algorithm. The patients were treated with a high-dose ivermectin of 0.4 mg/kg for one dose along with 5 days of azithromycin. Remarkably, only 16 of the 2688 patients (0.59%) required subsequent hospitalization with only a single death recorded.[61]

In another case series of 100 patients in Bangladesh, all treated with a combination of 0.2 mg/kg ivermectin and doxycycline, they found that no patient required hospitalization nor died, and all patients' symptoms improved within 72 hours.[62]

A case series from Argentina reported on a combination protocol that used ivermectin, aspirin, dexamethasone, and enoxaparin. In the 135 mild illness patients, all survived.[50] Similarly, a case series from Mexico of 28 consecutively treated patients with ivermectin, all were reported to have recovered with an average time to full recovery of only 3.6 days.[58]

Clinical studies of the efficacy of ivermectin in hospitalized patients

Studies of ivermectin among more severely ill hospitalized patients include 6 RCTs, 5 OCTs, and a database analysis study.[45,51–53,63–70]

The largest RCT in hospitalized patients was performed concurrent with the prophylaxis study reviewed above by Elgazzar et al.[45] Four hundred patients were randomized among 4 treatment groups of 100 patients each. Groups 1 and 2 included mild/moderate illness patients alone, with group 1 treated with one dose 0.4 mg/kg ivermectin plus standard of care (SOC) and group 2 received hydroxychloroquine 400 mg twice on day 1 then 200 mg twice daily for 5 days plus standard of care. There was a statistically significant lower rate of progression in the ivermectin-treated group (1% vs. 22%, $P < 0.001$), with no deaths and 4 deaths, respectively. Groups 3 and 4 included only severely ill patients, with group 3 again treated with a single dose of 0.4 mg/kg plus SOC, whereas group 4 received hydroxychloroquine plus SOC. In this severely ill subgroup, the differences in outcomes were even larger, with lower rates of progression 4% versus 30% and mortality 2% versus 20% ($P < 0.001$).

The one largely outpatient RCT conducted by Hashim reviewed above also included 22 hospitalized patients in each group. In the ivermectin/doxycycline-treated group, there were 11 severely ill patients and 11 critically ill patients, whereas in the standard of care group, only severely ill patients (n = 22) were included because of their ethical concerns of including critically ill patients in the control group (45). This decision led to a marked imbalance in the severity of illness between these hospitalized patient groups. However, despite the mismatched severity of illness between groups and the small number of patients included, beneficial differences in outcomes were seen, but not all reached statistical significance. For instance, there was a large reduction in the rate of progression of illness (9% vs. 31.8%, $P = 0.15$) and, most importantly, there was a large difference in mortality among the severely ill groups that reached a borderline statistical significance (0% vs. 27.3%, $P = 0.052$). Another important finding was the relatively low mortality rate of 18% found among the subset of critically ill patients, all of whom were treated with ivermectin.

A recent RCT from Iran found a dramatic reduction in mortality with ivermectin use.[65] Among multiple ivermectin treatment arms (different ivermectin dosing strategies were used in the intervention arms), the average mortality was reported as 3.3%, whereas the average mortality within the standard care and placebo arms was 18.8%, with an odds ratio (OR) of 0.18 (95% CI 0.06–0.55, $P < 0.05$).

Spoorthi[64] and Sasanak performed a prospective trial of 100 hospitalized patients whereby they treated 50 with ivermectin and doxycycline, whereas the 50 controls were given a placebo consisting of vitamin B6. Although no deaths were reported in either group, the ivermectin treatment group had a statistically significant shorter hospital length of stay (LOS) 3.7 days versus 4.7 days, $P = 0.03$, and shorter time to complete resolution of symptoms, 6.7 days versus 7.9 days, $P = 0.01$.

The largest OCT (n = 280) in hospitalized patients was conducted by Rajter et al at Broward Health Hospitals in Florida and was recently published in the major medical journal *Chest* (43). They performed a retrospective OCT using a propensity-matched design on 280 consecutive treated patients and compared those treated with ivermectin to those without. One hundred seventy-three patients were treated with ivermectin (160 received a single dose and 13 received a second dose at day 7) while 107 were not.[63] In both unmatched and propensity-matched cohort comparisons, similar, large, and statistically significant lower mortality was found among ivermectin-treated patients (15.0% vs. 25.2%, $P = 0.03$). Furthermore, in the subgroup of patients with severe pulmonary involvement, mortality was profoundly reduced when treated with ivermectin (38.8% vs. 80.7%, $P = 0.001$).

Another large OCT in Bangladesh compared 115 patients treated with ivermectin to a standard care cohort consisting of 133 patients.[51] Despite a significantly higher proportion of patients in the ivermectin group being men (ie, with well-described, lower survival rates in COVID), the groups were otherwise well matched, yet the mortality decrease was statistically significant (0.9% vs. 6.8%, $P < 0.05$). The largest OCT is a study from Brazil, published as a letter to the editor and included almost 1500 patients.[66] Although the primary data were not provided, they reported that in 704 hospitalized patients treated with a single dose of 0.15 mg/kg ivermectin, compared with 704 controls, overall mortality was reduced (1.4% vs. 8.5%, HR 0.2, 95% CI 0.12–0.37, $P < 0.0001$). Similarly, in the patients on mechanical ventilation, mortality was also reduced (1.3% vs. 7.3%). A small study from Baghdad, Iraq, compared 16 ivermectin-treated patients with 71

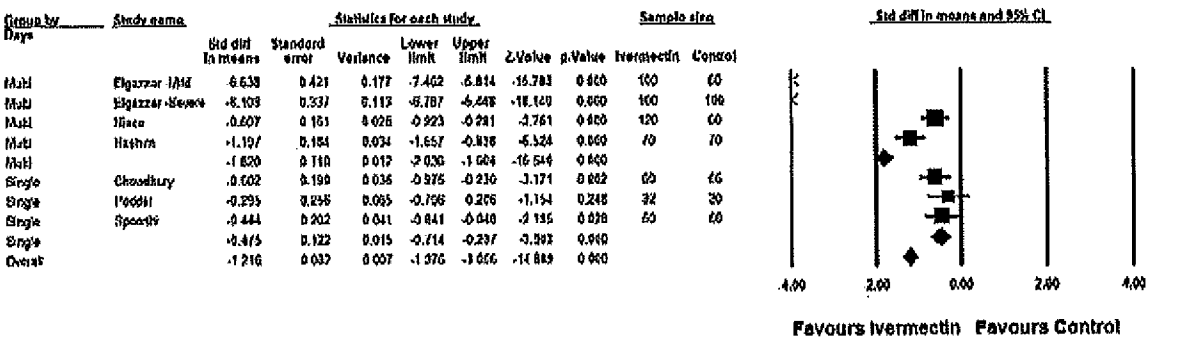

FIGURE 2. Meta-analysis of the outcome of time to clinical recovery from controlled trials of ivermectin treatment in COVID-19. OBS, observational study; RCT, randomized controlled trial. Symbols: Squares: Indicate treatment effect of an individual study. Large diamond: Reflect summary of study design immediately above. Small diamond: Sum effect of all trial designs. Size of each symbol correlates with the size of the confidence interval around the point estimate of treatment effect with larger sizes indicating a more precise confidence interval.

controls.[52] This study also reported a significant reduction in length of hospital stay (7.6 days vs. 13.2 days, $P < 0.001$) in the ivermectin group. In a study reporting on the first 1000 patients treated in a hospital in India, they found that in the 34 patients treated with ivermectin alone, all recovered and were discharged, whereas in more than 900 patients treated with other agents, there was an overall mortality of 11.1%.[70]

Meta-analyses of the above controlled treatment trials were performed by the study authors focused on the 2 important clinical outcomes: time to clinical recovery and mortality (Figures 2 and 3). The consistent and reproducible signals leading to large overall statistically significant benefits from within both study designs are remarkable, especially given that in several of the studies treatment was initiated late in the disease course.

Details of the prophylaxis, early, and late treatment trials of ivermectin in COVID-19 can be found in Table 3.

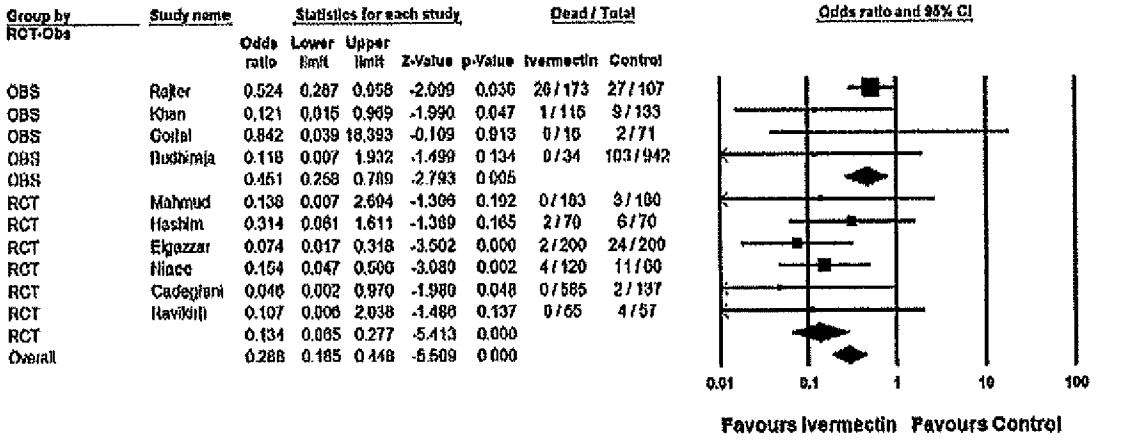

FIGURE 3. Meta-analysis of the outcome of mortality from controlled trials of ivermectin treatment in COVID-19. OBS, observational study; RCT, randomized controlled trial. Symbols: Squares: Indicate treatment effect of an individual study. Large diamond: Reflect summary of study design immediately above. Small diamond: Sum effect of all trial designs. Size of each symbol correlates with the size of the confidence interval around the point estimate of treatment effect with larger sizes indicating a more precise confidence interval.

Table 3. Clinical studies assessing the efficacy of ivermectin in the prophylaxis and treatment of COVID-19.

Prophylaxis Trials Author, Country, source	Study design, size	Study subjects	Ivermectin dose	Dose frequency	Clinical outcomes reported
Prophylaxis trials					
Shouman W, Egypt *www.clinicaltrials.gov* NCT04422561	RCT N = 340	Household members of pts with +COVID-19 PCR test	40–60 kg: 15 mg, 60–80 kg: 18 mg, and > 80 kg: 24 mg	Two doses, 72 hours apart	7.4% versus 58.4% developed COVID-19 symptoms, $P < 0.001$
Elgazzar A, Egypt ResearchSquare doi.org/10.21203/rs.3.rs-100956/v1	RCT N = 200	Health care and household contacts of pts with +COVID-19 PCR test	0.4 mg/kg	Two doses, day 1 and day 7	2% versus 10% tested positive for COVID-19 $P < 0.05$
Chala R, Argentina NCT04701710 *Clinicaltrials.gov*	RCT N = 234	Health care workers	12 mg	Every 7 d	3.4% versus 21.4%, $P = 0.0001$.
Carvallo H, Argentina *Journal of Biochemical Research and Investigation* doi.org/10.31546/2633–8653.1007	OCT N = 229	Healthy patients negative for COVID-19 PCR test	0.2 mg drops	1 drop 5 times a d x 28 d	0.0% versus 11.2% contracted COVID-19 $P < 0.001$
Alam MT, Bangladesh *European J Med Hlth Sciences* 10.24018/ejmed.2020.2.6.599	OCT N = 118	Health care workers	12 mg	Monthly	6.9% versus 73.3%, $P < 0.05$
Carvallo H, Argentina *Journal of Biochemical Research and Investigation* doi.org/10.31546/2633–8653.1007	OCT N = 1195	Health care workers	12 mg	Once weekly for up to 10 wk	0.0% of the 788 workers taking ivermectin versus 58% of the 407 controls contracted COVID-19.
Behera P, India *medRxiv* doi.org/10.1101/2020.10.29.20222661	OCT N = 186 case control pairs	Health care workers	0.3 mg/kg	Day 1 and day 4	2 doses reduced odds of contracting COVID-19 (OR 0.27 95% CI 0.16–0.53)
Bernigaud C, France *Annales de Dermatologie et de Venereologi* doi.org/10.1016/j.annder.2020.09.231	OCT N = 69 case control pairs	Nursing home residents	0.2 mg/kg	Once	10.1% versus 22.6% residents contracted COVID-19 0.0% versus 4.9% mortality
Hellwig M, USA *J Antimicrobial Agents* doi.org/10.1016/j.ijantimicag.2020.106,248	OCT N = 52 countries	Countries with and without IVM prophylaxis programs	Unknown	Variable	Significantly lower-case incidence of COVID-19 in African countries with IVM prophylaxis programs $P < 0.001$

Clinical trials–Outpatients

Prophylaxis Trials Author, Country, source	Study design, size	Study subjects	Ivermectin dose	Dose frequency	% Ivermectin versus % Controls Clinical outcomes reported
Mahmud R, Bangladesh *www.clinicaltrials.gov* NCT0452383	DB-RCT N = 363	Outpatients and hospitalized	12 mg + doxycycline	Once, within 3 days of PCR+ test	Early improvement 60.7% versus 44.4%, $P < 0.03$, deterioration 8.7% versus 17.8%, $P < 0.02$
Chowdhury A, Bangladesh *Research Square* doi.org/10.21203/rs.3.rs-38896/v1	RCT N = 116	Outpatients	0.2 mg//kg + doxycycline	Once	Recovery time 5.9 versus 9.3 days ($P = 0.07$)
Ravikirti, India *medRxiv* doi.org/10.1101/2021.01.05.21249310	DB-RCT N = 115	Mild–moderate illness	12 mg	Daily for 2 d	No diff in day 6 PCR + 0% versus 6.9% mortality, $P = 0.019$
Babalola OE, Nigeria medRxiv doi.org/10.1101/2021.01.05.21249131	DB-RCT N = 62	Mild–moderate illness	6 mg and 12 mg	Every 48 hours × 2 wk	Time to viral clearance: 4.6 days high dose versus 6.0 days low dose versus 9.1 days control ($P = 0.006$)
Podder CS, Bangladesh *IMC J Med Sci 2020;14(2)*	RCT N = 62	Outpatients	0.2 mg/kg	Once	Recovery time 10.1 versus 11.5 days (NS), average time 5.3 versus 6.3 (NS)
Chaccour C. Spain *Research Square* doi.org/10.21203/rs.3.rs-116547/v1	DB-RCT N = 24	Outpatients	0.4 mg/kg	Once	No diff in PCR+ day 7, lower viral load d 4 and 7, ($P < 0.05$), 76 versus 158 pts. d of anosmia ($P < 0.05$), 68 versus 98 pts. d of cough ($P < 0.05$)
Morgenstern J, Dominican Republic *medRxiv* doi.org/10.1101/2020.10.29.20222505	Case series N = 3099	Outpatients and hospitalized	Outpatients: 0.4 mg/kg hospital patients: 0.3 mg/kg	Outpatients: 0.3 mg/kg × 1 dose Inpatients: 0.3 mg/kg, days 1,2,6, and 7	Mortality = 0.03% in 2688 outpatients, 1% in 300 non-ICU hospital patients, and 30.6% in 111 ICU patients
Carvallo H, Argentina *medRxiv* doi.org/10.1101/2020.09.10.20191619	Case series N = 167	Outpatients and hospitalized	24 mg = mild, 36 mg = moderate, and 48 mg = severe	Days 0 and 7	All 135 with mild illness survived, 1/32 (3.1% of hospitalized) patients died
Alam A, Banglades *J of Bangladesh College Phys and Surg*, 2020; 38:10-15 doi.org/10.3329/jbcps.v38i0.47512	Case series N = 100	Outpatients	0.2 mg/kg/kg + doxycycline	Once	All improved within 72 h

(*Continued on next page*)

Table 3. (*Continued*) Clinical studies assessing the efficacy of ivermectin in the prophylaxis and treatment of COVID-19.

Clinical trials–Outpatients					% Ivermectin versus % Controls
Prophylaxis Trials Author, Country, source	Study design, size	Study subjects	Ivermectin dose	Dose frequency	Clinical outcomes reported
Espatia-Hernandez G, Mexico *Biomedical Research* www.biomedres.info/biomedi..-proof-of-concept-study-14435.html	Case series N = 28	Outpatients	6 mg	Days 1,2, 7, and 8	All pts recovered average recovery time 3.6 d

Clinical trials–Hospitalized patients					% Ivermectin versus % Controls
Prophylaxis Trials Author, Country, source	Study design, size	Study subjects	Ivermectin dose	Dose frequency	Clinical outcomes reported
Elgazzar A, Egypt ResearchSquare doi.org/10.21203/rs.3.rs-100956/v1	OL-RCT N = 400	Hospitalized patients	0.4 mg/kg	Daily for 4 days	Moderately ill: worsened 1% versus 22%, $P<0.001$. Severely ill: worsened 4% versus 30% mortality 2% versus 20% both with $P < 0.001$
Niaee S. M, Research Square doi.org/10.21203/rs.3.rs-109670/v1	DB-RCT N = 180	Hospitalized patients	0.2, 0.3, and 0.4 mg/kg (3 dosing strategies)	Once versus Days 1,3,5	Mortality 3.3% versus 18.3%. OR 0.18, (0.06–0.55, $P < 0.05$)
Hashim H, Iraq medRxiv doi.org/10.1101/2020.10.26.20219345	SB-RCT N=140	2/3 outpatients and 1/3 hospital pts	0.2 mg/kg + doxycycline	Daily for 2–3 d	Recovery time 6.3 versus 13.6 days ($P<0.001$), 0% versus 27.3% mortality in severely ill ($P = 0.052$)
Spoorthi S, India AIAM, 2020; 7(10):177-182	PCT N = 100	Hospitalized patients	0.2 mg/kg+ doxycycline	Once	Shorter hospital LOS, 3.7 versus 4.7 days, $P = 0.03$, faster resolution of symptoms, 6.7 versus 7.9 days, $P = 0.01$
Ahmed S. Dhaka, Bangladesh International journal of Infectious disease doi.org/10.1016/j.ijid.2020.11.191	DB-RCT N = 72	Hospitalized patients	12 mg	Daily for 5 d	Faster viral clearance 9.7 versus 12.7 days, $P = 0.02$
Chachar AZK, Pakistan Int J Sciences doi.org/10.18483/ijSci.2378	DB-RCT N = 50	Hospitalized patients-mild	12 mg	Two doses day 1 and one dose day 2	64% versus 60% asymptomatic by day 7
Portman-Baracco A, Brazil	OCT		0.15 mg/kg	Once	

(*Continued on next page*)

Table 3. (*Continued*) Clinical studies assessing the efficacy of ivermectin in the prophylaxis and treatment of COVID-19.

