Together • COVID-19 Clinical trials

Early Treatment of COVID-19 : The TOGETHER Adaptive Platform Trial

Effect of ivermectin on extended emergency room observation or hospitalization among outpatients with an early diagnosis of COVID-19

McMaster University

PUC Minas

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TOGETHER Trial Overview

- Randomized adaptive platform trial to investigate the efficacy of repurposed treatments for COVID-19 disease among high-risk adult outpatients
- Received ethics board approval in Brazil and Canada
- Data and Safety Monitoring Committee provides independent oversight
- The trial was initiated on June 2, 2020
- Enrollment into the ivermectin arm took place from March 23, 2021 until August 6, 2021

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In April 2020, emerging *in vitro* results suggested ivermectin inhibits replication of SARS-CoV-2

The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 *in vitro*

Leon Caly [a], Julian D. Druce [a], Mike G. Catton [a], David A. Jans [b], Kylie M. Wagstaff [b]

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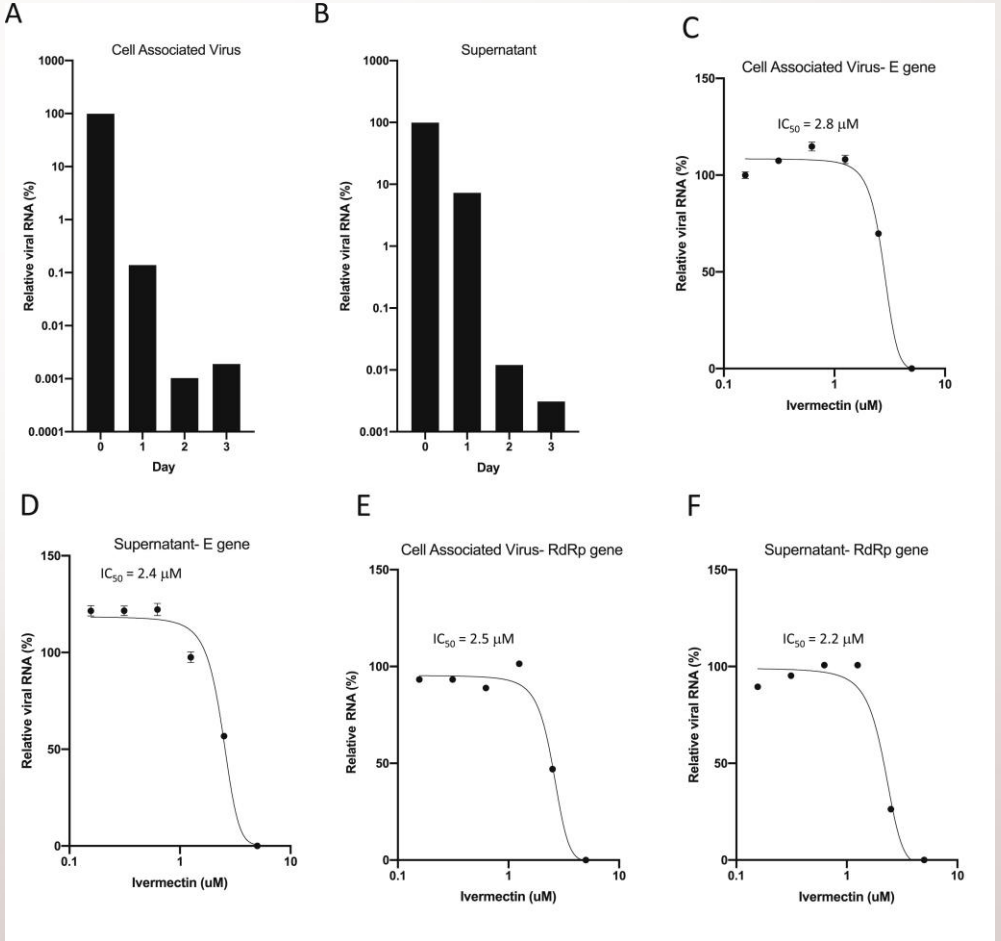
https://doi.org/10.1016/j.antiviral.2020.104787

Highlights

- Ivermectin is an inhibitor of the COVID-19 causative virus (SARS-CoV-2) *in vitro*.
- A single treatment able to effect ~5000-fold reduction in virus at 48 h in cell culture.
- Ivermectin is FDA-approved for parasitic infections, and therefore has a potential for repurposing.
- Ivermectin is widely available, due to its inclusion on the WHO model list of essential medicines.

In Vitro activity ivermectin vs DMSO in SARS-CoV-2- Australia/VIC01/2020 in Vero/hSLAM cells



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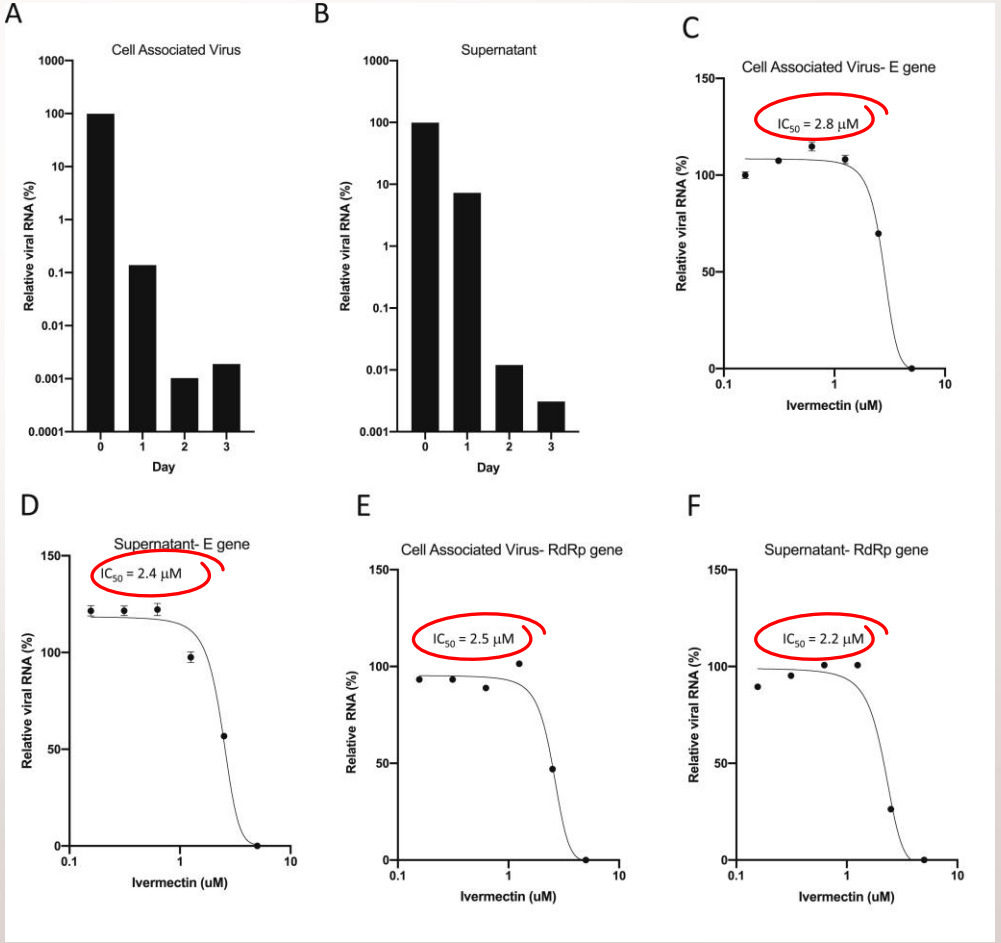

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Translation of Antiviral Pharmacology

- PBPK modelling was used to simulate time-course of ivermectin concentrations relative to *in vitro* susceptibility
- We simulated concentrations in plasma (black line) and lung tissue (blue line) relative to the IC50 following **600µg/kg QD for 3days** (9x cumulative highest labelled dose regimen)
- **Dose regimens many-fold higher than labelled would be insufficient to reach IC50 levels**


Contents lists available at ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

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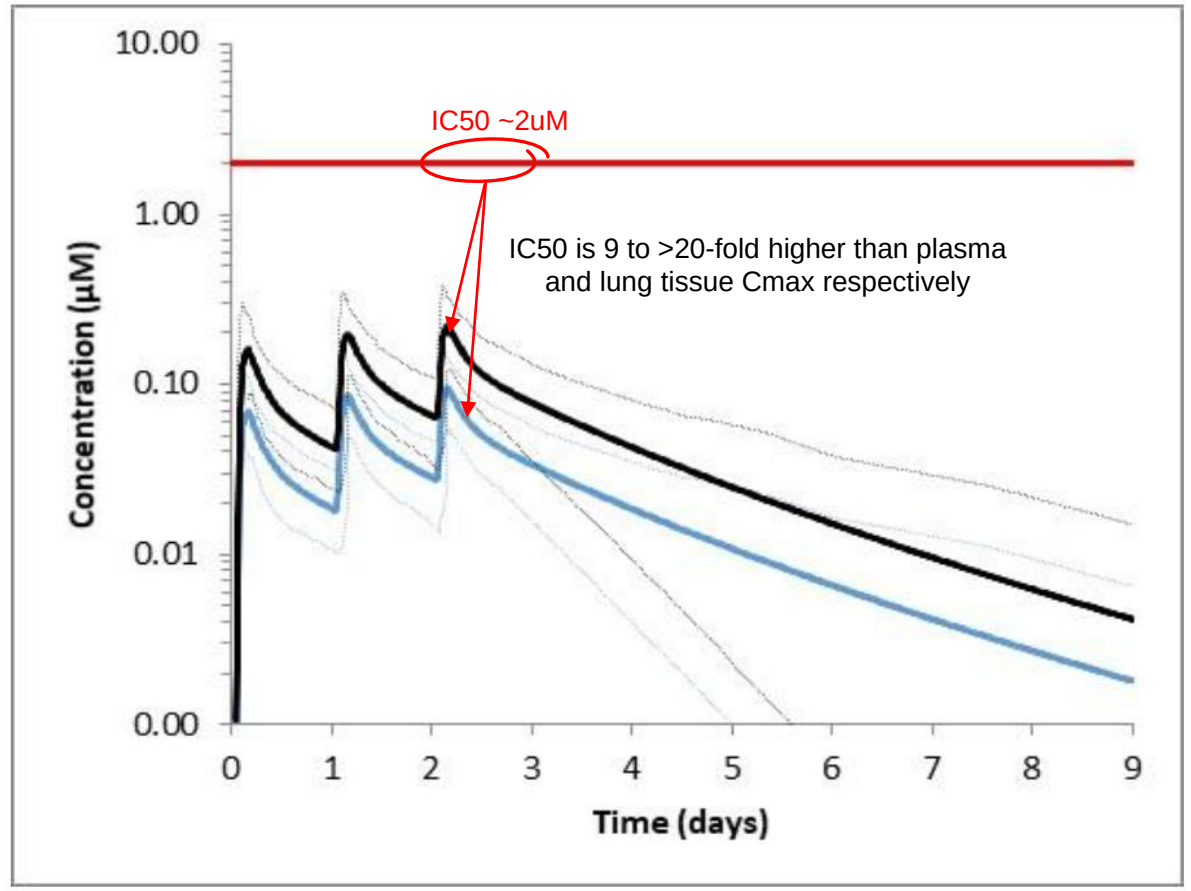
Simulated mean (5-95%) concentration-time profile



