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B/RD

British *Ivermectin* Recommendation Development

O Que é Ivermectina?

- Medicação antiparasitária com propriedades antiviral e antiinflamatórias
- Usada em medicina tropical há 40 years
- *Pertence a WHO's* Lista de Medicamentos Essenciais
- Prêmio Nobel da Medicina em 2015
- Ação in vitro contra Dengue, Zika, vírus da febre amarela, WNV

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Mechanism of action against SARS-CoV2

- Bloqueia a importação de proteínas virais para o núcleo da célula humana
- Impede a supressão viral da resposta imunológica humana
- Inibe as enzimas virais necessárias para a replicação
- Reduz a inflamação

Sources: Caly 2020, Heidary 2020, Anand 2003, Mody 2021, DiNicolantonio 2020

Revisão sistemática de ivermectina para prevenção e tratamento de covid-19

- A equipe incluiu 3 revisores sistemáticos, economista de saúde, 2 médicos especialistas e um representante do consumidor
- Protocolo de revisão enviado à Cochrane em 14 de janeiro de 2021
- Seguiu a Metodologia Cochrane estrita (apenas RCTs, avaliação de risco de viés, abordagem GRADE para avaliar a certeza da evidência)
- Atualizado em 31 de março de 2021 e enviado ao jornal sob revisão de pares

Por que foi importante fazer uma revisão sistemática?

- RSs com meta-análise de ensaios clínicos randomizados é considerado o mais alto nível de evidência
- Ensaios randomizados podem produzir resultados diferentes
- A maioria das autoridades de saúde usa RSs para apoiar as diretrizes de prática clínica
- Um grande corpo de evidências se acumulou

Como as evidências de Revisões Sistemáticas são avaliadas?

Avaliação de risco de viés

Geração de sequência aleatória

Ocultação de alocação

Cegamento dos participantes, equipe de saúde e avaliadores de resultados

Desgaste

Relatório seletivo

Outros vieses

Avaliação da certeza geral de evidência

A evidência do ensaio randomizado sinaliza uma ALTA CERTEZA

Rebaixada em -1 ou -2 por:

- ✓ Limitações do desenho do estudo
- ✓ Inconsistência
- ✓ Imprecisão
- ✓ Indireto
- ✓ Viés de publicação

ALTO - MODERADO - BAIXO - MUITO BAIXO

GRADEpro GDT

*WHO Standard Operating Procedure

Interpretação das evidências

MUITO BAIXA CERTEZA - estamos muito incertos sobre a estimativa

BAIXA CERTEZA - pesquisas futuras provavelmente mudarão a estimativa do efeito

CERTEZA MODERADA - pesquisas adicionais podem alterar a estimativa do efeito

ALTA CERTEZA - é improvável que pesquisas adicionais alterem a estimativa do efeito

Corticosteroides para pacientes criticamente enfermos covid-19 = evidência de certeza moderada

Remdesivir = low certainty evidence

Perguntas de revisão sistemática:

1. Para pessoas com covid, a ivermectina em comparação com nenhuma ivermectina melhora os resultados de saúde?

2. Para pessoas com maior risco de covid, a ivermectina comparada ao não uso de ivermectina melhora os resultados de saúde?

O que encontramos?

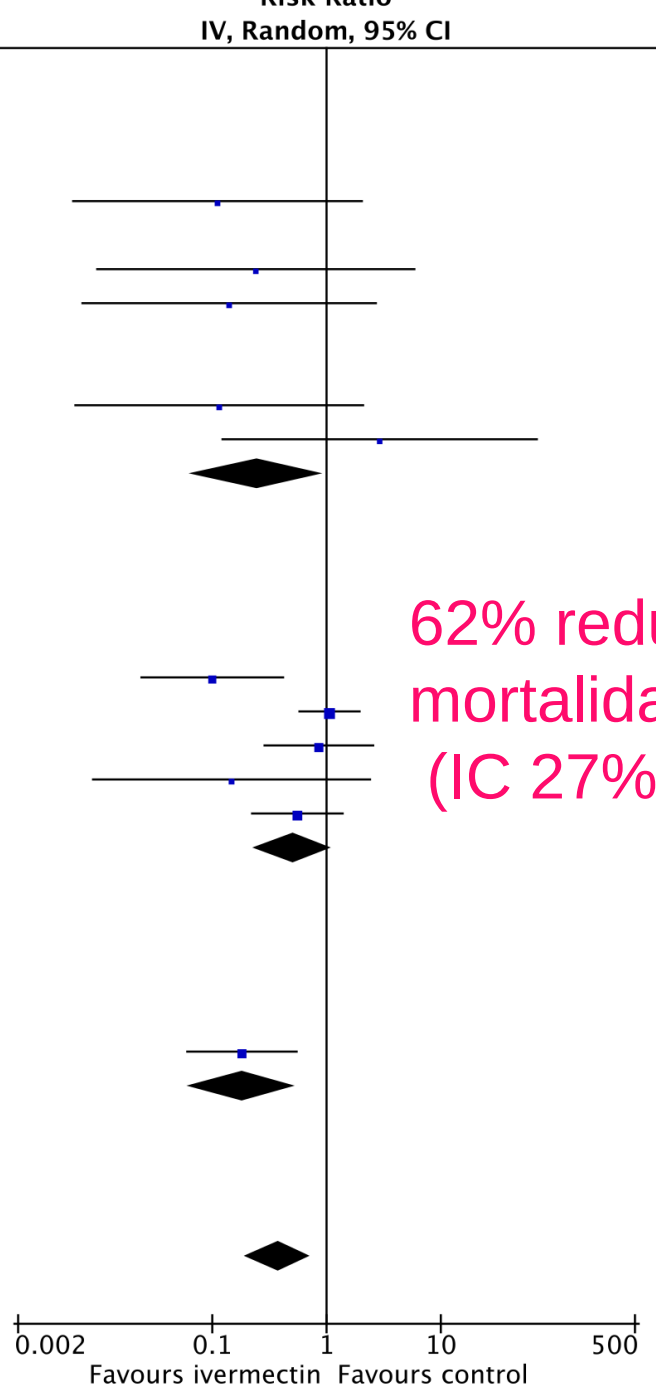
- Incluiu 24 ensaios clínicos randomizados (21 RCTs + 3 quase-RCTs)
- 21 ensaios de tratamento (2668 participantes)
- 3 ensaios de prevenção (738 participantes)
- O tamanho do teste variou de 24 a 473 pessoas
- A maioria dos ensaios foi registrada, autofinanciada, conduzida por médicos
- Sem conflitos de interesse óbvios

- Os ensaios de tratamento foram realizados na Argentina (1), Bangladesh (6), Brasil (1), Bulgária (1), Colômbia (1), Egito (1), Índia (2), Israel (1), Irã (2), Líbano (1), Nigéria (1), México (1), Paquistão (2), Espanha (1), Turquia (1)
- Os ensaios de prevenção foram conduzidos na Argentina (1) e no Egito (2)

Tratamento

Desfecho primário: Morte

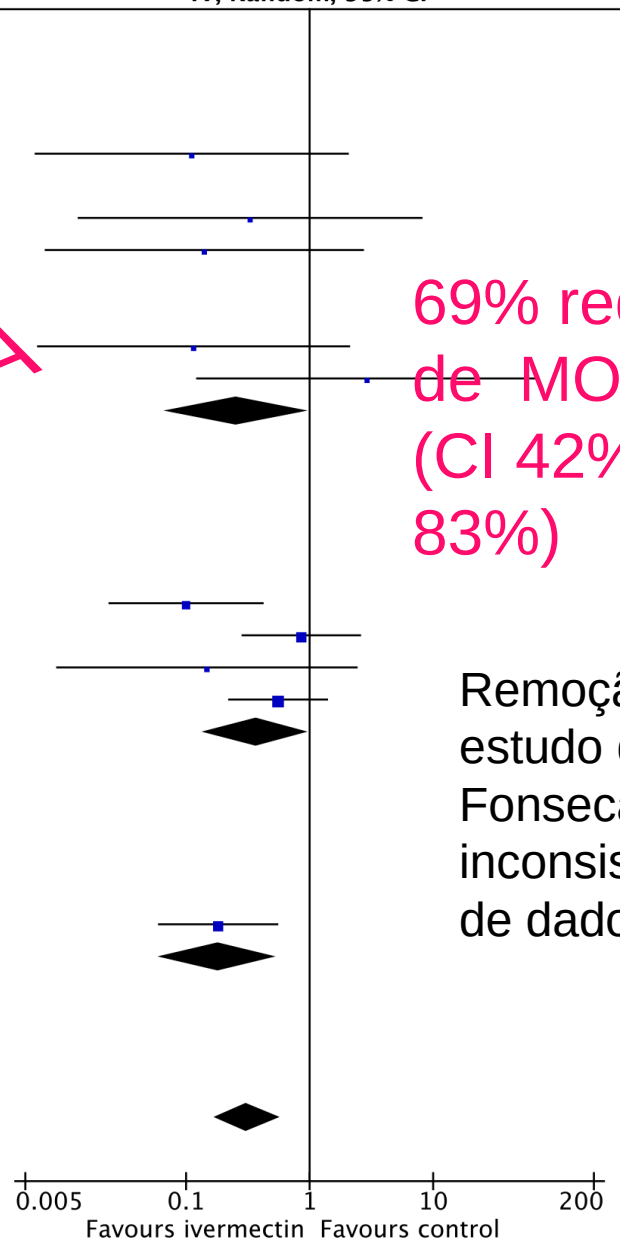
Study or Subgroup	Ivermectin Events	Ivermectin Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
1.1.1 Mild to moderate covid-19						
Ahmed 2020 (1)	0	45	0	23		Not estimable
Babaloa 2020 (2)	0	42	0	20		Not estimable
Chaccour 2020 (3)	0	12	0	12		Not estimable
Elgazzar 2020 (4)	0	100	4	100	4.3%	0.11 [0.01, 2.04]
Hashim 2020 (5)	0	48	0	48		Not estimable
Lopez-Medina 2021 (6)	0	275	1	198	3.6%	0.24 [0.01, 5.87]
Mahmud 2020 (7)	0	183	3	180	4.1%	0.14 [0.01, 2.70]
Mohan 2021 (8)	0	100	0	52		Not estimable
Petkov 2021 (9)	0	50	0	50		Not estimable
Ravikirti 2021 (10)	0	55	4	57	4.3%	0.12 [0.01, 2.09]
Rezai 2020 (11)	1	35	0	34	3.7%	2.92 [0.12, 69.20]
Subtotal (95% CI)		**945**		**774**	**20.0%**	**0.24 [0.06, 0.94]**
Total events	1		12			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.03$, df = 4 (P = 0.55); $I^2 = 0\%$						
Test for overall effect: Z = 2.05 (P = 0.04)						
1.1.2 Severe covid-19						
Elgazzar 2020 (12)	2	100	20	100	11.2%	0.10 [0.02, 0.42]
Fonseca 2021 (13)	12	52	25	115	19.5%	1.06 [0.58, 1.94]
Gonzalez 2021 (14)	5	36	6	37	14.3%	0.86 [0.29, 2.56]
Hashim 2020 (15)	0	11	6	22	4.5%	0.15 [0.01, 2.40]
Okumus 2021 (16)	6	36	9	30	16.2%	0.56 [0.22, 1.38]
Subtotal (95% CI)		**235**		**304**	**65.8%**	**0.51 [0.22, 1.14]**
Total events	25		66			
Heterogeneity: $Tau^2 = 0.48$; $Chi^2 = 10.52$, df = 4 (P = 0.03); $I^2 = 62\%$						
Test for overall effect: Z = 1.65 (P = 0.10)						
1.1.3 Mild, moderate and severe covid-19						
Niaee 2020 (17)	4	120	11	60	14.2%	0.18 [0.06, 0.55]
Subtotal (95% CI)		**120**		**60**	**14.2%**	**0.18 [0.06, 0.55]**
Total events	4		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.03 (P = 0.002)						
Total (95% CI)		**1300**		**1138**	**100.0%**	**0.38 [0.19, 0.73]**
Total events	30		89			
Heterogeneity: $Tau^2 = 0.49$; $Chi^2 = 19.78$, df = 10 (P = 0.03); $I^2 = 49\%$						
Test for overall effect: Z = 2.87 (P = 0.004)						
Test for subgroup differences: $Chi^2 = 2.38$, df = 2 (P = 0.30), $I^2 = 15.9\%$						



62% redução de mortalidade (IC 27% to 81%)

Tratamento Desfecho primário: Morte

Study or Subgroup	Ivermectin Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.2.1 Mild to moderate covid-19						
Ahmed 2020 (1)	0	45	0	23		Not estimable
Babalola 2020 (2)	0	42	0	20		Not estimable
Chaccour 2020 (3)	0	12	0	12		Not estimable
Elgazzar 2020 (4)	0	100	4	100	4.1%	0.11 [0.01, 2.04]
Hashim 2020 (5)	0	48	0	48		Not estimable
Lopez-Medina 2021 (6)	0	200	1	198	3.5%	0.33 [0.01, 8.05]
Mahmud 2020 (7)	0	183	3	180	4.0%	0.14 [0.01, 2.70]
Mohan 2021 (8)	0	100	0	52		Not estimable
Petkov 2021 (9)	0	50	0	50		Not estimable
Ravikirti 2021 (10)	0	55	4	57	4.2%	0.12 [0.01, 2.09]
Rezai 2020 (11)	1	35	0	34	3.5%	2.92 [0.12, 69.20]
Subtotal (95% CI)		**870**		**774**	**19.3%**	**0.26 [0.07, 1.00]**
Total events	1		12			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.06$, df = 4 (P = 0.55); $I^2 = 0\%$						
Test for overall effect: Z = 1.97 (P = 0.05)						
1.2.2 Severe covid-19						
Elgazzar 2020 (12)	2	100	20	100	13.6%	0.10 [0.02, 0.42]
Gonzalez 2021 (13)	5	36	6	37	19.4%	0.86 [0.29, 2.56]
Hashim 2020 (14)	0	11	6	22	4.5%	0.15 [0.01, 2.40]
Okumus 2021 (15)	6	36	9	30	23.9%	0.56 [0.22, 1.38]
Subtotal (95% CI)		**183**		**189**	**61.4%**	**0.37 [0.14, 0.98]**
Total events	13		41			
Heterogeneity: $Tau^2 = 0.51$; $Chi^2 = 6.40$, df = 3 (P = 0.09); $I^2 = 53\%$						
Test for overall effect: Z = 2.00 (P = 0.05)						
1.2.3 Mild, moderate and severe covid-19						
Niaee 2020 (16)	4	120	11	60	19.3%	0.18 [0.06, 0.55]
Subtotal (95% CI)		**120**		**60**	**19.3%**	**0.18 [0.06, 0.55]**
Total events	4		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.03 (P = 0.002)						
Total (95% CI)		**1173**		**1023**	**100.0%**	**0.31 [0.17, 0.58]**
Total events	18		64			
Heterogeneity: $Tau^2 = 0.20$; $Chi^2 = 11.48$, df = 9 (P = 0.24); $I^2 = 22\%$						
Test for overall effect: Z = 3.68 (P = 0.0002)						
Test for subgroup differences: $Chi^2 = 0.87$, df = 2 (P = 0.65), $I^2 = 0\%$						
Footnotes						



CERTEZA MODERADA

69% redução de MORTES (CI 42% to 83%)

Remoção do estudo de Fonseca- inconsistência de dados

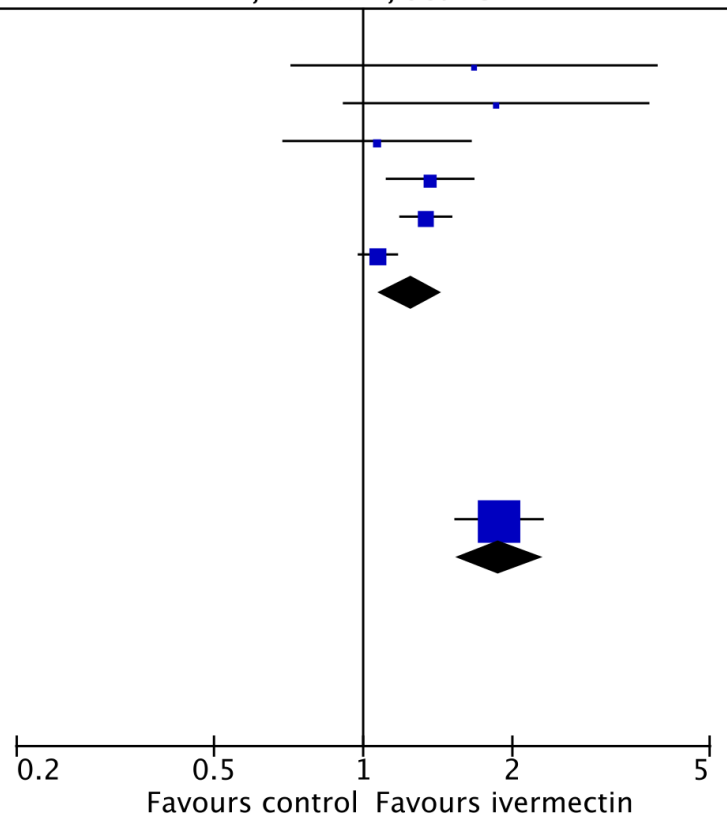
Desfechos secundários

- **25%** (8% a 45%) a mais com covid leve a moderado **melhorou** (5 ensaios, 1154 participantes)
- 65% (35% a 81%) **MENOR deterioração** (7 ensaios, 1587 participantes)
- **Tempo mais curto** para PCR negativo (eliminação viral)