Clinical trials–Hospitalized patients					% Ivermectin versus % Controls
Prophylaxis Trials Author, Country, source	Study design, size	Study subjects	Ivermectin dose	Dose frequency	Clinical outcomes reported
Arch Bronconeumol. 2020 doi.org/10.1016/j.arbres.2020.06.011	N = 1408	Hospitalized patients			Overall mortality 1.4% versus 8.5%, HR 0.2, 95% CI 0.12–0.37, $P < 0.0001$
Rajter JC, Florida Chest 2020 doi.org/10.1016/j.chest.2020.10.009	OCT N=280	Hospitalized patients	0.2 mg/kg + azithromycin	Day 1 and day 7 if needed	Overall mortality 15.0% versus 25.2%, $P = 0.03$, severe illness mortality 38.8% versus 80.7%, $P = 0.001$
Khan X, Bangladesh Arch Bronconeumol. 2020 doi.org/10.1016/j.arbres.2020.08.007	OCT N = 248	Hospitalized patients	12 mg	Once on admission	Mortality 0.9% versus 6.8%, $P <$ 0.05, LOS 9 versus 15 days, $P < 0.001$
Gorial FI, Iraq medRxiv doi.org/10.1101/2020.07.07.20145979	OCT N = 87	Hospitalized patients	0.2 mg/kg + HCQ and azithromycin	Once on admission	LOS 7.6 versus 13.2 days, $P <$ 0.001, 0/15 versus 2/71 died
Budiraja S. India medRxiv doi.org/10.1101/2020.11.16.20232223	OCT N = 1000 IVM=34	Hospitalized patients	n/a	n/a	100% IVM pts recovered 11.1% mortality in non-IVM-treated pts

DB-RCT, double-blinded randomized controlled trial; HCQ, hydroxychloroquine; IVM, ivermectin; LOS, length of stay; NS, nonstatistically significant, $P > .05$; OCT, observational controlled trial; OL, open label; PCR, polymerase chain reaction; RCT, randomized controlled trial; SB-RCT, single blinded randomized controlled trial.

Ivermectin in post-COVID-19 syndrome

Increasing reports of persistent, vexing, and even disabling symptoms after recovery from acute COVID-19 have been reported and that many have termed the condition as "Long COVID" and patients as "long haulers," estimated to occur in approximately 10%–30% of cases.[71–73] Generally considered as a postviral syndrome consisting of a chronic and sometimes disabling constellation of symptoms which include, in order, fatigue, shortness of breath, joint pains, and chest pain. Many patients describe their most disabling symptom as impaired memory and concentration, often with extreme fatigue, described as "brain fog," and is highly suggestive of the condition myalgic encephalomyelitis/chronic fatigue syndrome, a condition well reported to begin after viral infections, in particular with Epstein–Barr virus. Although no specific treatments have been identified for Long COVID, a recent manuscript by Aguirre-Chang et al from the National University of San Marcos in Peru reported on their experience with ivermectin in such patients.[74] They treated 33 patients who were between 4 and 12 weeks from the onset of symptoms with escalating doses of ivermectin; 0.2 mg/kg for 2 days if mild and 0.4 mg/kg for 2 days if moderate, with doses extended if symptoms persisted. They found that in 87.9% of the patients, resolution of all symptoms was observed after 2 doses with an additional 7% reporting complete resolution after additional doses. Their experience suggests the need for controlled studies to better test efficacy in this vexing syndrome.

Epidemiological data showing impacts of widespread ivermectin use on population case counts and case fatality rates

Similar to the individual cities in Brazil that measured large decreases in case counts soon after distributing ivermectin in comparison to neighboring cities without such campaigns, in Peru, the government approved the use of ivermectin by decree on May 8, 2020, solely based on the in vitro study by Caly et al from Australia.[48] Soon after, multiple state health ministries initiated ivermectin distribution campaigns in an effort to decrease what was at that time some of the highest COVID-19 morbidity and mortality rates in the world. Juan Chamie,[48] a data analyst and member of the FLCCC Alliance, recently posted an article based on 2 critical sets of data that he compiled and compared; first, he identified the timing and magnitude of each region's ivermectin interventions through a review of official communications, press releases, and the Peruvian Situation Room database to confirm the dates of effective delivery, and second, he extracted data on the total all-cause deaths from the region along with COVID-19 case counts in selected age groups over time from the registry of the National Computer System of Deaths (SINADEF) and from the National Institute of Statistics and Informatics.[48] It should be noted that he restricted his analyses to only those citizens older than 60 years to avoid the confounding of rises in the numbers of infected younger patients. With these data, he was then able to compare the timing of major decreases in this age group of both total COVID-19 cases and total excess deaths per 1000,000 people among 8 states in Peru with the initiation dates of their respective ivermectin distribution campaigns as shown in Figure 4.

Figure 5 from the same study presents data on the case fatality rates in patients older than 60 years, again among the 8 states in Peru. Note the dramatically decreased case fatality rates among older patients diagnosed with COVID-19 after ivermectin became widely distributed in those areas, a result which cannot be explained by changes in mask-wearing or lock-downs.

In an even more telling example, Chamie compared the case counts and fatality rates of the 8 states above with the city of Lima, where ivermectin was not distributed nor widely used in treatment during the same period. Figure 6 compares the lack of significant or sustained reductions in case counts or fatalities in Lima with the dramatic reductions in both outcomes among the 8 states with widespread ivermectin distribution.

Another example can be seen from the data compiled from Paraguay, again by Chamie who noted that the government of the state of Alto Parana had launched an ivermectin distribution campaign in early September. Although the campaign was officially described as a "deworming" program, this was interpreted as a guise by the regions' governor to avoid reprimand or conflict with the National Ministry of Health that recommended against the use of ivermectin to treat COVID-19 in Paraguay. The program began with a distribution of 30,000 boxes of ivermectin, and by October 15, the governor declared that there were very few cases left in the state as can be seen in Figure 7.

The evidence base for ivermectin against COVID-19

To date, the efficacy of ivermectin in COVID-19 has been supported by the following:

1. Since 2012, multiple in vitro studies have demonstrated that Ivermectin inhibits the replication of many viruses, including influenza, *Zika*, *Dengue*, and others.[9–17]
2. Ivermectin inhibits SARS-CoV-2 replication and binding to host tissue through several observed and proposed mechanisms.[18]
3. Ivermectin has potent anti-inflammatory properties with in vitro data demonstrating profound

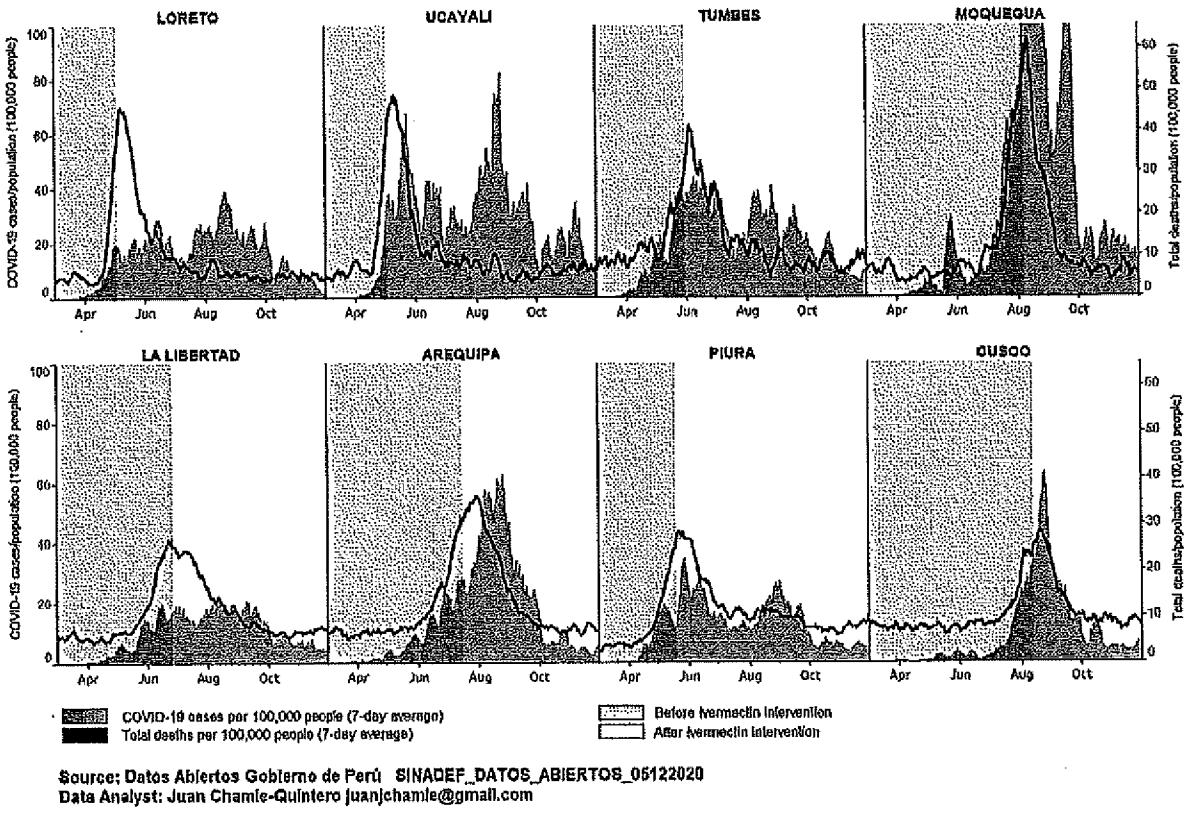

FIGURE 4. Decrease in total case incidences and total deaths/population of COVID-19 in the over 60 population among 8 Peruvian states after deploying mass ivermectin distribution campaigns.

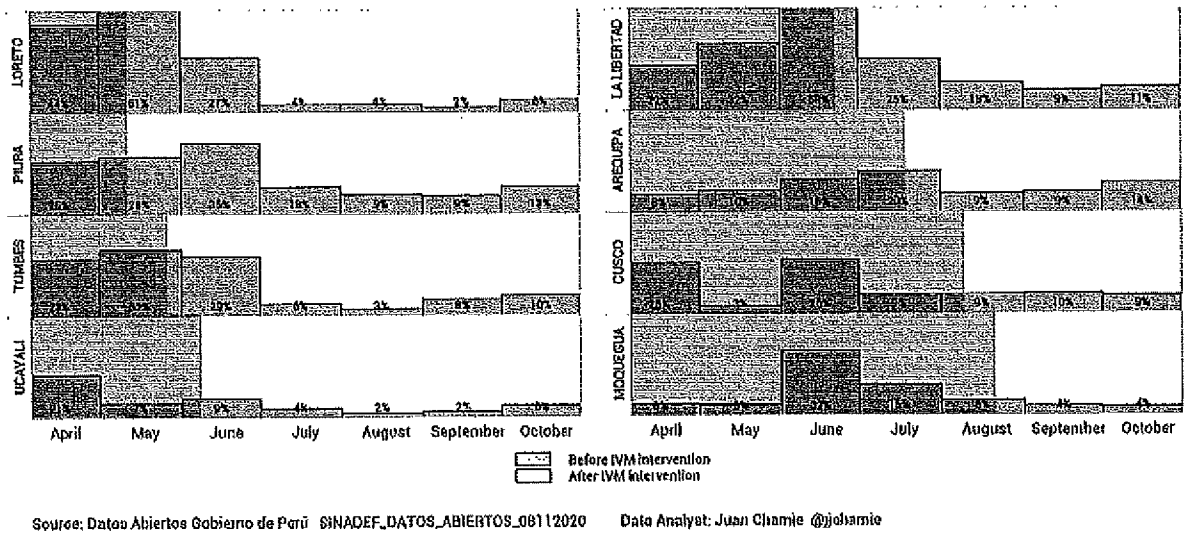

FIGURE 5. Daily total deaths, case fatalities, and case incidence for COVID-19 in populations of patients aged 60 and older for 8 states in Peru deploying early mass ivermectin treatments versus the state of Lima, including the capital city, where ivermectin treatment was applied months later.

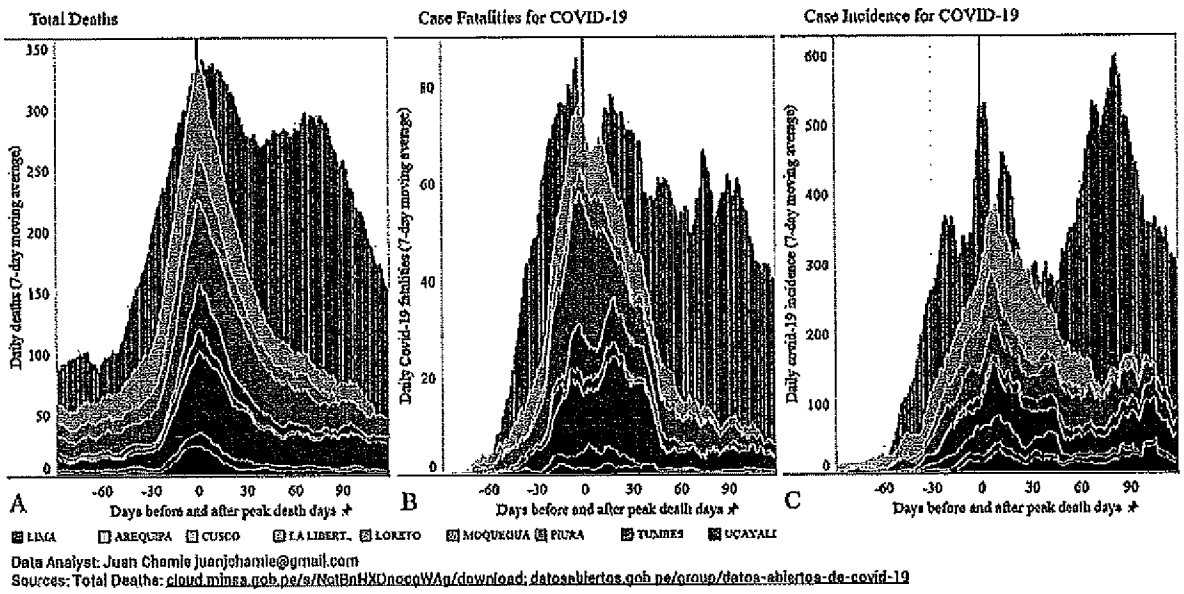

FIGURE 6. Covid-19 case fatalities and total deaths with and without mass ivermectin in different states of Peru.

inhibition of both cytokine production and transcription of nuclear factor-κB (NF-κB), the most potent mediator of inflammation.[37–39]

4. Ivermectin significantly diminishes viral load and protects against organ damage in multiple animal models when infected with SARS-CoV-2 or similar coronaviruses.[31,32]
5. Ivermectin prevents transmission and development of COVID-19 disease in those exposed to infected patients.[40–45]

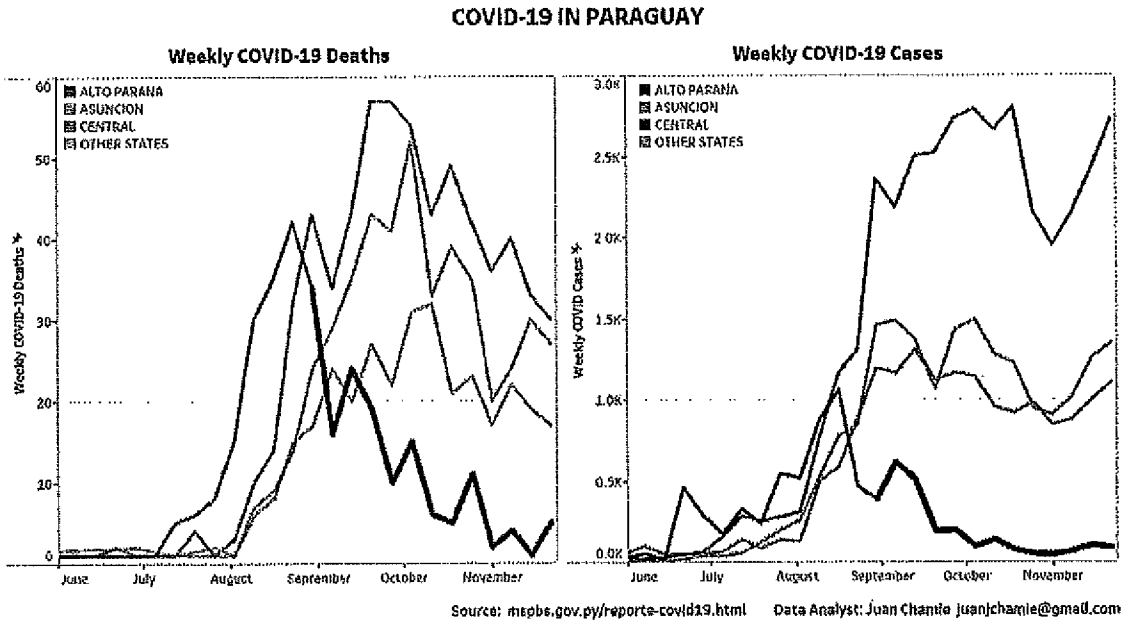

FIGURE 7. Paraguay – COVID-19 case counts and deaths in Alto Parana (bolded blue line) after ivermectin distribution began compared to other regions.

6. Ivermectin hastens recovery and prevents deterioration in patients with mild to moderate disease treated early after symptoms.[45,49–52,61,62]
7. Ivermectin hastens recovery and avoidance of ICU admission and death in hospitalized patients.[45,51,53,63–66]
8. Ivermectin reduces mortality in critically ill patients with COVID-19.[45,53,63]
9. Ivermectin leads to temporally associated reductions in case fatality rates in regions after ivermectin distribution campaigns.[48]
10. The safety, availability, and cost of ivermectin are nearly unparalleled given its low incidence of important drug interactions along with only mild and rare side effects observed in almost 40 years of use and billions of doses administered.[75]
11. The World Health Organization has long included ivermectin on its "List of Essential Medicines."