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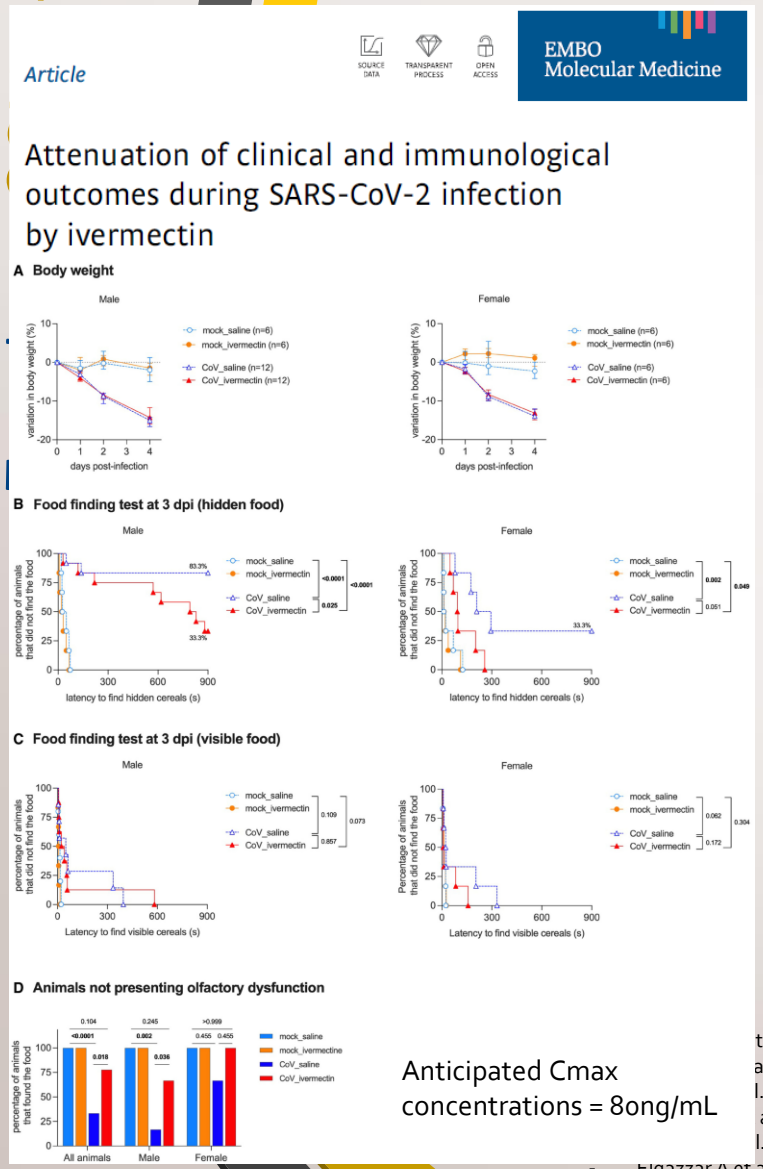

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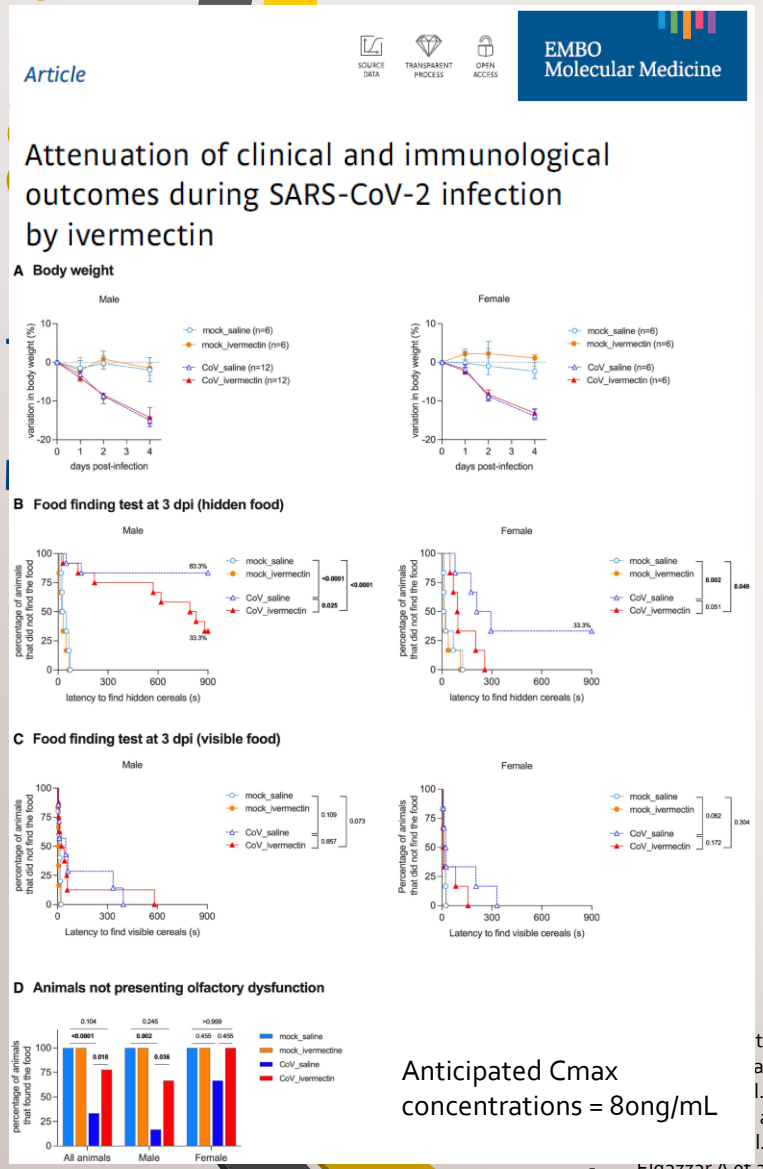

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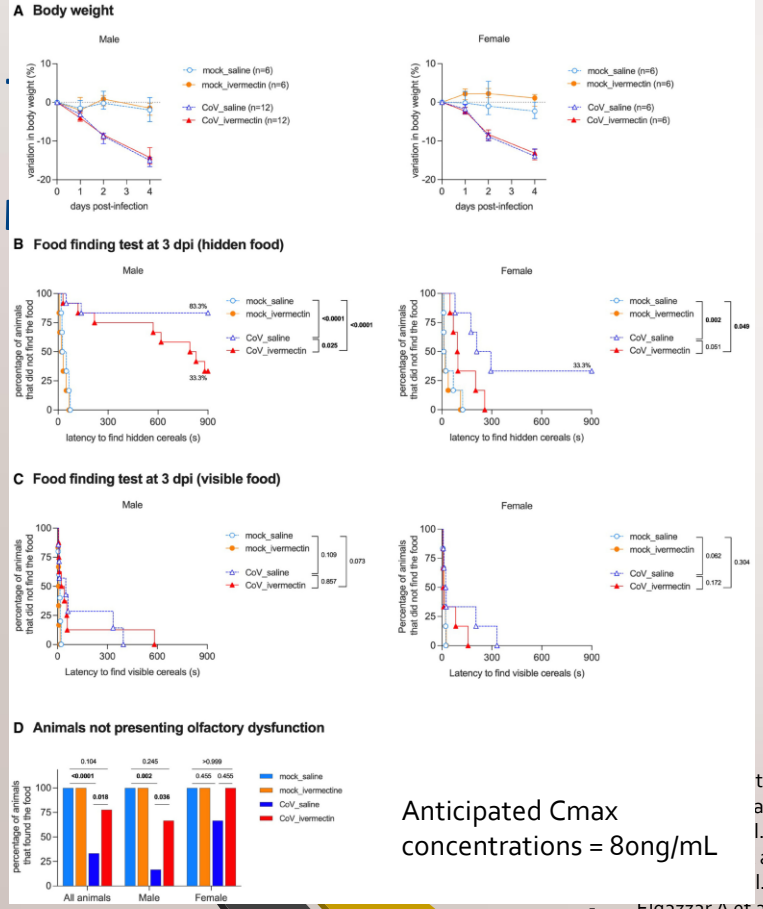

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Basma Hany
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Mohy Hafez
Benha Faculty of medicine
Hany Moussa
Kafr Elsheikh University, Faculty of medicine, Chest department

