repurposed drugs in Covid-19 treatment & prevention: *Ivermectin*

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EbMCsquared CIC, Bath

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Disclaimer

This presentation is a record of slides shown for a Scientific Conference of the Royal College of Emergency Medicine on 6 October 2021

Nothing in this material constitutes medical advice of any kind to any individual. It is a report of systematic reviews of clinical evidence but says nothing about the applicability to any individual patient.

Please consult your own medical advisor for any and all treatment options for any medical condition.

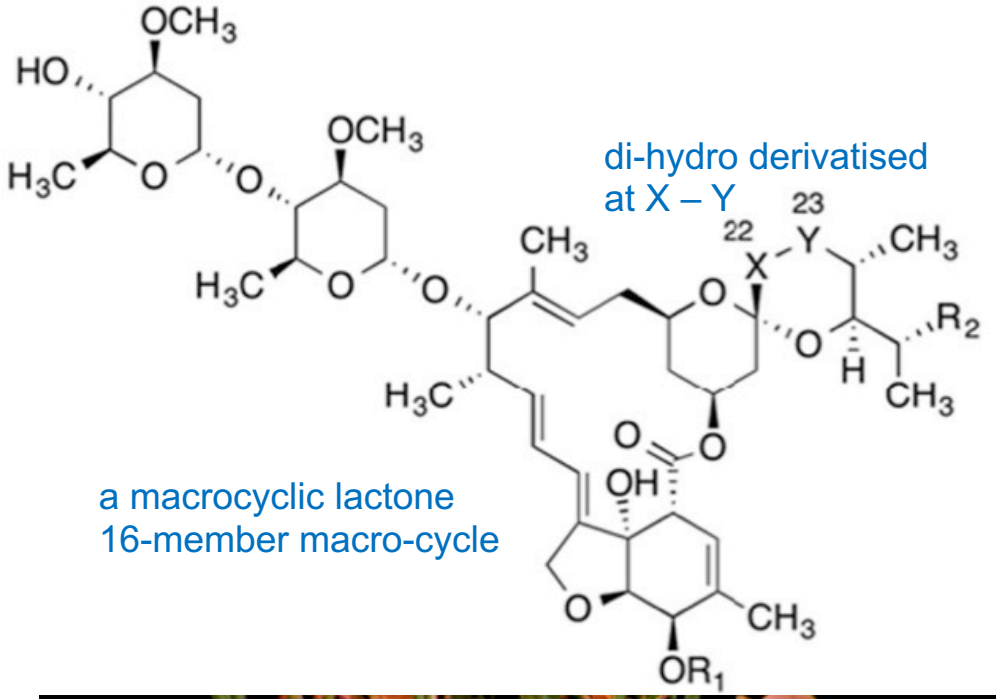
background

Outset of pandemic – no proven therapies

- identification of repurposed drugs
- highly politicised – Hydroxychloroquine & Remdesivir
- First proven therapy reducing mortality (in hospital)
  – corticosteroids (dexamethasone)
- Vaccines reduce severe disease but not always infection
- Early treatment rejected by most major health authorities
  - but widely practised with success in multiple settings
  - Perfect early therapy would be oral – efficacious, safe and well tolerated
  - Complementary to vaccination

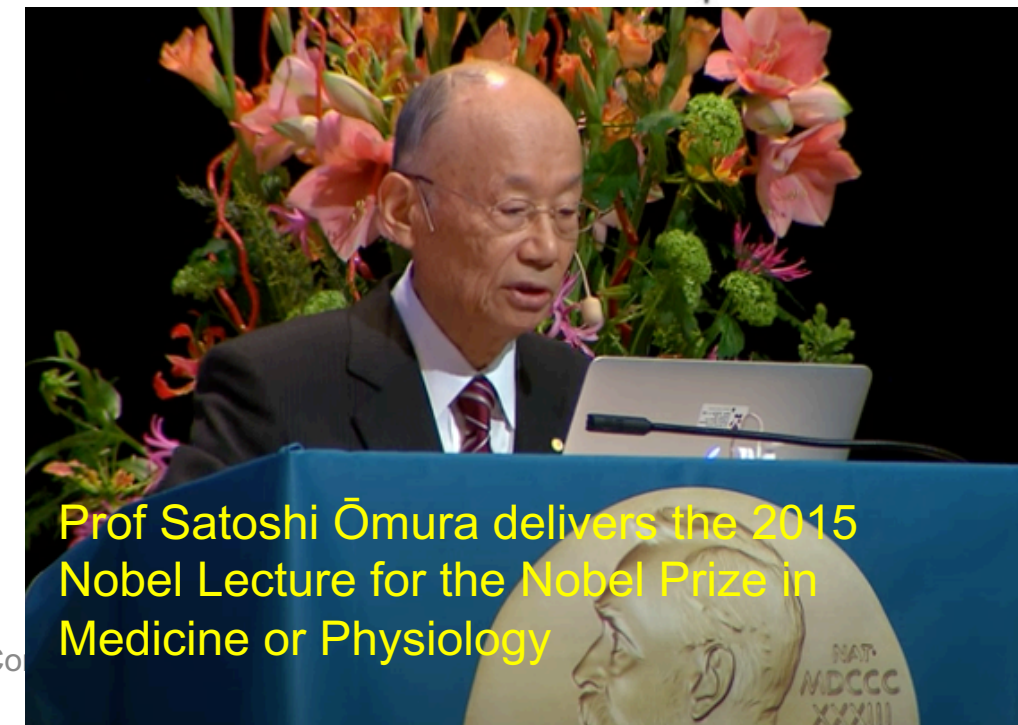
That safe, cheap, oral anti-viral already exists.

ivermectin, the WHO Essential Medicine



- Semi-synthetic derivative of bacterial fermentation product (*Streptomyces avermitilis*)
- Properties:
  anti-parasitic (helminths, arthropods)
  anti-viral (wide class RNA viruses)
  anti-inflammatory
  anti-neoplastic ?