A summary of the statistically significant results from the above controlled trials are as follows:

Controlled trials in the prophylaxis of COVID-19 (8 studies)

1. All 8 available controlled trial results show statistically significant reductions in transmission.
2. Three RCTs with large statistically significant reductions in transmission rates, N = 774 patients.[44–46]
3. Five OCTs with large statistically significant reductions in transmission rates, N = 2052 patients.[40–43,47]

Controlled trials in the treatment of COVID-19 (19 studies)

1. Five RCTs with statistically significant impacts in time to recovery or hospital length of stay.[45,49,53,64,65]
2. One RCT with a near statistically significant decrease in time to recovery, $P = 0.07$, N = 130.[54]
3. One RCT with a large, statistically significant reduction in the rate of deterioration or hospitalization, N = 363.[49]
4. Two RCTs with a statistically significant decrease in viral load, days of anosmia, and cough, N = 85.[57,60]
5. Three RCTs with large, statistically significant reductions in mortality (N = 695).[45,60,65]
6. One RCT with a near statistically significant reduction in mortality, $P = 0.052$ (N = 140).[53]
7. Three OCTs with large, statistically significant reductions in mortality (N = 1688).[51,63,66]

Safety of ivermectin

Numerous studies report low rates of adverse events, with the majority mild, transient, and largely attributed to the body's inflammatory response to the death of the parasites and include itching, rash, swollen lymph nodes, joint paints, fever, and headache.[75] In a study that combined results from trials including more than 50,000 patients, serious events occurred in less than 1% and largely associated with administration in Loa loa.[76] Furthermore, according to the pharmaceutical reference standard *Lexicomp*, the only medications contraindicated for use with ivermectin are the concurrent administration of antituberculosis and cholera vaccines while the anticoagulant warfarin would require dose monitoring. Another special caution is that immunosuppressed or organ transplant patients who are on calcineurin inhibitors, such as tacrolimus or cyclosporine, or the immunosuppressant sirolimus should have close monitoring of drug levels when on ivermectin given that interactions exist that can affect these levels. A longer list of drug interactions can be found on the *drugs.com* database, with nearly all interactions leading to a possibility of either increased or decreased blood levels of ivermectin. Given studies showing tolerance and lack of adverse effects in human subjects given escalating high doses of ivermectin, toxicity is unlikely, although a reduced efficacy because of decreased levels may be a concern.[77]

Concerns of safety in the setting of liver disease are unfounded given that, to the best of our knowledge, only 2 cases of liver injury have ever been reported in association with ivermectin, with both cases rapidly resolved without need for treatment.[78,79] Furthermore, no dose adjustments are required in patients with liver disease. Some have described ivermectin as potentially neurotoxic, yet one study performed a search of a global pharmaceutical database and found only 28 cases among almost 4 billion doses with serious neurological adverse events, such as ataxia, altered consciousness, seizure, or tremor.[80] Potential explanations included the effects of concomitantly administered drugs that increase absorption past the blood–brain barrier or polymorphisms in the mdr-1 gene. However, the total number of reported cases suggests that such events are exceedingly rare. Finally, ivermectin has been used safely in pregnant women, children, and infants.

DISCUSSION

Currently, as of December 14, 2020, there is accumulating evidence that demonstrates both the safety and efficacy of ivermectin in the prevention and treatment of COVID-19. Large-scale epidemiologic analyses validate the findings of in vitro, animal, prophylaxis, and clinical studies. Epidemiologic data from regions of the world with widespread ivermectin use have demonstrated a temporally associated reduction in case counts, hospitalizations, and fatality rates.

In the context of ivermectin's long-standing safety record, low cost, and wide availability along with the

consistent, reproducible, large magnitude of findings on transmission rates, need for hospitalization, and mortality, widespread deployment in both prevention and treatment has been proposed. Although a subset of trials are of an observational design, it must be recognized that in the case of ivermectin (1) half of the trials used a randomized controlled trial design (12 of the 24 reviewed above) and (2) observational and randomized trial designs reach equivalent conclusions on average as reported in a large Cochrane review of the topic from 2014.[81] In particular, OCTs that use propensity-matching techniques (as in the Rajter study from Florida) find near identical conclusions to later-conducted RCTs in many different disease states, including coronary syndromes, critical illness, and surgery.[82–84] Similarly, as evidenced in the prophylaxis (Figure 1) and treatment trial (Figures 2 and 3) meta-analyses as well as the summary trials table (Table 3), the entirety of the benefits found in both OCT and RCT trial designs aligns in both direction and magnitude of benefit. Such a consistency of benefit among numerous trials of varying sizes designs from multiple different countries and centers around the world is unique and provides strong, additional support.

The continued challenges faced by health care providers in deciding on appropriate therapeutic interventions in patients with COVID-19 would be greatly eased if more updated and commensurate evidence-based guidance came from the leading governmental health care agencies. Currently, in the United States, the treatment guidelines for COVID-19 are issued by the National Institutes of Health. Their most recent recommendation on the use of ivermectin in patients with COVID-19 was last updated on February 11, 2021, where they found that "there was insufficient evidence to recommend for or against ivermectin in COVID-19." For a more definitive recommendation to be issued by major leading public health agencies (PHA), it is apparent that even more data on both the quality and quantity of trials are needed, even during a global health care emergency, and in consideration of a safe, oral, low-cost, widely available and deployable intervention such as ivermectin.

Fortunately, large teams sponsored by 2 different organizations have embarked on this effort. One team, sponsored by the Unitaid/WHO's ACT Accelerator Program and led by the University of Liverpool Senior Research Fellow Dr. Andrew Hill, is performing a systematic review and meta-analysis focused solely on ivermectin treatment RCTs in COVID-19. Although a preliminary meta-analysis of 17 RCTs was posted to a preprint server in February, it is expected that by March 19, 2021, results from approximately 27–29 RCTs including almost 4500 patients will be presented to the WHO Guidelines Committee and that the epidemiologic studies reviewed above by Chamie et al were already presented to the committee in early March (personal communication with Dr. Andrew Hill). It is important to note that on February 5, the WHO Guidelines Committee announced that they had begun a review of the accumulating ivermectin data and expected to arrive at their own formal treatment recommendation within 4–6 weeks. If the above benefits in clinical outcomes continue to be reported in the remaining trials, it is hoped that this almost doubling of the current supportive evidence base would merit a recommendation for use by the WHO, NIH, and other PHA's would be forthcoming.

Because of the urgency of the pandemic, and in response to the surprising persistent inaction by the leading PHA's, the British Ivermectin Recommendation Development Panel was recently coordinated by the Evidence-Based Medicine Consultancy Ltd to more rapidly formulate an ivermectin treatment guideline using the standard guideline development process followed by the WHO. Made up of long-time research consultants to numerous national and international public health organizations including the WHO, they convened both a steering committee and a technical working group that then performed a systematic review and meta-analysis. On February 12, 2021, a meeting was held that included an international consortium of 75 practitioners, researchers, specialists, and patient representatives representing 16 countries and most regions of the world. This Recommendation Development Panel was presented the results of the meta-analysis of 18 treatment RCTs and 3 prophylaxis RCTs including more than 2500 patients along with a summary of the observational trials and the epidemiologic analyses related to regional ivermectin use. After a discussion period, a vote was held on multiple aspects of the data on ivermectin, according to standard WHO guideline development processes. The Panel *found the certainty of evidence for ivermectin's effects on survival to be strong and they recommended unconditional adoption for use in the prophylaxis and treatment of COVID-19.*

In summary, based on the totality of the trials and epidemiologic evidence presented in this review along with the preliminary findings of the Unitaid/WHO meta-analysis of treatment RCTs and the guideline recommendation from the international BIRD conference, ivermectin should be globally and systematically deployed in the prevention and treatment of COVID-19.

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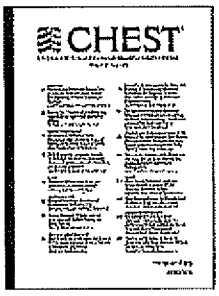

Use of Ivermectin Is Associated with Lower Mortality in Hospitalized Patients with COVID-19 (ICON study)

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Running head: Outcomes of Ivermectin use in Covid-19 infection

Abbreviation List:

OR: odds ratio
CI: confidence interval
BMI: body mass index
MAP: mean arteria pressure
SD: standard deviation
IQR: interquartile range
NNT: number needed to treat
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
COVID-19: Coronavirus Disease 2019
IRB: Institutional Review Board
FIO_2: Fraction of Inspired Oxygen

Keywords:

hospitalized COVID-19, survival, mechanical ventilation, severe pulmonary involvement, ivermectin, in-hospital mortality, NNT.

Abstract

Background:

Ivermectin was shown to inhibit SARS-CoV-2 replication in-vitro, which has led to off-label use, but clinical efficacy has not been previously described.

Research Question: Does ivermectin benefit hospitalized COVID-19 patients?

Study Design and Methods:

Charts of consecutive patients hospitalized at four Broward Health hospitals in Florida with confirmed COVID-19 between March 15 through May 11, 2020 treated with or without ivermectin were reviewed. Hospital ivermectin dosing guidelines were provided but treatment decisions were per treating physician's discretion. The primary outcome was all-cause in-hospital mortality. Secondary outcomes included mortality in patients with severe pulmonary involvement, extubation rates for mechanically ventilated patients, and length of stay. Severe pulmonary involvement was defined as need for FiO_2 ≥50%, noninvasive ventilation, or invasive ventilation at study entry. Logistic regression and propensity score matching were used to adjust for confounders.

Results:

280 patients, 173 treated with ivermectin and 107 without ivermectin, were reviewed. Most patients in both groups also received hydroxychloroquine and/or azithromycin. Univariate analysis showed lower mortality in the ivermectin group (15.0% versus 25.2%, OR 0.52, CI 0.29-0.96, P=0.03). Mortality was also lower among ivermectin-

treated patients with severe pulmonary involvement (38.8% vs 80.7%, OR 0.15, CI 0.05-0.47, p=0.001). There were no significant differences in extubation rates (36.1% vs 15.4%, OR 3.11 (0.88-11.00), p=0.07) or length of stay. After multivariate adjustment for confounders and mortality risks, the mortality difference remained significant (OR 0.27, CI 0.09-0.80, p=0.03).

196 patients were included in the propensity-matched cohort. Mortality was significantly lower in the ivermectin group (13.3% vs 24.5%, OR 0.47, CI 0.22-0.99, p<0.05); an 11.2% (CI 0.38%-22.1%) absolute risk reduction, with a number needed to treat of 8.9 (CI 4.5-263).

Interpretation:

Ivermectin treatment was associated with lower mortality during treatment of COVID-19, especially in patients with severe pulmonary involvement. Randomized controlled trials are needed to confirm these findings.

Introduction

Ivermectin has previously been studied as a therapeutic option for viral infections with data showing some in-vitro activity against a broad range of viruses, including HIV, Dengue, Influenza and Zika virus, likely through inhibition of IMP α/β1-mediated nuclear import of viral proteins.[1,2] Wagstaff et al, demonstrated that Ivermectin was a potent in-vitro inhibitor of SARS-CoV-2, showing a 99.8% reduction in viral RNA after 48 hours.[3] There are reports on the internet of physicians worldwide treating COVID-19 empirically with ivermectin since late April, 2020. Per ClinicalTrials.gov, there are currently 37 studies investigating the usefulness of ivermectin in COVID-19. However, in-vivo efficacy of ivermectin in SARS-CoV-2 infection in humans has not previously been reported.

In the late 1970s ivermectin was developed as a new class of drug to treat parasitic infections. Initially used in veterinary Medicine, it was soon found to be safe and effective in humans. It has successfully been used to treat onchocerciasis and lymphatic filariasis in millions of people worldwide as part of a global drug donation program. About 3.7 billion doses of ivermectin have been distributed in mass drug administration campaigns globally over the past 30 years. Presently, ivermectin is approved for use in humans in several countries to treat onchocerciasis, lymphatic filariasis, strongyloidiasis and scabies.[1]

Based on the data drug safety sheet for Ivermectin (NDA 50-742/S-022), side effects were uncommon and limited. Reported side effects with greater than 1% occurrence included, elevation in ALT/AST (2%), nausea (2%), diarrhea (2%), decreased leukocyte count (3%), peripheral edema (3%), tachycardia (3%), dizziness (3%), and pruritus (3%). A pharmacokinetic study of 166 patients reported side effects of headache (6%), dysmenorrhea (5.5%), URI symptoms (1.8%) and diarrhea (1.8%).[5]

Methods:

Patients

Sequentially consecutive hospitalized patients at four Broward Health associated hospitals in South Florida with laboratory-confirmed infection with SARS-CoV-2 during their admission were reviewed in this study. The list of confirmed cases was provided by the hospitals' epidemiology department. Enrollment dates ranged from March 15, 2020 through May 11, 2020. Confirmatory testing was performed by nasopharyngeal swab using an FDA Emergency Use Authorized COVID-19 molecular assay for the detection of SARS-CoV-2 RNA. Patients younger than 18 years old, pregnant, or incarcerated were excluded from data collection based on IRB requirements. Patients who had at least 2 separate admissions placing them in both groups were also excluded.

Study procedures

Records were abstracted by four of the authors and all data were subsequently reviewed and confirmed by the lead author. Baseline data were collected at the time of ivermectin

administration for the ivermectin group; for the usual care group baseline was either at the time of administration of hydroxychloroquine or, if not used, at the time of admission. Information collected included COVID-19 testing results, patient demographics, pre-existing comorbid conditions, initial vital signs, laboratory results, and the use of corticosteroids, hydroxychloroquine, and azithromycin in order to describe the cohort and to identify potential confounders between groups. Severity of pulmonary involvement was assessed at the time of baseline data collection and categorized as severe or non-severe. Patients were considered to have severe pulmonary involvement if they required an FiO_2 of 50% or greater, high-flow nasal oxygen, noninvasive ventilation, or intubation and mechanical ventilation. The non-severe pulmonary criteria encompassed patients who required no supplemental oxygen, or "low FIO_2" (i.e. Venturi mask 40% or less, or up to 6 L/min of low flow nasal cannula), independent of laboratory findings.

Patients were categorized into two treatment groups based on whether they received ivermectin at any time during the hospitalization. Patients in the ivermectin group received at least one oral dose of ivermectin at 200 micrograms/kilogram in addition to usual clinical care. A second dose could be given at the discretion of the treating physician at day 7 of treatment. Ivermectin is not currently FDA-approved for COVID-19. The decision to prescribe ivermectin, hydroxychloroquine, azithromycin, or other medications was at the discretion of the treating physicians, however hospital guidelines were established for the safe use and dosing of these agents. These guidelines included a

baseline EKG and mandatory cardiac and QTc monitoring for patients receiving hydroxychloroquine (alone or in combination with azithromycin) avoidance of azithromycin if patient's baseline QTc was greater than 460msec, and discontinuation of hydroxychloroquine if there was a concerning elevation in QTc or if the patient's cardiologist recommended discontinuation. Oxygen and ventilatory support were applied per the customary care. Empiric use of ivermectin was given explicitly for COVID-19.

Outcomes

The primary outcome was all-cause in-hospital mortality. Patient was considered a "survivor" if they left the hospital alive, or if their status in the hospital changed from active care to awaiting transfer to a skilled facility. Two consecutive negative nasopharyngeal swab specimens for SARS-CoV-2, collected ≥ 24 hours apart, were necessary for a patient to be accepted to the local skilled nursing facilities.

Secondary outcomes included subgroup mortality of patients with severe pulmonary involvement, extubation rates for patients requiring mechanical ventilation, and length of hospital stay. Length of stay was calculated from day of admission to either the day of discharge or to patient death.

Statistical analysis

Univariate analysis of the primary mortality outcome, and comparisons between treatment groups were determined by Student's t test for parametric continuous variables or Mann-Whitney U test for nonparametric continuous variables as appropriate, and by

Pearson Chi Square test for categorical variables. The method of Hodges-Lehman was used to estimate median differences with 95% confidence intervals.

To adjust for confounders and between-group differences, a multivariate analysis was performed using stepwise binary logistic regression. Patient variables included in the analysis were age, sex, comorbidities of diabetes, chronic lung disease, cardiovascular disease, and hypertension, smoking status, severity of pulmonary involvement, need for mechanical ventilation at study entry, body mass index (BMI), peripheral white blood count, absolute lymphocyte count, and use of corticosteroids based on bivariate associations within our data, a priori plausibility, and documented associations with mortality from previous studies. Adjusted odds ratio with 95% confidence intervals were computed to show level of certainty. Analyses were based on non-missing data and missing data were not imputed. Missingness of 1% was found for peripheral white blood cell count, 5% for smoking status, and 7% for absolute lymphocyte count.

We performed a secondary analysis using propensity score matching to reduce the effects of confounding and likelihood of selection bias. Propensity matching was performed using a nearest-neighbor algorithm with 1:1 matching without replacement, and a caliper distance of less than 0.2. Variables for propensity scoring included those variables from the univariate between-groups analysis of the unmatched cohort that had a P value less than 0.2 (age, sex, pulmonary condition, hypertension, HIV, severe pulmonary presentation, exposure to corticosteroids, hydroxychloroquine, or azithromycin). Race,

white cell count, absolute lymphocyte count, and need for mechanical ventilation prior to or on the day of study entry were also added as potential clinical confounders.

All tests were 2-sided and a p value <.05 was considered statistically significant. Statistical analyses were conducted using IBM SPSS v 26.0 software (Armonk, NY), R software v 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria), and SPSS PS-matching software (sourceforge.net).

This study was conducted in accordance with the amended Declaration of Helsinki. The protocol was approved by the Institutional Review Board for the Broward Health Hospital System, protocol approval number 2020-034-BHMC. The authors assume responsibility for the accuracy and completeness of the data and analyses, as well as for the fidelity of the study.

Results

Characteristics of the patients

307 patients were admitted for COVID-19 during the time period studied. 4 patients were not reviewed due to multiple admissions, 11 did not have COVID-19 confirmed at the time of the study, and 12 were excluded due to either age younger than 18 years old, pregnancy, or incarceration. The remaining cohort of 280 patients was comprised of 173 treated with ivermectin and 107 in the usual care group. Most patients received a single dose of ivermectin; however 13 patients received a second dose of ivermectin for ongoing signs or symptoms at day 7 of treatment. Follow up data for all outcomes were

available through May 19th, 2020. No patients were lost to follow-up for the primary outcome. At the time of analysis, all patients in both groups had met the endpoint of death, discharge alive, or awaiting transfer to a skilled facility. Of those awaiting transfer, in the control group, one patient was awaiting transfer to hospice due to an unrelated terminal illness, and one patient was awaiting a negative COVID-19 test to proceed with unrelated surgery. In the ivermectin group, five patients were in stable condition, awaiting transfer to skilled facility/rehab, and one patient was clinically improving. Baseline characteristics and between-group comparisons for unmatched and propensity-matched cohorts are shown in Table 1. Before matching, hypertension and corticosteroid use were more prevalent in the ivermectin group, whereas the use of hydroxychloroquine and hydroxychloroquine plus azithromycin were higher in the usual care group. Propensity score matching created a total of 98 matched pairs. After matching there were no statistically significant differences between the two groups. Eight patients in the propensity matched group received a second dose of ivermectin on day 7.

Outcomes

Unadjusted outcomes for the unmatched cohort, and outcomes in the propensity matched cohort are shown in Table 2. For the unmatched cohort, overall mortality was significantly lower in the ivermectin group than in the usual care group (15.0% vs 25.2%, for ivermectin and usual care respectively, p.03). Mortality was also lower for ivermectin treated patients in the subgroup of patients with severe pulmonary involvement (38.8%

vs. 80.7% for ivermectin and usual care respectively, p=.001). On univariate analysis, patients receiving corticosteroids had a higher mortality than those that did not (30.0% vs 13.7%, OR 2.7 (1.47 to 4.99; p=.001); however, corticosteroids were more likely to have been prescribed for severe patients (58.6% vs 22.4% for severe and nonsevere respectively, OR 4.91 (2.78 to 8.63, p<.001).