CERTEZA BAIXA

Melhora clínica

Study or Subgroup	Ivermectin Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.11.1 Mild to moderate covid-19						
Ahmed 2020 (1)	14	23	4	11	2.9%	1.67 [0.72, 3.91]
Ahmed 2020 (2)	17	22	5	12	4.0%	1.85 [0.91, 3.76]
Chachar 2020 (3)	16	25	15	25	8.9%	1.07 [0.69, 1.65]
Mahmud 2020 (4)	111	183	80	180	22.0%	1.36 [1.12, 1.67]
Elgazzar 2020 (5)	99	100	74	100	29.8%	1.34 [1.19, 1.51]
Lopez-Medina 2021 (6)	232	275	156	198	32.4%	1.07 [0.98, 1.17]
Subtotal (95% CI)		**628**		**526**	**100.0%**	**1.25 [1.08, 1.45]**
Total events	489		334			
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 13.43$, df = 5 (P = 0.02); $I^2 = 63\%$						
Test for overall effect: Z = 2.92 (P = 0.004)						
1.11.2 Severe covid-19						
Elgazzar 2020 (7)	94	100	50	100	100.0%	1.88 [1.54, 2.30]
Subtotal (95% CI)		**100**		**100**	**100.0%**	**1.88 [1.54, 2.30]**
Total events	94		50			
Heterogeneity: Not applicable						
Test for overall effect: Z = 6.12 (P < 0.00001)						



Footnotes

(1) IVM 12mg daily x 5 days
(2) IVM 12mg s+ doxy 200mg stat then 100 mg BD x 4 days
(3) IVM 12 mg at 0, 12, and 24 hours
(4) IVM 6mg once + Doxy 100 mg x 5 days
(5) IVM up to 24 mg daily for 4 days. Control group received hydroxychloroquine
(6) IVM 0.3mg/kg x 5 days
(7) IVM up to 24 mg daily for 4 days. Control group received hydroxychloroquine

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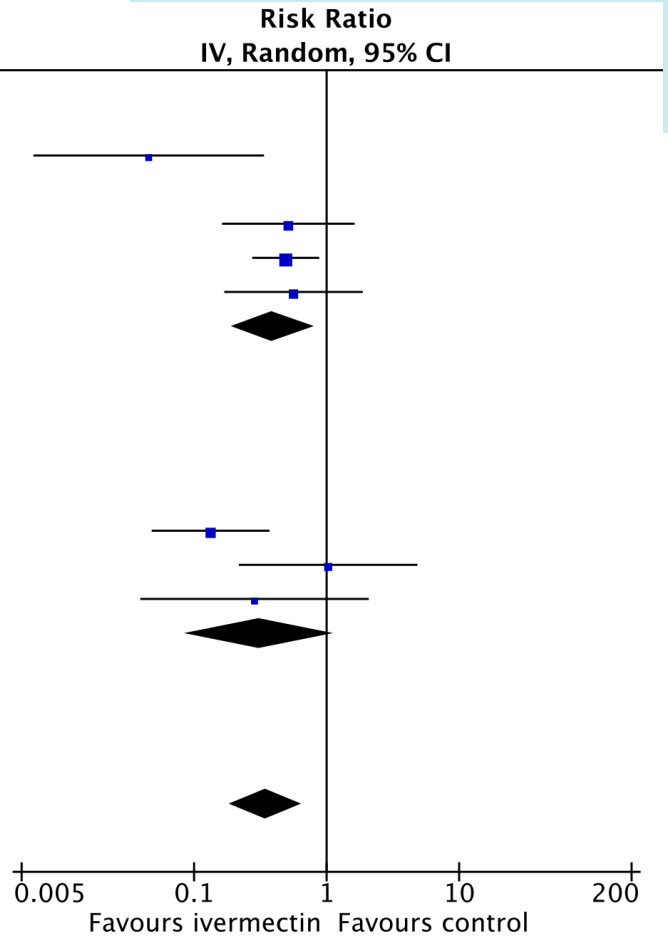
Deterioração (piora clínica)

Study or Subgroup	Ivermectin Events	Ivermectin Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
1.12.1 Mild to moderate covid-19						
Chaccour 2020 (1)	0	12	0	12		Not estimable
Elgazzar 2020 (2)	1	100	22	100	7.6%	0.05 [0.01, 0.33]
Hashim 2020 (3)	0	48	0	48		Not estimable
Lopez-Medina 2021 (4)	5	275	7	198	15.7%	0.51 [0.17, 1.60]
Mahmud 2020 (5)	16	183	32	180	25.5%	0.49 [0.28, 0.86]
Mohan 2021 (6)	5	80	5	45	15.0%	0.56 [0.17, 1.84]
Subtotal (95% CI)		**698**		**583**	**63.7%**	**0.40 [0.19, 0.82]**
Total events	27		66			
Heterogeneity: $Tau^2 = 0.24$; $Chi^2 = 5.41$, df = 3 (P = 0.14); $I^2 = 45\%$						
Test for overall effect: Z = 2.50 (P = 0.01)						
1.12.2 Severe covid-19						
Elgazzar 2020 (7)	4	100	30	100	17.6%	0.13 [0.05, 0.36]
Gonzalez 2021 (8)	3	36	3	37	11.0%	1.03 [0.22, 4.76]
Hashim 2020 (9)	1	11	7	22	7.7%	0.29 [0.04, 2.04]
Subtotal (95% CI)		**147**		**159**	**36.3%**	**0.31 [0.08, 1.15]**
Total events	8		40			
Heterogeneity: $Tau^2 = 0.77$; $Chi^2 = 4.78$, df = 2 (P = 0.09); $I^2 = 58\%$						
Test for overall effect: Z = 1.75 (P = 0.08)						
Total (95% CI)		**845**		**742**	**100.0%**	**0.35 [0.19, 0.65]**
Total events	35		106			
Heterogeneity: $Tau^2 = 0.32$; $Chi^2 = 11.75$, df = 6 (P = 0.07); $I^2 = 49\%$						
Test for overall effect: Z = 3.29 (P = 0.0010)						
Test for subgroup differences: $Chi^2 = 0.10$, df = 1 (P = 0.75), $I^2 = 0\%$						



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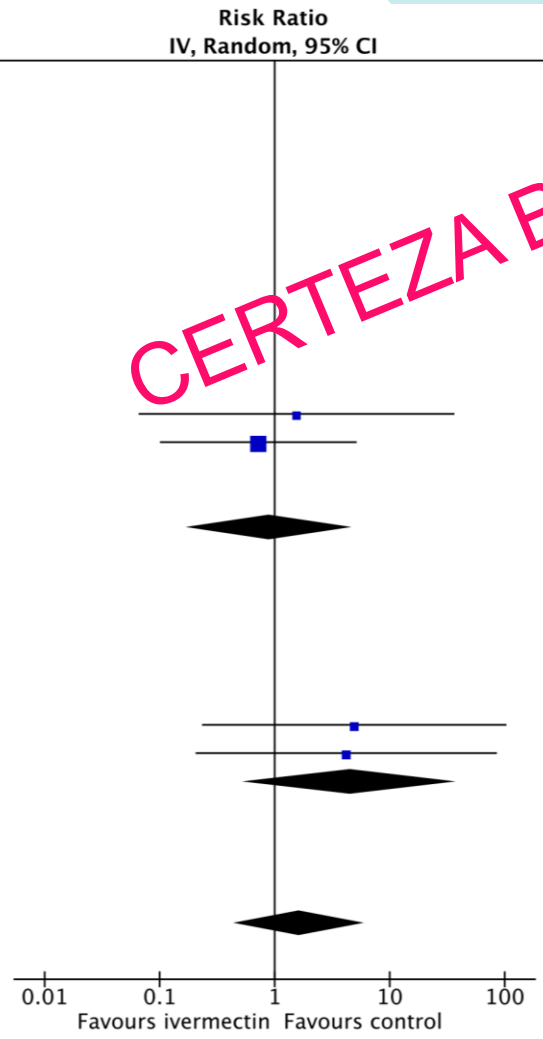
Desfechos secundários	Studies	Participants	Effect estimate
Tempo de recureração para PCR neg	4	375	MD = 3.20 menos dias [-5.99 to -0.40]
Admissão em UTI	2	279	RR 1.22 [0.75 to 2.00]
Ventilação mecânica	3	431	RR 0.66 [0.14 to 3.00]
Melhora clínica (Covid leve a moderado)	5	1154	RR 1.25 [1.08 to 1.45]
Deterioração	7	1587	RR 0.35 [0.19 to 0.65]
Hospitalização	2	194	RR 0.16 [0.02 to 1.32]

MD = Diferença média
RR= Risco Relativo

Eventos adversos graves

Study or Subgroup	Ivermectin Events	Ivermectin Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
1.14.1 Single dose						
Chaccour 2020 (1)	0	12	0	12		Not estimable
Hussein 2021 (2)	0	45	0	41		Not estimable
Mohan 2021 (3)	0	100	0	52		Not estimable
Subtotal (95% CI)		**157**		**105**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.14.2 IVM multi-dose						
Ahmed 2020 (4)	0	23	0	11		Not estimable
Babalola 2020 (5)	0	42	0	20		Not estimable
Krolewiecki 2020 (6)	1	30	0	15	17.3%	1.55 [0.07, 35.89]
Lopez-Medina 2021 (7)	2	275	2	198	45.0%	0.72 [0.10, 5.07]
Petkov 2021 (8)	0	50	0	50		Not estimable
Schwartz 2021 (9)	0	49	0	45		Not estimable
Subtotal (95% CI)		**469**		**339**	**62.3%**	**0.89 [0.17, 4.68]**
Total events	3		2			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.16$, df = 1 (P = 0.69); $I^2 = 0\%$						
Test for overall effect: Z = 0.14 (P = 0.89)						
1.14.3 IVM plus other drugs						
Ahmed 2020 (10)	0	22	0	12		Not estimable
Mahmud 2020 (11)	2	183	0	180	18.7%	4.92 [0.24, 101.74]
Okumus 2021 (12)	2	36	0	30	19.0%	4.19 [0.21, 84.03]
Subtotal (95% CI)		**241**		**222**	**37.7%**	**4.54 [0.54, 38.21]**
Total events	4		0			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.01$, df = 1 (P = 0.94); $I^2 = 0\%$						
Test for overall effect: Z = 1.39 (P = 0.16)						
Total (95% CI)		**867**		**666**	**100.0%**	**1.65 [0.44, 6.09]**
Total events	7		2			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.57$, df = 3 (P = 0.67); $I^2 = 0\%$						
Test for overall effect: Z = 0.75 (P = 0.46)						
Test for subgroup differences: $Chi^2 = 1.40$, df = 1 (P = 0.24), $I^2 = 28.3\%$						



CERTEZA BAIXA

Poucos eventos adversos

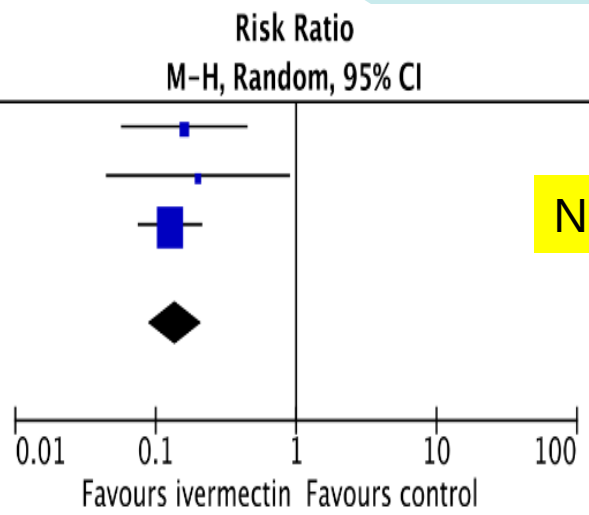
Prevenção

Desfecho primário: infecção por covid-19

Study or Subgroup	Ivermectin Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Chala 2021 (1)	4	117	25	117	18.4%	0.16 [0.06, 0.45]
Elgazzar 2020 (2)	2	100	10	100	8.7%	0.20 [0.04, 0.89]
Shouman 2020 (3)	15	203	59	101	73.0%	0.13 [0.08, 0.21]
Total (95% CI)		**420**		**318**	**100.0%**	**0.14 [0.09, 0.21]**
Total events	21		94			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.44$, df = 2 (P = 0.80); $I^2 = 0\%$

Test for overall effect: Z = 8.86 (P < 0.00001)



NNT = 4

Footnotes

(1) IVM 12 mg weekly + Iota-Carrageenan 6 sprays/day

(2) IVM up to 24mg weekly depending on weight x 2 doses

(3) IVM up to 24 mg depending on weight, given in 2 doses 72 hours apart

CERTEZA BAIXA

86% redução na infecção por Covid (IC 79% to 91%)

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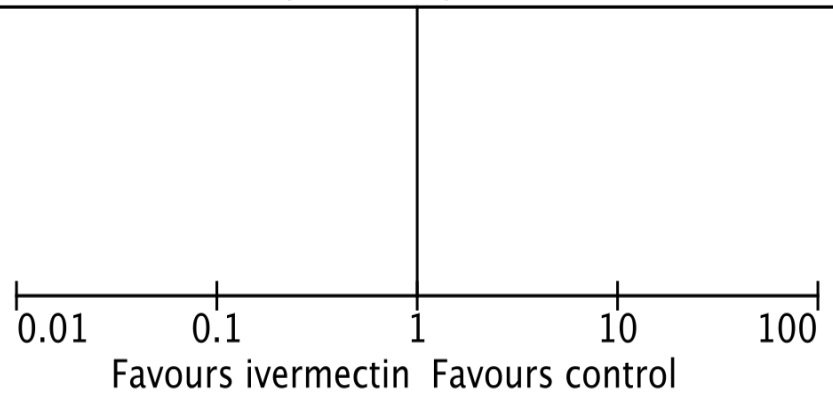
Prevenção

Eventos adversos graves

Study or Subgroup	Ivermectin Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Chala 2021 (1)	0	117	0	117		Not estimable
Shouman 2020 (2)	0	203	0	101		Not estimable
Total (95% CI)		**320**		**218**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable

Test for overall effect: Not applicable



Footnotes

(1) 12 mg (drops) and Iota-carrageena 6 sprays daily

(2) IVM up to 24 mg depending on weight, given in 2 doses 72 hours apart

Resumo dos efeitos da revisão sistemática

- IVM provavelmente **reduz o risco de morte de covid-19 em uma média de 62%** (27% a 81%).
- Mais pacientes podem melhorar e menos pacientes piorar
- IVM pode **reduzir infecções por Covid em 86%**
- Pode haver **pouca ou nenhuma diferença nos eventos adversos graves.**

Critérios de tomada de decisão da diretriz

- Efeitos
- Valores
- Recursos
- Equidade
- Aceitabilidade
- Viabilidade

IVM é custo-efetiva?

- Os custos associados à infecção por Covid são altos
- Taxas de hospitalização de 5 a 10% em alguns países
- 25% das hospitalizações requerem UTI
- UTI Reino Unido = £ 4.250
- EUA US $ 7.207 para moderado e $ 33.247 para covid grave
- Potencial para grande economia de custos

Ivermectina: custos

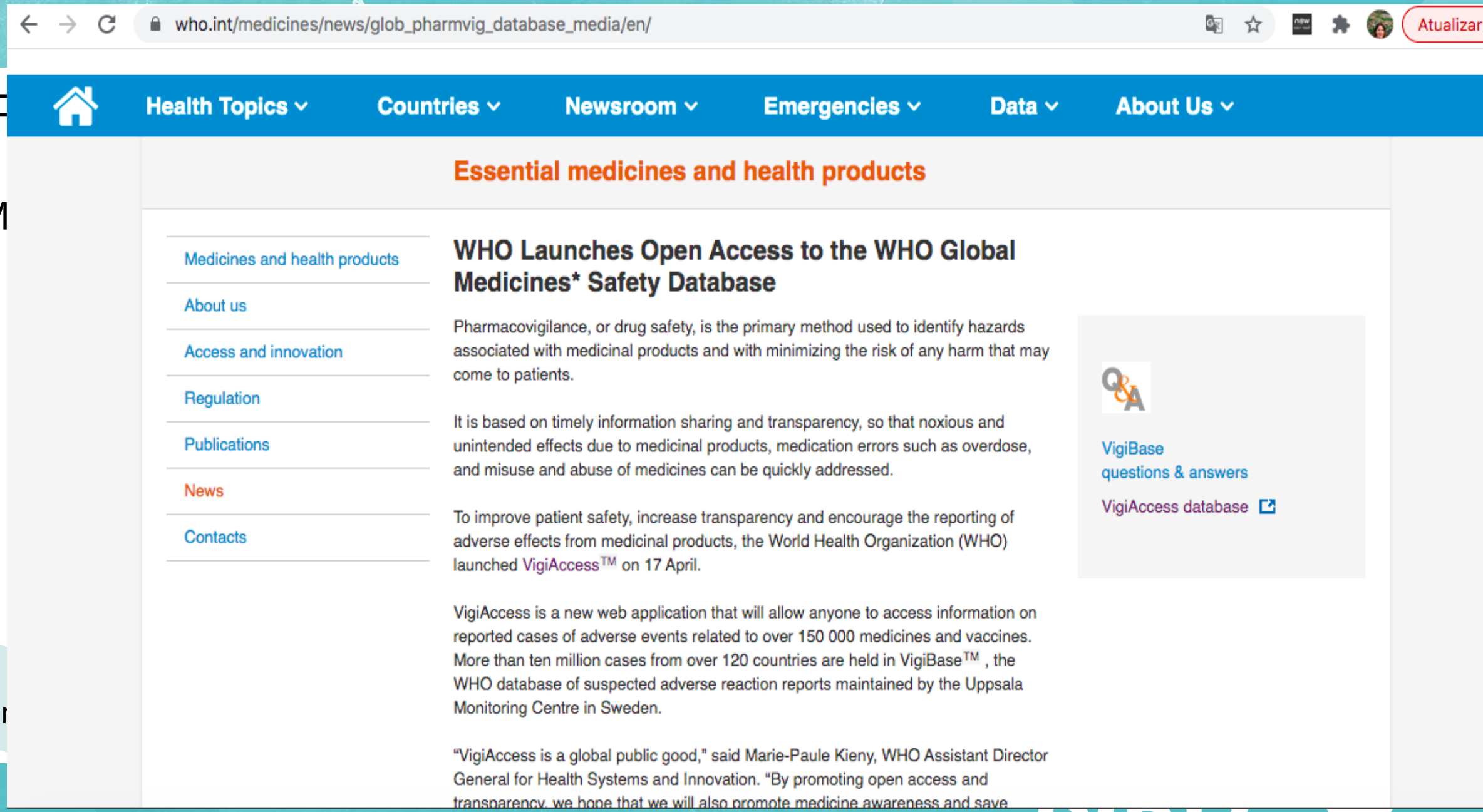
- IVM é barato
- Medicamento essencial da OMS = 3 centavos comprimido de 12 mg
- Genérico - muitos fabricantes em todo o mundo
- Sem refrigeração necessária
- Sem custos de administração, pode ser auto-administrada

Qual é o impacto do uso de ivermectina na equidade em saúde?