- WHO “Essential Medicine”
  “minimum medicine needs for a basic healthcare system”
  (so why not in NHS ?)
- Nobel Prize (2015) for eradication of “river blindness” (*Onchocerca volvulus*)



ivermectin, the *anti-viral* medicine

- Anti-viral over wide class RNA viruses

  Zika, dengue, yellow fever, West Nile,
  Chikungunya, avian influenza A, HIV-1 …

Ivermectin: a systematic review from antiviral effects to COVID-19 complementary regimen

J. Antibiotics **73**, 593-602 (2020)

Fatemeh Heidary[1] · Reza Gharebaghi[2,3]

- Specifically against SARS-CoV-2
  Caly *et al.*, Monash, April (2020)

  Monkey kidney cells *in vitro*
  Inspiration for many clinical trials

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

Antiviral Research **178**, 104787 (2020)

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

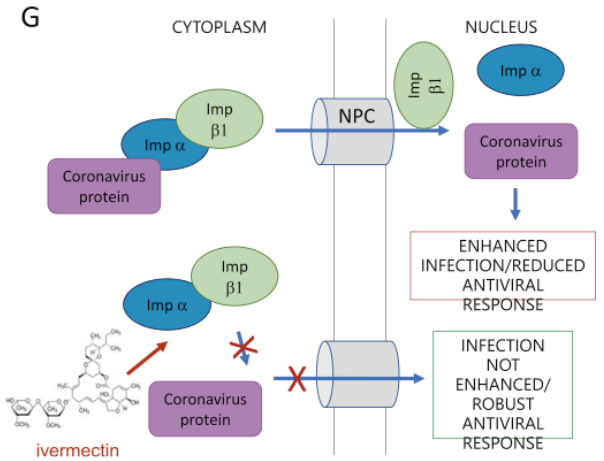
[a] *Victorian Infectious Diseases Reference Laboratory, Royal Melbourne Hospital, At the Peter Doherty Institute for Infection and Immunity, Victoria, 3000, Australia*
[b] *Biomedicine Discovery Institute, Monash University, Clayton, Vic, 3800, Australia*

- Mechanism(s) of action

  Both host-directed & virus-directed hypotheses:

  Blocks import of viral proteins to host cell nucleus

  Binding to spike protein, inhibition of RdRP, 3CLPro enzymes etc



ivermectin, the *safe* medicine

- Anti-parasitic dose to 200 µg / kg (1 or 2)
- Well-tolerated to 2 mg / kg (10 × higher)

  Guzzo *et al.* (2002) *J. Clin. Pharmacol.* **42**, 1122-1133

- 1 mg/kg daily for 6 mths reported in leukaemia

  de Castro *et al.* (2020) *Leukemia & Lymphoma*, **61**, 2536

- Safety profile from **3.7 *billion*** doses worldwide:

Ivermectin:	**20 deaths**	**5,484 AE reports**
C-19 vaccines:	6,667 deaths	1,198,200 AE reports

WHO's `Vigiaccess.org` at 24 June 2021

Ivermectin Safety:
Prof Christopher J M Whitty,
Chief Medical Officer for England

Effect of Ivermectin on *Anopheles gambiae* Mosquitoes Fed on Humans: The Potential of Oral Insecticides in Malaria Control

Carlos Chaccour, Jo Lines, and Christopher J. M. Whitty
Department of Infectious and Tropical Diseases, London School of Hygiene,

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J. Infectious Diseases, **202**, 113-116 **(2010)**

ivermectin in Covid-19: empirical regimens

Prophylaxis ivermectin (+ Vitamins D_3, C, Zinc, Quercetin, Melatonin)

Outpatient

- **I-MASK+** (FLCCC: Dr Pierre Kory *et al.*)
  PREVENTION & EARLY OUTPATIENT TREATMENT PROTOCOL FOR COVID-19

  EARLY TREATMENT PROTOCOL[3] (for Delta variant)

  as above + fluvoxamine or nitazoxanide + ASA

- ZIVERDOX (Prof Thomas Borody, Sydney)
  Zinc
  IVERmectin
  DOXycycline + Vitamins D_3, C

- SMDT (Dr Peter McCullough *et al.* Dallas)
  Sequential Multi-Drug Therapy – any *two* of **ivermectin**, hydroxychloroquine, ivermectin, favipiravir, Regeneron

Hospitalised

- MATH+ (FLCCC: Prof Paul Marik
  Dr Joseph Varon *et al.*)
  Methyprednisolone
  Ascorbic acid (IV)
  Thiamine
  Heparin
  + includes ivermectin as "core medication"

Hazan et al. (2021) *medRχiv* doi: 10.1101/2021.07.06.21259924
"Effectiveness of Ivermectin-Based Multidrug Therapy in Severe Hypoxic Ambulatory COVID-19 Patients"

Pathophysiological Basis and Rationale for Early Outpatient Treatment of SARS-CoV-2 (COVID-19) Infection

THE AMERICAN JOURNAL of MEDICINE®

Peter A. McCullough, MD, MPH,[a,b,c] Ronan J. Kelly, MD,[a] Gaetano Ruocco, MD,[d] Edgar Lerma, MD,[e] James Tumlin, MD,[f]

Also McCullough *et al.* (2020), *Revs. Cardiovasc. Med.* **21**, 517

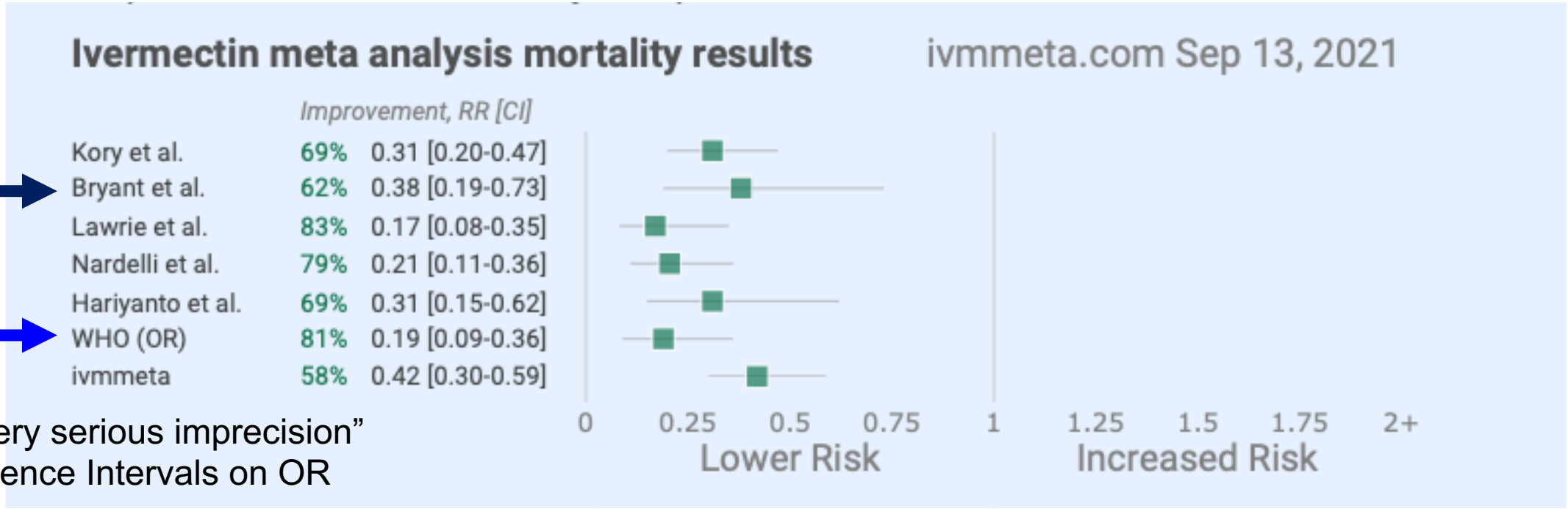
ivermectin: clinical trials

- 63 studies, 31 RCTs (as at 10 Sept)
- Several systematic reviews and meta-analyses: full list ivmmeta.com

