Causality inference with the Bradford Hill Criteria: The case of the Stone/Gill treatment protocol for COVID-19

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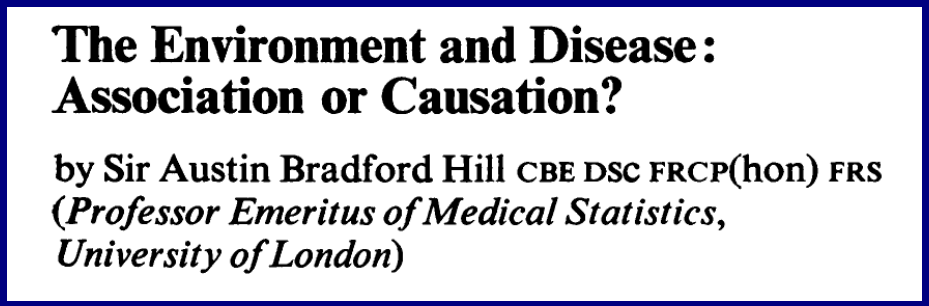
Publications

- The work is presented in detailed in a preprint which is currently available online:
  1. E. Gkioulekas, P.A. McCullough, C. Aldous: "Critical appraisal of multi-drug therapy in the ambulatory management of patients with COVID-19 and hypoxemia. Part I. Evidence supporting the strength of association", preprint
  2. E. Gkioulekas, P.A. McCullough, C. Aldous: "Critical appraisal of multi-drug therapy in the ambulatory management of patients with COVID-19 and hypoxemia. Part II: Causal inference using the Bradford Hill criteria", preprint
- Papers on the Bradford Hill criteria
  1. A.B. Hill. "The Environment and Disease: Association or Causation?", Proc R Soc Med. 58(5) (1965), 295-300.
  2. J. Howick, P. Glasziou, J.K. Aronson, "The evolution of evidence hierarchies: what can Bradford Hill's 'guidelines for causation' contribute?", Journal of the Royal Society of Medicine 102(5) (2009), 186-194.
  3. A.C. Ward, "The role of causal criteria in causal inferences: Bradford Hill's 'aspects of association'", Epidemiologic Perspectives & Innovations 6 (2009), 2.
- Stone case series
  1. J.C. Stone, P. Ndarukwa, D.E. Scheim, BM Dancis, J. Dancis, M.G.Gill, C. Aldous, "Changes in SpO2 on Room Air for 34 Severe COVID-19 Patients after Ivermectin-Based Combination Treatment: 62% Normalization within 24 Hours", *Biologics*. 2022 **2(3)** (2022), 196-210.
- We have used a case series threshold analysis technique to compare the case series against external/historical control groups:
  1. E. Gkioulekas, P.A. McCullough, V. Zelenko: "Statistical analysis methods applied to early outpatient COVID-19 treatment case series data", *COVID* 2(8) (2022), 1139-1182