Results were similar, with lower mortality in the ivermectin treated patients for the matched cohort for the group as a whole and for the subgroup with severe pulmonary involvement (Table 2). In the matched cohort, ivermectin was associated with an absolute risk reduction of 11.2% (CI 0.38%-22.1%) and a corresponding number needed to treat of 8.9 (CI 4.5-263) to prevent one death. We found no difference in median hospital length of stay or in extubation rates, in either the unmatched or matched cohorts. Of note, 1 of the 13 patients who received a second dose of ivermectin died; this patient was not in the propensity matched cohort.

Multivariate analysis was performed on the unmatched cohort, adjusting for demographic factors and between-group differences in mortality risks. Independent predictors of in-hospital mortality included treatment group, age, severe pulmonary disease category, and reduced lymphocyte count (Table 3). As race was not a significant predictor after adjustment, a further analysis was performed which showed white patients were significantly older than Black (66.8 vs 59.1 years; mean difference 7.7 years, CI 3.0 –

12.4, p=.001) and Hispanic patients (49.8 years, mean difference 17.0 years, CI 9.6 – 24.4, p<.001).

Discussion

In this multihospital retrospective cohort study, we observed a significant association with ivermectin on improved survival for patients admitted with COVID-19. This association was also seen in the subset of patients with severe pulmonary disease. These findings were confirmed after multivariate adjustment for comorbidities and differences between groups, and also in a propensity score matched cohort.

Similar to other studies, we noted that older age, cardiac disease, current or former smoking, more severe pulmonary involvement at presentation, higher white blood cell counts, and lower lymphocyte counts emerged as risk markers for in-hospital mortality. The overall mortality, and mortality in intubated patients, in our usual care group was similar to what was reported in previous studies. Richardson et al reported an overall mortality of 21% in their New York City cohort, with a mortality of 88% in intubated patients.[6] Fei Zhou et al reported a 28.2% mortality in their cohort of hospitalized patients in Wuhan, China; their intubated patients had a mortality of 96.9%.[7] In contrast to Ambati et al, we did not see a higher mortality effect for hydroxychloroquine.[8] This may have been due to the small number of patients who were not treated with these agents; our study was thus underpowered to detect a difference in mortality from hydroxychloroquine treatment. We also hypothesize that precautionary measures in the

hospitals' protocol for hydroxychloroquine use could have prevented them from developing fatal arrhythmias. These included baseline EKG and daily QTc monitoring by telemetry for any patient receiving hydroxychloroquine or combination therapy, avoidance of azithromycin if patient's baseline QTc was greater than 460msec, and discontinuation of hydroxychloroquine if there was a concerning elevation in QTc or if the patient's cardiologist recommended discontinuation. In contrast to Horby et al[9], we did not find a mortality benefit for patients who were prescribed corticosteroids on our multivariate analysis, which included several severity covariates. These findings are likely explainable by physicians' choice to reserve use of corticosteroids for the most seriously ill patients, as the study was performed prior to the results of the RECOVERY trial.[9]

We also did not confirm a higher risk of mortality in Black patients in comparison to white patients after controlling for age. Prior reports have shown lower survival rates among Black and Hispanic patients;[10] however Price et al also found no racial differences in mortality.[11] In our hospital population, white patients were significantly older, which is reflective of our catchment area and may be responsible for the discrepancy.

We did not observe a significant difference in hospital length of stay between the groups (median 7 days for both groups) despite the lower mortality. Possible explanation could include delay in discharging patients to other facilities (skilled nursing facilities, inpatient

rehabs, etc) due to lag in obtaining required repeat COVID-19 testing results. Patients who died were included in length of stay measurements.

Use of mechanical ventilation was not adopted as outcome of interest, as guidelines and practice patterns for intubation criteria changed throughout the length of the study. We were unable to determine ICU length of stay and ventilatory free days in the ICU, as overflow conditions during the pandemic placed critically patients in the emergency room and other non ICU environments and we could therefore not accurately determine ICU stay. We did not find a lower mortality in the subgroup of non-severe patients treated with ivermectin; however, our study was not powered to assess these differences as the overall mortality in non-severe patients was low. Similarly, the study was not powered to determine whether extubation rates were higher in the ivermectin group. These should be investigated further with a larger randomized controlled trial.

Interpretation

Our study has several limitations. Due to the retrospective observational nature of the study, despite adjustment for known confounders and propensity score matching, we cannot exclude the possibility of unmeasured confounding factors. Although more of the control group was enrolled in the first weeks of the study, suggesting the possibility of timing bias, this may be offset by preferential treatment of more severe patients with ivermectin early in the study due to low initial availability. We also did not find consistently different mortality outcomes with time over the short duration of this study.

We also did not find evidence of immortal time bias, as only one of the control patients died less than 5 days from admission, the average time from admission to death was 11 days, and the vast majority of patients received ivermectin in 2 days or less. If we omit the patient with potential immortal time from the analysis, the mortality difference remains significant in both unmatched (15.0% vs 24.5% for ivermectin and usual care respectively, $p<.05$) and matched (12.4% vs 25.0% for ivermectin and usual care respectively, $p<0.03$) cohorts. Most of our patients studied received hydroxychloroquine with or without azithromycin and we are unable to determine whether these medications had an added benefit, or whether mortality would have been better in both groups without these agents.

We have shown that ivermectin administration was significantly associated with lower mortality among patients with COVID-19, particularly in patients with more severe pulmonary involvement. Interpretation of these findings are tempered by the limitations of the retrospective design and the possibility of confounding. Appropriate dosing for this indication is not known; nor are the effects of ivermectin on viral load, or in patients with milder disease. Further studies in appropriately designed randomized trials are recommended before any conclusions can be made.

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Juliana C.Rajter, M.D.- lead author, had full access to all of the data in the study, contributed with study design, data collection and interpretation, writing of manuscript

Michael S. Sherman, M.D.- provided data analysis and interpretation, and contributed to writing of the manuscript

Naaz Fatteh, M.D. - contributed with data collection and literature search

Fabio Vogel, Pharm. D. - contributed to the study design and data collection

Jaime Sacks, Pharm. D. - contributed to data collection and data organization

Jean-Jacques Rajter, M.D.- corresponding author, contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

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"Take Home Point"

Question: Is Ivermectin associated with lower mortality rate in patients hospitalized with COVID-19?

Results: Retrospective cohort study of consecutive patients hospitalized with confirmed SARS-CoV-2 at a four- hospital consortium in South Florida. Analysis showed statistically significant lower mortality rates in the group treated with Ivermectin, as compared to the group treated with "usual care" (15.0% versus 25.2%).

Interpretation: Ivermectin was associated with lower mortality during treatment of COVID-19, especially in patients who required higher inspired oxygen or ventilatory support.

Table 1: Patient Characteristics by Treatment Group

	Unmatched Cohort				Matched Cohort			
Demographic characteristics	**Total (n=280)**	**Usual Care (n=107)**	**Ivermectin (n=173)**	**P value**	**Total (n=196)**	**Usual Care (n=98)**	**Ivermectin (n=98)**	**P value**
Age[a], years	59.6 (17.9)	58.6 (18.5)	60.2 (17.6)	0.45	59.6 (17.5)	59.04 (17.7)	60.07 (17.4)	0.68
Female sex	127 (45.4)	43 (41.2)	84 (48.6)	0.17	78 (39.8)	39 (39.8)	39 (39.8)	1.0
Race ethnicity				0.36				1.0
Black	153 (54.6)	55 (51.4)	98 (56.6)		108 (55.1)	54 (55.1)	54 (55.1)	
White	76 (27.1)	35 (32.7)	41 (23.7)		55 (28.1)	27 (27.6)	28 (28.6)	
Hispanic	33 (11.7)	12 (11.2)	21 (12.1)		23 (11.7)	12 (12.5)	111 (11.2)	
Other or not identified[c]	13 (4.6)	5 (4.7)	13 (7.5)		10 (5.1)	5 (5.1)	5 (5.1)	
Current or former smoker	46/255 (18.0)	22/99 (22.3)	24/156 (15.6)	0.40	31/180 (22.2)	20/90 (22.2)	11/90 (12.2)	0.11
Number of comorbidities[d]	1.66 (1.34)	1.60 (1.46)	1.70 (1.27)	0.57	1.56 (1.33)	1.58 (1.43)	1.53 (1.22)	0.79
Diabetes	90 (32.1)	31 (29.0)	59 (34.1)	0.37	59 (30.1)	30 (30.6)	29 (29.6)	0.88
Cardiac	43 (15.4)	18 (16.8)	25 (14.5)	0.59	27 (13.8)	16 (16.3)	11 (11.2)	0.30
Pulmonary	28 (10.0)	14 (13.1)	14 (8.9)	0.18	18 (10.1)	10 (10.2)	8 (8.2)	0.62
Obesity	114 (40.7)	42 (39.3)	72 (41.6)	0.70	79 (40.3)	39 (39.8)	40 (40.1)	0.88
Renal	24 (8.6)	10 (9.4)	14 (8.1)	0.72	16 (8.2)	9 (9.2)	7 (7.1)	0.60
Cancer	17 (6.1)	8 (7.5)	9 (5.2)	0.44	14 (7.1)	7 (7.1)	7 (7.1)	1.00
Hypertension	50 (17.9)	13 (12.2)	37 (21.4)	0.05	26 (13.2)	12 (12.2)	14 (14.3)	0.67
Neurologic	28 (10.0)	8 (7.5)	20 (11.6)	0.27	17 (8.7)	8 (8.2)	9 (9.2)	0.80
HIV infection	9 (3.2)	1 (1)	8 (4.6)	0.09	3 (1.5)	1 (1.0)	2 (2.0)	0.56
Thyroid	23 (8.2)	7 (6.6)	16 (9.3)	0.42	15 (7.7)	7 (7.1)	8 (8.2)	0.79
BMI[e]	30.0 (7.8)	29.8 (7.2)	30.1 (8.2)	0.81	29.4 (6.6)	29.4 (6.3)	29.4 (6.9)	0.95
Pulmonary severity				0.46				
Severe	75 (26.8)	26 (24.3)	49 (28.3)	0.12	47 (24.0)	22 (22.4)	25 (25.5)	0.62
Intubated at study entry	38 (13.6)	15 (14.0)	23 (13.3)	0.86	25 (12.8)	11 (11.2)	14 (14.3)	0.52
Heart rate[b]	86.0 (75.0, 98.0)	86.0 (74.0, 97.0)	86.0 (75.5, 98.0)	0.65	85.5 (74.0, 98.0)	86.0 (73.0, 97.5)	85.0 (74, 98.0)	0.88
MAP (mm Hg)[b]	93 (82.3, 103.0)	90 (81.0, 103.0)	94 (83, 103)	0.24	92.5 (82.0, 103.0)	91.0 (81.0, 103.2)	93.0 (82.0, 103.0)	0.74
MAP ≤ 70 mm Hg	13/260 (5.0%)	6/89 (6.7%)	7/171 (4.1%)	0.35	7 (3.6)	4 (4.1)	3 (3.1)	0.70
Corticosteroid	90 (32.1)	21 (19.6)	69 (39.8)	0.001	46 (23.2)	21 (21.4)	25 (25.5)	0.5
Hydroxychloroquine	260 (92.9%)	104 (97.2)	156 (90.2)	0.03	190 (96.9)	95 (96.9)	95 (96.9)	1.00
Azithromycin	243 (86.7%)	99 (92.5)	144 (83.2)	0.03	177 (90.3)	90 (91.8)	87 (88.7)	0.47
Peripheral white cell count ($X 10^9/L$)[b]	7.3 (5.6, 10.2) (n=277)	7.0 (5.7, 8.9) (n=106)	7.6 (5.5, 11.1) (n=171)	0.41	6.9 (5.3, 9.3)	7.0 (5.8, 9.0)	6.9 (5.2, 9.8)	0.69
Lymphocyte count (X	1.15 (0.78, 1.56)	1.14 (0.84, 1.49)	1.20 (0.77, 1.67)	0.62	1.13 (0.77, 1.52)	1.15 (0.87,	1.19 (0.75,	0.88

10^9/L)[b]	(n=260)	(n=102)	(n=158)			1.45)	1.57)	

BMI = body mass index. MAP = mean arterial pressure

[a] mean (± SD)

[b] median (interquartile range)

[c] Asian, Native American, Pacific Islander, or not identified

Table 2: Univariate Clinical Outcomes by Treatment Group

	Unmatched cohort				Matched cohort			
	Number/total number (%) or median (IQR)				Number/total number (%) or median (IQR)			
	Control (n=107)	Ivermectin (n=173)	OR or difference (CI)	P value	Control (n=98)	Ivermectin (n=98)	OR or difference (CI)	P value
Mortality								
Total	27 (25.2)	26 (15.0)	0.52 (0.29 to 0.96)	0.03	24 (24.5)	13 (13.3)	0.47 (0.22 to 0.99)	0.045
Severe	21/26 (80.7)	19/49 (38.8)	0.15 (0.05 to 0.47)	0.001	18/22 (81.8)	8/25 (32.0)	0.27 (0.08 to 0.92)	0.002
Non-severe	6/81 (7.4)	7/124 (5.6)	0.75 (0.24 to 2.3)	0.61	6/76(7.9)	4/74 (5.4)	0.97 (0.61 to 1.54)	0.78
Successful extubation	4/26 (15.4)	13/36 (36.1)	3.11 (0.88 to 11.00)	0.07	3/22 (15.4)	7/18 (38.9)	1.91 (0.43 to 8.46)	0.14
Length of stay (median, IQR)	7.0 (4.0, 10.0)	7.0 (4.0, 13.3)	0 (-1 to 2)	0.34	7.0 (4.0, 10.0)	7.0 (3.0, 13.0)	0 (-2 to 1)	0.88

IQR = interquartile range

Table 3: Multivariate analysis of factors associated with mortality

	OR (CI)	P value
Treatment group:		
Ivermectin	0.27 (0.09 to 0.80)	0.03
Control	Reference	
Age	1.05 (1.02 to 1.09)	0.003
Female sex	0.42 (0.24 to 1.82)	0.42
Male sex	Reference	
Current or former smoker	3.49 (0.71 to 17.32)	0.13
Nonsmoker	Reference	
Race		0.18
Black	0.64 (0.21 to 1.94)	0.43
Hispanic	0.14 (0.02 to 1.22)	0.08
Other	0.62 (0.05 to 7.92)	0.71
White	Reference	
Comorbidities		
Diabetes	1.17 (0.39 to 3.55)	0.78
Cardiac	1.51 (0.43 to 5.22)	0.52
Pulmonary	0.15 (0.20 to 1.84)	0.15
Hypertension	0.72 (0.17 to 3.08)	0.66
No comorbidities	Reference	
BMI	0.97 (0.89 to 1.07)	0.58
Severe presentation	11.41 (3.42 to 38.09)	<0.001
Intubated at study entry	2.96 (0.73 to 12.06)	0.13
MAP ≤ 70 mm Hg	1.82 (0.17 to 19.1)	0.62
Corticosteroid treatment	1.71 (0.52 to 5.16)	0.34
Peripheral white cell count	1.08 (0.96 to 1.23)	0.22
Lymphocyte count	3.65 (1.25 to 10.60)	0.02

Abbreviations: BMI – body mass index, MAP – mean arterial pressure.

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

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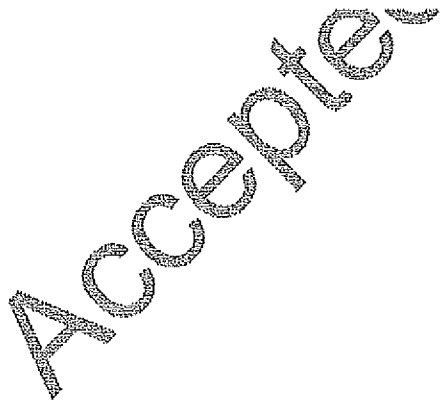
Abstract

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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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
González [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	18.4	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 Nlaee (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), $I^2 = 86.9\%$								