We are here (1 July)

WHO is here (March)

WHO states “very serious imprecision” but tight Confidence Intervals on OR

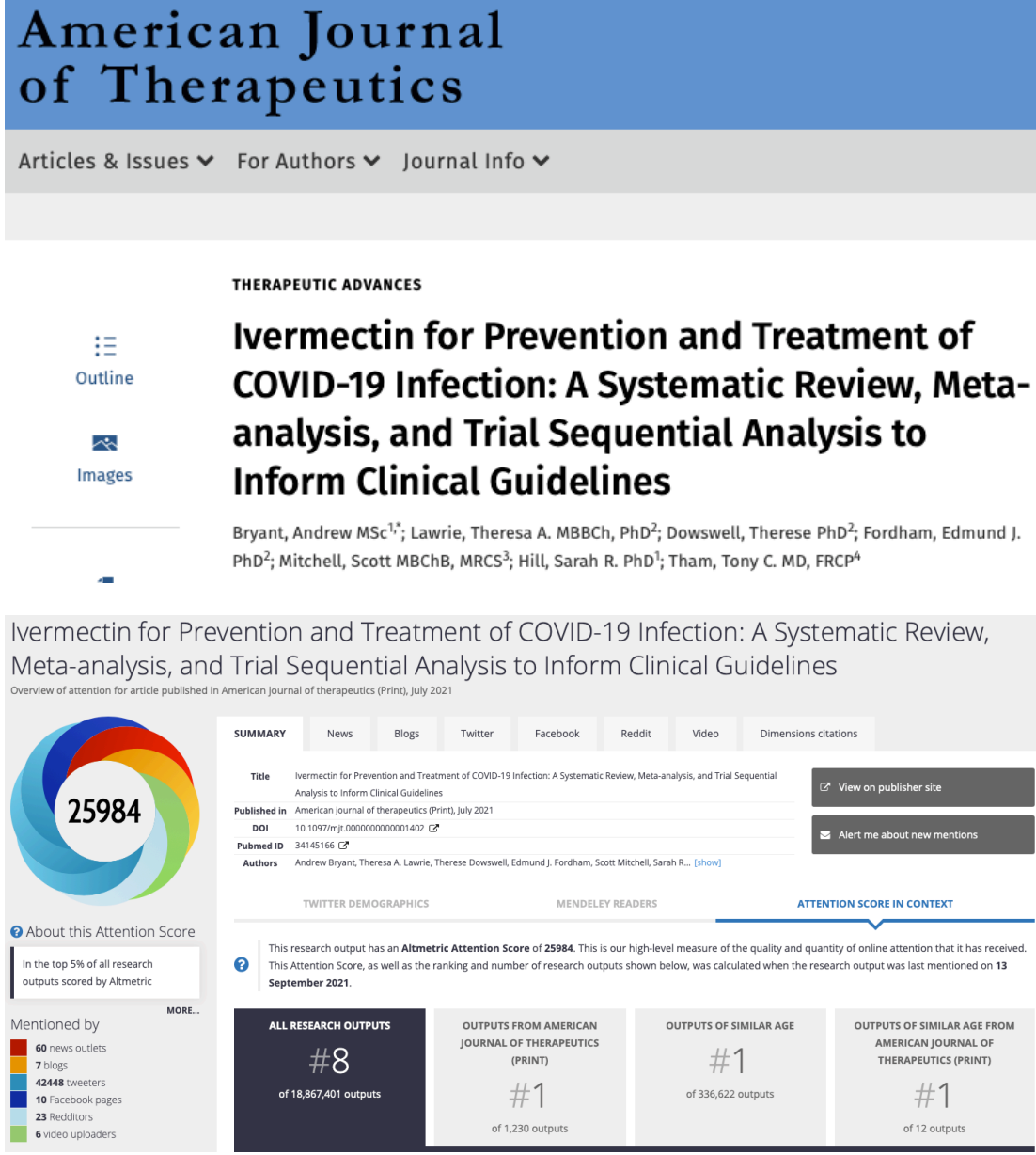


Everything here

Nothing here

systematic review & meta-analysis: Bryant *et al.*

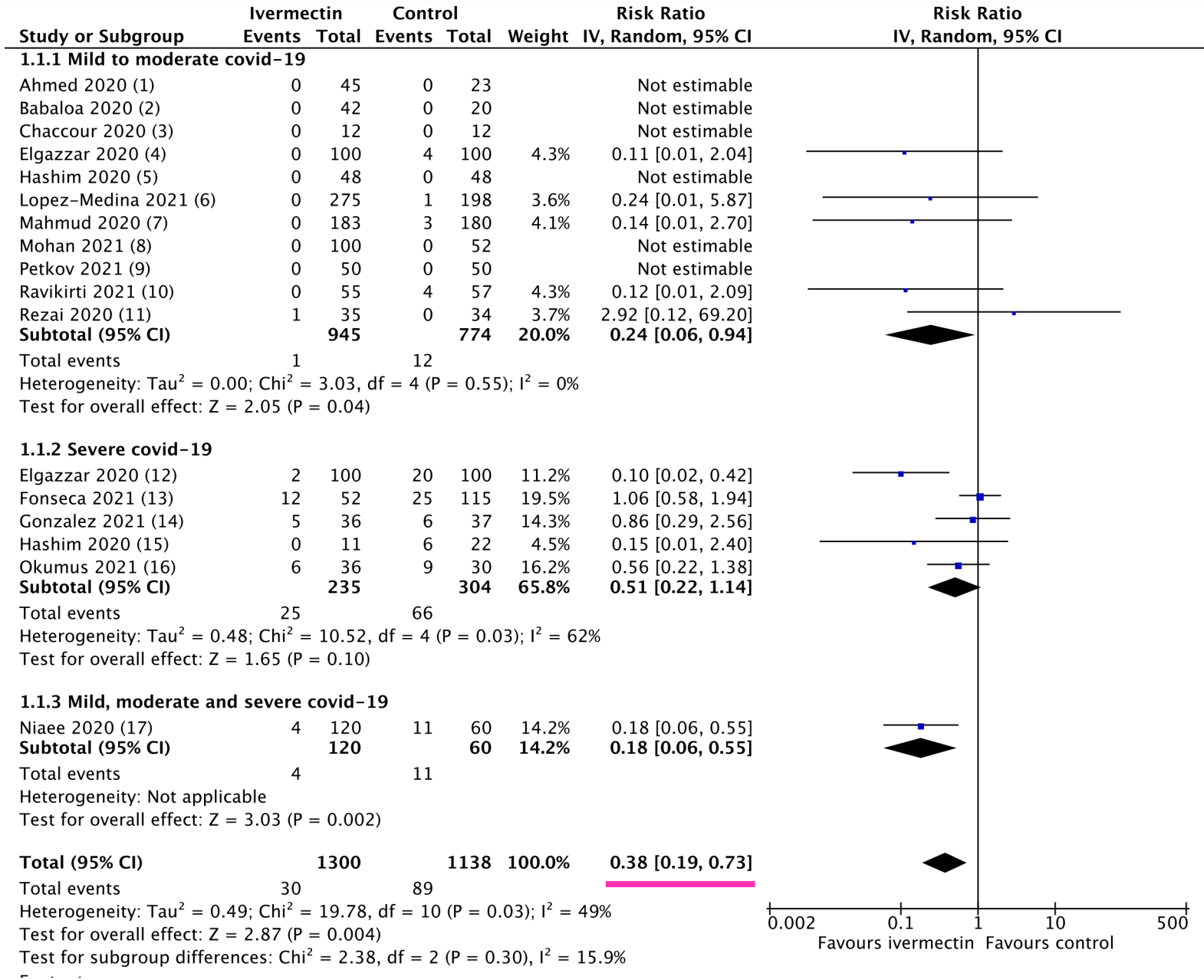
- First following strict PRISMA guidelines
  Preferred **R**eporting **I**tems for **S**ystematic **R**eviews and **M**eta-**A**nalyses
  Page *et al.* (2021) *BMJ*, **372,** 71
- Our PICO questions:
  [**P**opulation, **I**ntervention, **C**ontrol, **O**utcome(s)]
  1. "Ivermectin" *vs* "No Ivermectin" for Covid-19 treatment
  2. "Ivermectin" *vs* "No Ivermectin" for Covid-19 prevention
- Chose to restrict to *Randomised* trials only: 24 RCTs, 3406 patients
- Majority Registered, self-funded, physician-driven, w/o CoIs (1 exception)