Bradford Hill criteria for causal inference

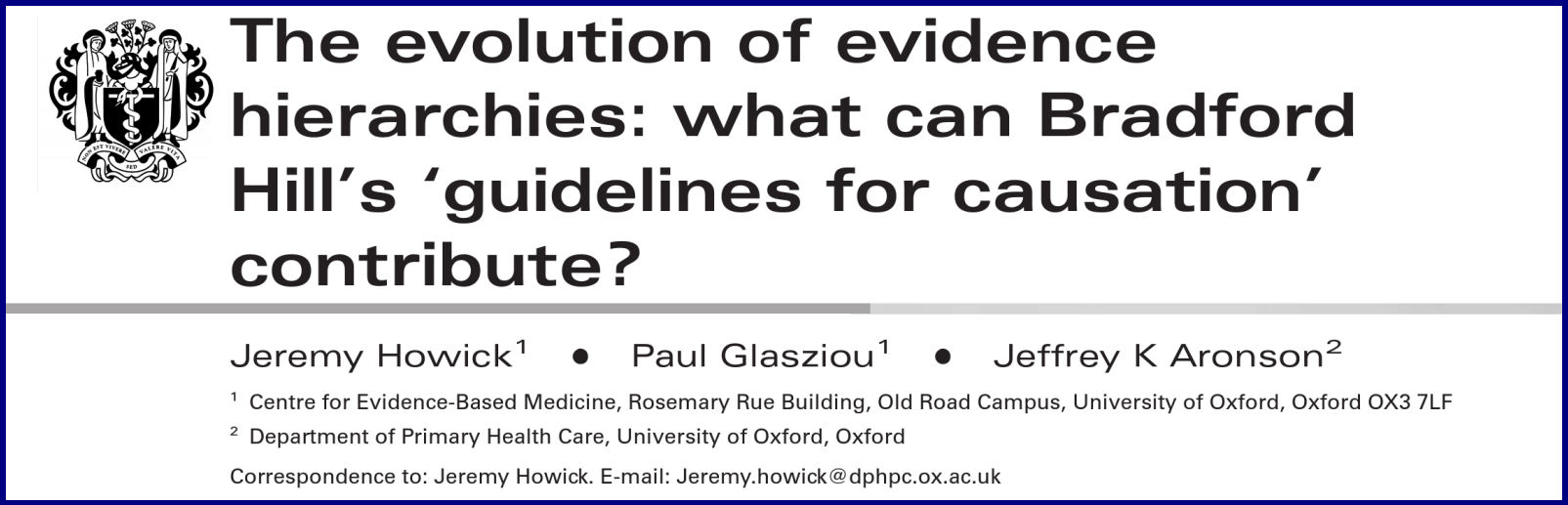


The Environment and Disease: Association or Causation?

by Sir Austin Bradford Hill CBE DSC FRCP(hon) FRS
(*Professor Emeritus of Medical Statistics, University of London*)

- The Bradford Hill criteria for a causal inference were introduced informally by Sir Austin Bradford Hill in 1965 in a paper published on the *Proceedings of the Royal Society of Medicine.*
- **The question of the day was:** *is smoking a cause of lung cancer?*
- **The problem:** *Association alone does not prove a causal relation.* For example: we may observe that coffee drinking is associated with lung cancer. However, the reason for the association could be that a large proportion of coffee drinkers are also smokers, and it is the smoking that causes the effect and not the coffee.
- Bradford Hill proposed the following criteria: *strength of association, consistency, specificity, temporality, biological gradient, biological plausibility, coherence, experiment, analogy.*
- The criteria were introduced in the context of an argument in favor of the causal relation between smoking and lung cancer.
- Some believe that randomized controlled trials (RCTs) are the only way one can establish causality. However, as a counter-example, we know that parachutes are effective in reducing mortality risk when someone jumps out of an airplane, without an RCT. *How do we know?*
- Easy exercise to apply Bradford Hill criteria on the parachute problem.

Howick's refinement of the Bradford Hill criteria. I



The evolution of evidence hierarchies: what can Bradford Hill's 'guidelines for causation' contribute?

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- In 2009 Howick proposed a refinement of the Bradford Hill criteria in which they were reorganized in three categories of evidence.
  1. *Direct evidence:* the association may be causal.
  2. *Mechanistic evidence:* there is a plausible causal chain that allows us to anticipate the causal relation between intervention and outcome.
  3. *Parallel evidence:* there is further support for the causal relation from similar epidemiological studies.
- Direct evidence play the decisive role for establishing causality whereas mechanistic and parallel evidence play only supporting roles to bolster our confidence in the existence of a causal relation.
- Howick proposed several examples of causal associations where the Bradford Hill criteria deliver a verdict of strong evidence for causation even without an RCT.