Ivermectin in COVID-19 Related Critical Illness

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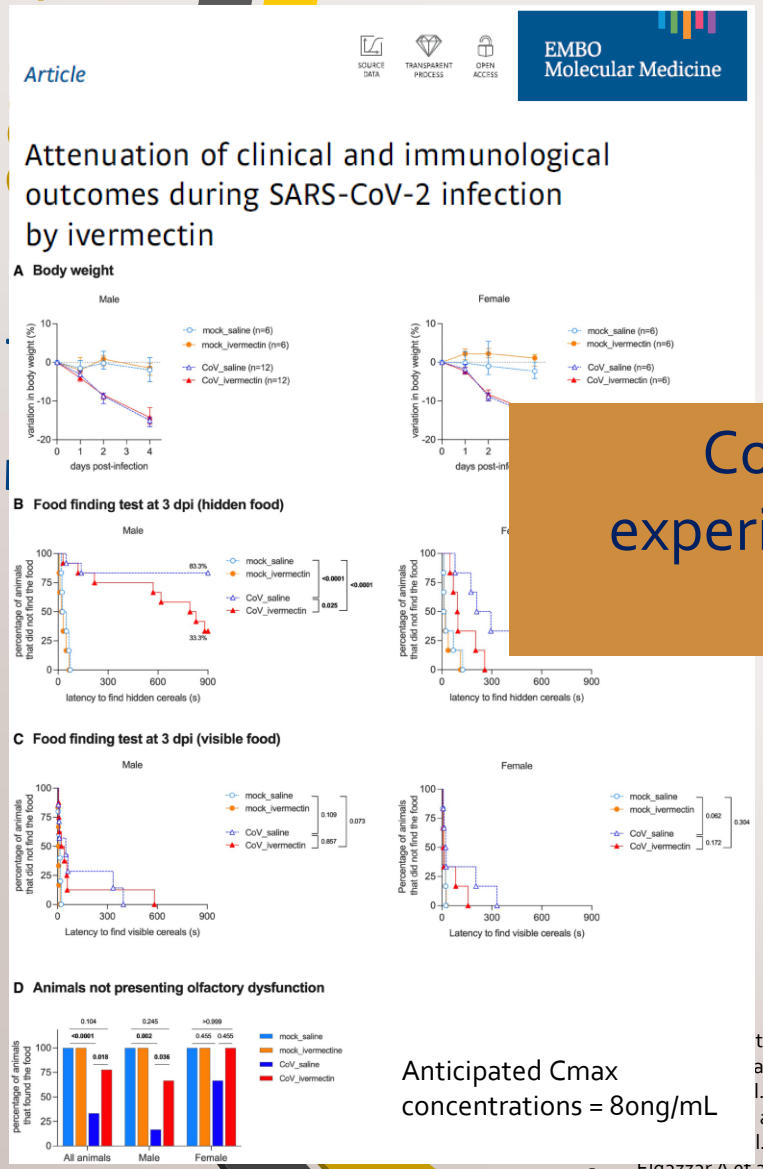
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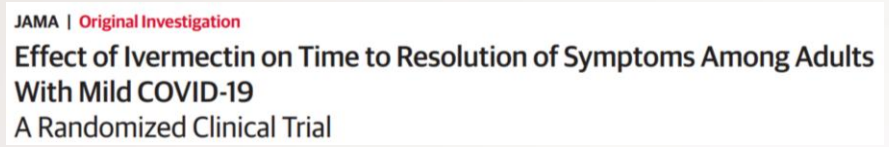
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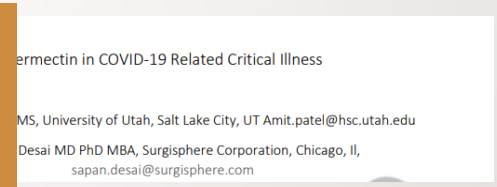
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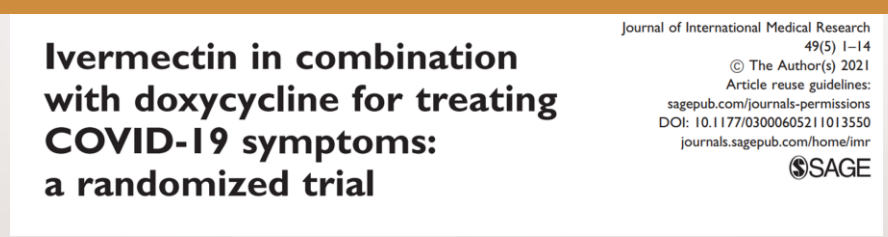
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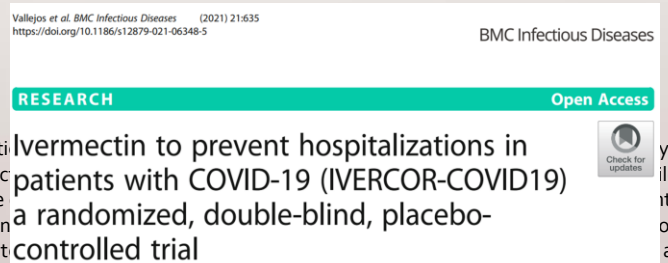
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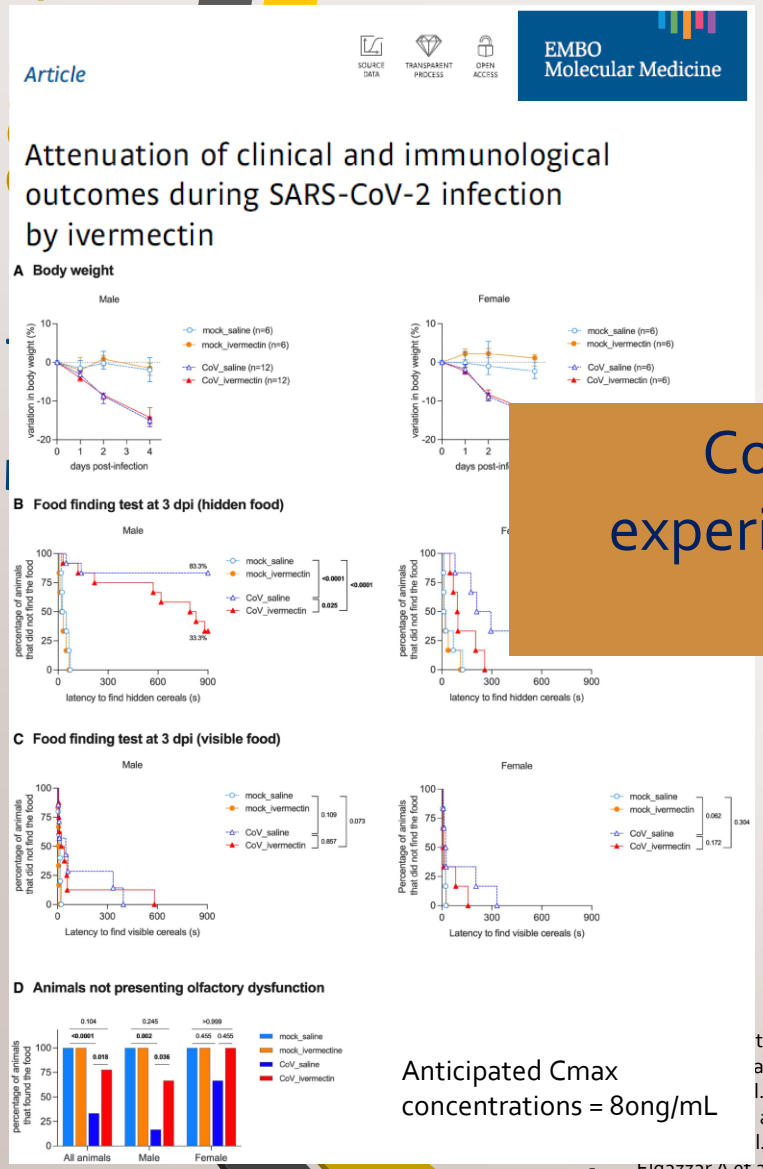
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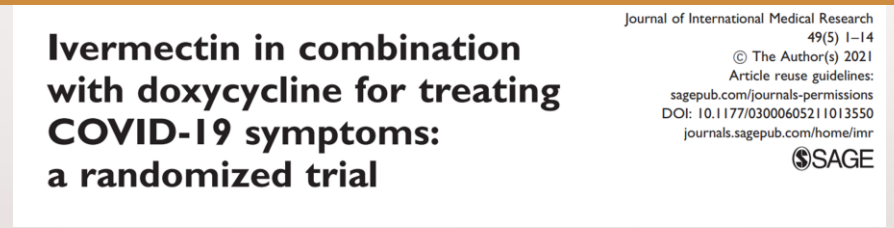
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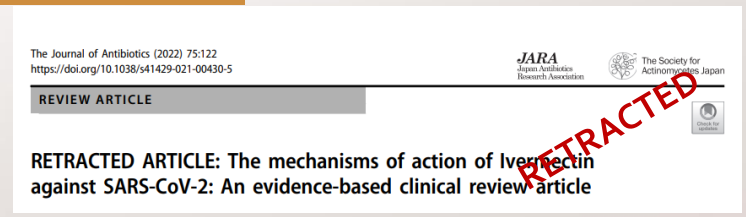
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JARA Japan Antibiotics Research Association

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RETRACTED ARTICLE: The mechanisms of action of Ivermectin against SARS-CoV-2: An evidence-based clinical review article

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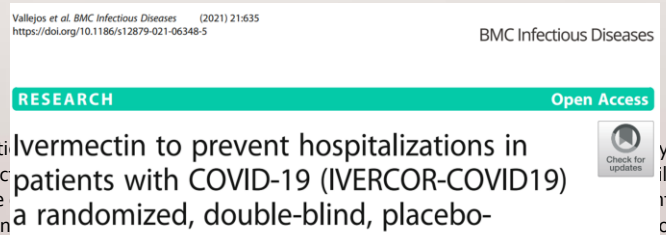
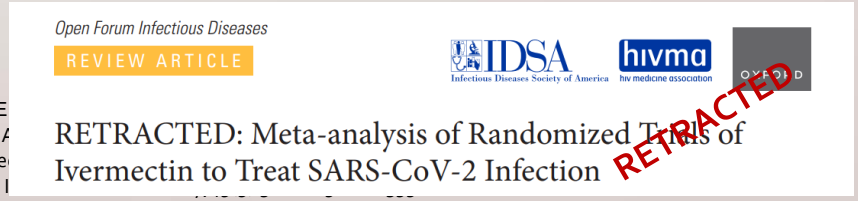