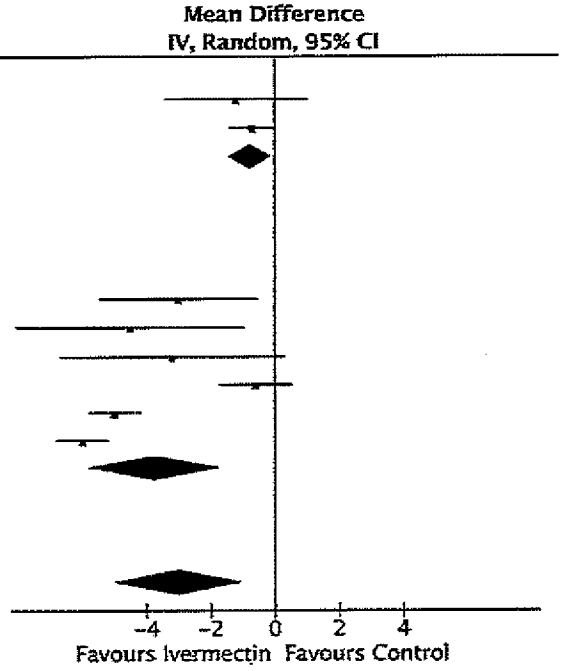


Figure 1B

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), $I^2 = 0\%$						

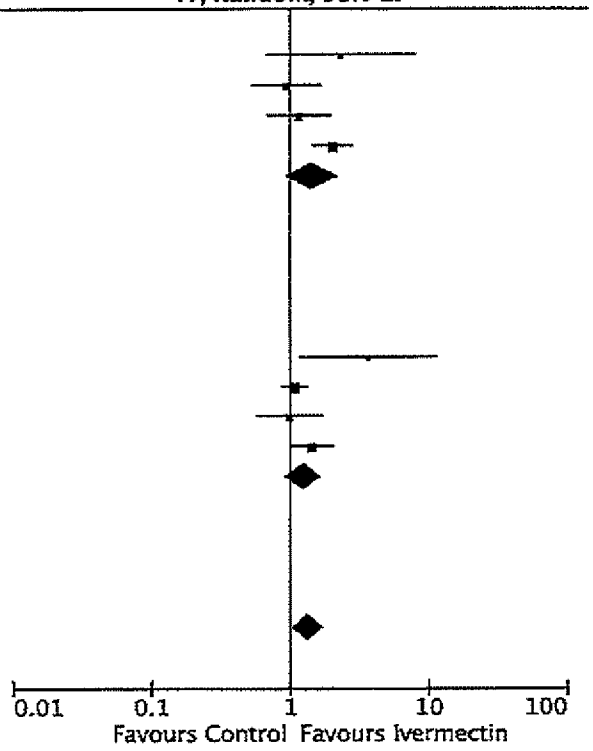


Figure 1C

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), $I^2 = 56.2\%$						

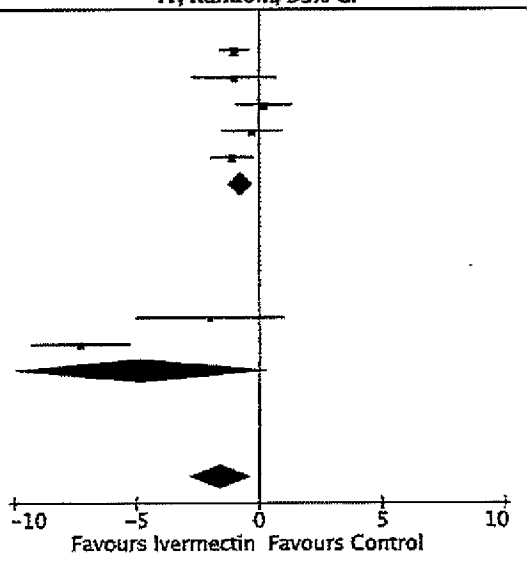


Figure 1D

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 ($P = 0.60$), $I^2 = 0\%$						

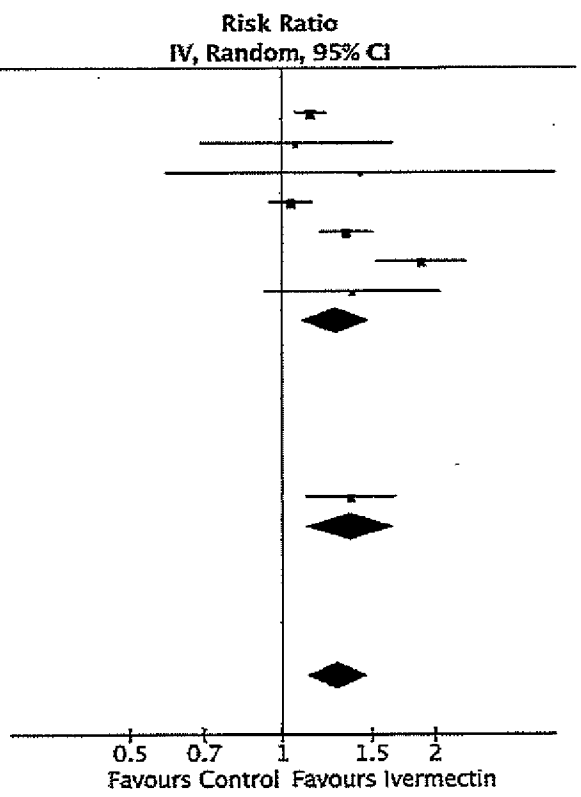


Figure 1E

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), $I^2 = 70.2\%$								

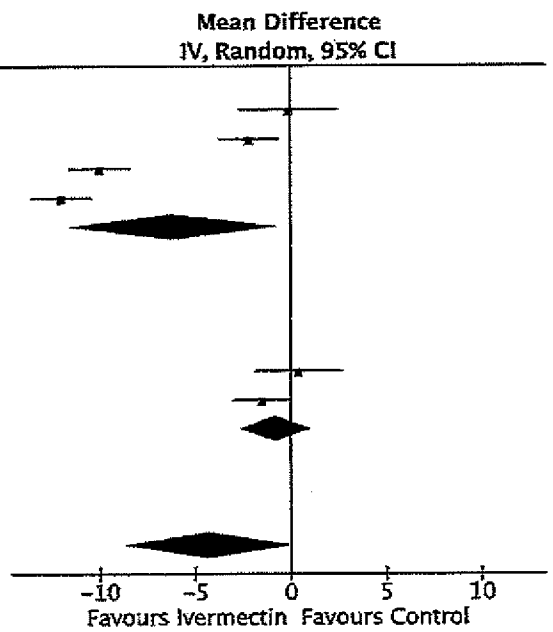


Figure 1F

1F) Study or Subgroup	Ivermectin Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Bangladesh Chowdhury et al	0	60	2	56	11.2%	0.19 [0.01, 3.81]
Colombia Lopez-Medina et al	4	200	6	198	65.2%	0.66 [0.19, 2.30]
Israel Schwartz et al	0	49	3	45	11.8%	0.13 [0.01, 2.48]
Lebanon Raad et al	0	50	3	50	11.8%	0.14 [0.01, 2.70]
Total (95% CI)		**359**		**349**	**100.0%**	**0.40 [0.14, 1.08]**
Total events	4		14			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.88$, $df = 3$ ($P = 0.60$); $I^2 = 0\%$

Test for overall effect: $Z = 1.80$ ($P = 0.07$)

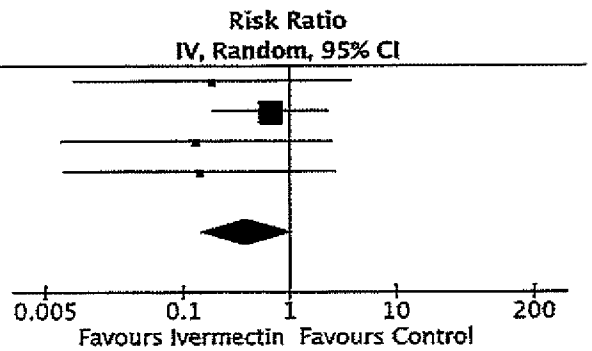


Figure 1G

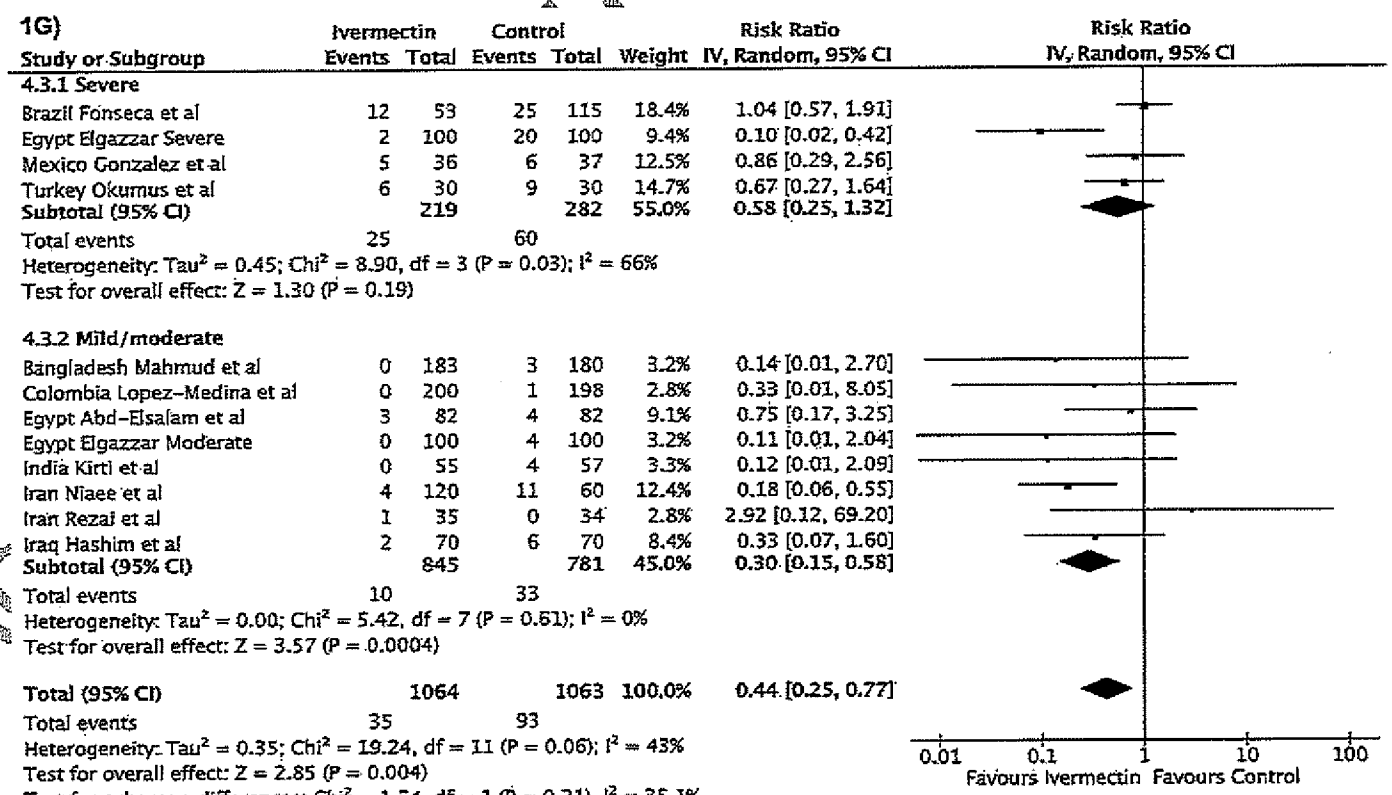


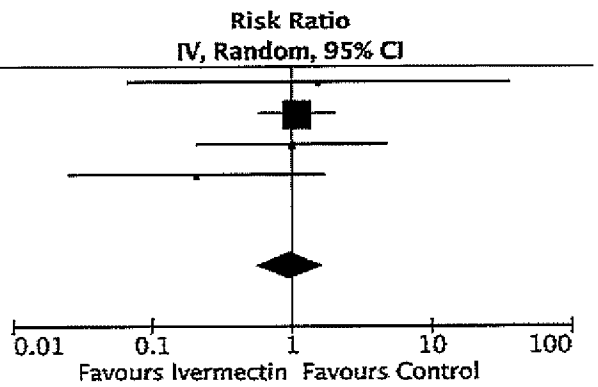
Figure 1H

1H)

Study or Subgroup	Ivermectin Events	Total	Control Events	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: $Z = 0.10$ ($P = 0.92$)



INDIAN BAR ASSOCIATION

(THE ADVOCATES' ASSOCIATION OF INDIA)

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Maharashtra (India) Tel: +91-22-49717796, Website: www.indianbarassociation.in

Contact us : dipaliojha@indianbarassociation.in

May 25, 2021

LEGAL NOTICE

To

Dr. Soumya Swaminathan

Chief Scientist,

World Health Organisation

Avenue Appia 20

1211 Geneva, Switzerland

Subject: 1. Running a disinformation campaign against Ivermectin by deliberate suppression of effectiveness of drug Ivermectin as prophylaxis and for treatment of COVID-19, despite the existence of large amounts of clinical data compiled and presented by esteemed, highly qualified, experienced medical doctors and scientists.

2. Issuing statements in social media and mainstream media, thereby influencing the public against the use of Ivermectin and attacking the credibility of acclaimed bodies/institutes like ICMR and AIIMS, Delhi, which have included 'Ivermectin' in the 'National Guidelines for COVID-19 management'

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Madam,

I, the undersigned, serve the following legal notice upon you:

1. This legal notice is divided in Eight sections:

Sr. Nos	Particulars	Para Nos
1.	Your views and statements against the use of Ivermectin for treatment of **COVID-19.**	**para 2 to 10, para 36, 37, 46**
2.	Extensive studies and trials that prove effectiveness of Ivermectin in treatment of **COVID-19.**	**para 11 to 20, para 30 to 35**
3.	Cases in the United States where older COVID-19 patients who were critically ill, either in comatose state or on ventilators, who have successfully recovered after Ivermectin was included in their line of treatment. Not to miss the crucial role of Courts, who intervened and directed the hospitals to administer Ivermectin on such patients who were at the doorstep of death.	**para 21 to 29**
4.	Cognizance taken of the 'Public Statement' issued by FLCCC on the Irregular Actions of Public Health Agencies and the Widespread Disinformation Campaign against Ivermectin.	**para 38 to 42**
5.	Ivermectin and 'The National Clinical Guidelines for Covid-19 management' issued by ICMR.	**para 43 to 45**

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6.	Main grounds for issuance of this legal notice.	**para 48 to 57**
7.	Falling standards of World Health Organization.	**Para 58 to 61**
8.	Commendable work by select courageous medical doctors who have lived up to their Hippocratic Oath.	**para 62 to 67**

2. That, you have tweeted the following on **May 10, 2021** on Twitter:

> *"Safety and efficacy are important when using any drug for a new indication. @WHO recommends against the use of Ivermectin for #COVID19 except within clinical trials https: //t.co/dSbDiW5tCW*
>
> *— Soumya Swaminathan (@doctorsoumya) May 10, 2021"*

3. That, the above-mentioned tweet came soon after the announcement from the State Health Minister of Goa, India on May 10, 2021 that all the adults in Goa would be given the oral drug **Ivermectin** (hereinafter referred to as '**Ivermectin**') as a prophylactic (Preventive) measure, irrespective of their coronavirus status, in a bid to bring down mortality. He stated that the reason behind such prescription was the study conducted by expert panels from the UK, Italy, Spain and Japan, who found a statistically significant reduction in mortality due to **Ivermectin**.

4. That, you have posted the above tweet in your official capacity as the Chief Scientist at the World Health Organisation (hereinafter referred to as WHO).

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5. That, you have included a hyperlink in your tweet **https://t.co/dSbDiW5t CW**, which upon clicking takes the reader to a page on the website of pharmaceutical company Merck, that displays a statement dated February 4, **2021** issued by Merck titled **'Merck Statement on Ivermectin use during Covid Pandemic'**. Refer **Annexure 1.**

6. That, you have appeared on YouTube channel **MOJO STORY** on **May 16, 2021**, wherein you have been interviewed by Ms. Barkha Dutt in a vlog titled **'Fears of "Prolonged Second Wave" says WHO Chief Scientist on India's COVID Calamity'**.

The link to access this vlog is as follows:
https://www.youtube.com/watch?v=N2lNIYXrLJA
That, in this vlog,

At **23:40** markup, Ms. Barkha Dutt has posed a question to you on effectiveness of medicines currently being administered to Covid-19 patients in the absence of vaccines and she specifically asks your views on **Ivermectin** to start with.

At **24:28** markup, you have replied;

> *"You know, evidence-based guidance and treatment, prevention is really the way to go and what we have tried at the WHO is to update our guidance as often as possible, based on the emerging data. So we have something called like the Living Guideline that we update whenever some new evidence comes out. So we got evidence on Hydroxychloroquine, Lupinavir, Ritonavir, Interferon,* ***Ivermectin*** *, Remdesivir and* ***all of these, the evidence does not support its use,*** *you know, on a wide scale for people infected with SARS CoV-2.*

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The one drug that has a big mortality benefit is simple Dexamethasone corticosteroids, given at the right stage of the disease because COVID-19 is a viral infection. As of now, we have no anti virals that really act very dramatically on this virus and they would need to be given in the early stage of the disease. We are hoping there are some anti virals in development that will come very soon. So the early stage, you can use monoclonal antibodies, again still under research antivirals and the second phase of the disease that is the anti-inflammatory – that's where the lungs are getting blocked with infection and people's oxygen levels are dropping and that's when steroids help and the anti-inflammatory drugs and the anti-IL-6 inhibitors, they help. That's when patients need oxygen. So what's lifesaving, its oxygen, its corticosteroids given to moderate and severely ill patients and perhaps the anti-IL-6 inhibitors. None of these other drugs which are widely being used including antibiotics has..." (not audible as Ms. Barkha Dutt has started her next question)

Ms. Barkha Dutt at **26:24** –...(sound interruption) Azithromycin, **Ivermectin**, Fabiflu that are now being given set base template. You would say none of these need to be given or should be given.

To which you have responded at **26:34** as under;

*"**There is no evidence that they have any impact on the disease progression so I would rather spend those resources on giving people good quality masks to wear**. In the absence of vaccines, masks are the only vaccines. Everybody wears good quality masks, covering their nose and mouth, that is going to make a big difference at the community level*

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and of course spend resources on ramping up of oxygen and other supplies that you need in the hospital, getting the work force there ready. You will have to supplement the work force because the existing doctors and nurses are not going to be enough to cope with the kind of load that we have seen, so those are the kind of investments that need to be made and you know these drugs really that's not going to be the ones that have an impact."

Ms. Barkha Dutt at 27:30 – Ok I know you are on limited time. I just have one more question on the drugs and then we will do the overall picture. Remdesivir and Plasma Therapy. These are two, again the obsessive things that continue in India. Your last word on those.

To which you have replied at **27:44** as under;

"Again, we had, don't have WHO guidance on plasma therapy but the trial which has just reported, the Recovery trial, in a very large number of patients showed clearly that the plasma therapy is of no benefit. The ICMR trial, many months ago showed the same thing in India. So plasma therapy again, you know, there is poor patient running around trying to get plasma for their relatives. I can understand the desperation, both on the side of patients and the side of doctors, just to do something, do everything possible just to save your loved ones but unfortunately, using these unproven therapies doesn't help, you know to save lives. So what is really critical is the oxygen at the right time and monitoring of people, making sure they get oxygen when they start de-saturating, they get the corticosteroids at the right time, they get the ICU care, the ventilation, the supportive care at the right time, that's really important and I think ongoing research, so again India has large

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number of scientific institutions, there are a number of early leads that different labs are talking about, all of these need to go through the clinical trials and should be tested to see whether they have, we desperately need better treatments for this virus, we don't have and so that should continue. But in the meantime, it is really the approach of testing, identifying people, following them up, monitoring them, getting them into care. Majority of the people will not need to be hospitalized obviously they can be managed at home but the ones who need to must get there and that's the only way to reduce the deaths that we have seen happening now."

7. That, your act of posting the said tweet on May 10, 2021 as well as responses to the questions in the interview on **MOJO STORY** on May 16, 2021 against the use of **Ivermectin** for treatment of COVID-19, are highly unconscionable, misleading and issued with ulterior purposes and deliberate intention to underplay the effectiveness of **Ivermectin** in treating the COVID-19 patients as well as its use as a prophylaxis and to dissuade people from using this drug by creating doubts in the minds of people around safety of **Ivermectin**.

8. That, you have deliberately disregarded the fact that there is loads of data to prove that **Ivermectin** is a safe drug and has no harmful effects in general. The drug **Ivermectin** which was discovered in 1975, has been around for around 40 years and has also won the Nobel Peace Prize. The 2015 Nobel Prize for medicine and physiology was shared between scientists which included Irish parasitologist William C. Campbell and Japanese microbiologist Satoshi Ōmura for discoveries that led to **Ivermectin**.

https://www.newscientist.com/article/dn28284-breakthrough-

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drugs-for-malaria-and-roundworm-win-medicine-nobel/

9. That, the **Ivermectin** is also recognized by WHO as one of the ten essential medications. Around 3.7 billion dosages of **Ivermectin** have been given out in last 40 years and there is sufficient data to prove its safety. That, you have wilfully ignored the mountains of data that shows that **Ivermectin** is undeniably helpful as prophylactic in preventing contracting COVID-19 and there is compelling evidence of its effectiveness in treating active COVID-19 in hospitalized patients.