Howick's refinement of the Bradford Hill criteria. II

Bradford Hill criterion/guideline		
Original designation	**Renamed designation**	**Description**
Direct evidence		
strength of association	size of effect	Epidemiological or experimental studies showing that the strength of association between intervention and outcome exceeds the combined effect of plausible confounders.
temporality	temporal and/or spatial proximity	A favorable response to the intervention follows shortly after the intervention. Shorter temporal proximity makes it less likely that confounding has occurred. This evidence is further strengthened when the favorable response reverses, when the intervention is withdrawn, and resumes, when the intervention is repeated (challenge and rechallenge). Howick extended temporality to include spatial proximity in addition to temporal proximity.
biological gradient	dose responsiveness	The outcome changes when the intensity of the intervention is increased. We have interpreted this to include both an increase in dose/duration of a medication and an expansion of a treatment protocol with additional medications.
Mechanistic evidence		
biological plausibility	plausible mechanism	Evidence of one or more complete causal link chains that connect the intervention with the purported outcome. Howick broadened this criterion to encompass both biological and non-biological mechanisms of action.
coherence	coherence	The causal hypothesis between intervention and outcome should be coherent with what is known from non-epidemiological studies about the intervention and the underlying condition treated. Included in this category are non-epidemiological studies that corroborate one part of the causal chain between the intervention and outcome, as opposed to corroborating the complete causal chain.
Parallel evidence		
consistency	replicability	Epidemiological studies that replicate the relationship between similar interventions and similar outcomes in similar populations. Replicability reduces the likelihood that the results can be attributed to selection bias.
analogy	similarity	Epidemiological studies that consider the relationship between interventions and outcomes where the intervention may differ either in its details (e.g. dosage, duration, addition or removal of medications) or its circumstances (e.g. different patient demographics, low vs high risk patients, early or late administration of treatment). Causal hypothesis is strongly supported when parallel studies agree on the outcomes, however it is also supported when the pattern of agreement and disagreement on the outcomes is coherent and can be explained.

Stone case series

biologics

MDPI

Article

Changes in SpO2 on Room Air for 34 Severe COVID-19 Patients after Ivermectin-Based Combination Treatment: 62% Normalization within 24 Hours

Jaqueline C. Stone [1], Pisirai Ndarukwa [2,3], David E. Scheim [4,*], Barry M. Dancis [5], Jerome Dancis [6], Martin G. Gill [7] and Colleen Aldous [8]

- 34 patient case series: 28 patients with baseline room air SpO2 $\leq$ 90%. All patients with baseline room air SpO2 $\leq$ 93%
- Between August 2020 and May 2021
- Three 10-day multidrug protocols for *mild disease*, *severe disease*, *salvage protocol*, that combined ivermectin, nanosilver nebulizations, doxycycline, zinc, vitamin C, vitamin D.
- Optional use of prednisone, enoxaparin, rivaroxaban, ceftriaxone, azithromycin, aspirin.
- Rule of thumb: Duration of ivermectin treatment and nanosilver nebulizations was continued for 48 hours after the resolution of symptoms.
- Availability of supplemental oxygen very limited
- 0 deaths and 0 hospitalizations; no supplemental oxygen.

Stone/Gill protocol used in Zimbabwe for in-person treatment

- *Initial treatment by trained nurses:* Administered, if baseline room air SpO2 $>$ 80%, not tachypneic, tachycardic, or confused (otherwise the *salvage protocol* is used). Initial administration of nanosilver nebulization 5-8 ml. Patient was then canulated. During canulation:
  1. Draw blood for bloodwork;
  2. Administer ivermectin at minimum dose 0.2mg/kg (increased to 0.6mg/kg during Delta);
  3. If patient is hypoxic, febrile, or systemically unwell: IV ceftriaxone 1g and either dexamethasone 8 mg stat or hydrocortisone 100-200 mg stat, as clinically indicated;
  4. Diabetes management, if needed.
- *Baseline protocol for mild disease:* ivermectin at 0.1-0.2 mg/kg on day 1, day 4, day 8; nanosilver nebulizations 5-8ml three times daily for 5-7 days; doxycycline 100 mg twice a day for 10 days, zinc 60mg per day for 10 days; vitamin C 1g three times daily and vitamin D 5000-10000 IU daily for 10 days. Ivermectin dose increased to 12 mg once a day for 5-7 days in December 2020 and later to 0.4-0.6 mg/kg for 5-7 days by July 2021, and was given for up to 48 hours after resolution of symptoms.
- *Additional medications:*
  1. If patient is hypoxic and CRP$>$ 20, then prednisone 40mg-60mg daily is added.
  2. If D-Dimer is raised, subcutaneous Enoxaparin at 80mg-100mg is administered followed by Rivaroxaban/Xarelto at 20mg daily for 30 days.
  3. If neutrophils are raised and the patient is canulated, ceftriaxone at 1g daily is given until oral treatment is considered adequate. Oral treatment replaces ceftriaxone with either doxycycline 100 mg twice a day for 10 days or azithromycin 500 mg twice a day and then 500 mg once a day for 5 days. Both are used, when coinfection with mycoplasma cannot be excluded.