Vallejos et al. BMC Infectious Diseases (2021) 21:635
https://doi.org/10.1186/s12879-021-06348-5

BMC Infectious Diseases

RESEARCH Open Access

Ivermectin to prevent hospitalizations in patients with COVID-19 (IVERCOR-COVID19) a randomized, double-blind, placebo-controlled trial


Open Forum Infectious Diseases

REVIEW ARTICLE

IDSA Infectious Diseases Society of America | hivma hiv medicine association

RETRACTED: Meta-analysis of Randomized Trials of Ivermectin to Treat SARS-CoV-2 Infection

RETRACTED

- Elgazzar A et al. Efficacy and safety of Ivermectin for treatment and prophylaxis of COVID-19 pandemic (Retracted) 4eee8c3c-3c9e-4f8d-bc73-c40b4137323b.pdf (researchsquare.com)
- Patel AN et al. Ivermectin in COVID-19 related critical illness (Retracted) fab19388-dc3e-4593-a075-db96f4536e9d (isglobal.org)
- Zaidi AK, Dehgani-Mobaraki P. The mechanisms of action of Ivermectin against SARS-CoV-2: An evidence-based clinical review article (Retracted). J Antibiot (Tokyo). 2022 Feb;75(2):122
- Hill A et al. Meta-analysis of Randomized Trials of Ivermectin to Treat SARS-CoV-2 Infection (Retracted) Open Forum Infect Dis. 2022 Feb 5;9(3):ofac05

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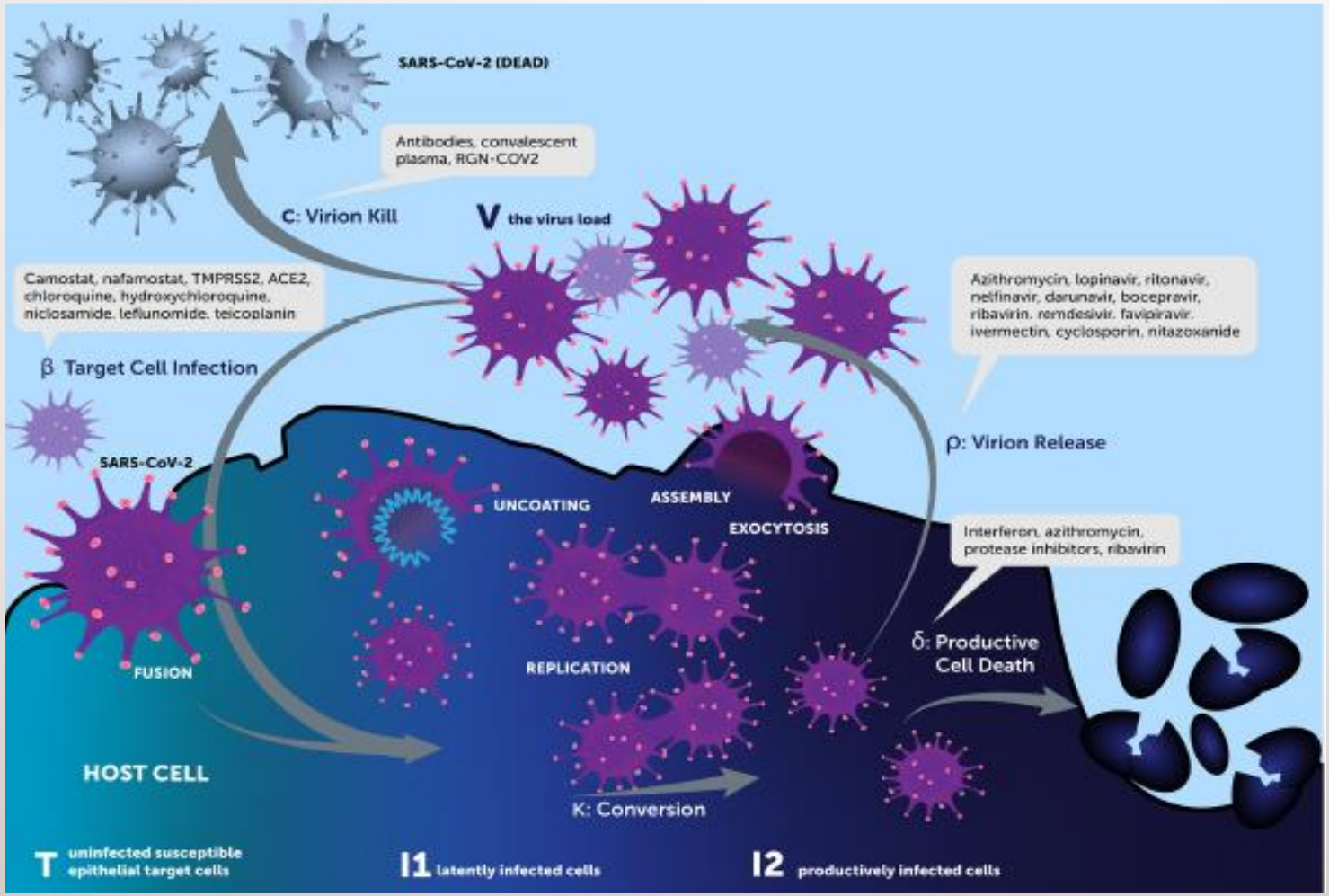
Timing Rationale: Viral Cell Cycle

SARS-CoV-2 cell cycle model used to inform treatment timing



- Patel K et al. Using in silico viral kinetic models to guide therapeutic strategies during a pandemic: An example in SARS-CoV-2. Br J Clin Pharmacol. 2021 Sep;87(9):3425-3438
- Dodds MG et al. Model-informed drug repurposing: Viral kinetic modelling to prioritize rational drug combinations for COVID-19. Br J Clin Pharmacol. 2021 Sep;87(9):3439-3450

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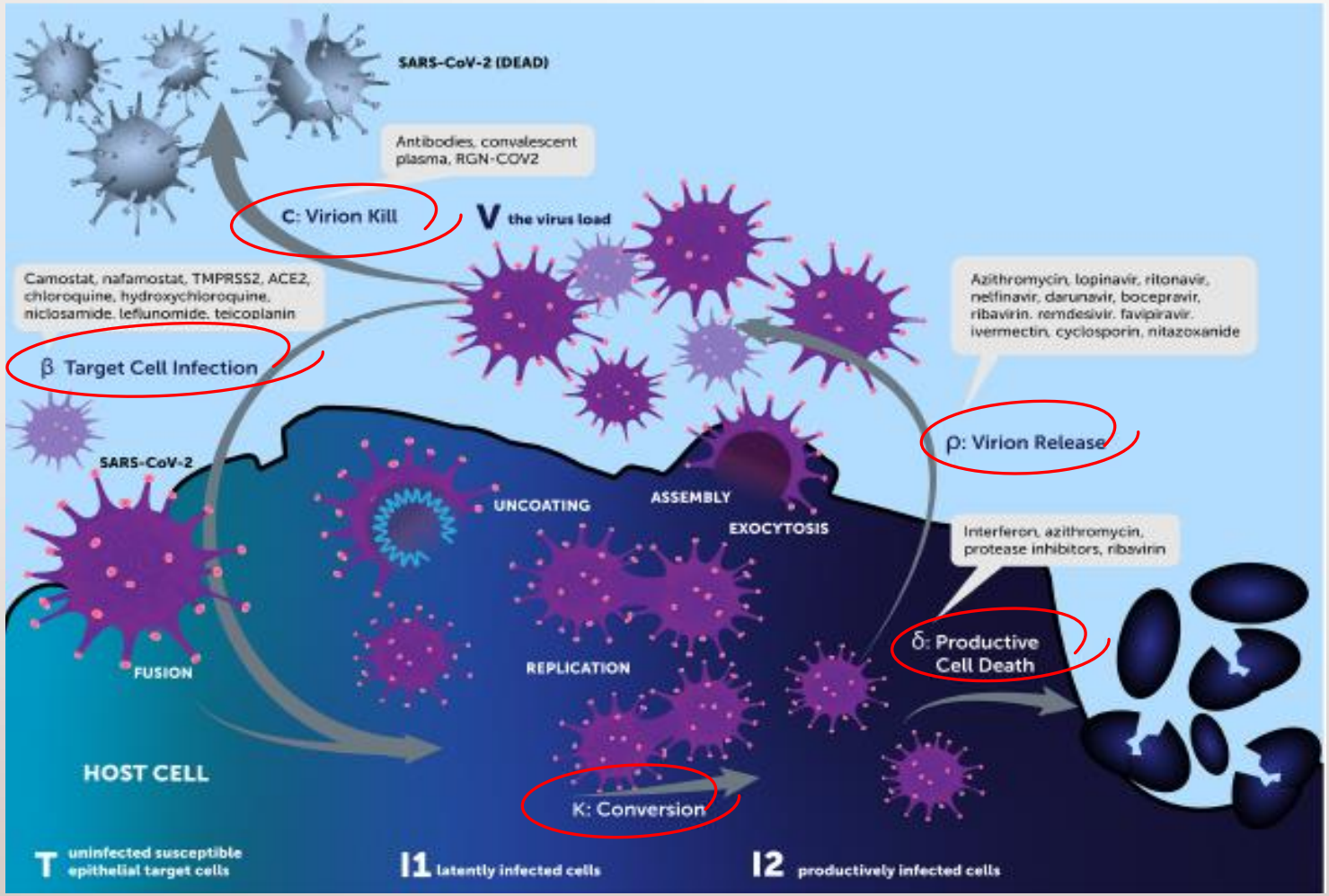