10. That, you have intentionally ignored the research undertaken by several doctors, scientists and their associations and alliances, who had started early on the pandemic, fervently searching for medicine/drug that would help in treatment of COVID-19. Their work which includes discussions, paper presentations, data on clinical trials, is readily available on the internet.

11. That, you have deliberately chosen to ignore the work of your own brethren of diligent doctors, physicians and scientists like the 'Front Line **COVID - 19** Critical Care Alliance' (hereinafter referred to as **'FLCCC'**) and the British **Ivermectin** Recommendation Development (hereafter referred to as 'BIRD') Panel

12. That, FLCCC is an alliance of experienced and esteemed medical doctors and scientists, who have come together at the start of the COVID-19 pandemic and are working tirelessly in conducting research, studies and Randomized Control Trial (hereafter referred to as RCTs).

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The website of FLCCC has ocean of information regarding treatment protocols for COVID-19, recommendations from esteemed and experienced medical professionals, testimonies of medical doctors and patients who have benefitted from the work of FCCCL.

https://covid19criticalcare.com/

13. That, the FLCCC team consists of experienced, respectable physicians and scientists who possess wealth of knowledge:

1. Dr. Paul E. Marik, MD
2. Dr. Pierre Kory, MD
3. Dr. G. Umberto Meduri, MD
4. Dr. Joseph Varon, MD
5. Dr. Jose Iglesias, MD
6. Dr. Keith Berkowitz, MD
7. Dr. Fred Wagshul, MD
8. Dr. Scott Mitchell, MBChB
9. Dr. Eivind Vinjevoli, MD
10. Dr. Eric Osgood, M.D.

Their profiles/Curriculum Vitae can be accessed on https://covid19criticalcare.com/about/the-flccc-physicians/

14. That, Dr. Pierre Kory, M.D., M.P.A., has testified twice on behalf of FLCCC, in two senate hearings of United States of America (hereinafter referred to as "US/USA") since the pandemic started. The first one on May 6, 2020 regarding recommendation of Corticosteroids to save lives of critically ill patients. The video of this hearing is available on the FLCCC

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website under **'Videos & Press section'** and under sub menu **'Official Testimony'**.

https://covid19criticalcare.com/videos-and-press/official-testimony/

The official transcript of this hearing is attached as **Annexure 2.**

15. That, Dr. Pierre Kory in his testimony on May 6, 2021 had advanced the case for use of corticosteroids at an appropriate time on critically ill COVID-19 patients, even when all the national and international organisations were against the use of corticosteroids. It is noteworthy that the results of the 'Recovery Trial' which came to be published in November 2020, hailed the effectiveness of Corticosteroids that led to overnight change in the protocol. Sadly, six precious months were lost from the time that Dr. Pierre Kory had testified, till the results of Recovery Trial were published.

16. That, Dr. Pierre Kory, on behalf of FLCCC, has testified before the US Senate for the second time on December 8, 2020 regarding the wonder drug **Ivermectin** and its potential as prophylaxis and also for treating COVID-19 patients. In this testimony, he has justified the use of **Ivermectin** for treating COVID-19 patients based on 10 RCTs undertaken (at the time he testified). The 28-minute video of his testimony is available on the FCCCL website under **'Videos & Press'** section and under sub menu **'Official Testimony'**.

https://covid19criticalcare.com/videos-and-press/official-testimony/

The official transcript of this hearing is attached as **Annexure 3.**

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17. That, Dr. Pierre Kory, in the US Senate hearing on December 8, 2020, has expressed his dismay over how some leading public health organisations including US FDA (US Food and Drug Administation), CDC (Centers for Disease Control and Prevention), NIH (National Institute of Health) were losing time in acknowledging the power of **Ivermectin** in treatment of COVID-19. **Dr. Pierre Kory, on behalf of FLCCC, had implored the Senate to have a look at their manuscript which covered the results of 10 Randomised Control Trials.**

Refer page 4 of the **Annexure 3**

18. That, the manuscript of FLCCC has passed a rigorous peer review by senior scientists at the US FDA and Defence Threat Reduction Agency. The same has been published by the **'American Journal of Therapeutics'**

https://eurekalert.org/pub_releases/2021-05/fccc-lpr050621.php

19. That the website of FLCCC has a special page dedicated to the **Ivermectin.**

https://covid19criticalcare.com/Ivermectin -in-covid-19/

20. That, the BIRD Panel has also conducted expansive studies and trials regarding effectiveness of **Ivermectin** as prophylaxis and for treatment of COVID-19 patients.

BIRD panel includes dozens of multinational scientists and doctors who have discussed the mounting data points and evidence supporting the use of **Ivermectin** in COVID-19 cases. The large, diverse group has reviewed the evidence associated with **Ivermectin** to potentially prevent and treat COVID-19, with a goal of reaching a consensus and making recommendations for further investigation and/or use.

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The details of BIRD are available on https://bird-group.org/

Refer **Annexure 4** for the details of recommendations by BIRD sent to WHO.

Doctors for Life in Brazil have supported BIRD's position and conclusions that contradict the WHO and claim there is much evidence to recommend Ivermectin for COVID-19, and each postponed day costs many lives.

The document can be accessed by clicking following link:
https://bird-group.org/evidence-to-recommend-ivermectin/

BIRD Panel had organized the **FIRST INTERNATIONAL IVERMECTIN FOR COVID CONFERENCE** on 24th and 25th April 2021.
The video is available on following link:

https://bird-group.org/conference-post-event/

Refer **Annexure 4** for the details of recommendations by BIRD sent to WHO.

21. That, it is disingenuous of you to have not acknowledged the cases of miraculous recovery of critically ill COVID-19 patients in the US, who were treated with **Ivermectin. That, you have wilfully neglected the exemplary work by FLCCC and all such physicians and scientists who have brought back critically ill, comatose and patients on ventilator from the doorsteps of death.**

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22. That, the patients were saved by the Courts of Law who passed orders to direct the concerned hospitals to administer **Ivermectin**, as US FDA has not yet approved **Ivermectin** for treatment of COVID-19.

23. That, **Ivermectin** has saved the life of one 81 year old male COVID-19 patient names John W. Swanson, whose chances of survival were minimal. Refer **Annexure 5**, a news article in **Buffalo News dated April 9, 2021** titled **'Judge orders Batavia hospital to treat coronavirus patient with Ivermectin '**

https://buffalonews.com/news/local/judge-orders-batavia-hospital-to-treat-coronavirus-patient-with-**Ivermectin** /article_53c8b32e-996c-11eb-87cf-2bd34f11d3c2.html

The article states;

> *"Swanson was on a ventilator and* ***"on death's doorstep,"*** *at the United Memorial Medical Center when doctors there gave him one dose of* ***Ivermectin*** *on April 1, according to an affidavit filed in court by attorneys for Swanson's wife, Sandra. "After that one dose,* ***he started breathing on his own. He was taken off the ventilator and was making great progress,"*** *said attorney Ralph C. Lorigo, who represents the Swanson family with Jon F. Minear. "Then, the hospital refused to give him additional doses." State Supreme Court Justice Frederick J. Marshall issued an order on April 2, directing the hospital to give Swanson four more doses of* ***Ivermectin*** *. As of late Friday afternoon, his attorneys described Swanson as "stable."*

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24. That, another 80 year old critical COVID-19 patient named Judith Smentkiewicz has had a miraculous recovery from the disease with the help of **Ivermectin** .

Refer **Annexure 6,** a news article in Buffalo News titled **'After experimental Covid-19 treatment, 80-year-old woman thankful to be home'**

https://buffalonews.com/news/local/after-experimental-covid-19-treatment-80-year-old-woman-thankful-to-be-home/article_df8ae9da-72e4-11eb-b544-2f9de5ae5d71.html

The article states;

> *"As Judith Smentkiewicz fought for her life in a local hospital last month, she had no idea that her struggle with Covid-19 was the subject of a heated court battle and stories in the news media. Until a few days ago, the 80-year-old woman was unaware that her family's lawyers had obtained a court order enabling her to receive doses of* ***Ivermectin****, a drug that has not yet been approved by the federal government as a Covid-19 treatment. Now that she's back at her Cheektowaga home and well on the road to recovery, Smentkiewicz is amazed at everything that happened to her.*
>
> *Smentkiewicz said she has "absolutely no memory" of a five-day period when she was on a ventilator at Millard Fillmore Suburban Hospital. According to family members, doctors there told them that her chances of survival were about 20%. "I remember being taken to the hospital in an ambulance on Dec. 31, and being put on a stretcher in a hallway," Smentkiewicz said. "I know they put me on the ventilator that*

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day, but I don't remember a single thing that happened until Jan. 4, when I was taken off the ventilator and able to sit up in my bed. I'm kind of glad I don't remember those days." Unapproved by FDA, ***Ivermectin*** *useful as Covid-19 treatment, local doctors say she now knows that her son, Michael, and daughter, Michelle Kulbacki, insisted that doctors give Smentkiewicz* ***Ivermectin*** *, a drug that has helped Covid-19 patients in other countries but has not yet been approved as a Covid-19 treatment in the U.*

She also realizes that, when doctors were reluctant to give her more than one dose of the drug, her son and daughter hired attorneys Ralph C. Lorigo and Jon F. Minear to get a court order that enabled her to get more doses. On Jan. 8, State Supreme Court Justice Henry J. Nowak ordered the hospital to resume treatment with ***Ivermectin*** *. After that, Smentkiewicz made a strong recovery. She was able to leave the hospital in mid-January.*

She then spent a month in the Harris Hill Nursing Facility in Amherst, and on Tuesday, she returned home. "I am so appreciative of my family, the lawyers, the judge, the doctors, and all these people who were praying for me and fighting for me," said Smentkiewicz, speaking to a reporter in a strong, clear voice. "I know I had a lot of prayer warriors on my side."

"While she was on the ventilator, we prayed for Mom. We prayed to God, and the answer that came back to us was Ivermectin ," *Kulbacki said. "My brother was doing some*

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research on his own and came up with the information about ***Ivermectin*** *. Nothing else was helping our mother. We read that* ***Ivermectin*** *was helping other people and had no dangerous side effects. We decided we had to try it."* ***Kulbacki said her mother made "a complete turnaround" within days of her first doses of Ivermectin .***

Smentkiewicz said she got "very good" care in the hospital and nursing home, and now feels she is "at about 85%" of where she was before she caught the virus. "I'm eating, walking, exercising, getting myself dressed and making my own bed, getting back to normal life little by little," she said. "I feel good, but I get out of breath if I try to do too much. I'm having a little trouble with balance and doing physical therapy twice a week." For years, she has been active as a volunteer at the Chapel in Cheektowaga, where she babysits young children while their parents attend Sunday services. Smentkiewicz said she is anxious to get back to that, and also wants to expand her volunteer activities. "One thing I saw in the nursing home was so many elderly people who just wanted someone to come in, help them open their mail and talk with them for a while," she said. "I think I would like to go in as a volunteer and visit with people who need that." ***She added that the publicity about her case will encourage families of suffering Covid19 patients to research the possibility of using Ivermectin to treat them.***

Doctors recently told The News that ***Ivermectin*** *has helped many patients at two of the region's busiest Covid-19*

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treatment centers – the Elderwood Health Care facility in Amherst and the McGuire Group's Harris Hill facility. Dr. Thomas Madejski, a former president of the New York State Medical Society, said he has also used ***Ivermectin*** *as an effective treatment for Covid-19 patients in Erie, Niagara and Orleans counties. "It has very benign side effects, and that is one reason I have been offering it to patients," said Madejski, who said he was speaking only for himself, and not for the state medical society. Smentkiewicz said* ***she has no way of knowing if Ivermectin is a miracle drug. She said she is thankful she did not become one of the nearly 500,000 Americans killed by Covid-19.***

"I can't say it will help everyone, but I definitely believe it helped me, with no side effects," Smentkiewicz said. "I feel that God kept me around for a reason. He had a plan for me," she added. ***"I believe that part of that plan is to get people to take a closer look at Ivermectin."***

25. That, in a third incident, a critically ill COVID-19 68 year old female patient named Nurije Fype, who was in a state of medically induced coma, at the Elmhurst Hospital in a comatose state and who was successful in dodging death due to inclusion of **Ivermectin** in her line of treatment.

Refer **Annexure 7,** an article published on Medical Brief titled **'US judge orders administration of Ivermectin to comatose patient'** dated **May 12, 2021:**

https://www.medicalbrief.co.za/archives/us-judge-orders-

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*administration-of-**Ivermectin** -to-comatose-patient/*

26. That, the case of Nurije Fype is a milestone in success of **Ivermectin** in the treatment of COVID-19. In this case, inspite of the court order to administer **Ivermectin** on Nurije Fype, the hospital had refused to act on the order. This left no option to the family of Nurije Fype but to consider filing a contempt of court petition against the Elmhurst hospital.

The article in Annexure 7 states that;

> *"At request of her family an **Illinois** judge has ordered that a comatose woman suffering from COVID-19 to be administered **Ivermectin** , against the advice of her doctors, reports the **Chicago Tribune**.*
>
> *Nurije Fype, 68, has been in intensive care at the hospital since early April and is now on a ventilator, according to testimony at the court hearing. Her daughter, Desareta Fype, is pushing for her mother to receive **Ivermectin** , a medication that the **US Food and Drug Administration** says may be unsafe.*
>
> ***Another federal agency,** the National Institutes of Health, has taken a more measured stance, saying that while the drug is well-tolerated when used for its intended purposes, there isn't enough information to allow a recommendation "for or against" using it to treat COVID-19.*
>
> ***Elmhurst Hospital's** attorney, Joseph Monahan, said at the hearing none of its doctors would agree to administer **Ivermectin** for COVID-19, and that an internal ethics panel concluded its use couldn't be justified. He argued that judges shouldn't overrule medical decisions.*

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"(The court) doesn't have the authority to order a medical corporation to use particular medications, particularly when it's an off-label use, particularly when the federal government has said it could be dangerous," he said.

He suggested Desareta Fype could transfer her mother to another facility where doctors would be willing to use the medication, but Judge James Orel seemed astonished at the suggestion. "Let me get this right: The hospital is willing to transfer a woman in a coma with COVID?" he said. "Is that what you're telling me?"

Judge Orel pointed to an affidavit from Fype's physician, Dr William Crevier, in which the doctor said he has used the drug successfully for COVID-19 patients since last year. If Elmhurst Hospital's doctors don't want to use ***Ivermectin*** *, Orel said, they should allow Crevier to administer it.*

"Why wouldn't this be tried if she's not improving?" Orel said. "Why does the hospital object to providing this medication? If someone has been in the ICU for a month and not improving, why would the hospital not consider another medication?"

It was still not clear, however, whether the hospital would allow Fype to receive the medication. Orel said he expected the case to head to an appellate court, and when he asked Monahan if the hospital was going to follow his order, the attorney replied, "I will talk to my client."

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For more details regarding Court hearing, click on link below;

*https://trialsitenews.com/when-nothing-else-works-judges-are-siding-with-**Ivermectin/***

On May 4, 2021, Judge Orel's response was pointed. ***"If there's a medicine out there that can assist a patient and nothing else is working and she's regressing to the point of near death, then, yes, I balance the equities." Meaning he weighed the evidence and sided with what many doctors call the "right to try".***

This news is covered by FOX 32 News channel and the same can be viewed on following link:

'COVID-19 patient shows 'improvement' after receiving Ivermectin following legal battle with hospital'

https://www.youtube.com/watch?v=qEAOICgDYhY

This video features patient Nurije Fype's daughter Desareta Fype and their Attorney Ralph Lorigo.

27. The news related to intervention of court in facilitating the administration of **Ivermectin** on Nurje Fupe is covered in detail on following websites:

News dated May 1, 2021 titled **'Court Battles Rage to save Lives. Attorney: 'Put Hospital Chief in Jail'**

*https://www.beckershospitalreview.com/pharmacy/illinois-hospital-gives-covid-19-patient-**Ivermectin** -following-court-order.html*

News dated April 16, 2021 titled **'Ivermectin goes to Court and the NIH relaxes its prohibition'**

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*https://www.thedesertreview.com/opinion/letters_to_editor/**Ivermectin** goes-to-court-and-the-nih-relaxes-its-prohibition/article_440b7300-59bf-11eb-b945-4f69ec28f4c0.html*

News dated April 21, 2021 titled **'Ivermectin Wins in Court Again: For Human Rights'**

*https://www.thedesertreview.com/opinion/letters_to_editor/**Ivermectin** wins-in-court-again-for-human-rights/article_98d26958-a13a-11eb-a698-37c06f632875.html*

28. That, Dr. Pierre Kory, who has expressed his anguish over refusal by the Elmhurst Hospital to administer **Ivermectin** on Nurije Fupe, despite having a court order and the subsequent consideration to initiate contempt of court proceeding by the patient's family, has been covered by FOX 32 on May 4, 2021and the same can be viewed on following

https://www.youtube.com/watch?v=eEF1eOeRlw0

In this video, Dr. Pierre Kory states;

> ***"They are behaving indefensibly. I think the Judge is dismayed, their horror at what they (hospital) are doing matches mine. It is inexcusable"***

https://trialsitenews.com/court-battles-rage-to-save-lives-attorney-put-hospital-chief-in-jail/

29. That, there are likely to be more cases of COVID-19 patients having benefitted from using **Ivermectin** in their line of treatment. However, due to stricter laws in the US around patient privacy, not all cases have made to the news and not all patients are forthcoming in sharing the details. But the

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testimonies of those who have dodged death and have survived, certainly make a strong case to use **Ivermectin.**

30. That, FLCCC based on its objective studies and RCTs has prevailed upon National Institute of Health (NIH) to change their guidance on **Ivermectin** to 'Neutral' on January 14, 2021, after referencing the increased numbers of clinical trials that have been done with positive results since their last update on August 27. They now recommend neither for nor against the use of **Ivermectin** for COVID-19.

https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/**Ivermectin /**

31. That, in India, Dr. Surya Kant Tripathi, Head of Respiratory Medicine Department, King George Medical University, Lucknow, along with some other health experts of India, has written a White Paper on **Ivermectin**, in which he has emphasized that this drug reduces the replication rate of the infection by several thousand times.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7434458/

32. That, the White paper by Dr. Surya Kant, the studies undertaken by AIIMS – Bhubaneswar and several other research and studies undertaken by medical doctors and scientists across the globe, have proved **Ivermectin** to be effective as a prophylaxis and also in the line of treatment for **COVID-19.**

33. That, the **FLCCC** in its Press Release on April 29, 2021 titled **'Front Line COVID-19 Critical Care Alliance Statement on New Guidance on**

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Ivermectin from the All India Institute of Medical Science' has praised the AIIMS for including **Ivermectin** in their national Covid-19 guidelines. FCCL has expressed their gratitude towards AIIMS for having followed the science on **Ivermectin** in creating the new Guidelines.