- Os grupos étnicos negros, asiáticos e minoritários são os mais afetados
- A ivermectina é segura para idosos e imunocomprometidos
- Trabalhadores da linha de frente correm maior risco de infecção
- Implementação lenta de vacinas em LMICs
- Alguns países aguardam mais dados de eficácia e segurança da vacina
- As listas de espera de cuidados de saúde estão crescendo para outras doenças

A Ivermectina seria aceitável e viável?

- Provavelmente reduz as mortes substancialmente com poucos SAEs - então, SIM
- Autorização de uso de emergência aceitável para vacinas e outros medicamentos novos com base em evidências de menor certeza
- IVM tem dados de segurança extensos e é usado em idosos e recomendado em pessoas imunocomprometidas


who.int/medicines/news/glob_pharmvig_database_media/en/
Atualizar
Health Topics
Countries
Newsroom
Emergencies
Data
About Us
Essential medicines and health products
Medicines and health products
About us
Access and innovation
Regulation
Publications
News
Contacts
WHO Launches Open Access to the WHO Global Medicines* Safety Database
Pharmacovigilance, or drug safety, is the primary method used to identify hazards associated with medicinal products and with minimizing the risk of any harm that may come to patients.
It is based on timely information sharing and transparency, so that noxious and unintended effects due to medicinal products, medication errors such as overdose, and misuse and abuse of medicines can be quickly addressed.
To improve patient safety, increase transparency and encourage the reporting of adverse effects from medicinal products, the World Health Organization (WHO) launched VigiAccess™ on 17 April.
VigiAccess is a new web application that will allow anyone to access information on reported cases of adverse events related to over 150 000 medicines and vaccines. More than ten million cases from over 120 countries are held in VigiBase™ , the WHO database of suspected adverse reaction reports maintained by the Uppsala Monitoring Centre in Sweden.
"VigiAccess is a global public good," said Marie-Paule Kieny, WHO Assistant Director General for Health Systems and Innovation. "By promoting open access and transparency, we hope that we will also promote medicine awareness and save
Q&A
VigiBase questions & answers
VigiAccess database

Licenciamento e uso off-label

- Suíça, USA CDC e uma autoridade de saúde do Reino Unido (BASH) já apoiam prescrições off-label de ivermectina
- As autoridades de saúde recomendam IVM para pessoas imunocomprometidas com Covid para prevenir infecções parasitárias

The BIRD Recommendation

O British Ivermectin Recommendation Development panel **recomenda ivermectina para a prevenção e tratamento da Covid-19** para reduzir a morbidade e mortalidade associada à infecção de covid-19 e prevenir a infecção de Covid-19 entre aqueles com maior risco.

Therapeutics and COVID-19

LIVING GUIDELINE
31 MARCH 2021

World Health Organization

Certainty of the evidence

For most key outcomes, including mortality, mechanical ventilation, hospital admission, duration of hospitalization and viral clearance, the panel considered the evidence of very low certainty. Evidence was rated as very low certainty primarily because of very serious imprecision for most outcomes: the aggregate data had wide confidence intervals and/or very few events. There were also serious concerns related to risk of bias for some outcomes, specifically lack of blinding, lack of trial pre-registration, and lack of outcome reporting for one trial that did not report mechanical ventilation despite pre-specifying it in their protocol (publication bias).

BIRD

British *Ivermectin* Recommendation Development

Metanálise da OMS: achados sobre mortalidade

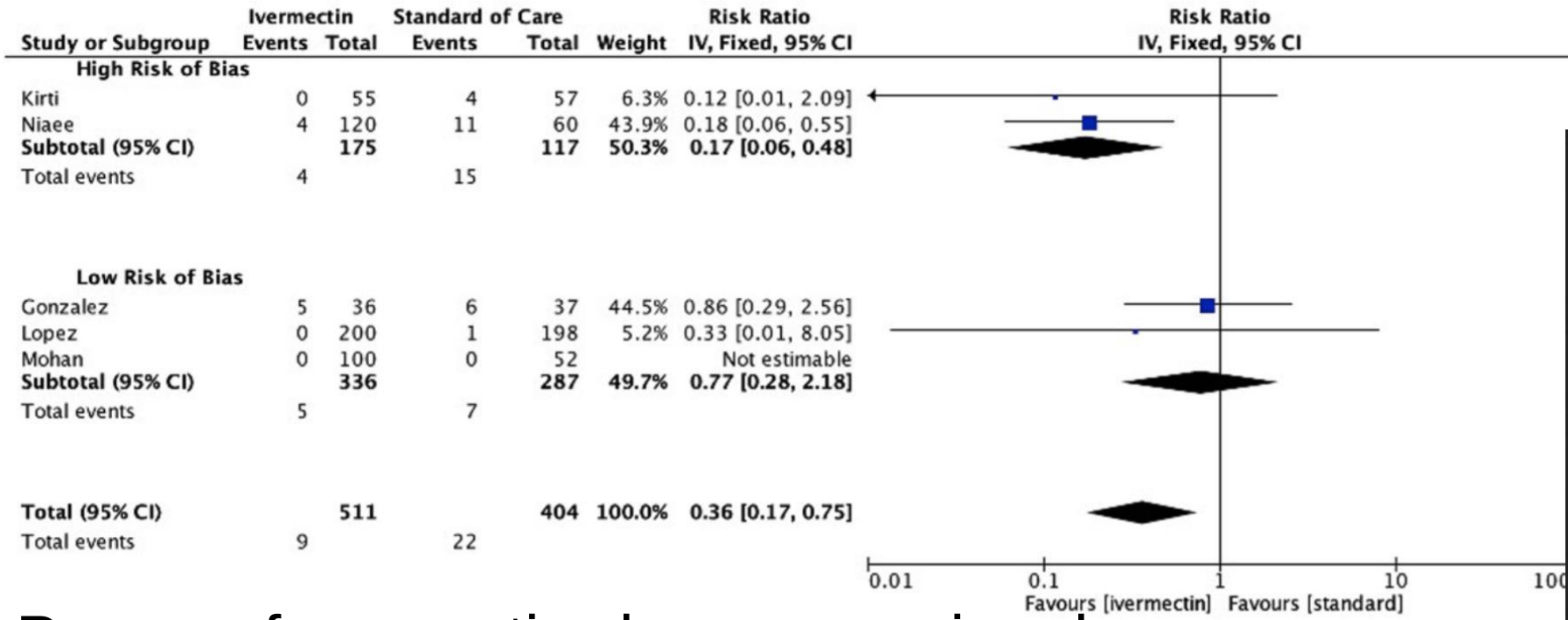
		GRADE	
Mortality	Odds ratio 0.19 (CI 95% 0.09 - 0.36) Based on data from 1,419 patients in 7 studies. [1] (Randomized controlled)	Very Low Due to serious risk of bias and very serious imprecision [2]	The effect of ivermectin on mortality is uncertain.

81% redução de mortalidade (IC 64% to 91%)

BIRD

British *Ivermectin* Recommendation Development

Metanálise OMS: desfecho morte



Por que foram retirados os ensaios de Hashim, Elgazzar, Okumus and Mahmud ….?

B/RD

British *Ivermectin* Recommendation Development

Metanálise da OMS : Eventos Adversos Graves

GRADE

Serious adverse events	Odds ratio 3.07 (CI 95% 0.77 - 12.09) Based on data from 584 patients in 3 studies. (Randomized controlled)	**Low** Due to very serious imprecision [6]	Ivermectin may increase the risk of serious adverse events leading to drug discontinuation.

Perfil de segurança da IVM e novas drogas

Data retrieved from VigiAccess.org (04.05.2021)			
Medicine	Year reporting started	Deaths	Adverse events
Ivermectin	1992	**19**	**5,267**
Remdesivir	2020	505	5,961
Covid-19 vaccine	2020	**4,108**	**623,804**

AIIMS/ ICMR-COVID-19 National Task Force/Joint Monitoring Group (Dte.GHS)

Ministry of Health & Family Welfare, Government of India

CLINICAL GUIDANCE FOR MANAGEMENT OF ADULT COVID-19 PATIENTS

22nd April 2021

COVID-19 patient

Mild disease

Upper respiratory tract symptoms (&/or fever) WITHOUT shortness of breath or hypoxia

Home Isolation & Care

MUST DOs

- Physical distancing, indoor mask use, strict hand hygiene.
- Symptomatic management (hydration, anti-pyretics, anti-tussive, multivitamins).
- Stay in contact with treating physician.
- Monitor temperature and oxygen

MAY DOs

Therapies based on low certainty of evidence

- Tab Ivermectin (200 mcg/kg once a day for 3 days). Avoid in pregnant and lactating women.

  OR
- Tab HCQ (400 mg BD for 1 day f/b 400 mg OD for 4 days) unless contraindicated.
- Inhalational Budesonide (given via Metered dose inhaler/ Dry powder inhaler) at a dose of 800 mcg BD for 5 days) to be given if symptoms (fever and/or cough) are persistent beyond 5 days of disease onset.

Moderate disease

Any one of:
1. Respiratory rate ≥ 24/min, breathlessness
2. SpO2: 90% to ≤ 93% on room air

ADMIT IN WARD

Oxygen Support:

- Target SpO_2: 92-96% (88-92% in patients with COPD).
- Preferred devices for oxygenation: non-rebreathing face mask.
- Awake proning encouraged in all patients requiring supplemental oxygen therapy (sequential position changes every 2 hours).

inflammatory or immunomodulatory therapy

Inj. Methylprednisolone 0.5 to 1 mg/kg in 2 divided doses (or an equivalent dose of dexamethasone) usually for a duration of 5 to 10 days.
Patients may be initiated or switched to oral route if stable and/or improving.

coagulation

Conventional dose prophylactic unfractionated heparin or Low Molecular Weight Heparin (weight based e.g., enoxaparin 0.5mg/kg per day SC). There should be no contraindication or high risk of bleeding.

itoring

Clinical Monitoring: Work of breathing, Hemodynamic instability, Change in oxygen requirement.

Serial CXR; HRCT chest to be done ONLY If there is worsening.

Lab monitoring: CRP and D-dimer 48 to 72 hrly; CBC, KFT, LFT 24 to 48 hrly; IL-6 levels to be done if deteriorating (subject to availability).

Severe disease

Any one of:
1. Respiratory rate >30/min, breathlessness
2. SpO2 < 90% on room air

ADMIT IN ICU

Respiratory support

- Consider use of NIV (Helmet or face mask interface depending on availability) in patients with increasing oxygen requirement, if work of breathing is LOW.
- Consider use of HFNC in patients with increasing oxygen requirement.
- Intubation should be prioritized in patients with high work of breathing /if NIV is not tolerated.
- Use conventional ARDSnet protocol for ventilatory management.

Anti-inflammatory or immunomodulatory therapy

- Inj Methylprednisolone 1 to 2mg/kg IV in 2 divided doses (or an equivalent dose of dexamethasone) usually for a duration 5 to 10 days.

Anticoagulation

- Weight based intermediate dose prophylactic unfractionated heparin or Low Molecular Weight Heparin (e.g., Enoxaparin 0.5mg/kg per dose SC BD). There should be no contraindication or high risk of bleeding.

Supportive measures

- Maintain euvolemia (if available, use dynamic measures for assessing fluid responsiveness).
- If sepsis/septic shock: manage as per existing protocol and local antibiogram.

Monitoring

- Serial CXR; HRCT chest to be done ONLY if there is worsening.
- Lab monitoring: CRP and D-dimer 24-48 hourly; CBC, KFT, LFT daily; IL-6 to be done if deteriorating (subject to availability).

After clinical improvement, discharge as per revised discharge criteria.

EUA/Off label use (based on limited available evidence and only in specific circumstances):

- Remdesivir (EUA) may be considered ONLY in patients with
  - Moderate to severe disease (requiring SUPPLEMENTAL OXYGEN), AND
  - No renal or hepatic dysfunction (eGFR <30 ml/min/m2; AST/ALT >5 times ULN (Not an absolute contradiction), AND
  - Who are within 10 days of onset of symptom/s.
    - Recommended dose: 200 mg IV on day 1 f/b 100 mg IV OD for next 4 days.
  - Not to be used in patients who are NOT on oxygen support or in home settings
- Tocilizumab (Off-label) may be considered when ALL OF THE BELOW CRITERIA ARE MET
  - Presence of severe disease (preferably within 24 to 48 hours of onset of severe disease/ICU admission).
  - Significantly raised inflammatory markers (CRP &/or IL-6).
  - Not improving despite use of steroids.
  - No active bacterial/fungal/tubercular infection.
    - Recommended single dose: 4 to 6 mg/kg (400 mg in 60kg adult) in 100 ml NS over 1 hour.
- Convalescent plasma (Off label) may be considered ONLY WHEN FOLLOWING CRITERIA ARE MET
  - Early moderate disease (preferably within 7 days of symptom onset, no use after 7 days).
  - Availability of high titre donor plasma (Signal to cut-off ratio (S/O) ≥3.5 or equivalent depending on the test kit being used).

Fonte: https://covid.aiims.edu/clinical-guidance-for-management-of-adult-covid-19-patients/

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.

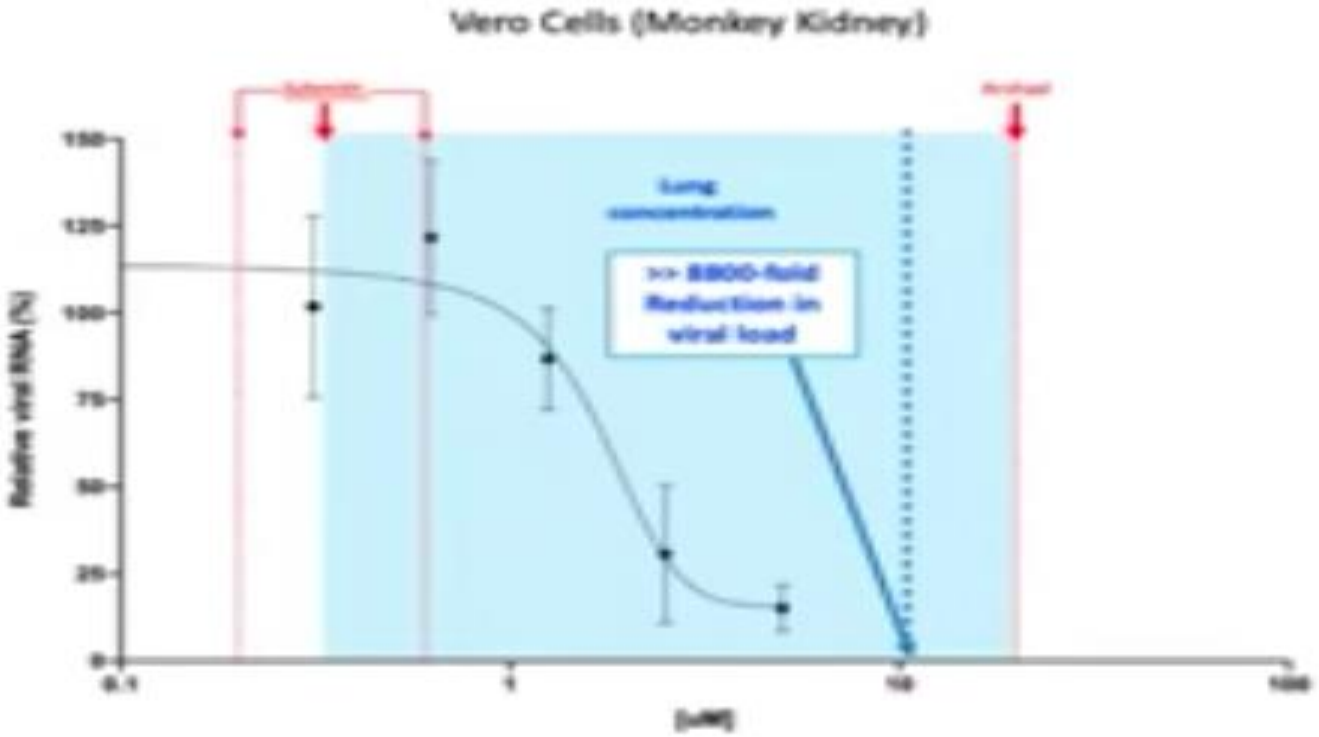
Areas of Uncertainty: The majority of trialed agents have failed to provide reproducible, definitive proof of efficacy in reducing the mortality of COVID-19 with the exception of corticosteroids in moderate to severe disease. Recently, evidence has emerged that the oral antiparasitic agent ivermectin 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

Ivermectin inhibits SARS-CoV-2 *in vitro*



Relevance of IC_{50} determined *in vitro* to clinical use?