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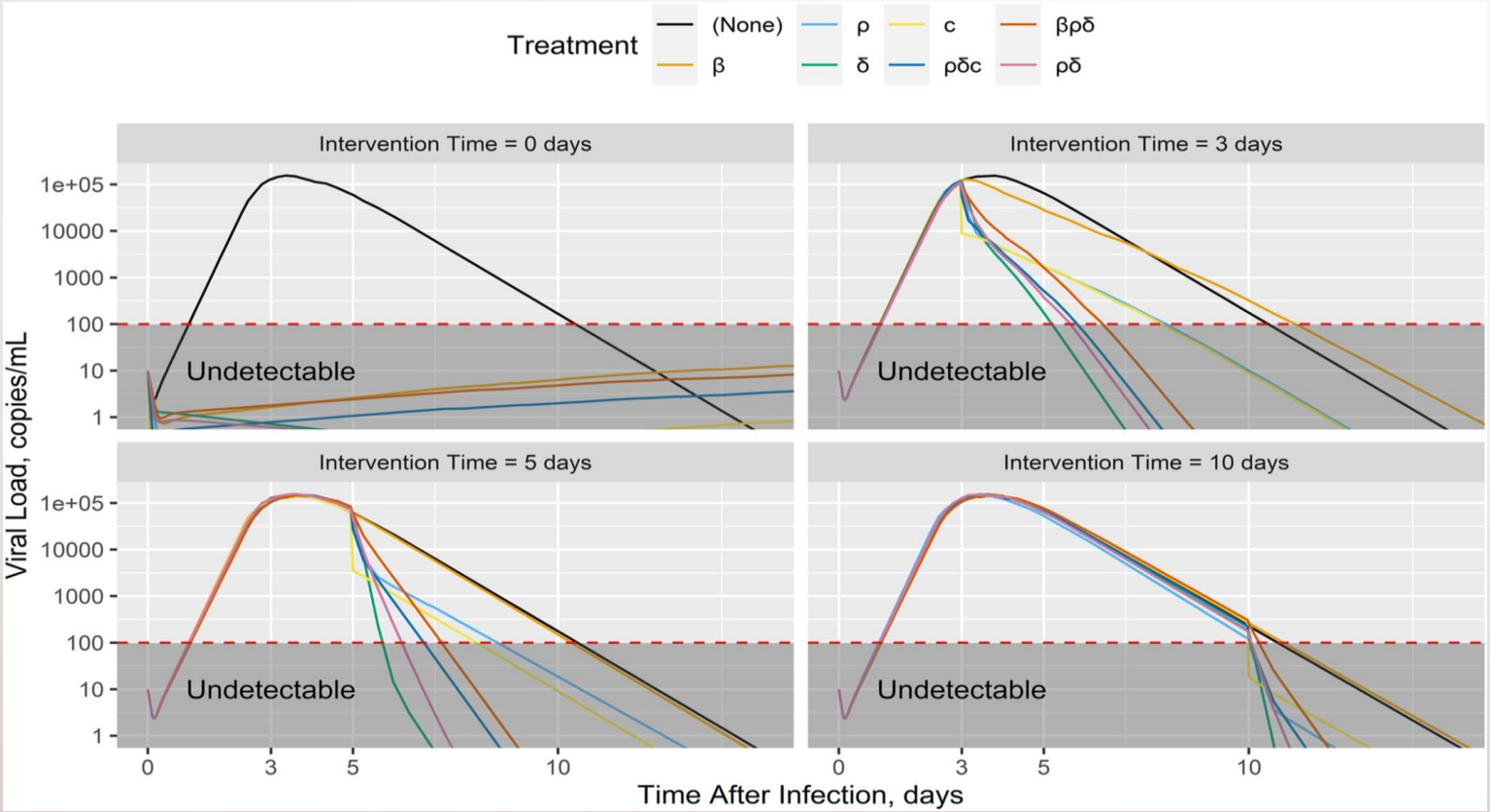
Timing Rationale: Early Intervention Most Sensitive

SARS-CoV-2 cell cycle model used to inform treatment timing



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Timing Rationale: Early Intervention Most Sensitive

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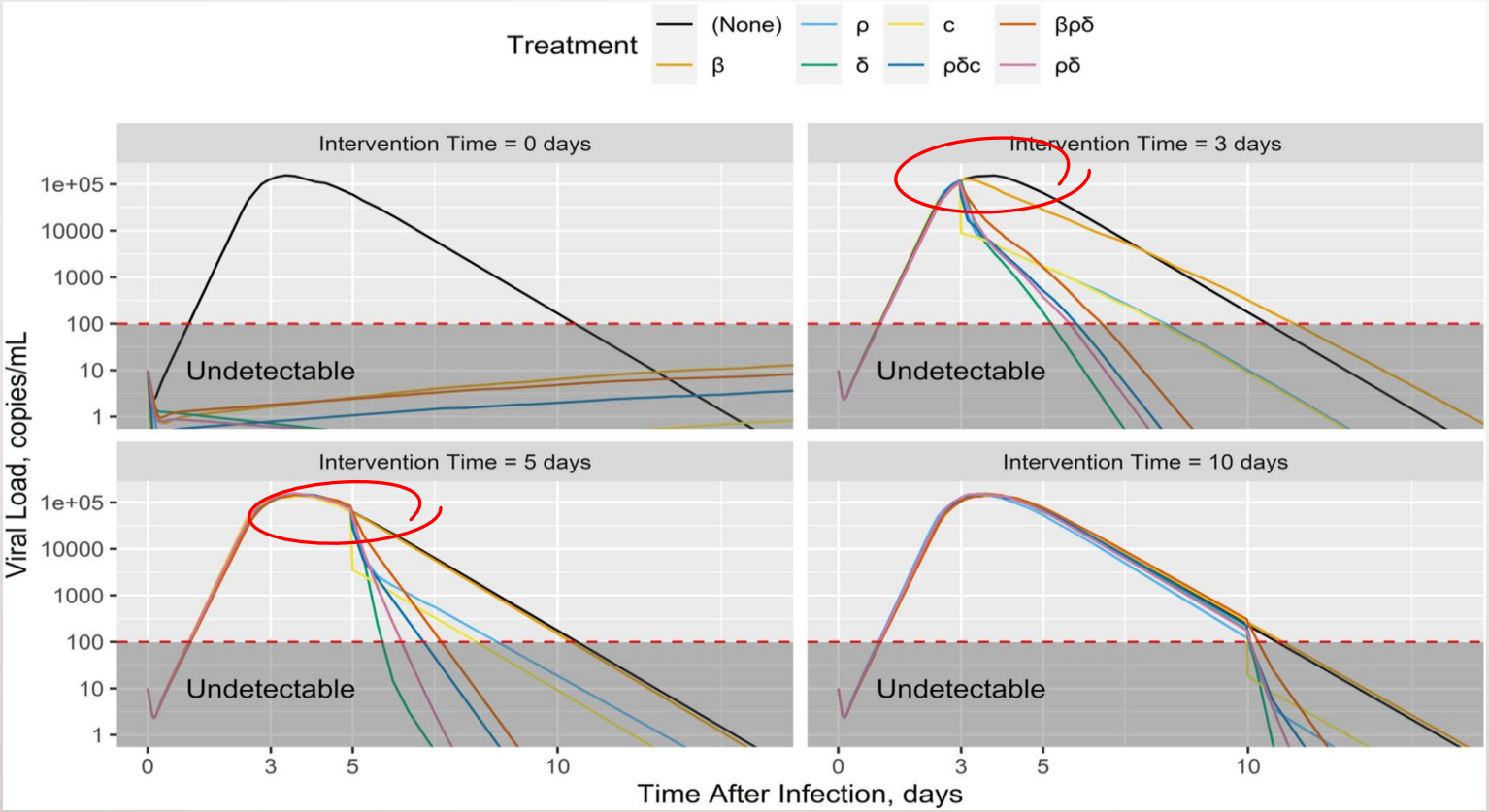

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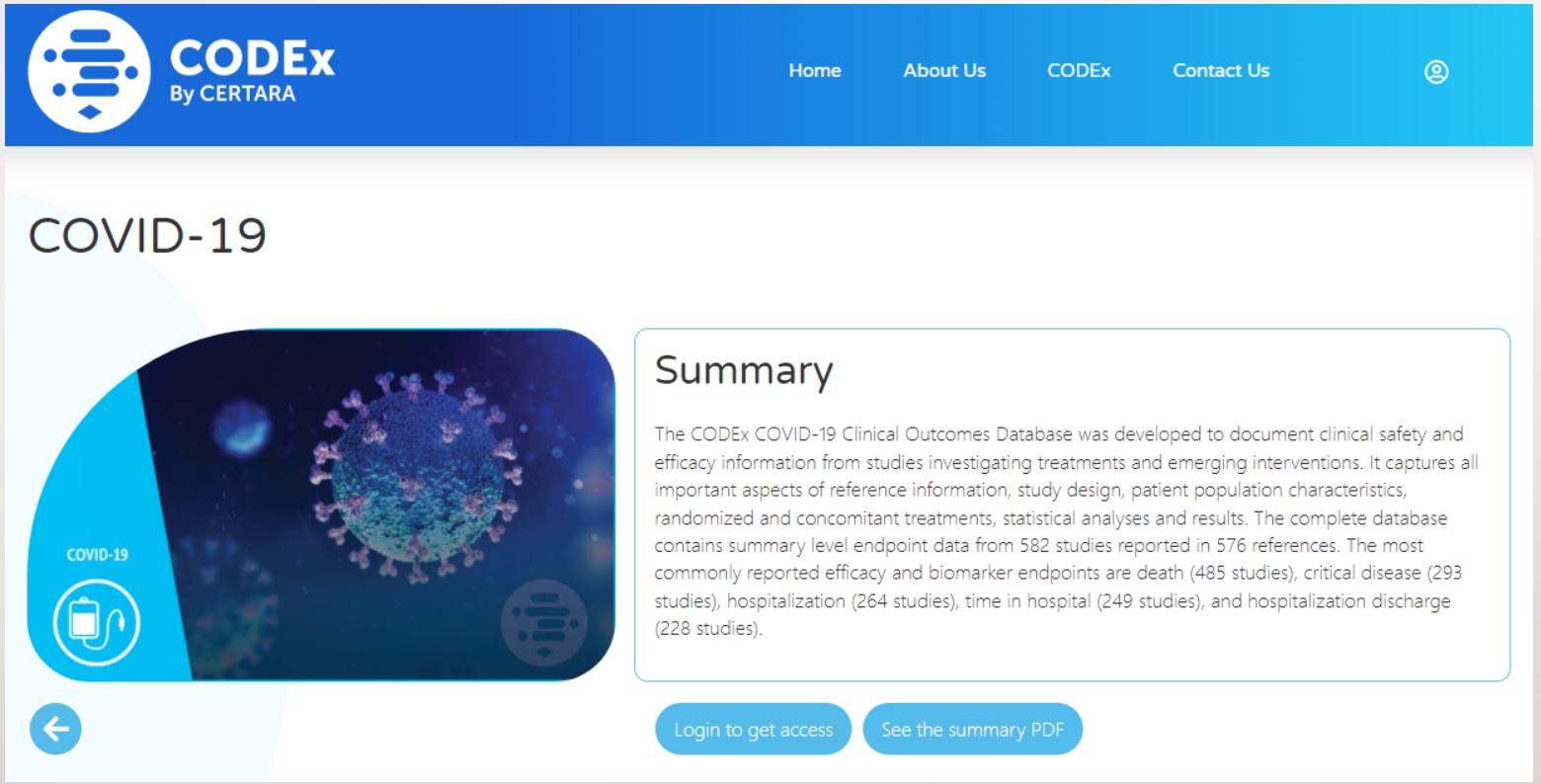
Dosing Rationale: 0.4mg/kg qd 3 days