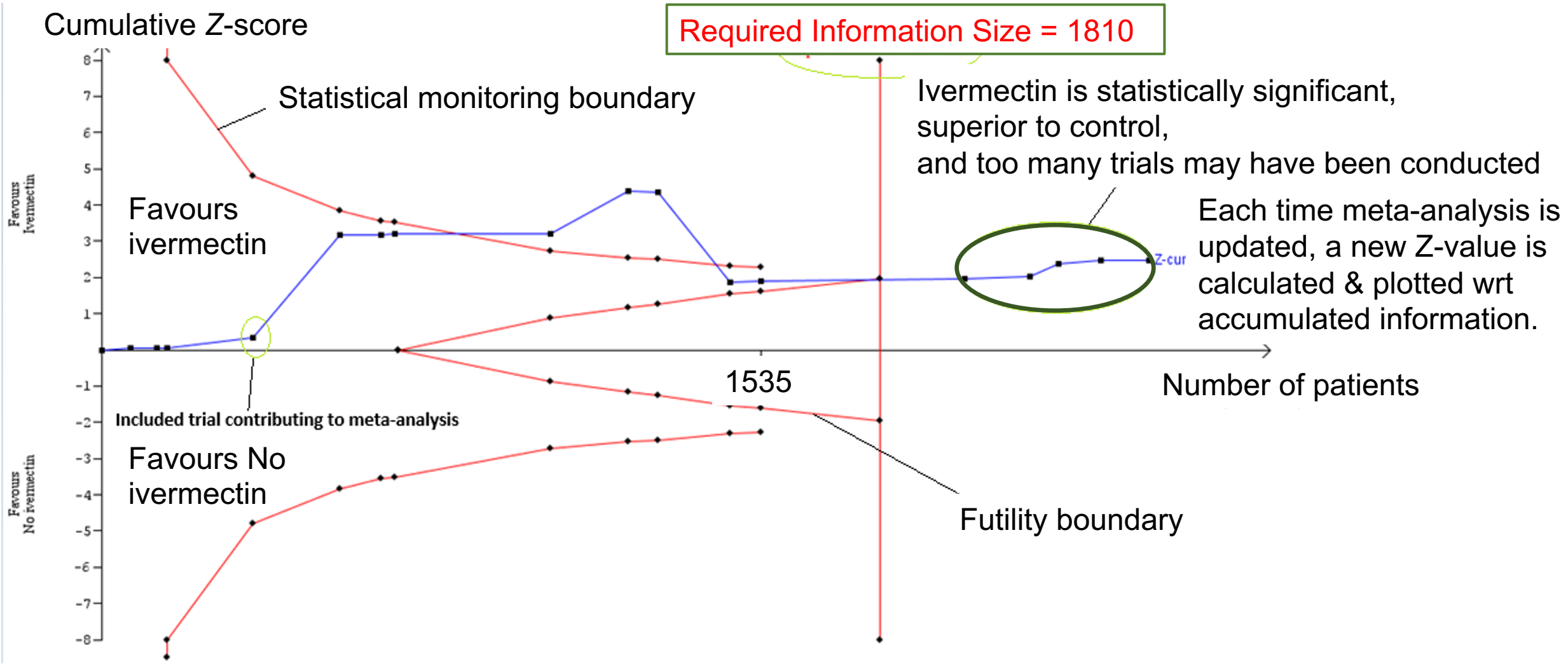
#8 out of 18,867,401 papers (13 Sept)

Headline outcome: mortality

- 62% reduction in mortality (by Risk Ratio)
- By GRADE of evidence *and* Trail Sequential Analysis (TSA) reported “Moderate” certainty
- Inverse variance, random effects model for meta-analysis
- Other Outcomes in paper