- In vitro assay very different from clinical situation
  - Vero/hSLAM cells- monkey kidney- do not produce IFN
  - Lack immune responses
- Ivermectin accumulates in lungs and other tissues (3x-10x serum levels)
- Human lung cells- better IC_{50}
- Short exposure vs extended exposure
- Single dose vs repeat dosing
- Taken with food (3x level)

Red- peer-reviewed, published modelling of IVM lung concentration after 200ug/kg dose

Reproduced with Permission from Wagstaff et al; Unpublished data 2021

Pharmacology

- 200ug/kg Tmax ~ 60 ug/ml (fasted)
- 200ug/kg Tmax about 150 ug/ml (with meal)
- 200ug/kg Lung concentration 180 ug/g tissue (fasted)
- 200ug/kg Lung concentration 450 ug/g tissue (with meal)

- IC_{50} for alveolar cells 0.41 uM (105 ug/g)
  (uM to ng/ml conversion: 1uM = 750 ng/ml)

Real-world effectiveness of hydroxychloroquine, azithromycin, and ivermectin among hospitalized COVID-19 patients: results of a target trial emulation using observational data from a nationwide healthcare system in Peru.

Methods: Retrospective cohort using nationwide data from the Peruvian Social Health Insurance April – July 2020. Five treatment groups (HCQ alone, IVM alone, AZIT alone, HCQ+AZIT, and IVM+AZIT within 48 hours of admission) were compared with SOC

Results: Among 5683 patients, 200 received HCQ, 203 IVM, 1600 AZIT, 692 HCQ+AZIT, 358 IVM+AZIT, and 2630 standard of care.

Mortality: IVM 23.2% vs SOC 15.2%; HR 1.40 (1.03-1.90)

Soto-Becerra P, et al MedRxiv Preprint

Real-world effectiveness of hydroxychloroquine, azithromycin, and ivermectin among hospitalized COVID-19 patients: results of a target trial emulation using observational data from a nationwide healthcare system in Peru.

- In this study all medications show higher mortality at day 30, which is consistent with asymptomatic (for COVID-19) or mild condition patients being more common in the control group…confounding by indication
- This study also does not compare treatments with a control group not receiving the treatment
- The excess mortality happened on the first day. This is consistent with treated patients being in more serious condition
- However, authors state that outcomes within 24 hours were excluded, however KM curves show significant mortality at day 1 (only for the treatment groups).
- IVM vs SOC: significantly older, male gender with more comorbidities and marked geographic variation
- No index of disease severity

Soto-Becerra P, et al MedRxiv Preprint

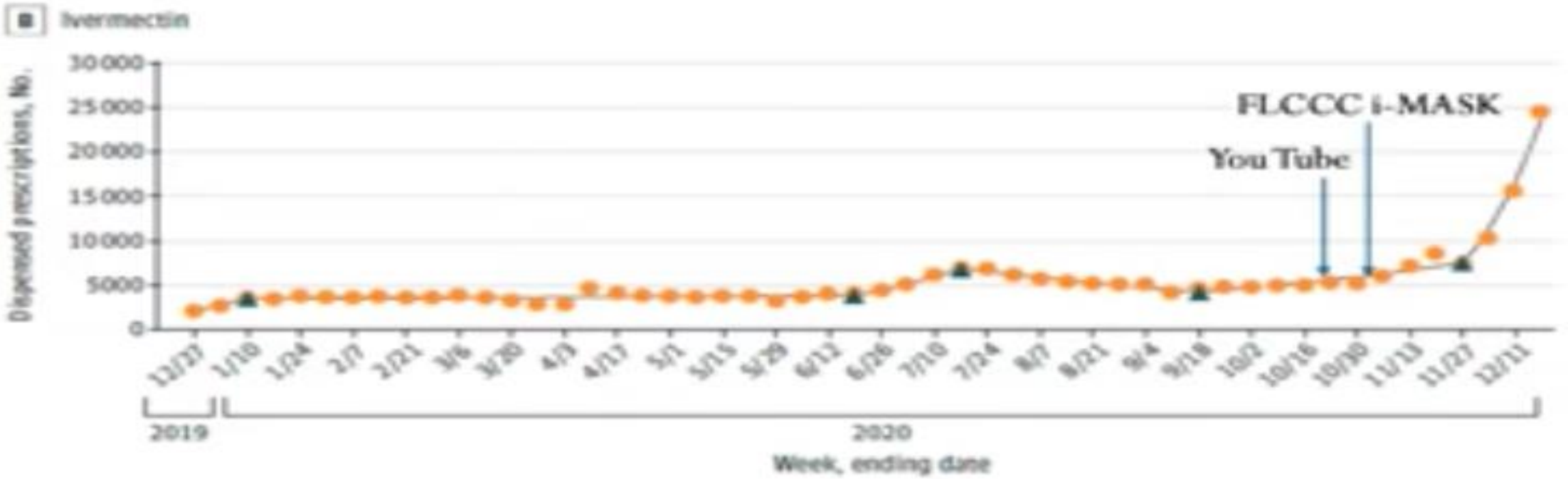
Dishonesty has Serious Consequences

Assessment of Outpatient Dispensing of Products Proposed for Treatment or Prevention of COVID-19 by US Retail Pharmacies During the Pandemic

Treatment[b]	Baseline No. of prescriptions dispensed per week[c]	Peak week, 2020 (end date)[d]	Peak No. of prescriptions dispensed per week, 2020[d]	No. of prescriptions dispensed above baseline in peak week, 2020	Increase in prescriptions dispensed above baseline in peak week, 2020, %
Ivermectin	3589	Dec 18, 2020	24 528	20 939	583.4
Chloroquine	499	Mar 20, 2020	2966	2467	494.4
Zinc[e]	1810	Dec 11, 2020	9110	7300	403.3
Hydroxychloroquine	93 640	Mar 20, 2020	267 308	173 668	185.5
Vitamin C[f]	9331	Dec 11, 2020	21 020	11 689	125.3
Dexamethasone	57 178	Dec 18, 2020	123 829	66 651	116.6
Lopinavir-ritonavir	492	Mar 20, 2020	954	462	93.8
Famotidine[g]	253 684	Dec 18, 2020	365 699	112 015	44.2

Geller AI, et al JAMA Intern Med 2021; ePub

Assessment of Outpatient Dispensing of Products Proposed for Treatment or Prevention of COVID-19 by US Retail Pharmacies During the Pandemic



Geller AI, et al JAMA Intern Med 2021; ePub

Open access, freely available online

Essay

Medical Journals Are an Extension of the Marketing Arm of Pharmaceutical Companies

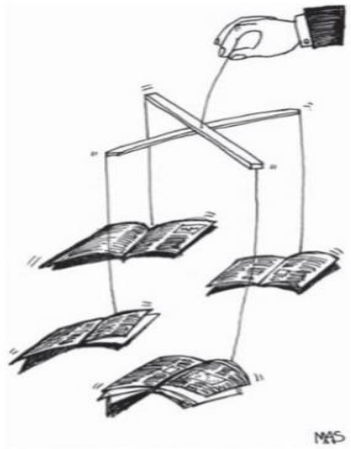
Richard Smith

"Journals have devolved into information laundering operations for the pharmaceutical industry", wrote Richard Horton, editor of the *Lancet*, in March 2004 [1]. In the same year, Marcia Angell, former editor of the *New England Journal of Medicine*, lambasted the industry for becoming "primarily a marketing machine" and co-opting "every institution that might stand in its way" [2]. Medical journals were conspicuously absent from her list of co-opted institutions, but she and Horton are not the only editors who have become increasingly queasy about the power and influence of the industry. Jerry Kassirer, another former editor of the *New England Journal of Medicine*, argues that the industry has deflected the moral compasses of many physicians [3], and the editors of *PLoS Medicine* have declared that they will not become "part of the cycle of dependency…between journals and the pharmaceutical industry" [4]. Something is clearly up.

The Problem: Less to Do with Advertising, More to Do with Sponsored Trials

The most conspicuous example of medical journals' dependence on the pharmaceutical industry is the substantial income from advertising, but this is, I suggest, the least corrupting form of dependence. The advertisements may often be misleading [5,6] and the profits worth millions, but the advertisements are there for all to see and criticise. Doctors may not be as uninfluenced by the advertisements as they would like to believe, but in every sphere, the public is used to discounting the claims of advertisers.

The much bigger problem lies with the original studies, particularly the clinical trials, published by journals. Far from discounting these, readers see randomised controlled trials as one of the highest forms of evidence. A large trial published in a major journal has the journal's stamp of approval (unlike the advertising), will be distributed around the world, and may well receive global media coverage, particularly if promoted simultaneously by press releases from both the journal and the expensive public-relations firm hired by the pharmaceutical company that sponsored the trial. For a drug company, a favourable trial is worth thousands of pages of advertising, which is why a company will sometimes spend upwards of a million dollars on reprints of the trial for worldwide distribution. The doctors receiving the reprints may not read them, but they will be impressed by the name of the journal from which they come. The quality of the journal will bless the quality of the drug.



DOI: 10.1371/journal.pmed.0020138.g001

(Illustration: Margaret Shear, Public Library of Science)

Fortunately from the point of view of the companies funding these trials—but unfortunately for the credibility of the journals who publish them—these trials rarely produce results that are unfavourable to the companies' products [7,8]. Paula Rochon and others examined in 1994 all the trials funded by manufacturers of nonsteroidal anti-inflammatory drugs for arthritis that they could find [7]. They found 56 trials, and not one of the published trials presented results that were unfavourable to the company that sponsored the trial. Every trial showed the company's drug to be as good as or better than the comparison treatment.

By 2003 it was possible to do a systematic review of 30 studies comparing the outcomes of studies funded by the pharmaceutical industry with those of studies funded from other sources [8]. Some 16 of the studies looked at clinical trials or meta-analyses, and 13 had outcomes favourable to the sponsoring companies. Overall, studies funded by a company were four times more likely to have results favourable to the company than studies funded from other sources. In the case of the five studies that looked at economic evaluations,

The Essay section contains opinion pieces on topics of broad interest to a general medical audience.

Citation: Smith R (2005) Medical journals are an extension of the marketing arm of pharmaceutical companies. PLoS Med 2(5): e138.

Richard Smith is Chief Executive of UnitedHealth Europe, London, United Kingdom. E-mail: richardswsmith@yahoo.co.uk

Competing Interests: RS was an editor for the *BMJ* for 25 years. For the last 13 of those years, he was the editor and chief executive of the BMJ Publishing Group, responsible for the profits of not only the *BMJ* but of the whole group, which published some 25 other journals. He stepped down in July 2004. He is now a member of the board of the Public Library of Science, a position for which he is not paid.

DOI: 10.1371/journal.pmed.0020138

Estudos observacionais IVM profilaxia

1) **Elgazzar e col, Universidade Benha, Egito, Observacional randomizado**

N=200 cuidados de saúde e contatos de COVID-19,
grupo de intervenção 100 prof. saúde IVM 0,4mg / kg no dia 1 e uma segunda
dose no dia 7 + EPI
grupo de controle de 100 prof. Saúde apenas EPI
RT-PCR positivos IVM 2%
RT-PCR positivos controles 10%, p <0,05.

2**) Carvallo et al Argentina estudo observacional controlado**

n=1.195 profissionais de saúde, por 3 meses
n=788 Grupo intervenção IVM 12mg.semanal
n= 407 Controle, após 3 meses:
0% infecções Grupo IVM
58% infecção no Grupo controle p<0,05

B/RD
British *Ivermectin* Recommendation Development

Estudos observacionais IVM profilaxia

3**)Shouman RCT na Universidade Zagazig no Egito,**
n= 340 (228 tratados, 112 controle)
Familiares de pacientes positivos para SARS-CoV-2 Ivermectina, 0,25mg / kg) D0 e 72h após.
Redução de sintomas Covid19 após 14 dias
Grupo IVM 7,4%
Grupo controle 58,4%, (p <0,001)

4**) Carvallo et al Argentina estudo observacional prospectivo n=229**

N=131 Intervenção : IVM (0,2mg.gotas 5xdia) + carragenina por 28 dias

N = 118 Controle. Após 28 dias:

Grupo IVM : 0% RT-PCR positivo

Grupo controle 11,2% e (p <0,001).

B/RD
British *Ivermectin* Recommendation Development

Estudos observacionais IVM profilaxia

5)Índia, Behera et al. estudo observacional de caso-controle retrospectivo N= 186 entre de profissionais de saúde, eles identificaram 169 participantes que tinham feito alguma dose de profilaxia

Profissionais com 2 doses de IVM profilaxia, o odds ratio para contrair COVID-19 RR = 0,27 (0,27, IC 95%, 0,15–0,51).

Com base no neste estudo e no de profilaxia egípcia, o Instituto de Ciências Médicas da Índia instituiu um protocolo de profilaxia para seus profissionais de saúde

2 Doses de ivermectina com 72 horas de intervalo e repetem a dose mensalmente.

Estudos observacionais IVM profilaxia

6) Behera et al., 2020,França, estudo retrospectivo caso controle residentes de lares de idosos e surto de escabiose (Março-Maio 2020)
Grupo intervenção: IVM para todos os 69 residentes e 52 funcionários
Grupo controle: demais lares de idosos do condado
Ao final da observação pareada dos asilos:

- Grupo intervenção

10,1% com sintomas Covid19 (7/69 residentes)
1% necessitou de oxigênio suplementar (1/69)
0% letalidade

- grupo de controle

22,6% dos residentes adoeceram
4,9% letalidade

Ensaios clinicos randomizados Profilaxia IVM

1)Protocolo Carvallo IVERCAR ECR prospectivo
Ministério da Saúde de Tucumán, Argentina, n=234 profissionais de saúde,
grupo de intervenção IVM 12 mg.semanal,
grupo controle . Incidência de Covid19 após 4 meses:

- Grupo IVM 3,4%
- grupo controle 21,4% p <0,0001 (Chala, 2020).

2)Alam et al. Dhaka, Bangladesh, ECR por 4 meses
grupo de intervenção (n = 58) 12 mg.mês
grupo controle . Incidência de infecção após 4 meses:

- grupo IVM 6,9%
- grupo controle 73,3%, p <0,05

EVIDENCIAS TRATAMENTO
IVM PACIENTES COVID19 MODERADOS/GRAVE

- 5 ECR com impactos no tempo de recuperação ou tempo de internação hospitalar

(Elgazzar et al., 2020; Hashim et al., 2020; Mahmud, 2020; Niaee et al., 2020; Spoorthi V, 2020)

- 1 ECR com redução na taxa de deterioração ou hospitalização,

N = 363

(Mahmud, 2020)

EVIDENCIAS TRATAMENTO
IVM PACIENTES COVID19 MODERADOS/GRAVE

2 ECR com uma diminuição estatisticamente significativa na carga viral, dias de anosmia e tosse, N = 85 (Chaccour et al., 2020; Ravikirti et al., 2021)

• 3 ECR com grandes reduções estatisticamente significativas na mortalidade

(N = 695) (Elgazzar et al.,2020; Niaee et al., 2020; Ravikirti et al., 2021)

• 1 ECR com uma redução quase estatisticamente significativa na mortalidade, p =

0,052 (N = 140) (Hashim et al., 2020)

• 3 EOC com reduções na mortalidade (p<0,05)(N = 1.688)

(Khan et al., 2020; Portmann-Baracco et al., 2020; Rajter et al., 2020

EVIDENCIAS TRATAMENTO
IVM PACIENTES COVID19 MODERADOS/GRAVE

1 ECR com uma redução quase estatisticamente significativa na mortalidade, p =

0,052 (N = 140) (Hashim et al., 2020)

- 3 EOC com reduções na mortalidade (p<0,05)(N = 1.688)

(Khan et al., 2020; Portmann-Baracco et al., 2020; Rajter et al., 2020

ENSAIOS CLINICOS RANDOMIZADOS PACIENTES COVID MODERADO/GRAVE

1)Mahmud et al ECR duplo-cego Dhaka, Bangladesh e N=363
Grupo intervenção IVM + doxiciclina ou azitromicina
Grupo controle: doxiciclina ou azitromicina

Problemas: dados publicados não especificam quantidade de pacientes ambulatoriais levemente enfermos vs. pacientes hospitalizados tratados, Desfechos clínicos importantes
Aumento de taxas de melhora precoce (60,7% vs. 44,4% p <0,03)
Redução de taxas de deterioração clínica (8,7% vs 17,8%, p <0,02).
02 óbitos no grupo controle

2) Ravikirti et al, 2021 realizou um RCT duplo-cego
N= 115 pacientes,
Desfecho primário: positividade da PCR no Dia 6 não foi diferente,
Desfecho secundário: mortalidade foi de 0% vs. 6,9%, p = 0,019 (Ravikirti et al., 2021).
Babalola et al, Nigéria, ECR duplo-cego
N=62 pacientes
diferença significativa na depuração viral entre ambos os
grupos de tratamento de baixa e alta dose e controles de forma dependente da dose, p = 0,006

Ivermectina é o mito da hepatotoxicidade

Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines: Drug-induced liver injury☆