ICODA
International COVID-19 Data Alliance



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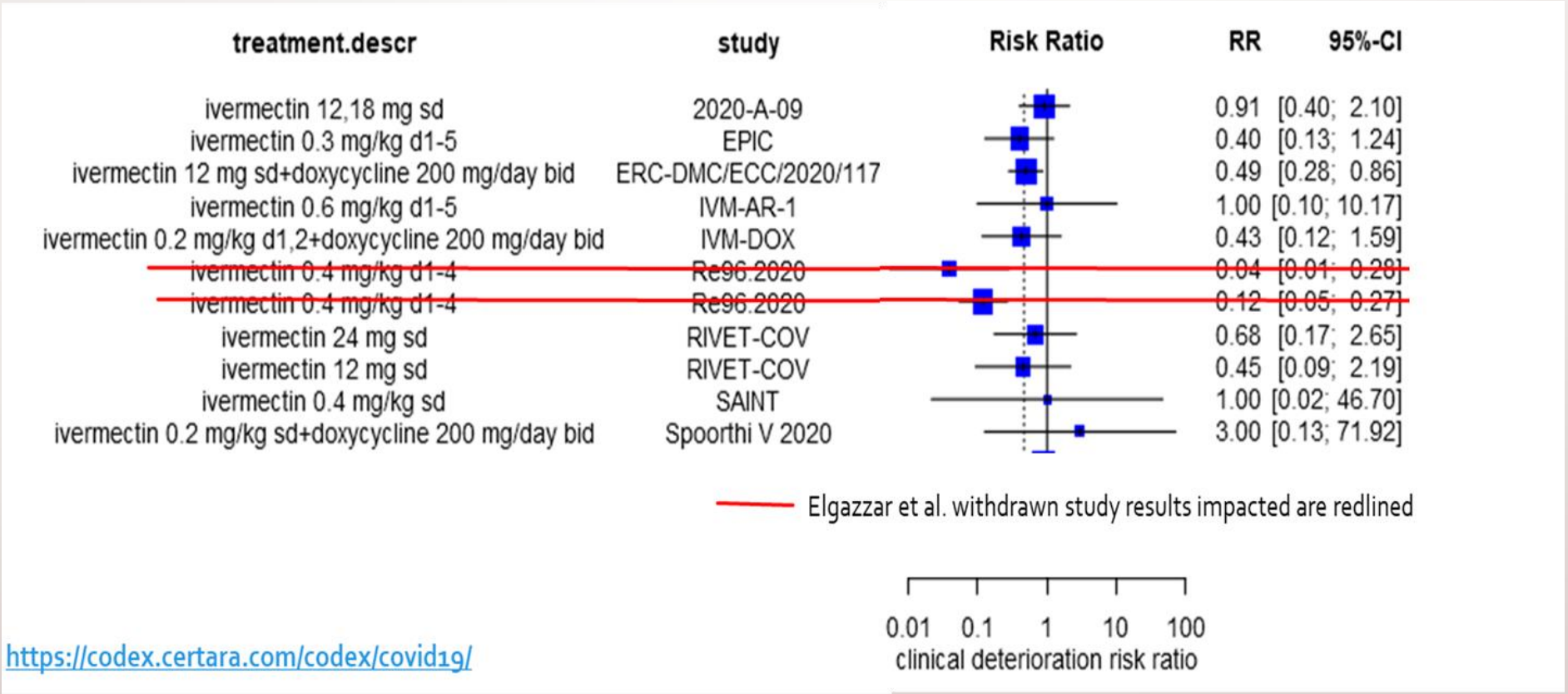

https://codex.certara.com/codex/covid19/

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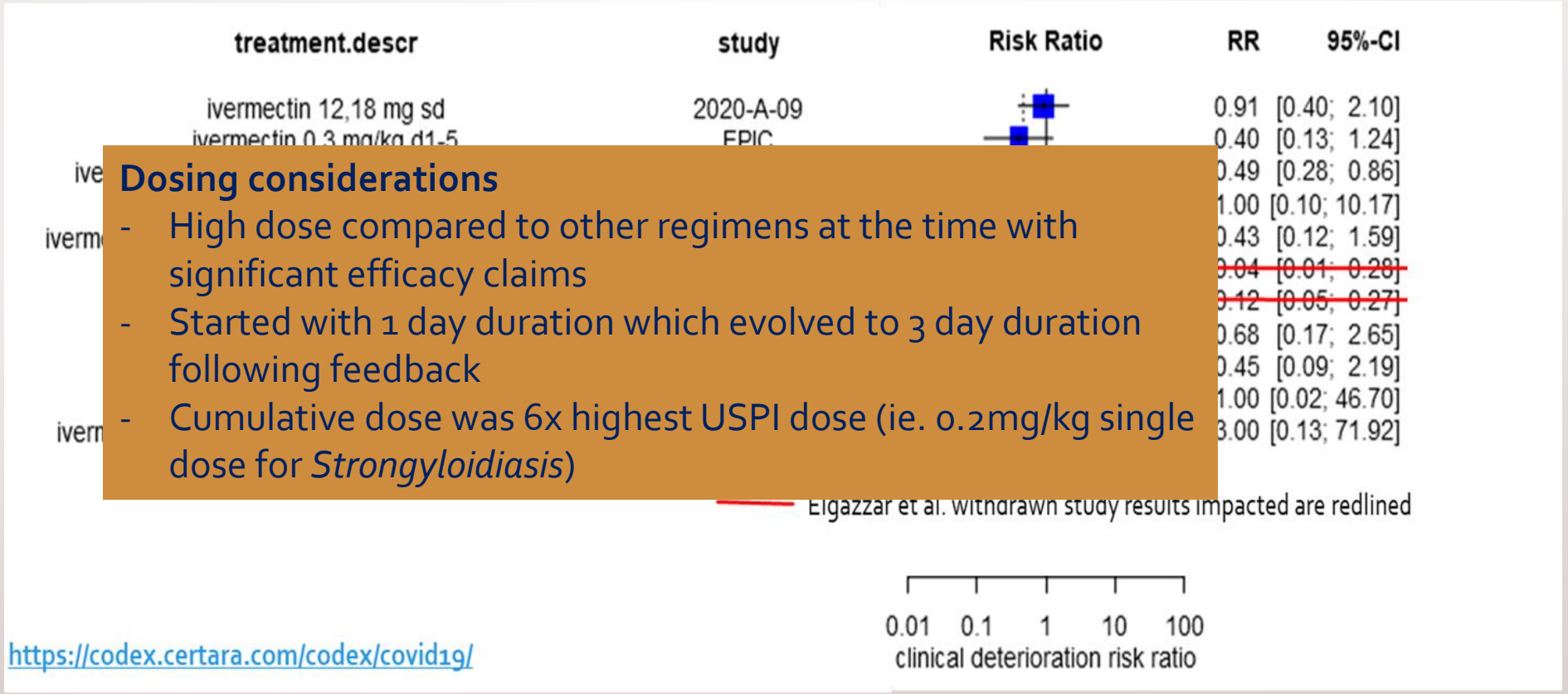

Dosing considerations

- High dose compared to other regimens at the time with significant efficacy claims
- Started with 1 day duration which evolved to 3 day duration following feedback
- Cumulative dose was 6x highest USPI dose (ie. 0.2mg/kg single dose for *Strongyloidiasis*)

https://codex.certara.com/codex/covid19/

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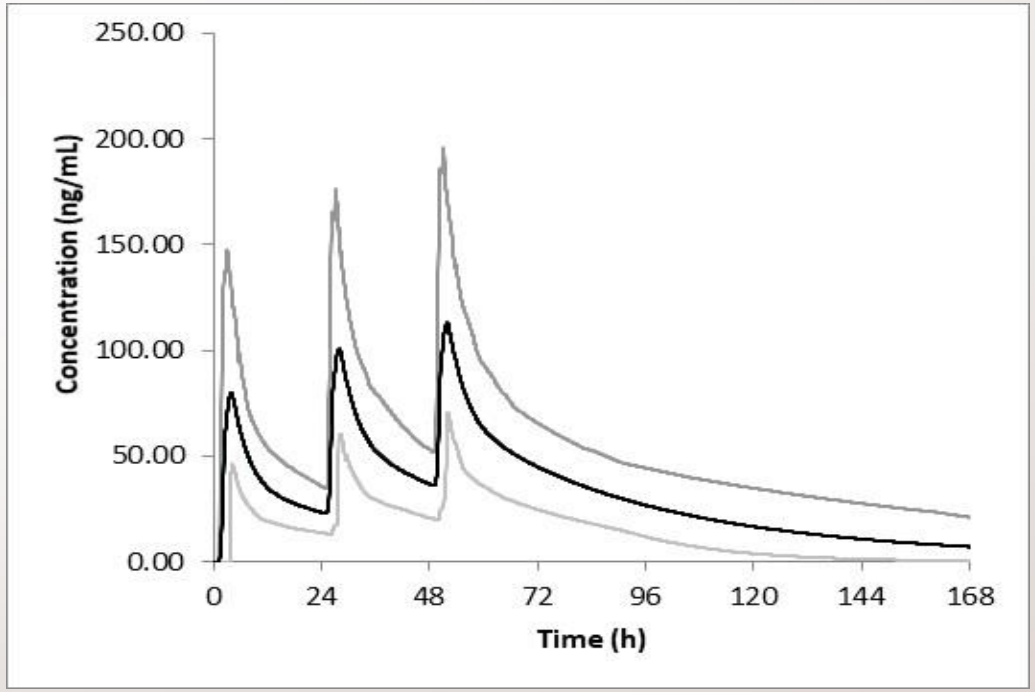
Dosing Rationale: 0.4mg/kg qd 3 days (fasted)