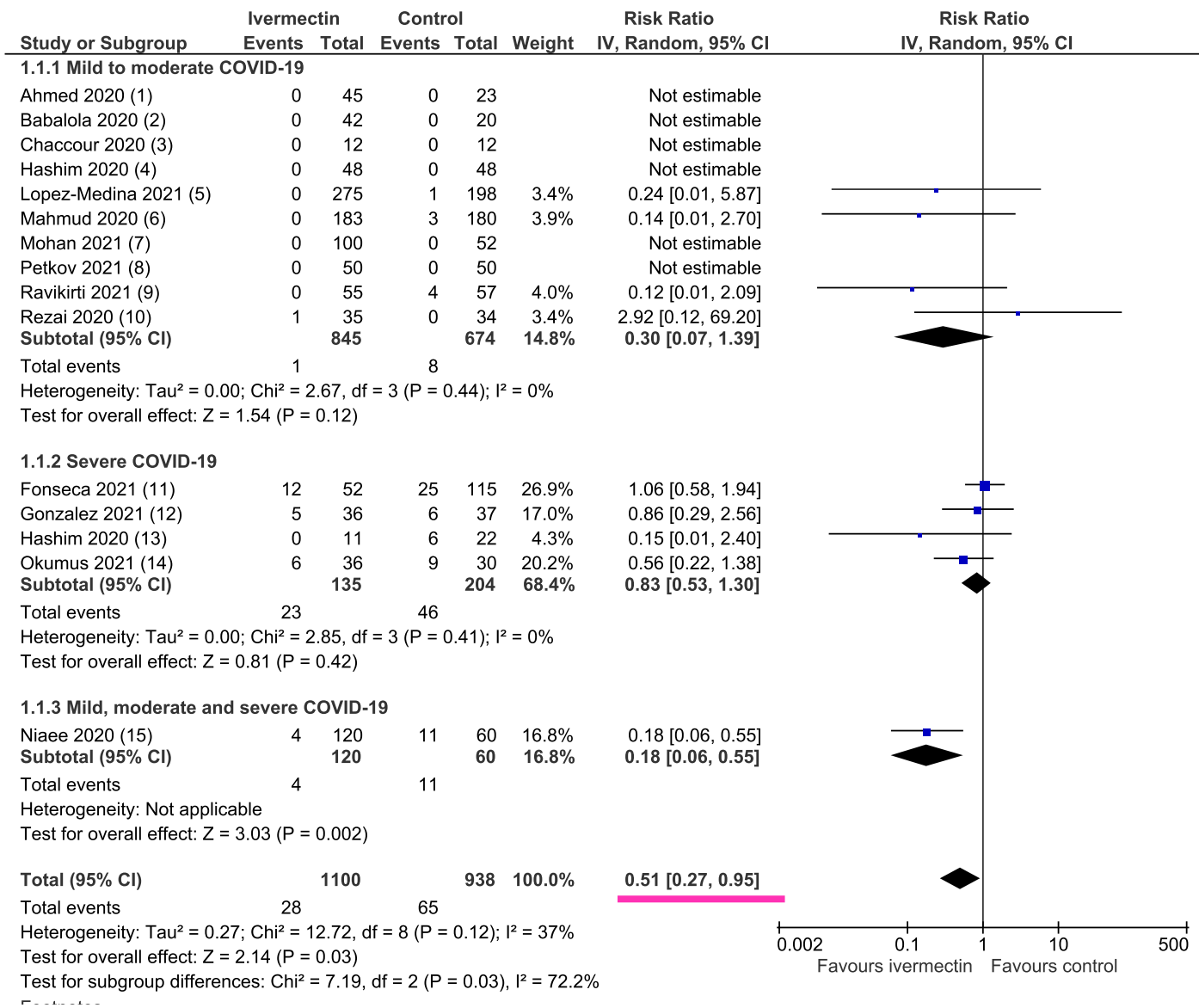


Trial Sequential Analysis



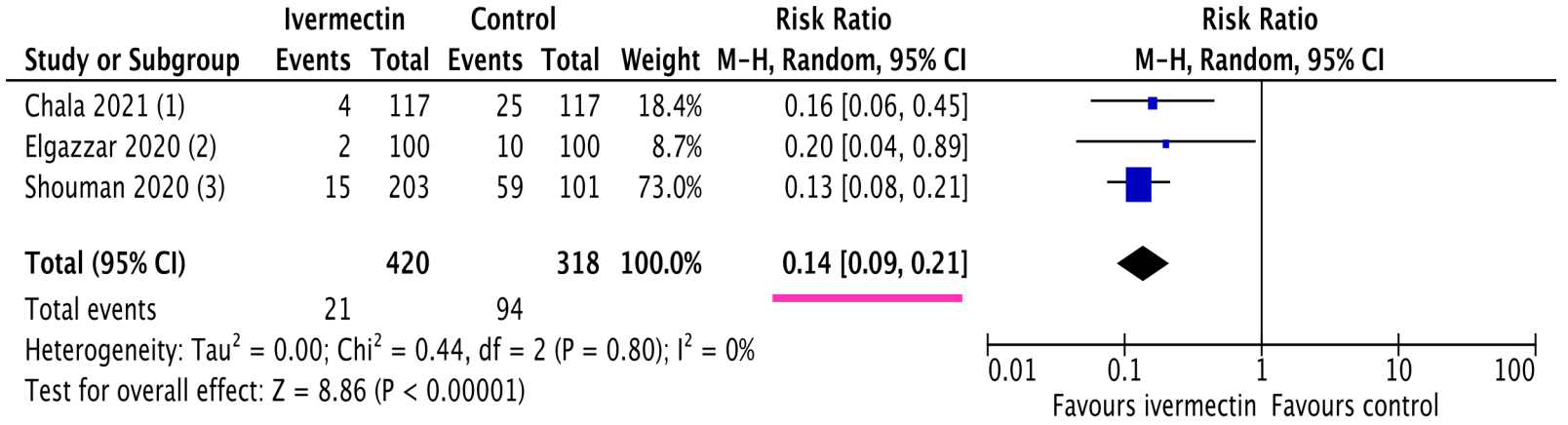
Sensitivity: removing a disputed trial

- Accusation of fraud (denied) against Prof Elgazzar
- Removal of Elgazzar changes headline mortality advantage to 49% improvement but does not remove it
- Review will be updated



prophylaxis outcome

- Powerful reduction in Risk of infection in prophylaxis
- Excluding disputed trial makes no difference …
- results consistent with observational trials



Study or Subgroup	Ivermectin Events	Ivermectin Total	Control Events	Control 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)

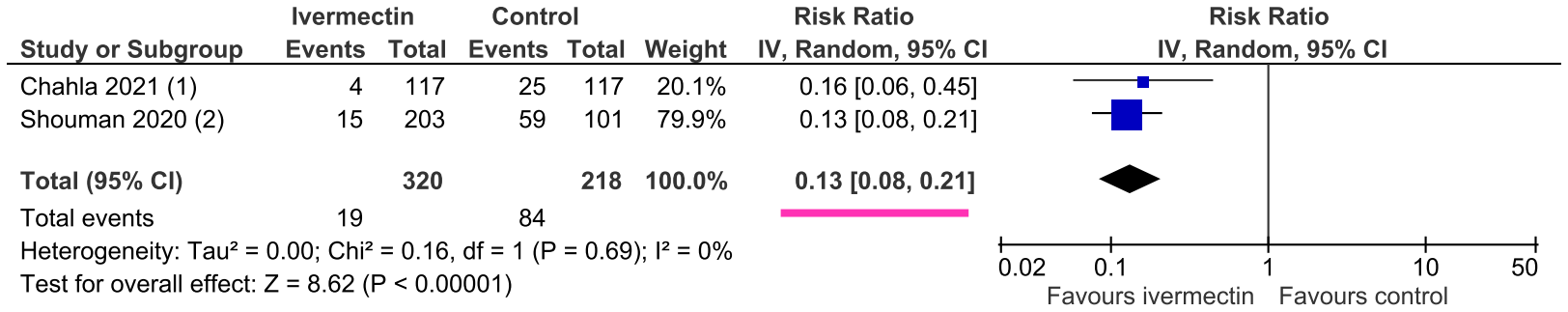
Footnotes

(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

86% reduction in Risk of infection



Study or Subgroup	Ivermectin Events	Ivermectin Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Chahla 2021 (1)	4	117	25	117	20.1%	0.16 [0.06, 0.45]
Shouman 2020 (2)	15	203	59	101	79.9%	0.13 [0.08, 0.21]
Total (95% CI)		**320**		**218**	**100.0%**	**0.13 [0.08, 0.21]**
Total events	19		84			