European Association for the Study of the Liver *

Summary

Idiosyncratic (unpredictable) drug-induced liver injury is one of the most challenging liver disorders faced by hepatologists, because of the myriad of drugs used in clinical practice, available herbs and dietary supplements with hepatotoxic potential, the ability of the condition to present with a variety of clinical and pathological phenotypes and the current absence of specific biomarkers. This makes the diagnosis of drug-induced liver injury an uncertain process, requiring a high degree of awareness of the condition and the careful exclusion of alternative aetiologies of liver disease. Idiosyncratic hepatotoxicity can be severe, leading to a particularly serious variety of acute liver failure for which no effective therapy has yet been developed. These Clinical Practice Guidelines summarize the available evidence on risk factors, diagnosis, management and risk minimization strategies for drug-induced liver jury.

stress), interfere with bile acid transport and either lead to lethal consequences (necrosis or apoptosis) or induce adaptive

Table 1. Drugs associated with intrinsic vs. idiosyncratic DILI.*

Intrinsic	Idiosyncratic	
Acetaminophen	Allopurinol	Lapatinib
Amiodarone§	Amiodarone§	Methyldopa
Anabolic steroids	Amoxicillin-clavulanate	Minocycline
Antimetabolites	Bosentan	Nitrofurantoin
Cholestyramine**	Dantrolene	Pazopanib
Cyclosporine	Diclofenac	Phenytoin
Valproic acid	Disulfiram	Pyrazinamide
HAART drugs	Felbamate	Propylthiouracil
Heparins**	Fenofibrate	Statins§
Nicotinic acid	Flucloxacillin	Sulfonamides
Statins§	Flutamide	Terbinafine
Tacrine**	Halothane	Ticlopidine
	Isoniazid	Tolvaptan
	Ketoconazole	Tolcapone
	Leflunomide	Trovafloxacin
	Lisinopril	

- de ácidos graxos, enquanto suprimiu genes rel
esteatose. Em comparação, a ivermectina inibi
farnesóide X, que regula positivamente a oxida

Pediatr Gastroenterol Hepatol Nutr. 2021 Mar;24(2):119-126
https://doi.org/10.5223/pghn.2021.24.2.119
pISSN 2234-8646·eISSN 2234-8840

Pediatric Gastroenterology, Hepatology & Nutrition
pghn

Guideline

Check for updates

Coronavirus Disease 2019-Liver Injury-Literature Review and Guidelines Based on the Recommendations of Hepatological Societies

Joanna Pawlowska,[1] **Dariusz M. Lebensztejn**,[2] **and Irena Jankowska** [1]

[1]Department of Gastroenterology, Hepatology, Feeding Disorders and Pediatrics, The Children's Memorial Health Institute, Warsaw, Poland
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OPEN ACCESS

Table 1. Papers evaluating liver function in adult patients infected with SARS-CoV-2

Author	Patient number	Abnormal value of laboratory result				Comments
		ALT, AST, LDH U/L – elevated	PT increased	Albumin deceased	Total bilirubin increased	
Chen et al. [4]	99	ALT 28 (28.3), AST 35 (35.4), LDH 75 (75.8)	5 (5.1)	97 (98.0)	18 (18.2)	(only in one pts AST-1,445 U/L, ALT-7,590 U/L)
Huang et al. [5]	41	AST 15 (36.6), LDH 29/40 (72.5)	-	-	-	Elevated: AST "ICU care" 8/13 (61.5), AST "no ICU care" 7/28 (25.0), median PT 12.2 s [IQR 11.2–13.4]; higher than "non-ICU patients" (median PT 10.7 s [9.8–12.1], p–0.012)
Wu et al. [6]	80	ALT 3 (3.8), AST 3 (3.8), LDH 17 (21.3)	-	2 (2.5)	1 (1.23)	No pts with increased PT
Xu et al. [7]	62	AST 10 (16.1), LDH 17 (27.4)	-	-	-	
Wang et al. [8]	138	Significantly higher ALT AST, LDH in "ICU cases" (maximum value: ALT 57 U/L, AST 70 U/L, LDH-596 U/L)	-	-	Significantly higher total bilirubin (max value 18.6 µmoL/L)	
Shi et al. [9]	81	AST 43 (53.1)	-	-	-	7 (8.6) had hepatitis or liver cirrhosis in anamnesis
Yang et al. [10]	52	Liver dysfunction 15 (28.8) - all critically ill adult patients	12.9% in non-survivors	-	-	Liver dysfunction: survivors (n–20) 6 pts (30.0) non-survivors (n–32) 9 pts (28.1)
Mo et al. [11]	155	Significantly higher AST (max 65 U/L), LDH (max 437 U/L) in refractory cases	-	Significantly lower albumin (min. 32 g/L) in refractory cases	-	On admission total chronic liver disease 7 (4.5)
Zhou et al. [12]	191	ALT 59/189 (31.2), LDH 123/184 (66.8)	11/182 (6.0)	Significantly lower albumin in "non-survivors" 29.1 g/L (26.5–31.3)	-	Abnormal ALT: "survivors" 24% vs. "non-survivors" 48% Abnormal LDH: "survivors" 54% vs. "non-survivors" 98% coagulopathy 37 (19.4)
Guan et al. [13]	1,099	ALT 158/741 (21.3), AST 168/757 (22.2), LDH 277/675 (41.0)	-	-	76/722 (10.5)	HBV infection in 23 pts (2.1)
Xie et al. [14]	79	ALT 25 (31.6), AST 28 (35.4)	-	-	5.1%	Median value of ALT, AST and bilirubin for entire cohort was 36.5 (17.5–71.5) U/L, 34.5 (25.3–55.3) U/L and 12.7 (8.1–15.4) mmoL/L respectively
Fan et al. [15]	148	ALT 27 (18.2), AST 32 (21.6)	-	-	9 (6%)	55 pts (37.2) had abnormal liver function at hospital admission; abnormal GGT 26 (17.6), and ALP 6 (4.1).
Singh and Khan [16]	250	ALT 60/130 (46.2), AST 80/130 (61.5)	-	-	(>2 mg/dL) 30/120 (25.0)	Patient with pre-existing liver disease: abnormal GGT-10/10 (100.0)
	2,530	ALT 390/770 (50.6), AST 520/770 (67.5)	-	-	(>2 mg/dL) 70/770 (9.1)	Patient without pre-existing liver disease: abnormal GGT-20/30 (66.7)

Ivermectina e o mito de carcinogênese

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Comment > Leuk Lymphoma. 2020 Oct;61(10):2536-2537.
doi: 10.1080/10428194.2020.1786559. Epub 2020 Jul 1.

Continuous high-dose ivermectin appears to be safe in patients with acute myelogenous leukemia and could inform clinical repurposing for COVID-19 infection

Claudio Galvao de Castro Jr [1], Lauro Jose Gregianin [2 3], Jan A Burger [4]

Affiliations + expand

PMID: 32611256 DOI: 10.1080/10428194.2020.1786559

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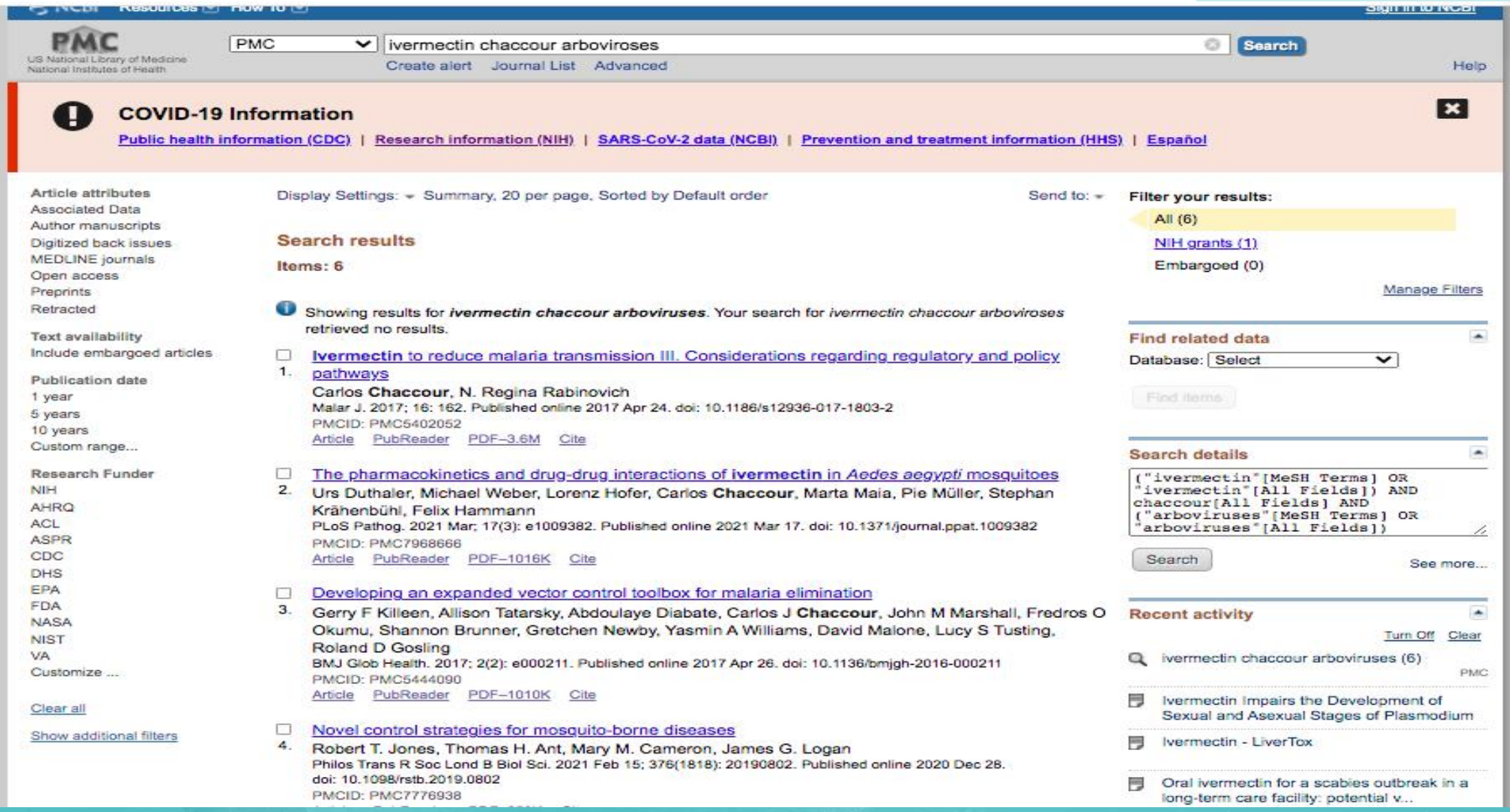
Ivermectina e o mito da infertilidade

Onde estão as arboviroses em meio a Pandemia da Covid?



02 FEBRUARY 2021 | STATEMENTS

Unitaid statement regarding Ivermectin as a potential COVID-19 treatment

Ivermectin, as well as other repurposed products, has been suggested as a potential treatment for COVID-19 based on preliminary promising evidence – further data is needed to support a definitive recommendation either for or against its use for COVID-19.

Unitaid has collaborated with the University of Liverpool to conduct the preliminary desk analysis of existing trials evaluating ivermectin in different countries of the world, in order to facilitate a review by WHO.

The preliminary analysis has incorporated data from randomised clinical studies that have been completed in Bangladesh, Egypt, Iran, India, Iraq, Lebanon, Pakistan, Turkey, Nigeria, Argentina, Mexico, and Spain.

In the coming weeks, results from additional trials in other countries are expected, and an in-depth analysis will be conducted by WHO to determine next steps, including the potential need for further targeted clinical studies.

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Ivermectin and Long Haul COVID

- Acute COVID:
  - Mild cases lasts up to 11 days
  - Severe cases can last up to 28 days
    - Hospital Cases (severe pulmonary phase) can be many weeks/months
- Long Haul COVID – defined as symptoms beyond 4-6 weeks
- Typical case
  - Starts out mild and does not improve
  - May worsen over time, also can wax/wane with flare-ups
    - Some are repeatedly hospitalized but that is unusual

FLCCC "Long-Hauler" COVID-19 TREATMENT PROTOCOL?

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- **High frequency of a constellation of persistent symptoms post-acute illness**
  - Fatigue, aches, palpitations, rash, dizziness, headaches, poor concentration
  - Similar post-viral syndromes associated with Epstein-Barr and others
  - Often an absence of "objective findings" – frustrating for patient/physician/family
- **Does Ivermectin have a role in these prolonged phases?**
  - Encouraging reports from case series and increasing anecdotes
  - Aguirre-Chang, Peru: 33 patients with symptoms present > 4 weeks after COVID-19
    - 0.2mg/kg x 2 days: 88% of patients reported "total improvement"
    - Dose then increased to 0.4mg/kg x 2 days: 94% of patients reported "total improvement"

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"Therapeutic Test"of Aguirre-Chang

- Ivermectin – 0.2- 0.3 mg/kg twice daily for 5 days
- Aspirin – 600-650mg/day divided into 2-3 doses daily
- Symptoms that respond best are
  - Anosmia, nasal congestion, tachycardia, chest pain, night sweats, low grade fever, shortness of breath, wheezing
  - Poor concentration/memory, mental fatigue/confusion
- RESPONSE:
  - If after 5 days IVM/ASA, if symptoms improve by 40%, continue both medicines until symptoms have completely resolved
  - Personal communication: **approximately 300 patients treated, approximately 75% -85% have responded**
    - If predominant symptoms are muscular or chronic fatigue – he adds HCQ, Vitmains B, Zinc, responses more variable, treatment required is prolonged

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The BIRD Recommendations on the Use of Ivermectin for Covid-19

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British
Ivermectin
Recommendation
Development

Proceedings and conclusions of the British Ivermectin Recommendation Development meeting held on the 20th February 2021 in Bath, United Kingdom.

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The Latest: The "BIRD" Meeting

- BIRD = **British Ivermectin Recommendation Development Meeting**
- International Collaboration of 75 researchers, specialists, generalists and patient representatives
  - Coordinated by the "Evidence Based Medicine Consultancy" based in the UK
  - No financial ties/support – organizers/participants volunteered "for the good of humankind"
  - Followed a standard "evidence to decision" framework
    - Systematic review and meta-analysis of randomized controlled trials of ivermectin in COVID-19
    - Meta-analysis provide the highest level of evidence, used for guideline development
      - WHO, NICE, NHS, NIH etc
  - If health emergency: accelerate process while maintain transparency and reporting
    - Core principle underlying NICE guideline and standards

BIRD

British *Ivermectin* Recommendation Development

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BIRD Summary Document

- Released Feb 23, 2021
  - Conclusions of the meeting held on Feb 21, 2021 between
    - BIRD Steering Group
    - BIRD Technical Working Group
    - BIRD Recommendation Development Panel
    - Can be viewed here: https://www.youtube.com/watch?v=7gQbi7LZvPw
  - Core Assessments of the Evidence
    - Desirable Effects, Undesirable effects
    - Certainty of the Evidence, Balance of Effects
    - Values and Preferences
    - Resources – costs, certainty of evidence on costs
    - Equity – impacts of ivermectin
    - Acceptability – would it be acceptable to all stakeholders?
    - Feasibility – is ivermectin feasible?