Dose (mg)	Subjects	Study design	Food effect
12	15 healthy subjects	POP-PK analysis of clinical data from 2 studies – one with a high fat breakfast and the other in the fasted state	1.18 (95% CI: 1.10-1.67)
12	13 elderly Japanese subjects (73-95 years)	Food effect study (high fat meal) crossover	1.25 (90% CI: 1.09-1.43)
30	12 healthy subjects (21-45 years)	Dose escalation study including food effect arm (high fat breakfast) – crossover	2.57 (95% CI: 2.16-3.05)

Dosing considerations

- Fasted conditions consistent with USPI
- Cmax exceeded those in Syrian Hamster model
- Cumulative exposures 6x labelled dose

PBPK modelling of ivermectin with 0.4 mg/kg dosing for 3 days in fasted state



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- Duthaler U et al. The effect of food on the pharmacokinetics of oral ivermectin. J Antimicrob Chemother. 2020 Feb 1;75(2):438-440
- Miyajima A et al. Effect of high-fat meal intake on the pharmacokinetic profile of ivermectin in Japanese patients with scabies. J Dermatol. 2016 Sep;43(9):1030-6
- Stromectol USPI: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/050742s026lbl.pdf

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Clinical Pharmacology Summary

- Based on the rationale presented, ivermectin entered into the TOGETHER platform RCT
  - Viral cell cycle model supported early treatment (suitable for TOGETHER trial)
  - 0.4mg/kg d, based on emerging clinical evidence at time and limited preclinical rationale
  - Fasting conditions, consistent with USPI
  - Duration: initially 1 day, following feedback, increased to 3 days

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Trial Setting

Clinical Sites In Minas Gerais:

1. Sete Lagoas
2. Ibirite
3. Brumadinho
4. Gov Valadares
5. Montes Claros
6. Nova Lima
7. Santa Luzia
8. Ouro Preto
9. Betim
10. Sabará
11. Contagem
12. Belo Horizonte


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Intervention Timeline

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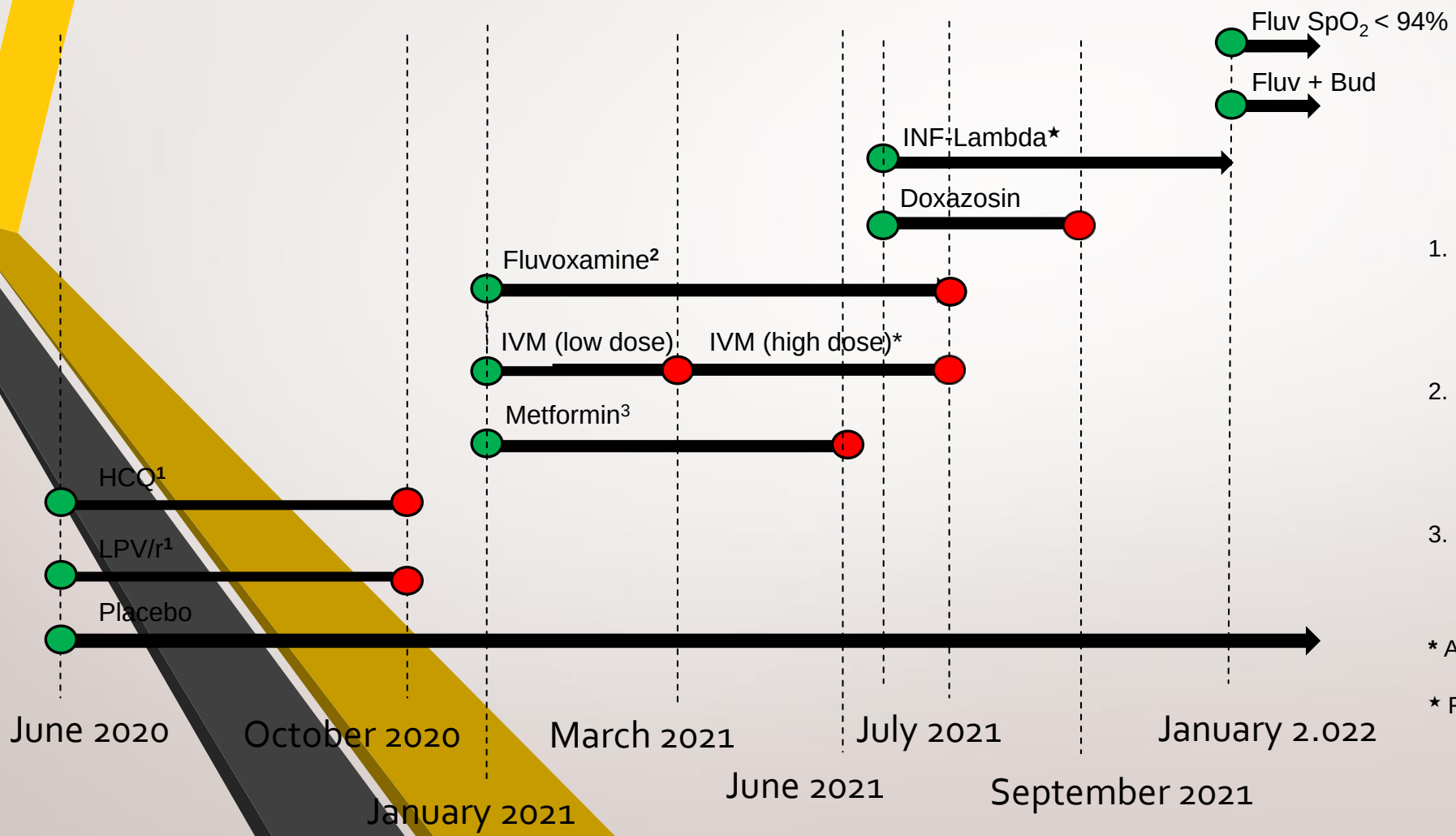

1. Reis G et al. JAMA Netw Open. 2021 Apr 1;4(4):e216468. doi: 10.1001/jamanetworkopen.2021.6468

2. Reis G et al. Lancet Glob Health. 2021 Oct 27:S2214-109X(21)00448-4. doi: 10.1016/S2214-109X(21)00448-4

3. Reis G et al. Lancet Reg Health Am. 2022 Feb;6:100142. doi: 10.1016/j.lana.2021.100142.

* Accepted manuscript

⋆ Finished arm

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Randomization

- Patients screened for eligibility
- Informed consent obtained
- Randomized to ivermectin (400ug/kg once a day) or placebo for 3 days
- Randomization stratified:
  - To account for other arms in the trial
  - Clinical site
  - Age (≥50 years *vs* <50 years)

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Key Eligibility Criteria

1. Patients over the age of 18
2. Presenting to an outpatient care setting with an acute clinical condition consistent with COVID-19 and symptoms beginning within 7 days of the screening date
3. Positive rapid test for SARS-CoV-2 antigen
4. At least one additional criterion for high-risk:
    - Diabetes mellitus
    - Systemic arterial hypertension
    - Symptomatic lung disease
    - Symptomatic asthma patients
    - Smoking
    - Obesity
    - Transplant patients
    - Patient with stage IV chronic kidney disease or on dialysis
    - immunosuppressed
    - History of cancer in the last 0.5 years or undergoing current cancer treatment.
    - Age greater than 50 years

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Exclusion Criteria

1. Diagnostic examination for SARS-CoV2 negative associated with acute flu-like symptoms
2. Acute respiratory condition compatible with COVID-19 treated in the primary care and requiring hospitalization
3. Acute respiratory condition due to other causes
4. Patients who have received vaccination for SARS-CoV2
5. Dyspnea secondary to other acute and chronic respiratory causes or infections
6. Acute flu showing at least one of the criteria below:
   - Respiratory Rate > 28 / min;
   - SaO_2 < 90% or < 93% on nasal oxygen therapy at 10 L / min;
   - PaO_2 / FIO_2 < 300 mm Hg;
7. Use of study drugs for COVID
8. Patient risks

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Outcomes

Primary Outcomes:

- Emergency room visits due to the clinical worsening of COVID-19 (defined as participant remaining under observation for > 6 hours)
- Hospitalization due to the progression of COVID-19 (defined as worsening of viral pneumonia) and/or complications within 28 days of randomization.