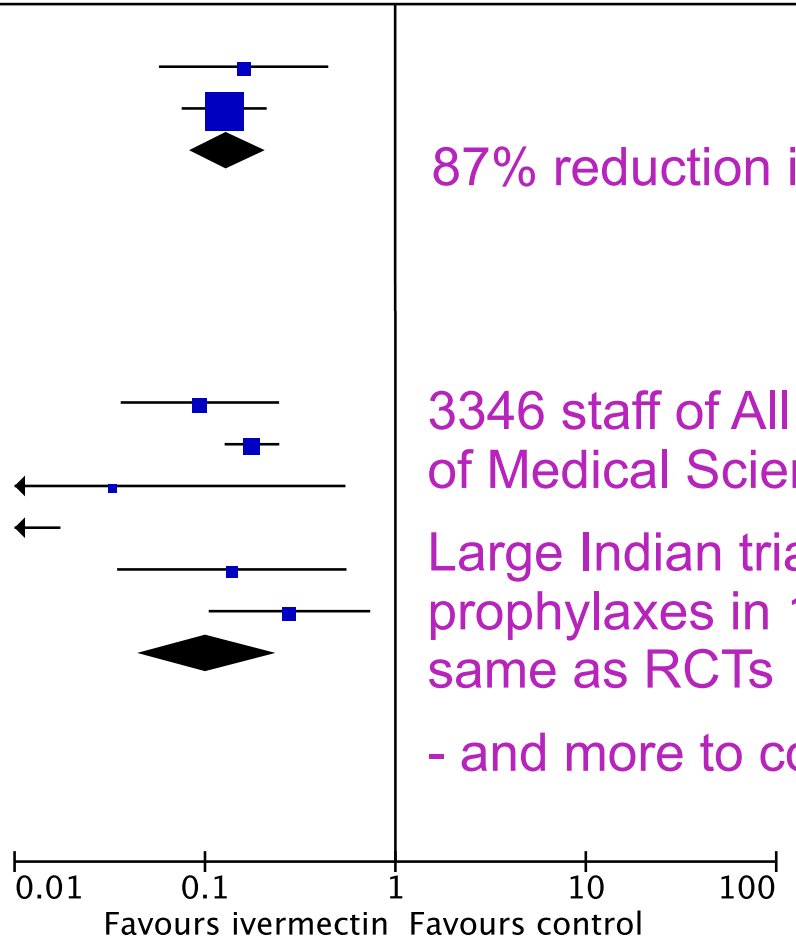
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.16$, df = 1 (P = 0.69); $I^2 = 0\%$

Test for overall effect: Z = 8.62 (P < 0.00001)

Exclusion of Elgazzar makes little change – in fact improves point estimate

multiple prophylaxis trials show strong effect

Study or Subgroup	Ivermectin Events	Ivermectin Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
3.1.1 Randomized Trials (RCTs)						
Chahla 2021	4	117	25	117	20.1%	0.16 [0.06, 0.45]
Shouman 2020	15	203	59	101	79.9%	0.13 [0.08, 0.21]
Subtotal (95% CI)		**320**		**218**	**100.0%**	**0.13 [0.08, 0.21]**
Total events	19		84			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.16$, df = 1 (P = 0.69); $I^2 = 0\%$						
Test for overall effect: Z = 8.62 (P < 0.00001)						
3.1.2 Observational Trials (OCTs)						
Alam 2020b	4	58	44	60	21.2%	0.09 [0.04, 0.25]
Behera 2021	45	2199	133	1147	28.2%	0.18 [0.13, 0.25]
Carvallo 2020b	0	131	11	98	6.7%	0.03 [0.00, 0.55]
Carvallo 2020b	0	788	237	407	6.9%	0.00 [0.00, 0.02]
Mondal 2021	2	154	126	1342	16.2%	0.14 [0.03, 0.55]
Morgenstern 2021	5	271	18	271	20.9%	0.28 [0.10, 0.74]
Subtotal (95% CI)		**3601**		**3325**	**100.0%**	**0.10 [0.04, 0.24]**
Total events	56		569			
Heterogeneity: $Tau^2 = 0.61$; $Chi^2 = 16.46$, df = 5 (P = 0.006); $I^2 = 70\%$						
Test for overall effect: Z = 5.37 (P < 0.00001)						



87% reduction in infection Risk

3346 staff of All India Institute of Medical Sciences agree

Large Indian trial of different prophylaxes in 1496 HCWs – same as RCTs

- and more to come …

a unique study in household contacts

Shouman et al NCT04422561 (RCT)
J Clin Diag Res (2021) **15**(2) OC27-OC32

	index cases	Infected contacts	total contacts	average household
Control	24	59	101	5.2
Ivermectin	52	15	203	4.9
			304	

confirmed cases — *Household members falling sick* — *all contacts*

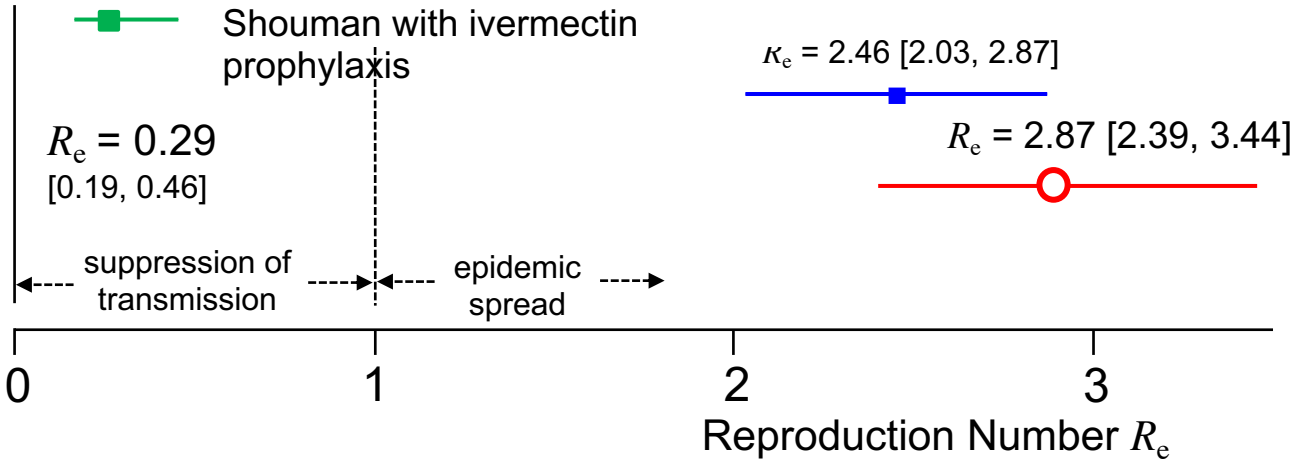
$p = 10^{-22}$

Ivermectin prophylaxis kills off onward transmission

$$R_e = \frac{new\ infections}{index\ cases}$$

The Reproduction Number

95% Confidence Intervals after Clopper & Pearson (1934) *Biometrika*, **26,** 404