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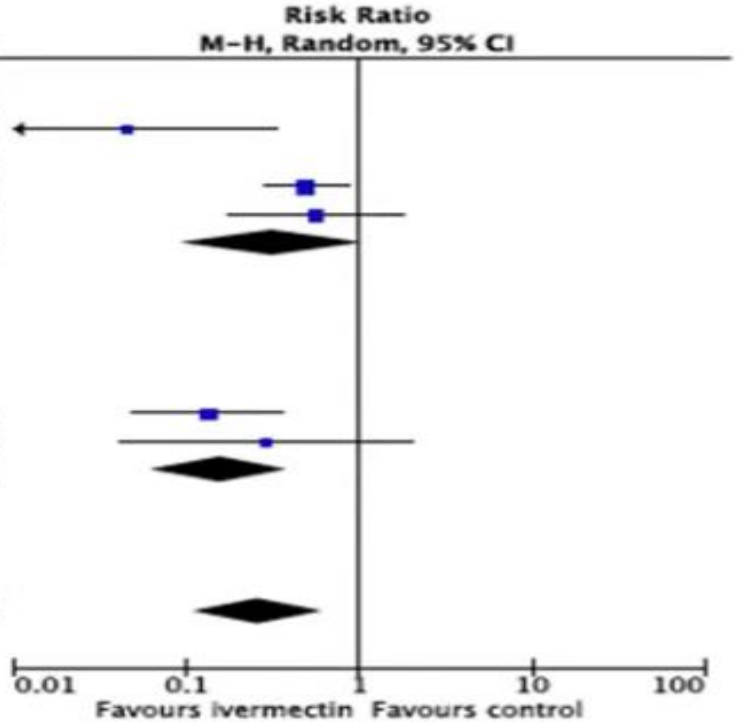
BIRD Conclusions

Forest plot: Deterioration

Study or Subgroup	Ivermectin Events	Ivermectin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.12.1 Mild to moderate covid-19						
Chaccour 2020 (1)	0	12	0	12		Not estimable
Elgazzar 2020 (2)	1	100	22	100	12.3%	0.05 [0.01, 0.33]
Hashim 2020 (3)	0	48	0	48		Not estimable
Mahmud 2020 (4)	16	183	32	180	30.5%	0.49 [0.28, 0.86]
Mohan 2021 (5)	5	80	5	45	21.1%	0.56 [0.17, 1.84]
Subtotal (95% CI)		**423**		**385**	**63.9%**	**0.31 [0.10, 1.02]**
Total events	22		59			
Heterogeneity: $Tau^2 = 0.72$; $Chi^2 = 6.35$, df = 2 (P = 0.04); $I^2 = 69\%$						
Test for overall effect: Z = 1.92 (P = 0.05)						
1.12.2 Severe covid-19						
Elgazzar 2020	4	100	30	100	23.7%	0.13 [0.05, 0.36]
Hashim 2020	1	11	7	22	12.4%	0.29 [0.04, 2.04]
Subtotal (95% CI)		**111**		**122**	**36.1%**	**0.16 [0.06, 0.38]**
Total events	5		37			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.46$, df = 1 (P = 0.50); $I^2 = 0\%$						
Test for overall effect: Z = 4.06 (P < 0.0001)						
Total (95% CI)		**534**		**507**	**100.0%**	**0.26 [0.11, 0.61]**
Total events	27		96			
Heterogeneity: $Tau^2 = 0.55$; $Chi^2 = 10.79$, df = 4 (P = 0.03); $I^2 = 63\%$						
Test for overall effect: Z = 3.07 (P = 0.002)						
Test for subgroup differences: $Chi^2 = 0.84$, df = 1 (P = 0.36), $I^2 = 0\%$						



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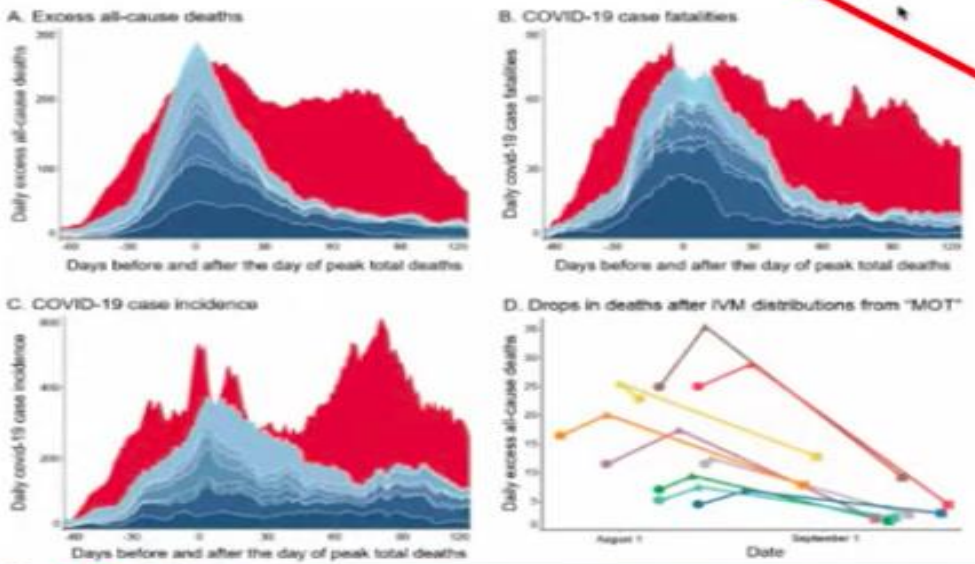
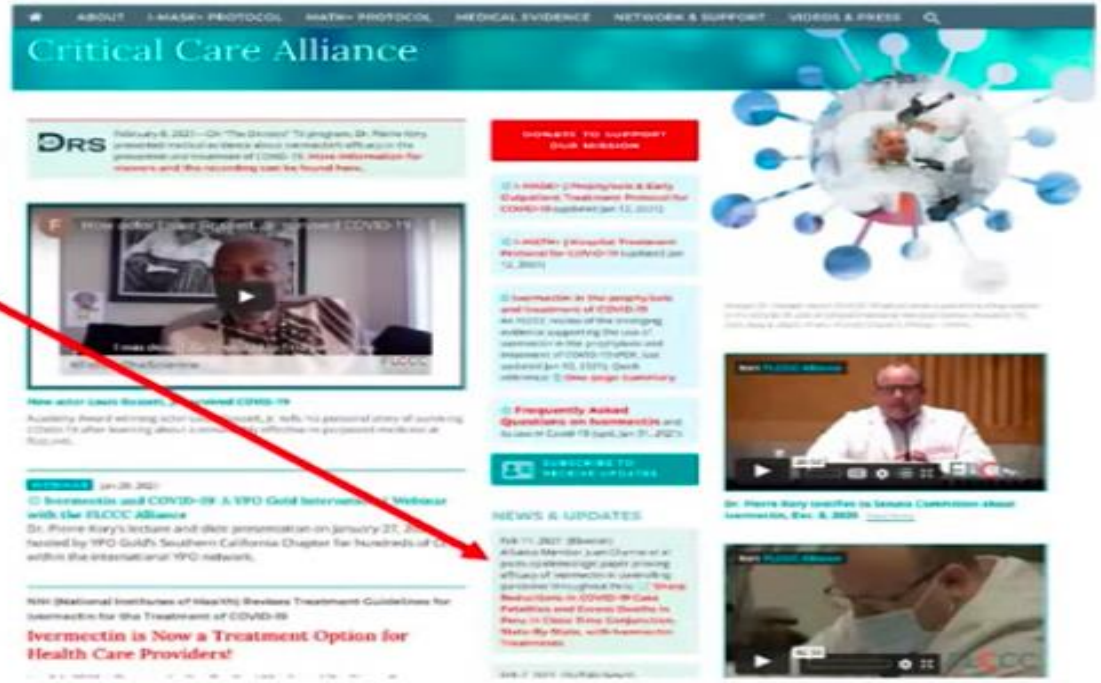
HISTORIC, LANDMARK PAPER COMPLETED
Chamie J, Hibberd J, Scheim D.

Sharp reductions in COVID-19 case fatalities and excess deaths in Peru in close time conjunction, state-by-state, with ivermectin treatments

Juan J. Chamie-Quintero,[a] Jennifer A. Hibberd,[b] David E Scheim[c]





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THE MEXICO CITY STORY – DEC 29: Mexican Social Security Institute (IMSS)

- Instituto Mexican del Seguro Social
  - Assists public health, pensions, social security
  - On December 29th, decision made to adopt am ivermectin protocol in Mexico City
  - All PCR+ patients at 250 testing locations were given ivermectin
    - Rapid tests were used, patients received ivermectin before going hime

THE MEXICO CITY STORY – DEC 29: IMSS Adopts Ivermectin as Treatment for all PCR+ Patients

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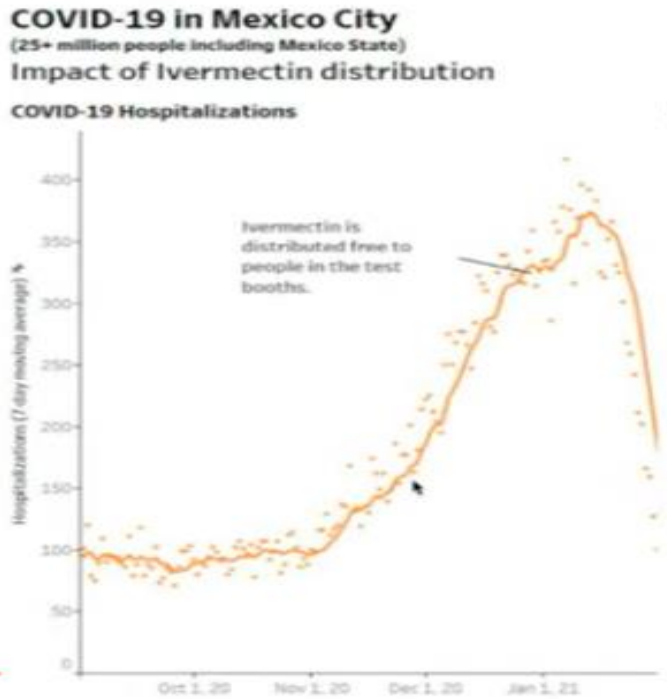

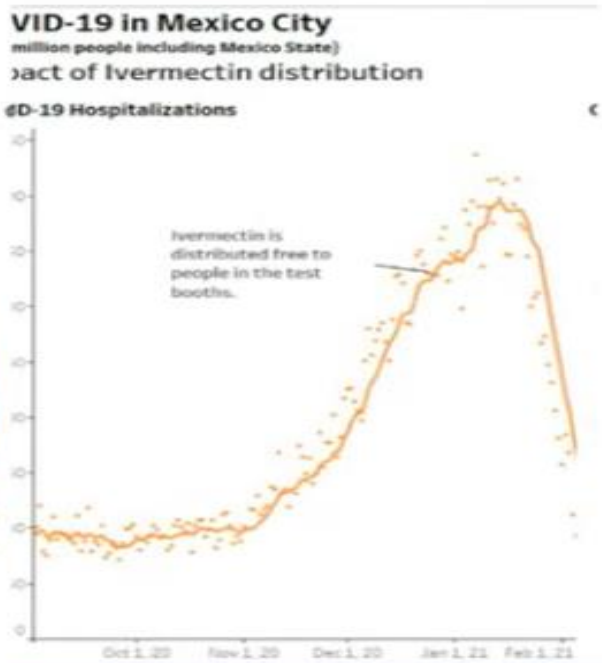

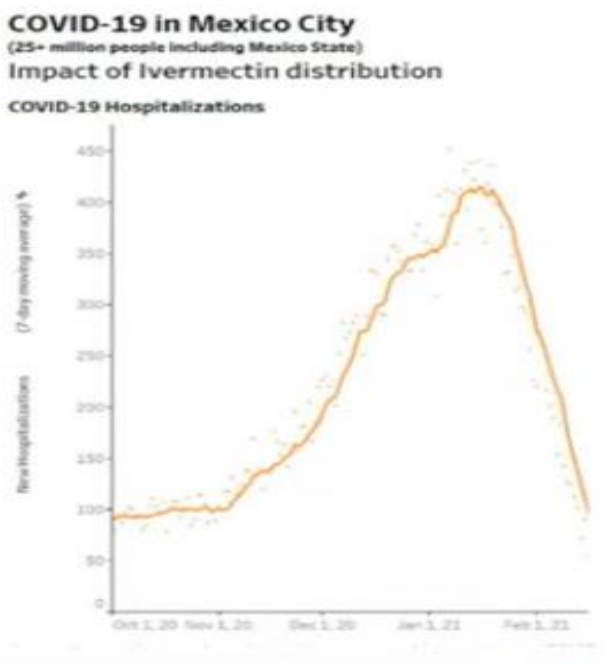

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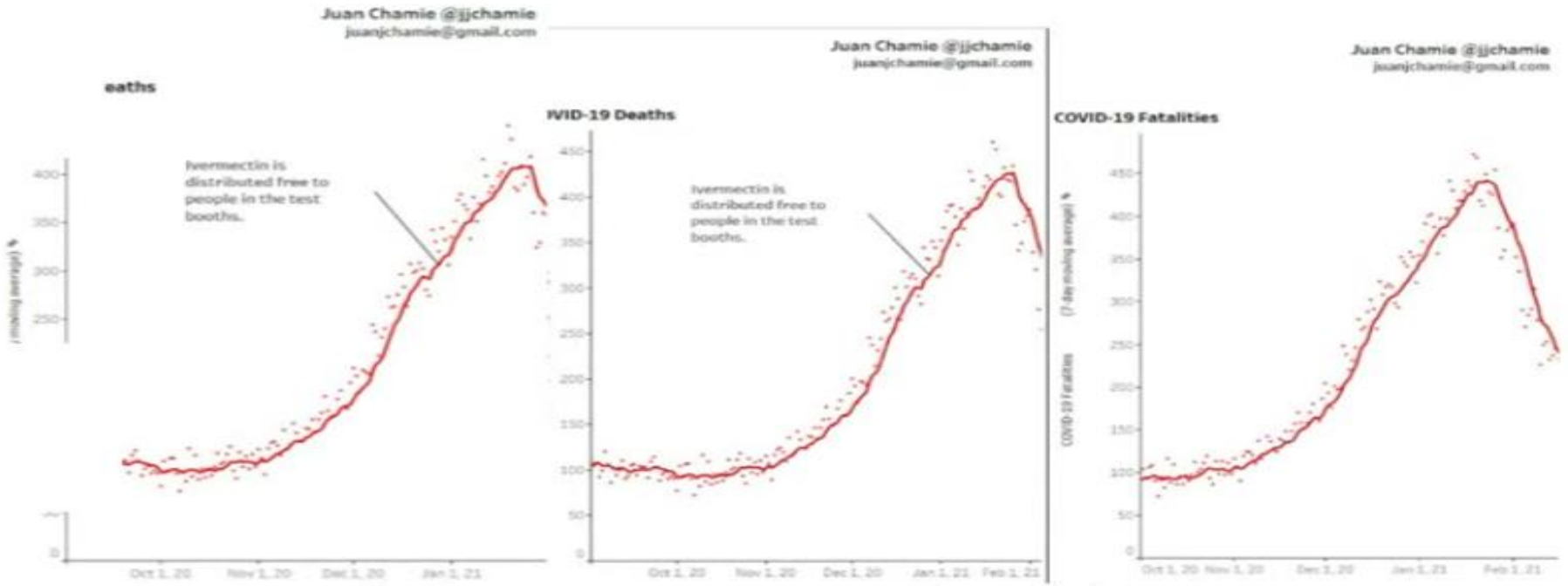
MEXICO CITY – DEATH RATES



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Infectious Disease Society of America

Recommendations 18-19: Ivermectin vs. no ivermectin for hospitalized patients and outpatients outside the context of a clinical trial

New section developed 1/29/21

Recommendation 18: In hospitalized patients with severe COVID-19, the IDSA panel suggests against ivermectin use outside of the context of a clinical trial. (Conditional recommendation, very low certainty of evidence)

Recommendation 19: In outpatients with COVID-19, the IDSA panel suggests against ivermectin use outside of the context of a clinical trial. (Conditional recommendation, very low certainty of evidence)

The last literature search was conducted January 27, 2021.

Other considerations

The panel determined the certainty of evidence of treatment of ivermectin for hospitalized and non-hospitalized patients to be very low due to concerns with risk of bias and imprecision. In addition, there were concerns about publication bias, as the available evidence consisted mostly of positive trials. The guideline panel made a conditional recommendation against treatment of COVID-19 with ivermectin outside of the context of a clinical trial for both patients with COVID-19 hospitalized or in the outpatient setting.

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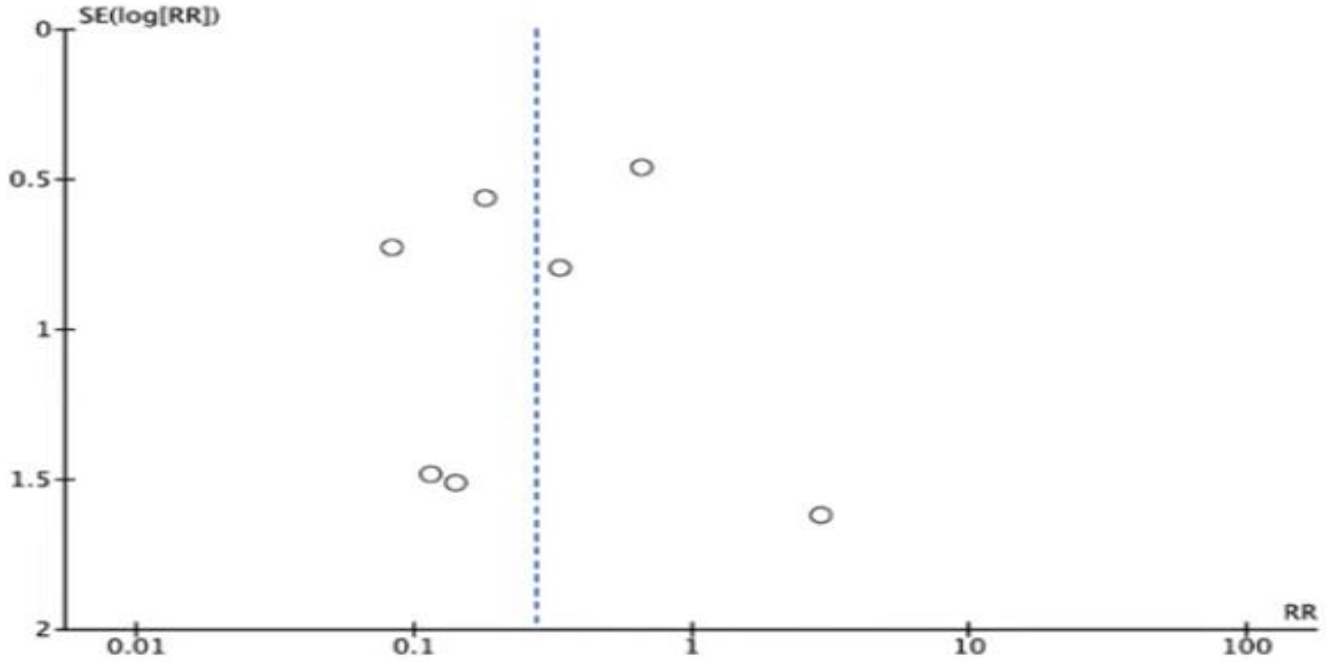
Funnel plot – no significant risk of publication bias



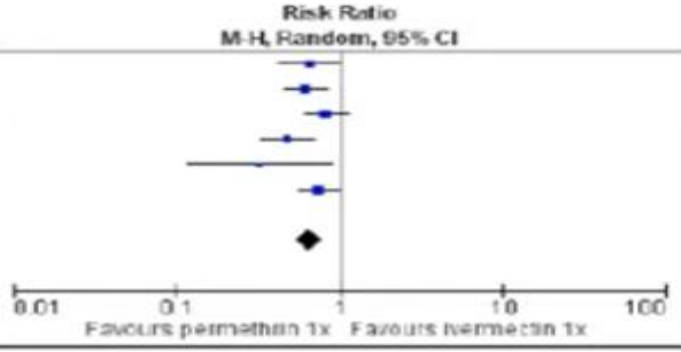
P-value estimated from the regression-based Harbord test for small study effects (p=0.934)

IVERMECTIN META-ANALYSES – WHICH ONE LED TO W.H.O APPROVAL?