Refer **Annexure 8.**

34. That, FLCCC and BIRD have issued a **'Joint Statement on Widespread use of Ivermectin in India for Prevention and Early Treatment'** on May 3, 2021.

https://www.einnews.com/pr_news/540334684/medical-organizations-in-the-uk-u-s-join-the-government-of-india-to-recommend-**Ivermectin** -to-end-the-covid-19-crisis

https://covid19criticalcare.com/videos-and-press/flccc-releases/joint-statement-may-03-2021-joint-statement-on-widespread-use-of-**Ivermectin** -in-india-for-prevention-and-early-treatment

Refer **Annexure 9.**

35. That, the **Ivermectin** has been widely used to treat Covid-19 in South Africa, Czech Republic, Bolivia, Honduras, Peru, Slovakia, Zimbabwe Bangladesh.

The link https://ivmstatus.com/ gives pictorial representation of global **Ivermectin** adoption for COVID-19. The status is updated regularly.

36. That, in your interview on Mojo Story on **May 16, 2021**, while Ms. Barkha Dutt has asked you a pointed question at 22:40 whether to continue using Remdesivir and **Ivermectin**, you have deliberately misled the audience by

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not revealing the mountains of evidence on effectiveness of **Ivermectin**. You, instead of giving a balanced response, that was expected from someone of your stature, have resorted to strawman argument and diverted the attention of people to areas totally unrelated to the specific question posed to you. You have responded by saying;

> *"There is no evidence that they have any impact on the disease progression so I would rather spend those resources on giving people good quality masks to wear. In the absence of vaccines, masks are the only vaccines. Everybody wears good quality masks, covering their nose and mouth, that is going to make a big difference at the community level and of course spend resources on ramping up of oxygen and other supplies that you need in the hospital, getting the work force there ready. You will have to supplement the work force because the existing doctors and nurses are not going to be enough to cope with the kind of load that we have seen, so those are the kind of investments that need to be made and you know these drugs really that's not going to be the ones that have an impact."*

37. That, in the said interview on Mojo Story, you have mentioned about the Living Guidelines issued by WHO on March 31, 2021.

The Living Guideline can be accessed from the website of WHO:

- *https://www.who.int/news-room/feature-stories/detail/who-advises-that-**Ivermectin** -only-be-used-to-treat-covid-19-within-clinical-trials*
- *https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021.1*

Refer **Annexure 10** for document titled **'Therapeutics and COVID-19'**

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LIVING GUIDELINE DATED MARCH 31, 2021 issued by WHO.

38. MALAFIDES OF 'WHO' IN MISLEADING THE PUBLIC WITH ULTERIOR PURPOSES:

38.1. That, the LIVING GUIDELINE dated March 31, 2021 includes recommendations of WHO on several drugs including **Ivermectin**. The WHO panel has made a recommendation not to use **Ivermectin** in patients with COVID-19 except in the context of a clinical trial.

The document also states the studies and finding of the Global Development Group (GDG), which supposedly served as the rationale for such recommendation regarding **Ivermectin**.

38.2. That, the explanation provided by WHO in the said Living Guideline dated March 31, 2021 is debunked by FLCCC by exposing the severe fallacies and bias on the part of WHO which was pre-determined to block the cheap drug **Ivermectin** from being discovered as effective drug in prevention and treatment of COVID-19.

Refer **Annexure 11 - Public Statement** dated May 12, 2021 issued by FLCCC titled **'Irregular Actions of Public Health Agencies and the Widespread Disinformation Campaign against Ivermectin'**

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Refer the following link:
https://covid19criticalcare.com/videos-and-press/flccc-releases/flccc-alliance-statement-on-the-irregular-actions-of-public-health-agencies-and-the-widespread-disinformation-campaign-against-ivermectin/

39. That, the para 3 to 8 of the **Public Statement** dated May 12, 2021 issued by FLCCC titled **'Irregular Actions of Public Health Agencies and the Widespread Disinformation Campaign against Ivermectin'**

read as under;

> *"The following accounting and analysis of the WHO **Ivermectin** panel's highly irregular and inexplicable analysis of the **Ivermectin** evidence supports but one rational explanation: the GDG Panel had a predetermined, nonscientific objective, which is to recommend against **Ivermectin**. This is despite the overwhelming evidence by respected experts calling for its immediate use to stem the pandemic. Additionally, there appears to be a wider effort to employ what are commonly described as "disinformation tactics" in an attempt to counter or suppress any criticism of the irregular activity of the WHO panel.*
>
> *The WHO **Ivermectin** Guideline Conflicts with the NIH Recommendation*
>
> *The FLCCC Alliance is a nonprofit, humanitarian organization made up of renowned, highly published, world-expert clinician-researchers whose sole mission over the past year has been to develop and disseminate the most effective treatment protocols for COVID-19. In the past six months,*

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much of this effort has been centered on disseminating knowledge of our identification of significant randomized, observational, and epidemiologic studies consistently demonstrating the powerful efficacy of ***Ivermectin*** *in the prevention and treatment of COVID-19. Our manuscript detailing the depth and breadth of this evidence passed a rigorous peer review by senior scientists at the U.S Food and Drug Administration and Defense Threat Reduction Agency. Recently published, our study concludes that, based on the totality of the evidence of efficacy and safety,* ***Ivermectin*** *should be immediately deployed to prevent and treat COVID-19 worldwide.*

The first "red flag" is the conflict between the March 31, 2021, WHO ***Ivermectin*** *Panel's "against" recommendation and the NIH's earlier recommendation from February 12th of a more supportive neutral recommendation based on a lower amount of supportive evidence of* ***Ivermectin****'s efficacy at that time.*

Two flawed lines of analysis by the WHO appear to account for this inconsistent result:

1) The WHO arbitrarily and severely limited the extent and diversity of study designs considered (e.g., retrospective observational controlled trials (OCT), prospective OCTs, epidemiological, quasi-randomized, randomized, placebo-controlled, etc.).

2) The WHO mischaracterized the overall quality of the trial data to undermine the included studies.

The Severely Limited Extent and Diversity of ***Ivermectin*** *Data Considered by the WHO's* ***Ivermectin*** *Panel*

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*The WHO **Ivermectin** Panel arbitrarily included only a narrow selection of the available medical studies that their research team had been instructed to collect when formulating their recommendation, with virtually no explanation why they excluded such a voluminous amount of supportive medical evidence. This was made obvious at the outset due to the following:*

1) No pre-established protocol for data exclusion was published, which is a clear departure from standard practice in guideline development.

*2) The exclusions departed from the WHO's own original search protocol it required of Unitaid's **Ivermectin** research, which collected a much wider array of randomized controlled trials (RCT).*

*Key **Ivermectin** Trial Data Excluded from Analysis*

1) The WHO excluded all "quasi-randomized" RCTs from consideration (two excluded trials with over 200 patients that reported reductions in mortality).

*2) The WHO excluded all RCTs where **Ivermectin** was compared to or given with other medications. Two such trials with over 750 patients reported reductions in mortality.*

*3) The WHO excluded from consideration 7 of the 23 available **Ivermectin** RCT results. Such irregularities skewed the proper assessment of important outcomes in at least the following ways:*

a) Mortality Assessment

i) WHO Review: Excluded multiple RCTs such that only 31 total trials deaths occurred; despite this artificially meager

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sample, an estimate of up to a 91% reduction in the risk of death was found.

ii) Compared to the BIRD Review: Included 13 RCTs with 107 deaths observed and found a 2.5% mortality with ***Ivermectin*** *vs. 8.9% in controls; estimated reduction in risk of death=68%; highly statistically significant, (p=.007).*

b) Assessment of Impacts on Viral Clearance

i) WHO Review: 6 RCTs, 625 patients. The Panel avoided mention of the important finding of a strong dose-response in regard to this outcome.

ii) This action in (i) is indefensible given that their Unitaid research team found that among 13 RCTs, 10 of the 13 reported statistically significant reductions in time to viral clearance, with larger reductions with multiday dosing than single-day, consistent with a profound dose-response relationship.

c) Adverse Effects

i) WHO: Only included 3 RCTs studying this outcome. Although no statistical significance was found, the slight imbalance in this limited sample allowed the panel to repeatedly document concerns for "harm" with ***Ivermectin*** *treatment.*

ii) Compare (a) to the WHO's prior safety analysis in their 2018 Application for Inclusion of ***Ivermectin*** *onto Essential Medicines List for Indication of Scabies:*

(1) "Over one billion doses have been given in large-scale prevention programs."

(2) "Adverse events associated with ***Ivermectin*** *treatment are primarily minor and transient."*

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*4) The WHO excluded all RCTs studying the prevention of COVID-19 with **Ivermectin,** without supporting rationale. Three RCTs including almost 800 patients found an over 90% reduction in the risk of infection when **Ivermectin** is taken preventively.*

*5) The WHO excluded observational controlled trials (OCT), with 14 studies of **Ivermectin.** These included thousands of patients, including those employing propensity matching, a technique shown to lead to similar accuracy as RCTs.*

*a) One large, propensity-matched OCT from the US found that **Ivermectin** treatment was associated with a large decrease in mortality.*

*b) A summary analysis of the combined data from the 14 available **Ivermectin** OCTs found a large and statistically significant decrease in mortality.*

6) The WHO excluded numerous published and posted epidemiologic studies, despite requesting and receiving a presentation of the results from one leading epidemiologic research team. These studies found:

*a) In numerous cities and regions with population-wide **Ivermectin** distribution campaigns, large decreases in both excess deaths and COVID-19 case fatality rates were measured immediately following the campaigns.*

*b) Countries with pre-existing **Ivermectin** prophylaxis campaigns against parasites demonstrate significantly lower COVID-19 case counts and deaths compared to neighboring countries without such campaigns.*

Assessment of the Quality of the Evidence Base by WHO Guideline Group

The numerous above actions minimizing the extent of the evidence

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base were then compounded by the below efforts to minimize the quality of the evidence base:

The WHO mischaracterized the overall quality of the included trials as "low" to "very low," conflicting with numerous independent expert research group findings:

1) An international expert guideline group independently reviewed the BIRD proceeding and instead found the overall quality of trials to be "moderate."

2) The WHO's own Unitaid systematic review team currently grade the overall quality as "moderate."

3) The WHO graded the largest trial it included to support a negative assessment of ***Ivermectin's*** *mortality impacts as "low risk of bias." A large number of expert reviewers have graded that same trial as "high risk of bias," detailed in an open letter signed by over 100 independent physicians.*

We must emphasize this critical fact: If the WHO had more accurately assessed the quality of evidence as "moderate certainty," consistent with the multiple independent research teams above, ***Ivermectin*** *would instead become the standard of care worldwide, similar to what occurred after the dexamethasone evidence finding decreased mortality was graded as moderate quality, which then led to its immediate global adoption in the treatment of moderate to severe COVID-19 in July of 2020.*

Further, The WHO's own guideline protocol stipulates that quality assessments should be upgraded when there is the following:

1) a large magnitude of effect (despite their data estimating a survival benefit of 81%, the low number of studies and events included allowed them to dismiss this finding as "very low certainty") or;

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2) evidence of a dose-response relationship. The WHO shockingly omits the well-publicized reports by their Unitaid research team of a powerful dose-response relationship with viral clearance.

*In sum, the WHO's recommendation that "**Ivermectin** not be used outside clinical trials" is based entirely upon:*

1) the dismissal of large amounts of trial data;

2) the inaccurate downgrading of evidence quality; and

3) the deliberate omission of a dose-response relationship with viral clearance.

Consequently, these actions formed the basis of their ability to avoid a recommendation for immediate global use.

Even more surprising is that based on their "very low certainty" finding, the panel goes on to "infer" that "most patients would be reluctant to use a medication for which the evidence left high uncertainty regarding effects on outcomes they consider important."

This statement is insupportable in light of the above actions. No patient could ever rationally consent to a trial in which they were acutely ill and would be subject to the possibility of receiving a placebo, once informed of; the large amount of relevant and positive trials that the WHO removed from consideration, their avoidance of reporting a large dose-response relationship, and their widely contradicted "very low certainty" grading of large mortality benefits. Such a trial would result in a historic ethical research violation, causing both a widespread loss of life and a resultant loss of trust in PHAs and research institutions for decades to come.

The many methods employed by the WHO to distort the evidence base and arrive at a non-recommendation are made even more suspicious and questionable by the following:

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1) The WHO GDG did not hold a vote on the use of ***Ivermectin*** *. This highly irregular decision was purportedly based on the* ***Ivermectin*** *Panel's "consensus on evidence certainty."*

2) Unitaid Sponsors allegedly inserted multiple limitations and weakened the conclusions in the preprint, systematic review manuscript by the Unitaid research team, which has recently led to formal charges of scientific misconduct.

3) Recent WHO whistleblower complaints of external influences in other WHO Covid reports, as well as attempts by massive external funding organizations to increase their influence in formulating WHO policies.

4) The finding of marked differences in the evidence bases used to support prior WHO/BIRD guideline recommendations for ***Ivermectin*** *in other diseases:*

a) WHO: Approved ***Ivermectin*** *in the treatment of scabies based on 10 RCTs that included only 852 patients, despite it being inferior to the standard of care.*

b) FDA: Approved ***Ivermectin*** *in the treatment of strongyloidiasis based on 5 RCTs that included only 591 patients.*

c) BIRD: Approved ***Ivermectin*** *in March, 2021, for the prevention and treatment of COVID-19 based on 21 RCTs and 2,741 patients.*

Conclusion

As expert clinician-researchers in society, we are firmly committed to ensuring that public health policy decisions derive from scientific data. Disturbingly, after extensive analysis of the recent WHO ***Ivermectin*** *guideline recommendation, we could not arrive at a*

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credible scientific rationale to explain the numerous irregular, arbitrary, and inconsistent behaviors documented above. Further, after consultation with numerous physicians, guideline reviewers, legal experts, and veteran PHA scientists, we identified two major socio-political-economic forces that serve as the main barrier influences preventing ***Ivermectin*** *'s incorporation into public health policy in major parts of the world. They are:*

1) The modern structure and function of what we will describe as "Big Science" and;

2) The presence of an active "Political-Economic Disinformation Campaign."

40. That, the said Public Statement also states that (page 2);

"A similar conclusion has also been reached by an increasing number of expert groups from the United Kingdom (UK), Italy, Spain, United States (US), and a group from Japan headed by the Nobel Prize-winning discoverer of ***Ivermectin,*** *Professor Satoshi Omura. Focused rebuttals that are backed by voluminous research and data have been shared with PHAs over the past months.* ***These include the WHO and many individual members of its guideline development group (GDG), the FDA, and the NIH. However, these PHAs continue to ignore or disingenuously manipulate the data to reach unsupportable recommendations against Ivermectin treatment. We are forced to publicly expose what we believe can only be described as a "disinformation" campaign astonishingly waged with full cooperation of those authorities whose mission is to maintain the integrity of scientific research and protect public health."***

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41. That, we as members of public, have taken cognizance of the said Public Statement dated May 12, 2021, issued by FLCCC and we call upon you to provide your response as the Chief Scientist at WHO, to the fallacies pointed out by FLCCC regarding the Living Guideline of WHO dated 31.03.2021 based on the study conducted by Development Guideline Group regarding **Ivermectin**.

42. That, your failure to provide rebuttal to the contents mentioned in **para 39** supra, shall be taken as acceptance of the fallacies in the Living Guideline Report of WHO dated **31.03.2021**.

43. That, 'The Indian Council for Medical Research' (hereafter referred to as ICMR) which is the one of the oldest and largest medical bodies in the world and which is the apex medical research organization, has listed the drug **Ivermectin** as a possible treatment option for mild Covid-19 patient under home isolation in the **'May Do'** category on April 22, 2021. The National Clinical Guidelines for Covid-19 management are developed by All India Institute of Medical Sciences (hereinafter referred to as AIIMS), Delhi and ICMR joint taskforce. Refer **Annexure 12.**

44. That, the **Ivermectin** continues to be part of the National Protocol issued by the ICMR even at the time of drafting this legal notice. Refer **Annexure 13** for the National Protocol as updated on May 17, 2021.

45. That, you are a qualified medical doctor possessing the degree of MBBS and MD in Pediatrics from AIIMS Delhi. You have served as Director General of the ICMR and Secretary of the Department of Health Research (Ministry of

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Health and Family Welfare) for the Government of India from August 2015 to November 2017. That, going by your educational qualifications and work experience, you are deemed to be competent enough to understand the significance of statements/protocols/notifications issued by the esteemed organizations of India like ICMR and AIIMS, which you yourself were associated with at some point in time. But you have been repeatedly issuing statements against the use of **Ivermectin** with a malafide intention to misguide, mislead and create confusion in the minds of Indians in order to dissuade us from knowing about **Ivermectin** which has brought back few critically ill COVID-19 patients from the doors of death.

46. That, while you have attached the company statement issued by Merck in your tweet on May 10, 2021, you have intentionally ignored the fact that Merck, which is the manufacturer of **Ivermectin** may have a conflict of interest in issuing the said statement against the use of **Ivermectin** in treatment of COVID-19 as mentioned in para 4, since Merck is in process of making its own COVID-19 drug and that clinical trials for the same are in progress.

Refer the following link:

https://whyy.org/segments/some-doctors-think-theyve-found-a-cheap-generic-drug-which-treats-covid-19-so-why-hasnt-anyone-heard-of-it/

An excerpt from the above news article titled **'Some doctors think they've found a cheap, generic drug which treats COVID-19. So why hasn't anyone heard of it?'** states;

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*"Merck, which originally developed **Ivermectin** but whose patent on it expired, does not endorse its use for COVID-19 treatment. In a statement, a Merck representative said that "following detailed review of the evidence available for **Ivermectin** we calculated that the dose required to attain an antiviral effect would significantly exceed the doses known to be safe and well tolerated," referencing the in vitro study. "We therefore concluded that further research to evaluate the clinical potential of **Ivermectin** for the treatment of SARS-CoV-2 was not warranted."*

Merck is in the process of developing its own new therapy for COVID-19, which it would presumably patent. It is also involved in vaccine trials."

Merck has issued a statement January 25, 2021 regarding development of its two investigational therapeutic candidates for treatment of COVID 19. Refer **Annexure 14.**

47. That, the **Ivermectin** is off-patent since 1996 and therefore it is available at a cheap rate at present.

48. That, your malafides are proven through your act of attaching the public statement of a pharmaceutical company Merck dated February 4, 2021 instead of the Report of WHO dated March 31, 2021 in your tweet on May 10, 2021. That, you were aware that the said WHO report on Living Guideline dated March 31, 2021 is an eyewash as far as the recommendation on **Ivermectin** is concerned and hence you deliberately attached an older statement of Merck dated February 4, 2021.

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49. That, it was your malfeasance reflecting in the tweet on May 10, 2021 against the use of **Ivermectin** in desperate hope to dissuade people of India from discovering the effectiveness of **Ivermectin** and that they keep falling sick and are available as a huge market for several drugs which are being launched now and which are in the pipeline and would be launched soon once the Emergency Use Authorisation (EUA) is granted for their public use.