Secondary Outcomes:

- WHO clinical worsening scale
- PROMIS global health scale
- Mortality defined and all-cause
- Cause-specific hospitalization
- Viral clearance and viral load
- Respiratory symptoms
- Adverse events
- Adverse drug reactions
- Adherence with medication


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Data Collection

- Participants were contacted on Days 1, 2, 3, 4, 5, 7, 10, 14, and 28 via telephone and social media applications
- Participants were contacted up to day 60 to assess long-term outcomes
- All SAEs were documented and reported as per local regulatory requirements
- Data were entered into the trial's EDC system (IBM Clinical Development)

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Primary Outcome

- 14.7% (100 of 679) of participants allocated to ivermectin experienced a primary outcome event
- 16.3% (111 of 679) of participants allocated to placebo in the ITT population experienced a primary outcome event

(Relative Risk [RR]: 0.90; 95% Bayesian Credible Interval [BCI]: 0.70 – 1.16)

- **mITT population** (24h treatment before event)**:** (RR: 0.89; 95% BCI: 0.69 – 1.15)
- **PP population** (100% adherence): (RR: 0.94; 95% BCI: 0.67 – 1.35)
- 81% of events were hospitalization in the ITT population

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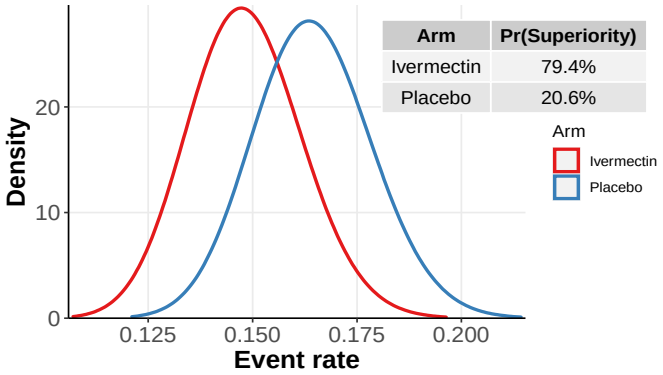
Intention−to−treat analysis

Arm	Pr(Superiority)
Ivermectin	79.4%
Placebo	20.6%



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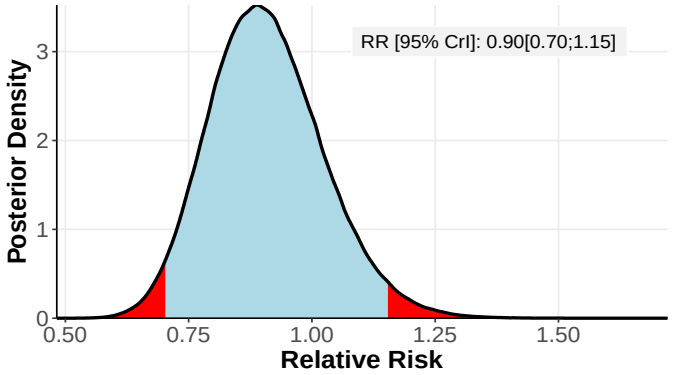
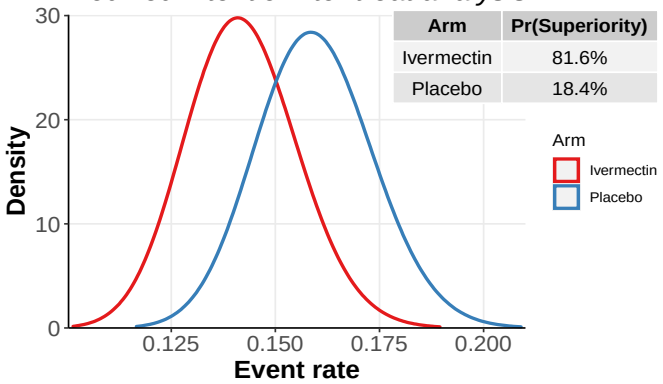
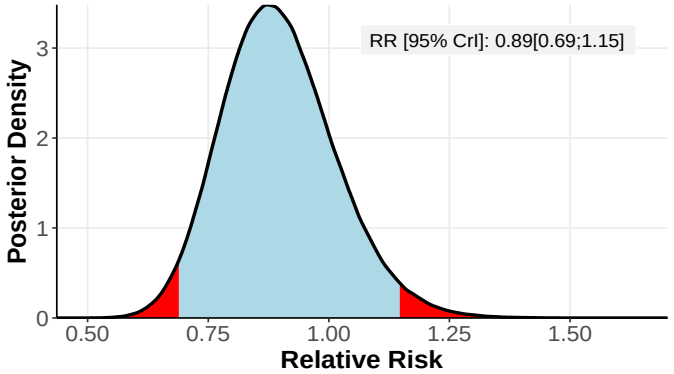


Modified intention−to−treat analysis

Arm	Pr(Superiority)
Ivermectin	81.6%
Placebo	18.4%

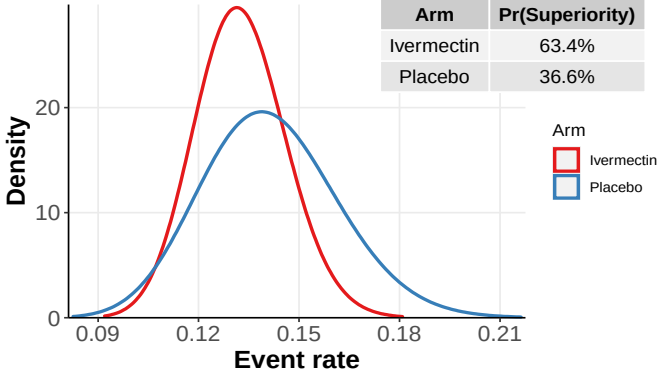


Modified intention−to−treat analysis



Per−protocol analysis

Arm	Pr(Superiority)
Ivermectin	63.4%
Placebo	36.6%



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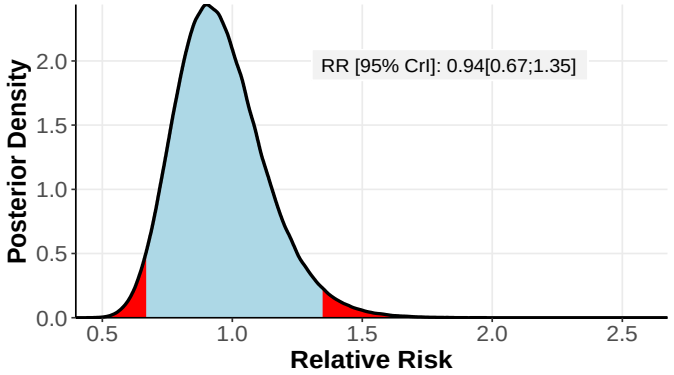

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Primary Outcome

Intention to treat (ITT)			
	N	**n (%)**	**RR (95% BCI)**
Ivermectin	679	100 (14.7)	0.90 (0.70 - 1.16)
Placebo	679	111 (16.3)	1.00 (Ref)
All	1358	211 (15.5)	--
Modified Intention to Treat (mITT)			
	N	**n (%)**	**RR (95% BCI)**
Ivermectin	674	95 (14.1)	0.89 (0.69 - 1.15)
Placebo	675	107 (15.9)	1.00 (Ref)
All	1349	202 (15.0)	--
Per Protocol (PP)*			
	N	**n (%)**	**RR (95% BCI)**
Ivermectin	624	82 (13.1)	0.94 (0.67 – 1.35)
Placebo	288 **	40 (13.9)	1.00 (Ref)
All	912	122 (13.4)	--

*(PP) population was defined by 100% self-reported adherence.

**The PP population compared only those with 100% adherence to both ivermectin and 3-day matched placebo-control.

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Secondary Outcomes

	Ivermectin	Placebo	Estimated treatment effect (95% BCI)
Viral clearance (Day 7)	36/142 (25.4%)	42/165 (25.5%)	1.00 (0.68, 1.46)
Hospitalized for COVID-19	78/679 (11.5%)	93/679 (13.7%)	0.84 (0.63, 1.11)
All-cause hospitalization	79/679 (11.6%)	95/679 (14%)	0.83 (0.63, 1.10)
Days to hospitalization	5 days [3 to 7]	5 days [3 to 7.5]	0.83 (0.61, 1.13)+
Days of hospitalization	6 days [3.75 to 10]	6 days [3 to 11]	0.99 (0.80, 1.24)‡
Emergency room visit for at least 6 hours	36/679 (5.3%)	31/679 (4.6%)	1.16 (0.73, 1.85)
Days to the emergency visit for at least 6 hours	5 days [4 to 7]	5 days [3 to 8]	1.15 (0.71, 1.89)+
Death	20/679 (2.9%)	24/679 (3.5%)	0.84 (0.46, 1.50)
Days to death	13.5 days [8.75 to 19.25]	14 days [8 to 20]	0.84 (0.46, 1.50)+

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Secondary Outcomes

	Ivermectin	Placebo	Estimated treatment effect (95% BCI)
Mechanical ventilation required	19/679 (2.8%)	25/679 (3.7%)	0.77 (0.43, 1.36)
Days on mechanical ventilator	6 days [3 to 15.5]	7 days [2 to 12]	1.06 (0.63, 1.75)‡
PROMIS Global Physical	49.6 [42.6 to 53.1]	49.6 [42.6 to 56.6]	-0.43 (-1.37, 0.55)§
PROMIS Global Mental	52.5 [43.5 to 58.6]	52.5 [46.5 to 58.6]	6.05 [-104.1;116.7]§§
Medicine Adherence 100%	624/679 (91.9%)	547/679 (80.6%)*	1.14 (1.09, 1.19)
Grade 1 TEAE	16/679 (2.4%)	12/679 (1.8%)	1.32 (0.64, 2.76)
Grade 2 TEAE	49/679 (7.2%)	76/679 (11.2%)	0.65 (0.46, 1.04)
Grade 3 TEAE	41/679 (6%)	50/679 (7.4%)	0.82 (0.55, 1.22)
Grade 4 TEAE	17/679 (2.5%)	18/679 (2.7%)	0.95 (0.49, 1.80)
Grade 5 TEAE	20/679 (2.9%)	25/679 (3.7%)	0.81 (0.45, 1.42)

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Subgroup Analyses

- We found no evidence of moderation of treatment effect for ivermectin compared to placebo, for sub-groups of:
  - age, sex, days since symptom onset, BMI, smoking status, or lung or cardiovascular disease
  - We observed no benefit among those initiating ivermectin within 3 days of symptom onset over placebo (RR: 1.14; 95% CI: 0.76 – 1.74)
  - Events in our trial happened an average of 5 days post-randomization.

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Conclusions

- In this trial, we did not find a significant effect of ivermectin for the treatment of early COVID
- But we cannot rule out a small treatment effect

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The TOGETHER Team

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