SCABIES

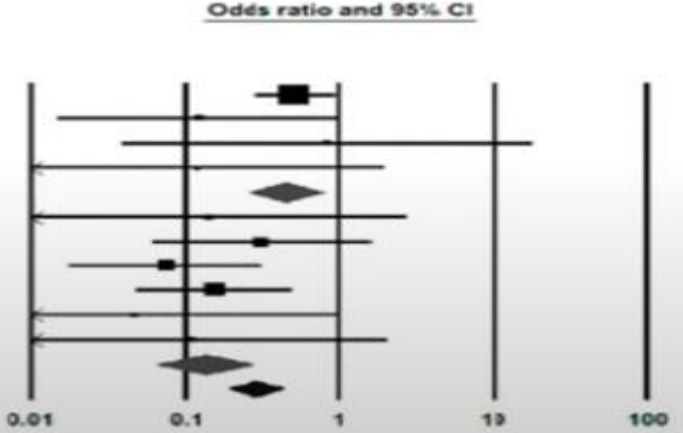
Study or Subgroup	Ivermectin (single dose) Events	Total	Permethrin (once applied) Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bachewar 2009 (1)	15	34	23	34	13.1%	0.65 [0.42, 1.02]
Meenakshi 2014 (2)	32	70	52	70	22.7%	0.62 [0.46, 0.82]
Rohatgi 2013 (3)	28	50	34	50	21.0%	0.82 [0.60, 1.12]
Sharma 2011 (4)	26	60	27	40	16.2%	0.48 [0.33, 0.71]
Usha 2000 (5)	4	40	14	45	3.1%	0.32 [0.12, 0.90]
Wankhade 2016 (6)	29	50	39	50	23.6%	0.74 [0.56, 0.98]
Total (95% CI)		324		289	100.0%	0.65 [0.54, 0.78]
Total events	134		189			

Heterogeneity: Tau² = 0.02; Chi² = 7.66, df = 5 (P = 0.18); I² = 35%
Test for overall effect: Z = 4.52 (P < 0.00001)



COVID-19

Group by RCT-Obs	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Dead / Total Ivermectin	Dead / Total Control
OBS	Rajter	0.524	0.287	0.958	-2.099	0.036	26 / 173	27 / 107
OBS	Khan	0.121	0.015	0.969	-1.990	0.047	1 / 115	9 / 133
OBS	Gorial	0.842	0.039	18.393	-0.109	0.913	0 / 16	2 / 71
OBS	Budhiraja	0.118	0.007	1.932	-1.499	0.134	0 / 34	103 / 942
OBS		0.451	0.258	0.789	-2.793	0.005		
RCT	Mahmud	0.138	0.007	2.894	-1.306	0.192	0 / 183	3 / 180
RCT	Hashim	0.314	0.061	1.611	-1.389	0.165	2 / 70	6 / 70
RCT	Elgazzar	0.074	0.017	0.318	-3.502	0.000	2 / 200	24 / 200
RCT	Nisee	0.154	0.047	0.506	-3.080	0.002	4 / 120	11 / 60
RCT	Cadegiani	0.040	0.002	0.970	-1.980	0.048	0 / 585	2 / 137
RCT	Ravikirti	0.107	0.006	2.038	-1.486	0.137	0 / 55	4 / 57
RCT		0.134	0.065	0.277	-5.413	0.000		
Overall		0.266	0.165	0.440	-5.509	0.000		



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npr WISCONSIN PUBLIC RADIO

The Mystery Of India's Plummeting COVID-19 Cases

February 1, 2021 · 3:29 PM ET

AP

India's dramatic fall in virus cases leaves experts stumped

By KRUTIKA PATHI and ANIRUDDHA GHOSAL yesterday

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COULD IT BE POSSIBLE?

Sales of Ivermectin, drug to treat parasitic infections, jump fourfold

SOHINI DAS &
RUCHIKA CHITRAVANSHI
Mumbai/New Delhi, 5 February

Ivermectin, a drug used to treat parasitic infections, rose to prominence in 2020 as a treatment for Covid-19, pushing its sales up by more than 25 times, prompting more drug firms to launch the product.

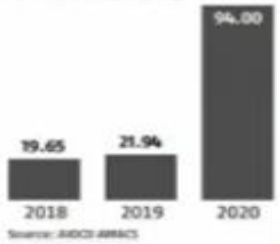
Though demand for Ivermectin slowed with the rise of antivirals like remdesivir and favipiravir, experts feel its relevance as a prophylaxis remains. Annual sales of Ivermectin were around ₹19 crore in 2018 and went up to ₹21 crore in 2019. In 2020 it shot up to ₹94 crore. The drug's sales grew from ₹1.7 crore in April to ₹26.8 crore in September, riding on Covid-19 demand, shows data from market research firm AIOCD AWACS.

Mumbai-based pulmonologist Dr Agam Vora said in the first few months of the pandemic, the line of treatment was not established. "Ivermectin emerged as one of the better options around at the time as it has hardly any side effects and has no drug-to-drug interaction. It is inexpensive and easily available. The best part is its prophylactic properties," Dr Vora said. He has published papers on the role of Ivermectin in treating mild cases of Covid-19.

Dr Vora said by the time Ivermectin popularity grew, antivirals like favipiravir and remdesivir came along. This hit demand for the drug, which saw sales dip to ₹8.6 crore in December.

BOOSTER DOSE

Sales value (₹ crore)



Source: AIOCD AWACS

Several firms launched the drug last year, including Mumbai-based JB Chemicals. Nikhil Chopra, chief executive officer of JB Chemicals, said they launched the drug in November. It also launched favipiravir and Chopra feels Ivermectin has not lost its relevance as it has prophylactic properties.

Dr Vora said, "The vaccine would take some time to cover a sizeable population. Until then, safe drugs like Ivermectin can be used as prophylactic to stop the spread of infection."

Firms like Cipla, Sun Pharmaceuticals, Zuventus have popular Ivermectin brands in the market. Kedar Upadhye, global CFO of Cipla, too, said Ivermectin was considered good for Covid-19 before other molecules came along. Sales of the drug first picked up in states like Uttar Pradesh, West Bengal, and it still seems to be doing well in the North.

"We are giving Ivermectin to those who are getting admitted in the hospitals with Covid as well as family members and contacts of the patient.... This is in the government protocol," said Subodh Kumar Adarsh, chief medical officer, Agra.

A chief medical officer in Aligarh said the drug, unlike HCQ, which was also a part of the protocol, does not have any major side effects and is easier to use. Medical professionals believe the repurposed drug controls the replication of the virus in the body. However, it works for mild cases and doesn't prevent deaths, a Delhi-based doctor said.

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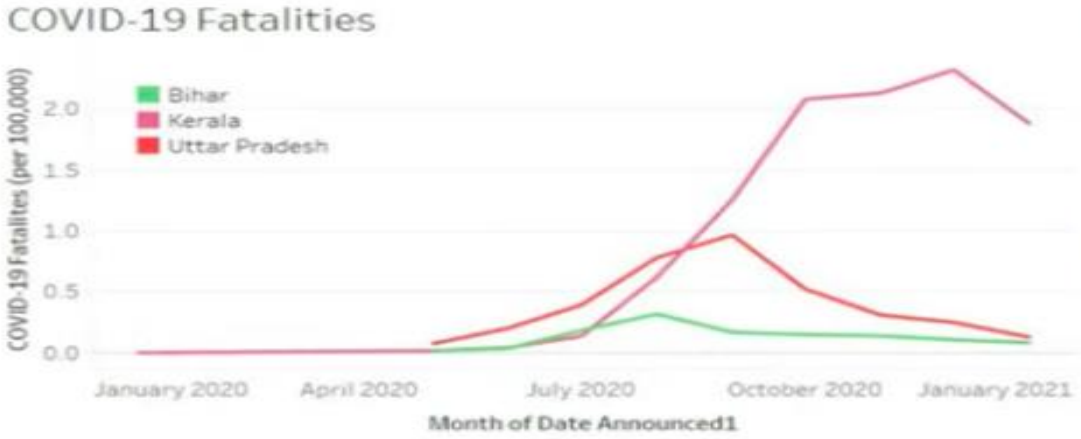
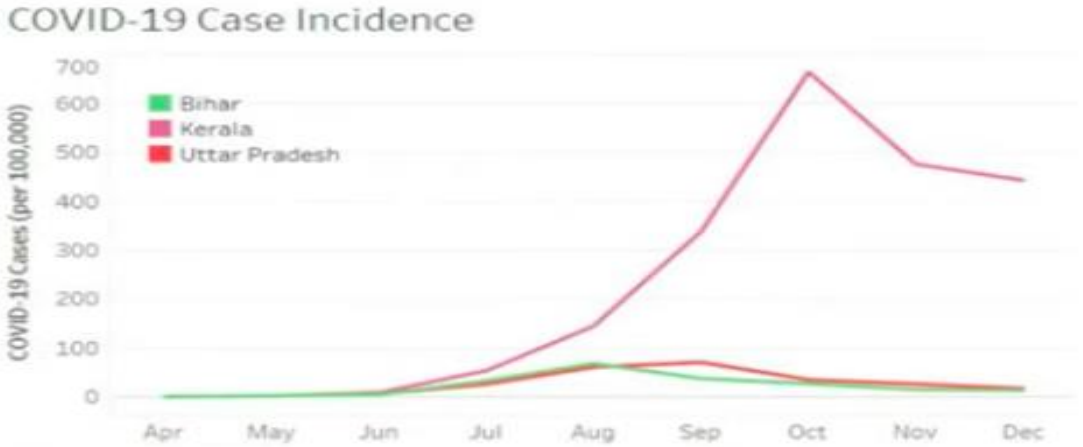
FRONT LINE COVID-19 CRITICAL CARE ALLIANCE · FLCCC.NET
PROPHYLAXIS & TREATMENT PROTOCOLS FOR COVID-19

COVID-19 in India

Case incidence and fatalities in Uttar Pradesh, Bihar and Kerala.



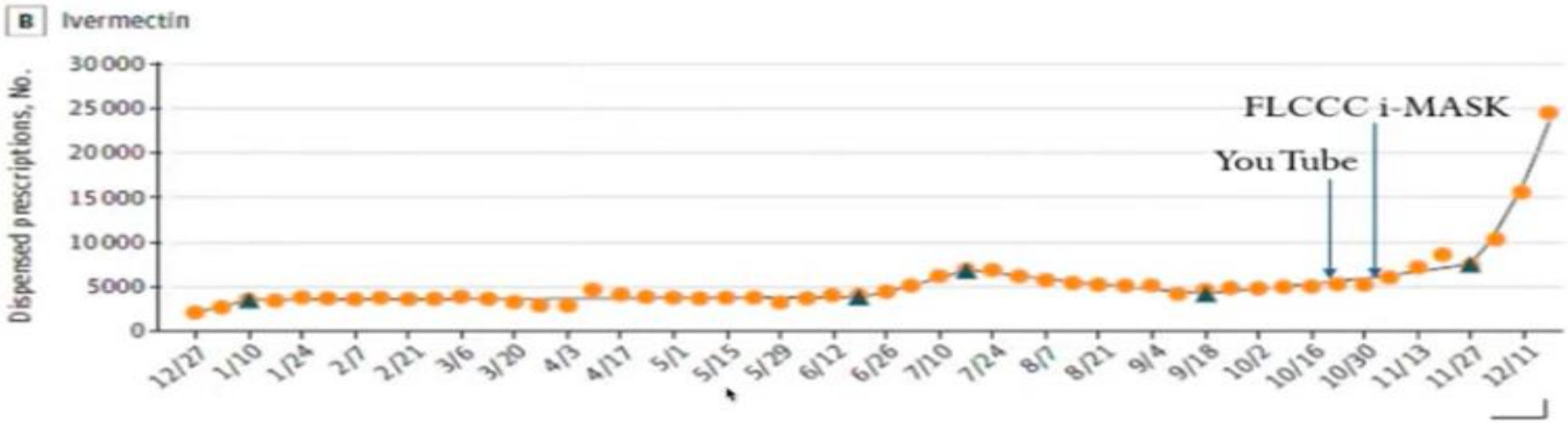


Uttar Preadesh and Bihar goverments promote ivermectin as a COVID-19 treatment. Bihar started first.

Source: api.covid19india.org
Data Analyst: Juan Chamie juanjchamie@gmail.com

IVERMECTIN PRESCRIPTIONS IN THE US

Assessment of Outpatient Dispensing of Products Proposed for Treatment or Prevention of COVID-19 by US Retail Pharmacies During the Pandemic



Geller AI, et al JAMA Intern Med 2021; ePub

IVERMECTIN USE IN THE U.S - LATELY

Table. Estimated Increases in Dispensed Retail Prescriptions for Selected Products Proposed to Treat or Prevent COVID-19—United States, March-December 2020 vs 2019[a]

Treatment[b]	Baseline No. of prescriptions dispensed per week[c]	Peak week, 2020 (end date)[d]	Peak No. of prescriptions dispensed per week, 2020[d]	No. of prescriptions dispensed above baseline in peak week, 2020	Increase in prescriptions dispensed above baseline in peak week, 2020, %	Weeks >50% above baseline, 2020, No.
Ivermectin	3589	Dec 18, 2020	24 528	20 939	583.4	12
Chloroquine	499	Mar 20, 2020	2966	2467	494.4	2
Zinc[e]	1810	Dec 11, 2020	9110	7300	403.3	32
Hydroxychloroquine	93 640	Mar 20, 2020	267 308	173 668	185.5	4
Vitamin C[f]	9331	Dec 11, 2020	21 020	11 689	125.3	30
Dexamethasone	57 178	Dec 18, 2020	123 829	66 651	116.6	6
Lopinavir-ritonavir	492	Mar 20, 2020	954	462	93.8	1
Famotidine[g]	253 684	Dec 18, 2020	365 699	112 015	44.2	0
Tocilizumab	293	Dec 4, 2020	400	107	36.4	0
Sarilumab	123	Aug 14, 2020	154	31	25.2	0
Janus kinase inhibitors	2171	Dec 4, 2020	2960	789	36.4	0
Tyrosine kinase inhibitors	1770	Mar 20, 2020	1966	196	11.1	0
Azithromycin[h]	860 605	Mar 20, 2020	953 074	92 469	10.7	0
Colchicine	54 564	Mar 20, 2020	60 294	5730	10.5	0
Vitamin D[i]	568 481	Mar 20, 2020	624 726	56 245	9.9	0

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IVERMECTIN ADOPTION ACROSS THE WORLD...

Select U.S. Hospitals & Other Providers Utilizing Ivermectin

Dayton Ohio VA Hospital

Univ. Tennessee Hospital

Lincoln Hospital &

N. Basin Medical Clinics, WA

Los Robles Hospital

Thousand Oaks, CA

Lexington Medical Center Hospital, SC

DeTar Hospital

Citizens Medical Center Hospital

Post-Acute Medical (PAM) Rehabilitation Hospital, Texas

Fort Duncan Regional Medical Center, Texas

Hendrick Heath Hospital, Texas

Urgent Care Chain

Florida Keys

Operator of 23 Assisted Living Facilities

Southern U.S.

10 Multi-State Tele-Health Operators

7 SNF's, Buffalo, NY – Dt. Majeskie
Maguire SNF, Harrishill , NY
Elderwood SNF, Amherst
7 Virginia SNF's – Dr. David Chesler

Prof. Eli Schwartz

- Director of the Center for Geographic Medicine at Sheba Medical Center in Tel-Hashomer Israel, first introduced the field of travel medicine to Israel .
- His practice became the recognized center by the Ministry of Health of Israel for tropical and travel diseases. Dr Schwartz is currently serving as the president of the Israeli Society of Parasitology and Tropical Diseases and past president of the Asia-Pacific Travel Health Society. He is a full Professor (clinical) at the Sacker faculty of Medicine, Tel-Aviv University.

The International Ivermectin for Covid Conference 24-25 April 2021

Ivermectin vs. Placebo treatment in non-hospitalized patients with COVID-19 – A double blind , randomized controlled trial

Prof. Eli Schwartz, MD, DTMH,

The Center of Geographic & Tropical Med.