κ_e = 2.46 [2.03, 2.87]

R_e = 2.87 [2.39, 3.44]

Shouman w/o prophylaxis

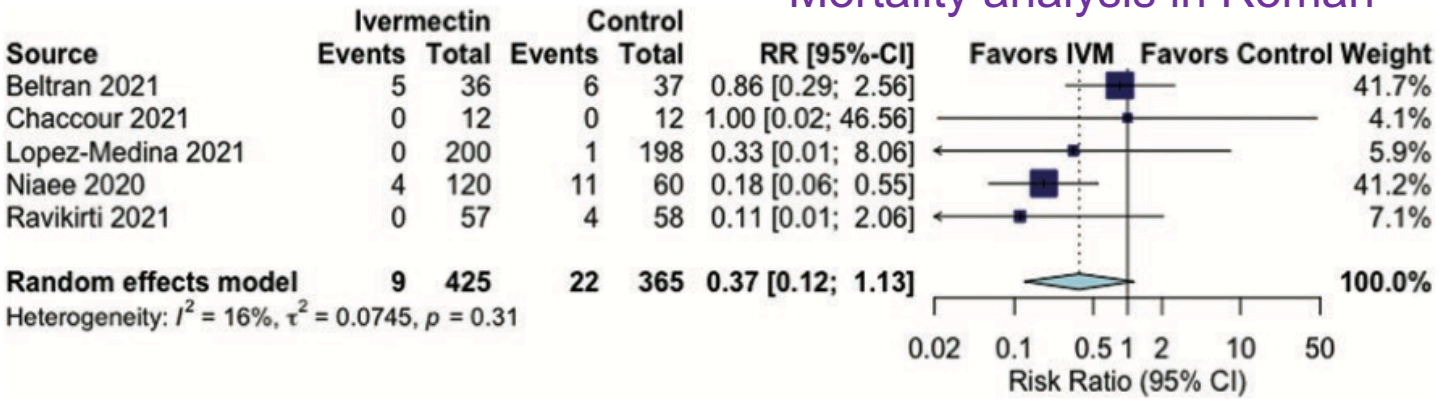
SARS-CoV-2 infectivity: meta-analysis of all literature

Billah *et al.* (2020) *PLoS ONE* doi: 10.1371/journal.pone.0242128

controversies

- Attack by Roman *et al.* (*Clin. Infect. Dis.*)
- Elgazzar dispute – effect shown, updates published
- A recent Cochrane Review by Popp *et al.*

Mortality analysis in Roman



conclude no effect of ivermectin – in defiance of the evidence showing 63% reduction in mortality …

Bryant *et al.* (2021) *Am. J. Therapeutics* **28**, e573-e576

Popp *et al. Cochrane Database Sys. Revs.* **7**
Many rejections of trials using “unapproved” drugs
Rejection of active comparators inconsistent
Fragmentation by location of treatment
Few meta-analyses: single studies for most comparisons
Mortality: from 185 patients in 2 studies “we don’t know”

Bayesian approaches

Neil, M & Fenton, N (2021)
Am. J. Therapeutics. **28**(5):e576-e579

- Probability that mortality depends on *both* severity *and* (ivermectin) treatment: **> 99 %**
- Full distributions for Risk Ratio and Risk Difference
- Even after removing Elgazzar *and* Niaee, sensitivity analysis still supports hypothesis of mortality benefit with 77% probability

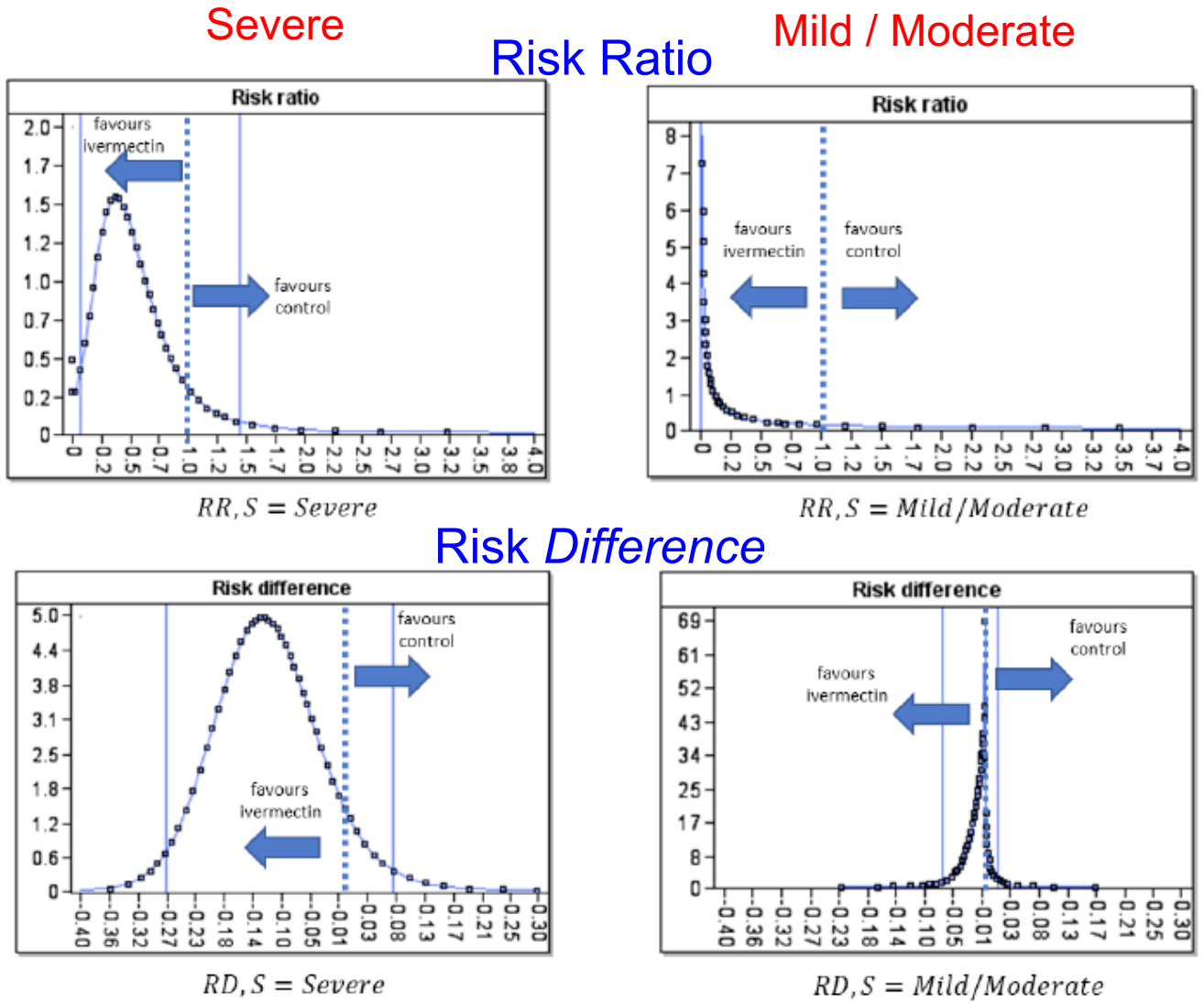


Figure 3: Posterior marginal probability distributions for RR and RD from meta-analysis

experience-based medicine

- 600 µg/kg loading dose
- 400 µg/kg × 10 days
- + doxycycline, zinc & nebulised nano-silver (Ag)