50. That, you are wilfully speaking against the use of **Ivermectin** for COVID-19 patients as you are aware that in the event of **Ivermectin** being declared as an **'existing and adequate drug'** to treat COVID-19, the Emergency Use Authorisation (EUA) currently granted for variety of vaccines and drugs would stand revoked and this will severely impact the prospects of new vaccines and drugs being manufactured to combat COVID-19.

51. That, you have abused your position as the Chief Scientist at WHO to adversely influence the people including medical doctors and scientists, by trying to impose upon them the fact that WHO does not support the use of **Ivermectin** either as prophylactic or in treatment of COVID-19.

52. It seems that you have deliberately opted for deaths of people to achieve your ulterior goals and this is a sufficient ground for criminal prosecution against you and also for initiating action for revocation of your degrees in medical field.

53. That, it is highly unbecoming of you as a physician and scientist, to insist on Randomized Control Trials amidst pandemic, to ascertain the efficacy of **Ivermectin** in treatment of COVID-19. This is equivalent to you taking a stand

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that allows people to fall sick and probably die of COVID-19, but does not allow them to take a drug which has not only been proven to be safe with no harmful effects, but has also been proved to be effective as prophylaxis and in treatment of COVID-19 in numerous cases across the globe. This is juxtaposed to the fact that precious time was lost in conducting the solidarity trial by WHO that concluded that most of the drugs or therapies did not work viz. Hydroxychloroquine, Remdesivir and the convalescent plasma.

54. You are deliberately ignoring the medical ethics and principles that you are bound to follow;

1. The Declaration of Geneva of the World Medical Association (WMA) binds the physician with the words, "The health and wellbeing of my patient will be my first consideration,"

   https://www.wma.net/policies-post/wma-declaration-of-geneva/

2. International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

   https://www.wma.net/wp-content/uploads/2006/09/International-Code-of-Medical-Ethics-2006.pdf

3. Article 37 of the WMA declaration of Helsinki, titled: ***"Unproven Interventions in Clinical Practice" It is paraphrased as "In the treatment of an individual patient, where proven interventions do not exist, a physician may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering***

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https://www.wma.net/wp-content/uploads/2016/11/DoH-Oct2013-JAMA.pdf

55. That, you are called upon to read Article 37 of the WMA declaration of Helsinki mentioned in **para 54** supra, at least a hundred times and provide a cogent explanation for:

1. Not supporting the use of **Ivermectin** in treatment of COVID-19, given the fact that **Ivermectin** is proven to be safe with no harmful effects.

2. Ignoring the presence of voluminous data that proves the effectiveness of **Ivermectin**, not to forget the cases where patients have been taken off ventilator soon after **Ivermectin** was administered (Refer para 21 to 28)

56. That, your misleading tweet on May 10, 2021 against the use of **Ivermectin** had the effect of the State of Tamil Nadu withdrawing **Ivermectin** from the protocol on May 11, 2021 just a day after the Tamil Nadu Government had included the same for treatment of COVID-19 patients.

https://science.thewire.in/health/tn-revises-protocols-leaves-out-Ivermectin-for-covid-patients/

57. That, the re-purpose drugs which were included in the solidarity trials like Remdesivir, hydroxychloroquine have proved to be 'Ineffective', so did the convalescent plasma therapy. Your concerns around use of **Ivermectin** for COVID-19 are totally misplaced given the fact that **Ivermectin** has no harmful side effects unlike corticosteroids and Remdesivir. Hence, resistance to use of

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Ivermectin on flimsy grounds and that too by wilfully ignoring the voluminous data that proves the effectiveness of the drug, is not at all tenable, rather it proves your malafides and ulterior purposes.

58. That, the credibility and integrity of WHO has been severely eroded and continues to wane with each passing day due to its miserable failure in handling the pandemic. Also, the reports issued by WHO are increasingly been seen as biased and totally lacking in quality, authenticity and rational approach. The latest the report regarding investigation into the origins of the Corona Virus is also being questioned by the scientists' community. As many as eighteen eminent scientists have written to WHO asking for detailed investigation.

https://www.wsj.com/articles/scientists-call-for-deeper-investigation-into-covid-19-origin-11620928801

The above article states;

> *"In a letter published Thursday in the journal Science, an international group of 18 biologists, immunologists and other scientists criticized the findings of a report released in March by a World Health Organization-led team into the pandemic's origin and called for a more extensive evaluation of the two leading hypotheses: that the pandemic virus entered the human population and began spreading after escaping from a lab or after jumping to humans from infected animals.*
>
> *TheWHO-led team, which included scientists from China and several other countries, reported no definitive proof of either hypothesis. Yet, the scientists wrote, the team nevertheless concluded that an animal origin for the pandemic was the likelier scenario and devoted only*

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four out of the report's 313 pages to the possibility of a lab accident."

59. That, the WHO report published in March 2021 regarding the investigation into the origins of Corona virus is found to be severely lacking in many aspects, which is explained in following article;

https://science.thewire.in/the-sciences/scientists-litter-fuller-investigation-origins-novel-coronavirus-lab-natural-spillover/

The article states;

> *"This was evidently a comment on the WHO's investigation into the origins of the virus. Under the terms of reference of this investigation, the information, data, and samples for the study's first phase were collected and summarised by a team of Chinese scientists. The rest of the team only built on this analysis, which found no clear evidence either to support a natural spillover or a lab accident. However, the team said a zoonotic spillover from an intermediate host was "likely to very likely," and a laboratory incident was "extremely unlikely".*
>
> *Even before the WHO report was released in March this year, reports said in November 2020 that the WHO had 'ceded' control of the investigation to China in a bid to gain access to the source of coronavirus. The reports argued that the WHO was eager to "win access and coordination" from China but achieved neither."*

60. That, several nations are calling out WHO for its falling standards, biased approach and its deliberate acts of omission and commission that are causing loss of human lives.

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While the WHO flaunts itself like 'know it all', it is akin to the vain Emperor in new clothes, while the entire world has realized by now that the Emperor (WHO) has no clothes at all.

61. That, you and WHO have misled and misguided all the people throughout the pandemic, starting from the delay in raising alarm soon after SARS-CoV2 was detected in China, your failure to prevail over China in conducting an impartial investigation into the origins of the virus, inordinate time consumed before declaring Remdesivir, Hydroxychloroquine, convalescent plasma as 'ineffective' in treatment of COVID-19, ever changing theories around SARS-CoV2 being transmitted through droplets or it being air borne and many more. The world is gradually waking up to your absurd, arbitrary and fallacious approach in presenting concocted facts as 'scientific approach'. As the famous quote of Abraham Lincoln goes –

> ***"You can fool all the people some of the time and some of the people all the time, but you cannot fool all the people all the time."***

62. That, the team of FLCCC have beseeched all countries to use **Ivermectin** which according to them is the only way to end this pandemic.

Refer the article below titled **'immediate global Ivermectin use can end Covid-19 pandemic: Scientists'** published online on The Free Press Journal on May 10, 2021:

> *https://www.freepressjournal.in/health/immediate-global-**Ivermectin** - use-can-end-covid-19-pandemic-scientists*

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63. That, the article mentioned in para 55 states;

"Peer reviewed by medical experts that included three US government senior scientists and published in the American Journal of Therapeutics, the research is the most comprehensive review of the available data taken from clinical, in vitro, animal, and real-world studies.

Led by the Front Line COVID-19 Critical Care Alliance (FLCCC), a group of medical and scientific experts reviewed published peer-reviewed studies, manuscripts, expert meta-analyses, and epidemiological analyses of regions with ***Ivermectin*** *distribution efforts all showing that* ***Ivermectin*** *is an effective prophylaxis and treatment for COVID-19.*

"We did the work that the medical authorities failed to do, we conducted the most comprehensive review of the available data on Ivermectin," said Pierre Kory, MD, president and chief medical officer of the FLCCC. "We applied the gold standard to qualify the data reviewed before concluding that Ivermectin can end this pandemic."

A focus of the manuscript was on the 27 controlled trials available in January 2021, 15 of which were randomised controlled trials (RCT's). Consistent with numerous meta-analyses of ***Ivermectin*** *RCT's since published by expert panels from the UK, Italy, Spain and Japan, they found large, statistically significant reduction in mortality, time to recovery and viral clearance in Covid-19 patients treated with* ***Ivermectin*** *.*

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"Our latest research shows, once again, that when the totality of the evidence is examined, there is no doubt that ***Ivermectin*** *is highly effective as a safe prophylaxis and treatment for Covid-19," said Paul E. Marik, founding member of the FLCCC and Chief, Pulmonary and Critical Care Medicine at Eastern Virginia Medical School.*

Many regions around the world now recognise that Ivermectin is a powerful prophylaxis and treatment for Covid-19. South Africa, Zimbabwe, Slovakia, Czech Republic, Mexico, and India have approved the drug for use by medical professionals.

The results as seen in this latest study demonstrate that the ***Ivermectin*** *distribution campaigns repeatedly led to "rapid population-wide decreases in morbidity and mortality."*

"We are calling on regional public health authorities and medical professionals around the world to demand that ***Ivermectin*** *be included in their standard of care right away so we can end this pandemic once and for all," Marik noted."*

64. That, the work done by FLCCC, BIRD and similar groups, has ruffled the feathers of many including WHO, whose inefficiencies and failures have been exposed time and again.

65. That, there is a vicious attempt by some individuals including doctors, scientists and leading public health organisations, to suppress all the news regarding effectiveness of Ivermectin. This Syndicate has managed to capture considerable portion of scientific and medical community, who

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continuously discredit any reports/news around the effectiveness of **Ivermectin** in treating COvid-19 patients.

Such deliberate actions are explained in detail in the Public Statement by FLCCC (Refer Annexure 11, page 8 to 13)

66. That the FLCCC and BIRD have shown exemplary courage in building a formidable force to tackle the challenges in the form of disinformation, resistance and rebuke from pharma lobbies, powerful health institutions like WHO, NIH, CDC and regulators like US FDA.

67. That, in the time of this crisis, there are few doctors who are living up to their Hippocratic Oath, by putting the patients' interest first and not being complicit in the agenda of spreading disinformation. These brave and courageous doctors, who are morally upright, have chosen to support the truth rather than yielding meekly to authoritative and unscientific mandates.

These doctors are your very own brethren who are highly qualified, experienced and more importantly humane and conscientious.

The FLCCC site has a video dated April 19, 2020 that features following brave doctors, who have been forthcoming in declaring the effectiveness of **Ivermectin:**

1. *Dr. Paul E. Marik – M.D., FCCCM, FCCP*

   Norfolk, Virginia
2. *Dr. Bruce Boros – M.D.*

   Key West, Florida
3. *Dr. Keith Berkowitz – M.D., MBA*

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New York

4. *Dr. Eric Osgood – M.D.*

   Trenton, New Jersey

5. *Dr. Colleen Aldous – PhD*

   Durham, South Africa

6. *Dr. Alexis Lieberman– M.D.*

   Philadelphia, Pennsylvania

7. *Dr. Randy Grellner – M.D.*

   Cushing, Oklahoma

8. *Dr. Jackie Stone – M.D.*

   Harare, Zimbabwe

9. *Dr. Syed Haider – M.D.*

   Asheville, North Carolina

10. *Dr. Fred Wagshul – M.D.*

    Dayton, Ohio

11. *Dr. William Crevier – M.D.*

    Orland Park, Illinois

12. *Dr. Arezo Fathie – M.D.*

    Las Vegas, Nevada

13. *Dr. Bruce Patterson – M.D.*

    Palo Alto, California

14. *Dr. Miguel Antonatos – M.D.*

    Chicago, Illinois

15. *Dr. Matt Erickson – M.D.*

    Gainesville, Florida

16. *Dr. Ram Yogendra – M.D.*

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Pawtucket, Rhode Island

17. *Dr. Tess Lawrie – MBBCH, PHD*

Bath, United Kingdom

The video can be accessed on *https://covid19criticalcare.com/videos-and-press/flccc-alliance-videos/*

The description of video reads thus:

They are truly adhering to their Hippocratic Oath and Putting patients – not profits first.

> *"These brave doctors are rising to the highest ideals of the Hippocratic Oath they took to save the lives of the patients who come into their care. These are the truest heroes of this ruthless pandemic. They have chosen to #followthescienceand save lives—and have refused to be party to the corruption that is endemic among the world's health authorities. There are more brave doctors out there."*

That, Dr. Paul E. Marik, towards the end of the video, states the following regarding **Ivermectin** ;

> *"The statistics for us is, we know this can make a difference and save lives. And it seems like nobody really cares and wants to listen to us. We have this massive force that is trying to silence us and yet we feel we can't be silenced. We can't be, because you know the truth will ultimately prevail".*

68. That, the Constitution of India, as per Article 51 A (h), casts a solemn duty upon me to develop scientific temper, humanism and the spirit of inquiry and

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reform. Therefore, I shall relentlessly pursue and question anything that is found to be unscientific, biased, arbitrary, flawed and irrational, especially in these times when several people are losing their lives, which could have been saved but for the vicious attempts by a few to suppress vital information.

69. That, you are called upon to:

(1) Provide your and WHO's response to each and every finding shared by FLCCC in their Public Statement issued on May 12, 2021 regarding the fallacies in the Living Guideline issued by WHO on March 31, 2021

(2) Furnish the study papers, research, knowledge resources relied upon by you, based on which, you have tweeted against the use of **Ivermectin** on May 10, 2021.

(3) Explain the rationale for attaching the notification of Merck dated Feb 4, 2021 instead of the Living Guideline issued by WHO on March 31, 2021, in your tweet on May 10, 2021.

(4) Explain with facts and figures that support your stand that **Ivermectin** is not safe.

(5) Strictly refrain from sharing your views on Ivermectin for COVID-19 till you address points 1, 2, 3 and 4 above.

70. That, your failure to provide any response or a clear response to all of the points in para 69, shall be deemed as acceptance of all claims and allegations

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against you in this notice and we reserve all the rights to initiate legal action against you, which will be at your peril.

71. This notice is issued by reserving our rights to initiate prosecution under sections 302, 304 (II), 88, 120 (B) and 34 and other provisions of the Indian Penal Code and under Disaster Management Act, 2005 in the appropriate Courts of Law having jurisdiction for each death caused due to your act of commission and omission.

Date: 25.05.2021

Place: Mumbai

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Adv. Dipali N. Ojha
Head – Legal Cell
Indian Bar Association
www.indianbarassociation.in

Copy to,

1. **Hon'ble President of India**
2. **Hon'ble Prime Minister of India**
3. **Hon'ble Governors of all States of India**
4. **Hon'ble Minister of Home Affairs**
5. **Hon'ble Minister of Health and Family Welfare**
6. **The Director, Intelligence Bureau**
7. **The Director, CBI**
8. **Hon'ble Chief Ministers of all States of India**

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9. The Director General of Indian Council of Medical Research (ICMR)

10. The Director, All India Institute of Medical Sciences, Delhi (AIIMS)

11. The National President, Indian Medical Association

12. The Drugs Controller of India

13. The Director, The National Institute of Virology, Pune

14. The Chairman, National Medical Commission (NMC)

15. South East Asia Office WHO, Delhi, India

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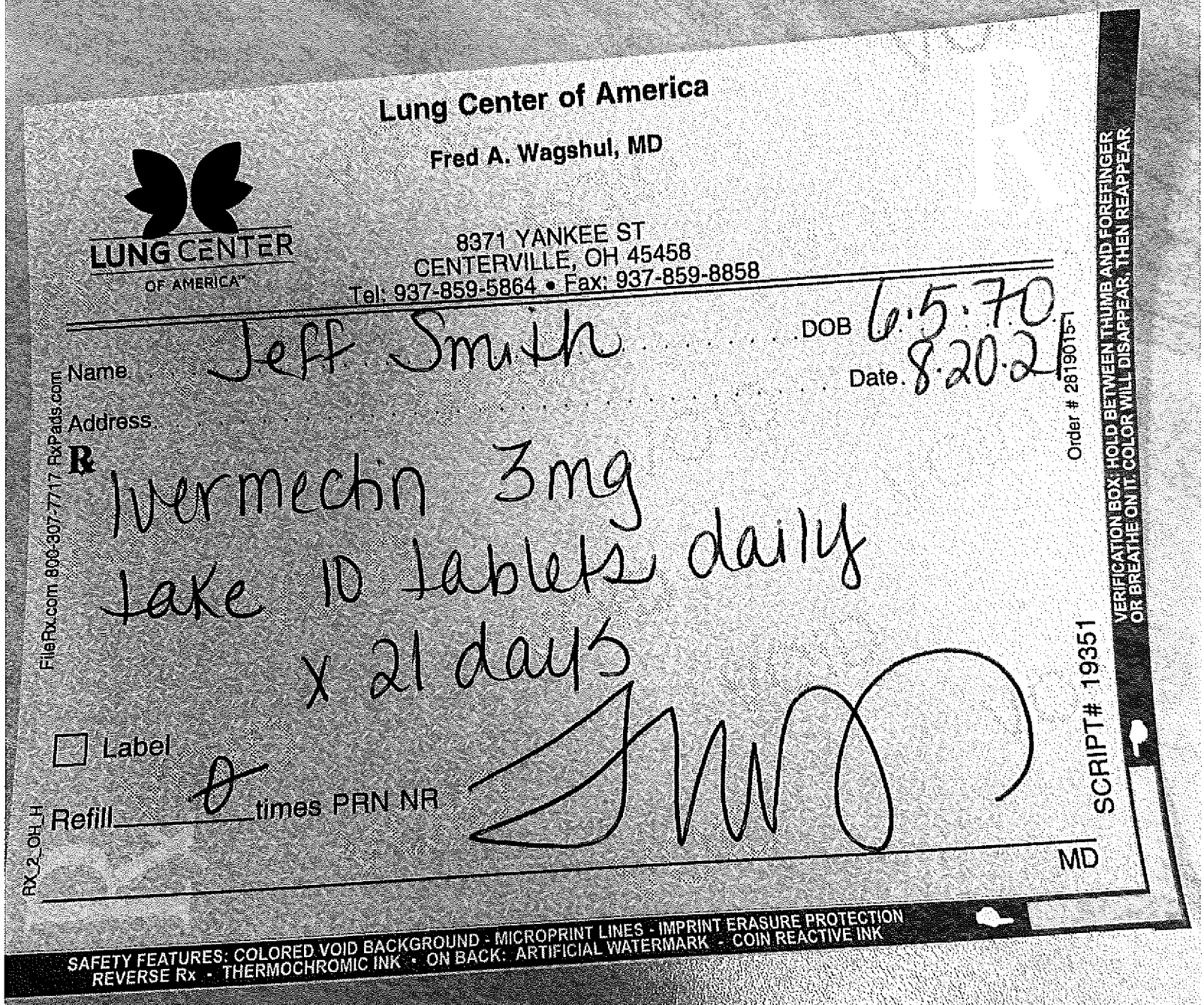
EXHIBIT "M"



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Fred A. Wagshul, MD

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