Sheba Medical Center,Tel Hashomer,, Sackler Faculty of Medicine, Tel-Aviv Univ. Israel

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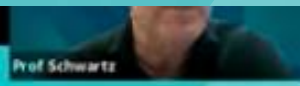

The study

- **Objectives:**
- Reduction of viral shedding among mild to moderate COVID-19 patients.
- To evaluate the effect of Ivermectin in prevent progression of clinical disease

Prof Schwartz

Follow up

- **Clinical follow up**: performed on daily basis for 14 days (Tel. interview) –for monitoring symptoms, clinical deterioration and AE.
- + a last call on day 30
- **Swab PCR: 6 times:** at randomization, **days: 6**, 8, 10, 12, & 14

  Change to : 2, 4

Sample size and actual recruitment

- **Sample size calculation: 50 patients for Ivermectin vs. 50 for Placebo**
- [Outcome: decrease from 90% positive at day 6 -to 67.5% (25% decrease) = **48 patients** per **group** (alpha 0.05, power 80%)]
- Total **96 patients**
- **Final recruitment = 116 patients**
- **Drop-out=30 (Placebo-14, Ivermectin-8)-due to negative results (Ct>35) on admission, 8 left the study/no results**
- **Final number: Ivermectin=47**

  Placebo= 42

	Ivermectin	Placebo	P
N	47	42	N.S
Age –years (Range)	39.8 (22-72)	39.2 (20-71)	N.S
Age>50 y.	12 (24%)	11(24%)	N.S
Age>60 y.	5(10%)	4(9%)	N.S
Other risk factor	10 (20%)	9 (20%)	N.S
Gender	9F, 40M	9F, 36M	N.S
Weight (mean) Kg	78.2	81.5	N.S
%Asymptomatic	18.0	13.3	N.S
Recruitment: post-symptoms onset –Days (mean±SD)	4±2	4±2	N.S
Ct level at recruitmnt	23.8	22.4	N.S

Patients Characteristic

Legendas/legendas ocultas (c)

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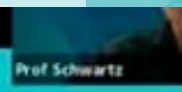


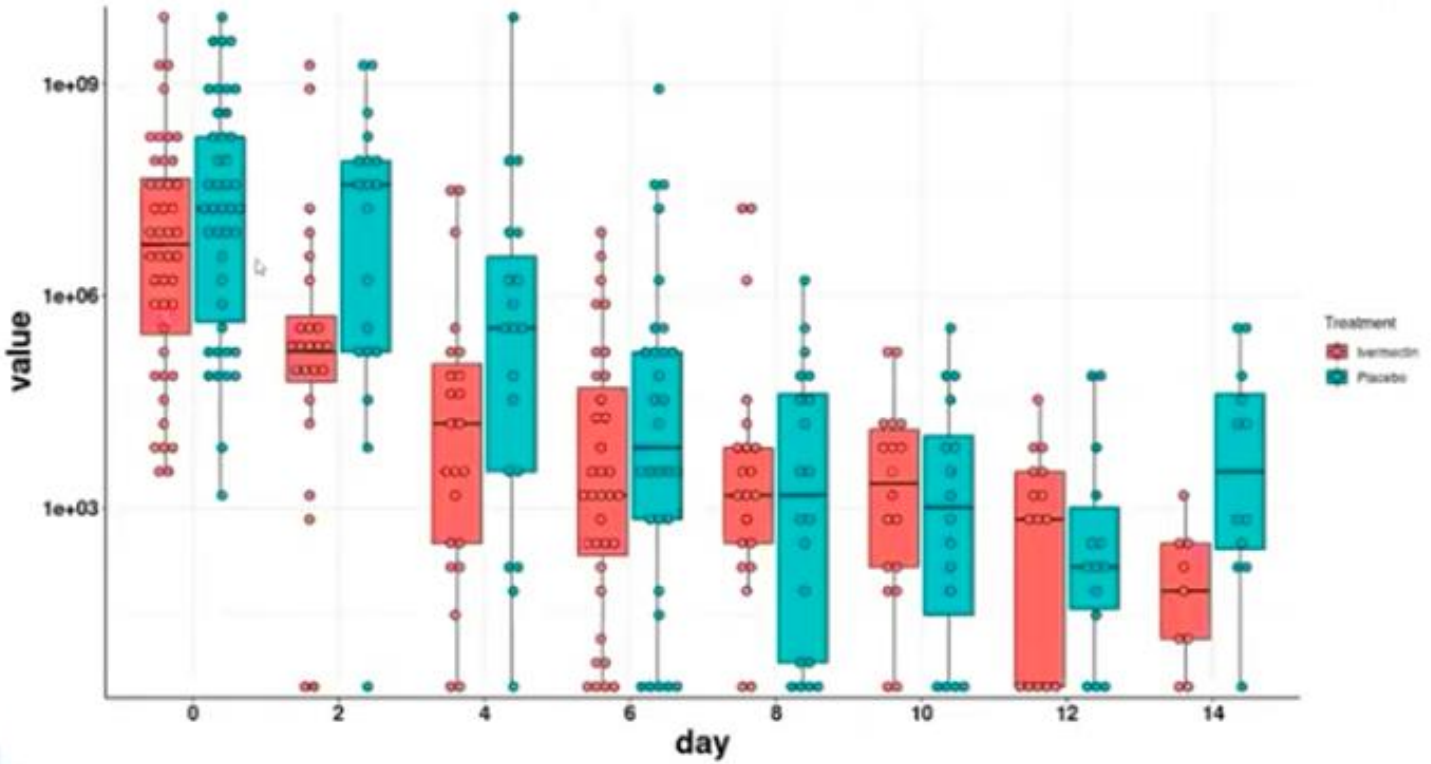
Safety

- No Safety issues were reported
  - *Diarrhea: IVM-2, P-1*
  - *Rash: P-2*

Prof Schwartz

Viral load evolution by study arm.

Viral load values were log-transformed. The boxes show the interquartile range. Dots represent each individual value



Negative samples (Ct>30) from initiation of treatment

	N	Ivermectin	Placebo	P value*	OR	95% CI	
Negative at Day 4	50	15/28 (54%)	7/22 (32%)	0.12	2.47	0.77	7.92
Negative at Day 6	89	34/47 (72%)	21/42 (50%)	0.03	2.58	1.09	6.31
Negative at Day 8	89	39/47 (83%)	25/42 (59%)	0.01	3.32	1.25	8.22
Negative at Day 10	89	40/47 (85%)	29/42 (69%)	0.07	2.56	0.91	7.72

Multivariable logistic regression model

Variable	Odds Ratio	95% Confidence Interval		P value
female	0.926	0.281	3.047	0.8993
Age	0.980	0.946	1.016	0.2719
weight	1.006	0.976	1.037	0.6966
symptoms	0.824	0.234	2.904	0.7636
Ivermectin	2.640	1.055	6.609	0.0381

In the multivariable logistic regression model, the adjusted odds ratio of *Ct>30* at day 6 for the Ivermefctin group was 2.64-fold higher than for the placebo group (95% confidence interval [CI]: 1.06–6.61, P=0.04)

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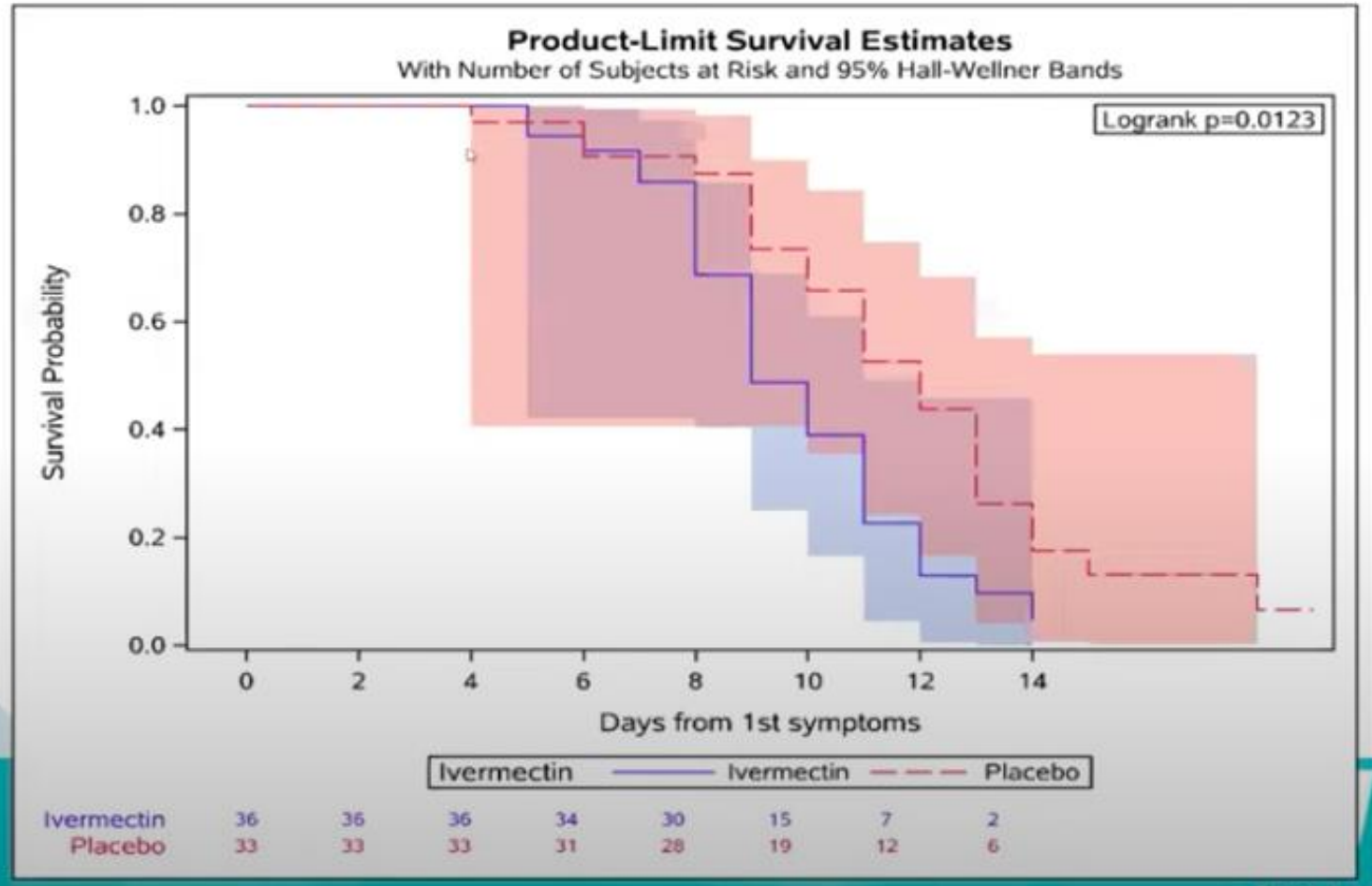
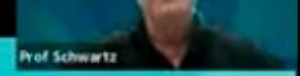
Kaplan-Meier analysis of Symptomatic patients (N=69) till negative result (Ct >30)





Clinical deterioration- our study

	Ivermectin	Placebo	P
N	47	42	N.S
Age –years (Range)	39.8 (22-72)	39.2 (20-71)	N.S
Age>50 y.	12 (24%)	11(24%)	N.S
Other risk factor	10 (21%)	9 (21%)	N.S
Hospitalization	1*	3	
From Asymtomatic- to Symptomatic	0	1	

* Within 12 h. of treatment

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Conclusions

- Ivermectin demonstrated an anti-SARS-CoV-2 activity
- It reduces the viral-shedding period
- It shorten the infectivity time

Viral Culture

Number	Day	Ct -Swab	Ct-culture (day 10)	Interpretation
141(P)	4	23	28	Negative
147 (P)	4	25	5	Positive

In vitro study;
Viable Cell culture: 4-6 days

	No. tested	No. positive	%
Placebo	18	6	33%
Ivermectin	14	1	7%

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Composite Calculation: Non-Infectious samples (Ct>30, and Non-viable culture) from initiation of treatment

	Ivermectin N=47	Placebo N=42	P value
Negative at Day 6	43/47 (91%)	30/42 (73%)	0.01

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Conclusions

- Ivermectin demonstrated an anti-SARS-CoV-2 activity
- It reduces the viral-shedding period
- It shorten the infectivity time

- Therefore it may have a significant public-health impact
- It may block transmission chain
- **It may shorten the isolation time**

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Development

The
Evidence-Based
Medicine
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Resposta à declaração da EMA sobre ivermectina para Covid-19

Em 22 de março, a Agência Europeia de Medicamentos (EMA) emitiu um comunicado 1 no qual, após a revisão das evidências, recomenda contra o uso de ivermectina para a prevenção e tratamento de covid-19, fora dos ensaios clínicos "bem planejados". A EMA diz ter evidências de estudos de laboratório, ensaios clínicos, estudos observacionais e meta-análises, mas não fornece fontes, especificações ou citações. Corrigiremos essas omissões abaixo.

AO MINISTÉRIO PÚBLICO FEDERAL – PROCURADORIA DA REPÚBLICA EM GOIÁS.

AS EVIDÊNCIAS CIENTÍFICAS ACERCA DO ATENDIMENTO INTEGRAL DAS PESSOAS ACOMETIDAS COM A COVID-19: O ESTADO DA ARTE ATUAL, COM ÊNFASE NO TRATAMENTO NA FASE INICIAL (REPLICAÇÃO VIRAL) DA DOENÇA.

Responsáveis pela elaboração:

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Biomédica, mestre em fisiopatologia médica e doutora em ciências pela Universidade Estadual de Campinas (UNICAMP) e pós doutora pelo Laboratório Nacional de Biociências (LNBio) e pela *Harvard Medical School*.

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Fonte: http://www.mpf.mp.br/go/sala-de-imprensa/docs/not%202541-nota%20tecnica.pdf

“Penso que na discussão dos problemas da natureza deveríamos começar não pelas escrituras, mas antes pelas experiências e demonstrações.”

Galileu Galilei

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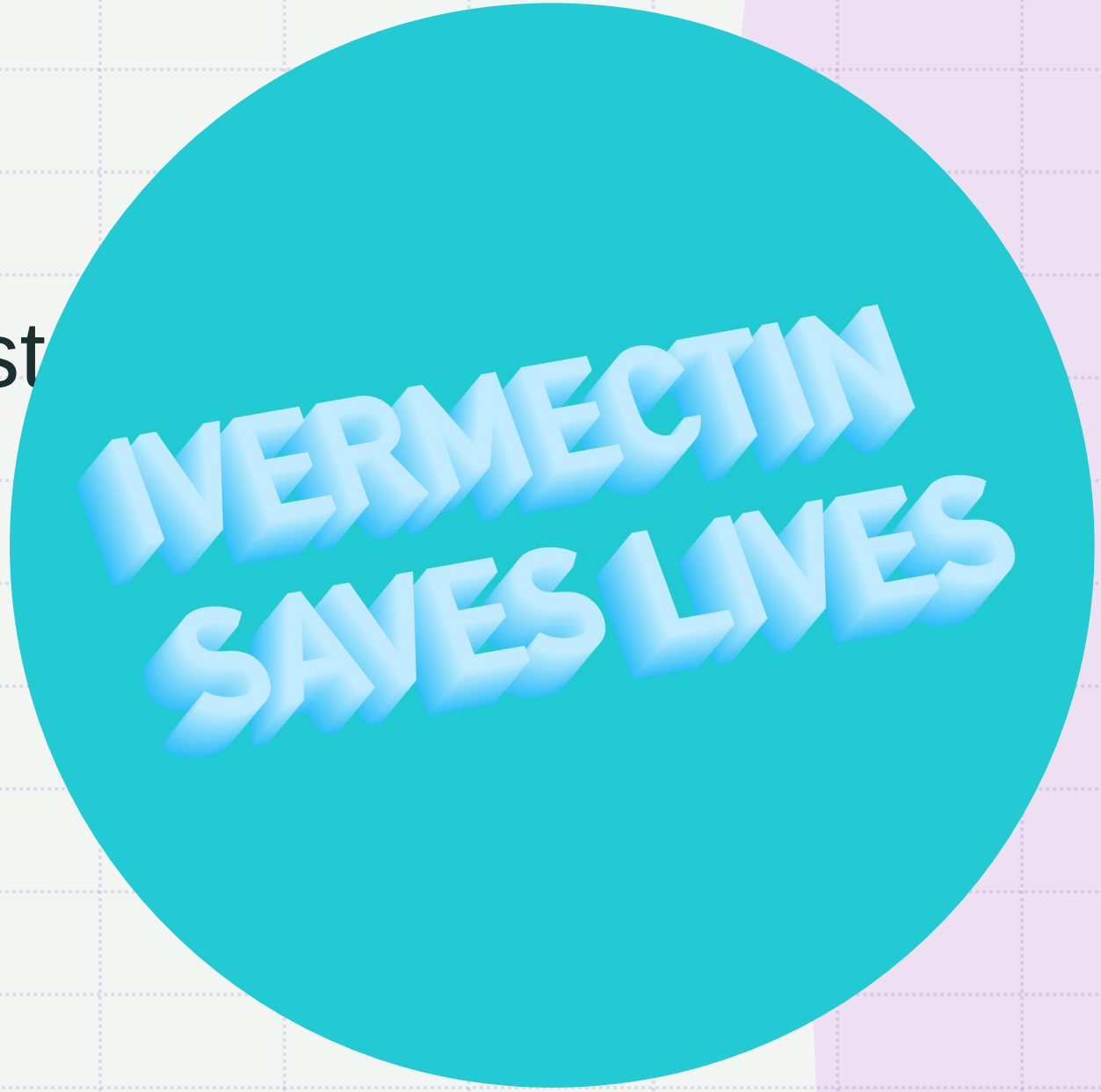
Obrigada,
Profa Dra. Tess Lawrie!

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



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- .Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects. Guzzo CA1, Furtek CI, Porras AG, Chen C, Tipping R, Clineschmidt CM, Sciberras DG, Hsieh JY, Lasseter KC.
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- **Overview**: A summary of international ivermectin covid studies (c19ivermectin.com)
- **Review**: Ivermectin – A Potential Global Solution to the Covid-19 Pandemic (FLCCC)
- **Review**: Meta-analysis of randomized trials of ivermectin to treat SARS-CoV-2 infection (Andrew Hill et al., Research Square, January 2021)
- Review of the Emerging Evidence Supporting the Efficacy of Ivermectin in the Prophylaxis and Treatment of COVID-19 FLCCC Alliance; updated Jan 12, 2021

Caly et al The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Research, doi:10.1016/j.antiviral.2020.104787 Caly et al

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