Dr Jackie Stone MB ChB BSc MRCP FRACGP DAvMed FACASM
Harare, Zimbabwe (outpatients)

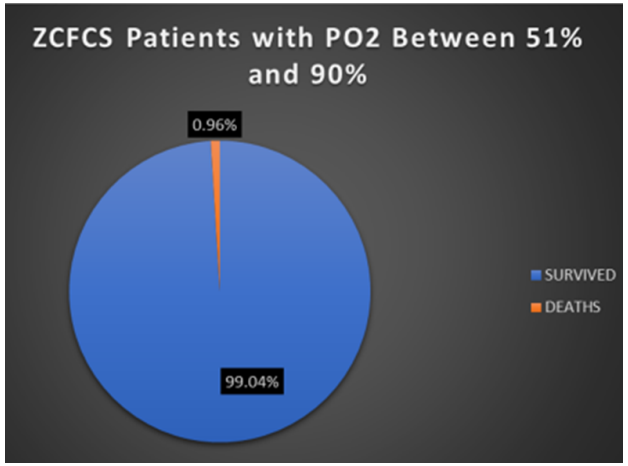
Prof Nathi Mdladla (South Africa, ICU chief George Mukhari Hospital, intensivist managing 60 beds, 26 ICU)

Moderate to Severe patients pO_2 51-90%

Mortality 1/104 < 1%

cf 35% state hospital

95% stay at home



(International Covid Symposium, Rome, 13 Sept 2021)

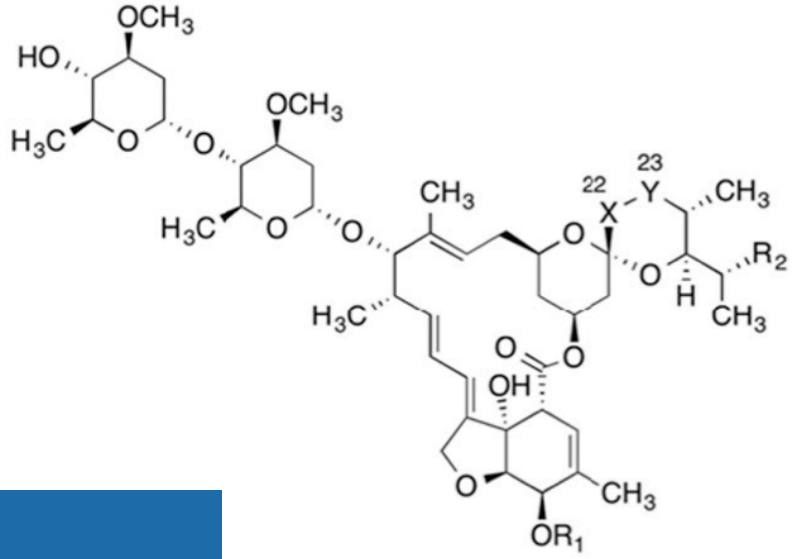
" The question is no longer whether it works: it is at what dose & in what combinations "

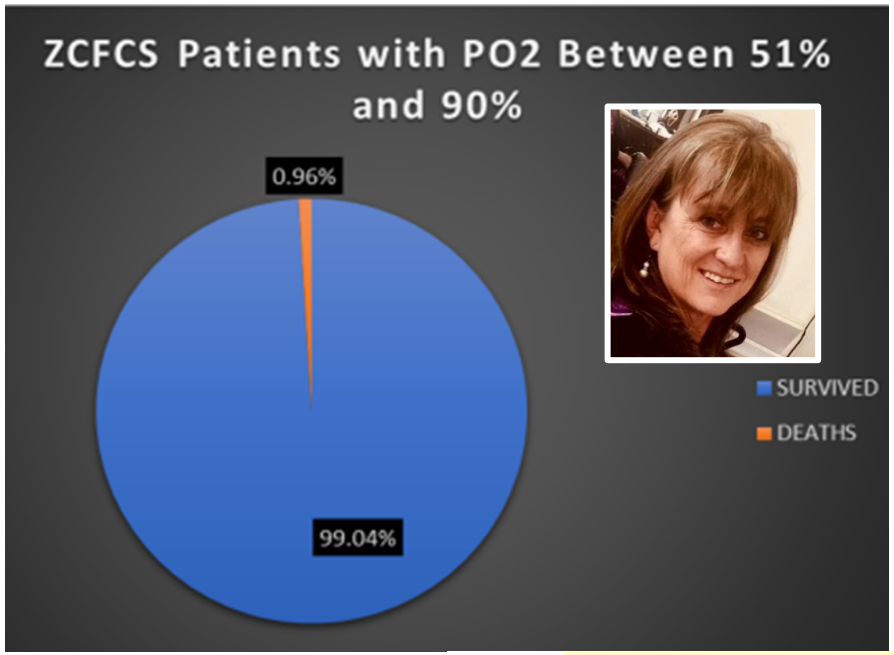
17 July 2021 presentation to Malaysian Alliance For Effective Covid Control MAECC

conclusions

- an exceptionally safe medicine of negligible cost
- known anti-viral action; multiple candidate mechanisms
- Extensive clinical experience in USA, Peru, India, Zimbabwe – especially outpatient & prophylaxis
- *“ The question is no longer whether it works: it is at what dose & in what combinations ”*
- Meta-analyses of controlled trials important for quantitative metrics, but not the totality of the evidence base

Thank you for your attention





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WHO's `Vigiaccess.org` at 24 June 2021

- Independent expert safety reviews:

Jacques Descotes MD, PharmD, PhD
Professor Emeritus, Claude Bernard University of Lyon
Fellow, US Academy of Toxicological Sciences
Eurotox Registered Toxicologist

ImmunoSafe

Ivermectin Safety Endorsement
by Prof Christopher J M Whitty,
Chief Medical Officer for England:

Effect of Ivermectin on *Anopheles gambiae* Mosquitoes Fed on Humans: The Potential of Oral Insecticides in Malaria Control

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