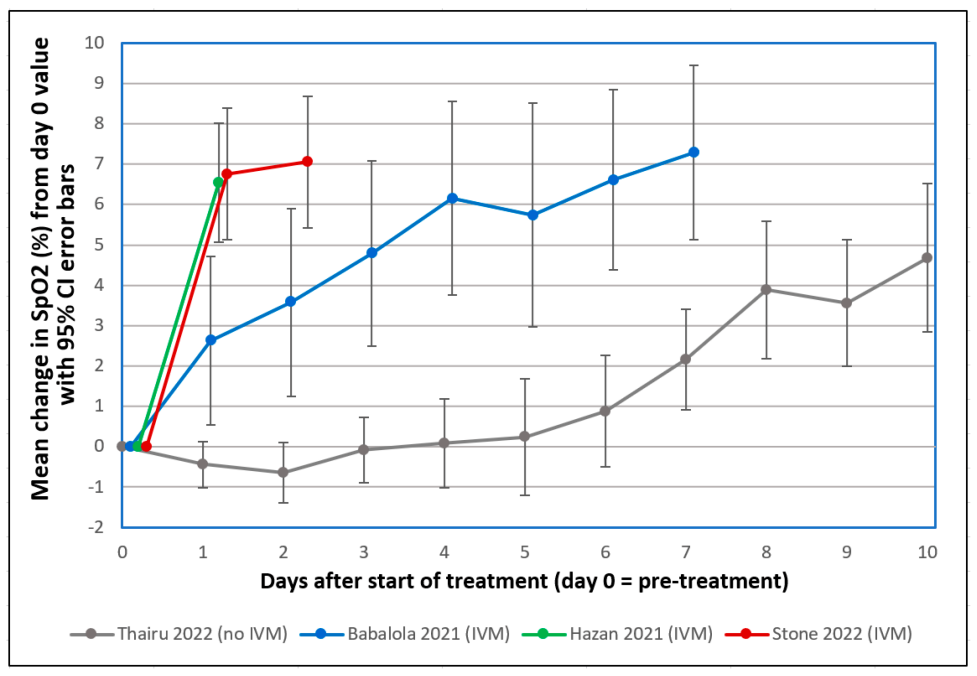
Stone/Gill protocol: severe disease

- *Criteria for baseline protocol for severe disease*: If any of the following were present:
  1. The Lymphocyte to LDH ratio was over 210
  2. The D-Dimer was raised
  3. The CRP was raised
  4. The patient was in stage 3 (thrombosis) of the disease as per McCullough's definitions.
- *Baseline protocol for severe disease:*
  1. ivermectin 0.2mg to 0.3mg/kg daily for 5 days, during the Beta wave and 0.4-0.6 mg/kg during the delta wave for 10 days
  2. silver nebulizations 5-8ml at least three times per day and continuously as needed when room air SpO2 $\leq$ 90%
  3. doxycycline 100mg twice daily for 10 days
  4. zinc 20mg twice daily for 10 days; vitamin C 1g three times daily and vitamin D 5000-10000 IU daily for 10 days.
- *Additional medications:*
  1. If patient is hypoxic and CRP$>$ 20, then prednisone 40mg-60mg daily is added.
  2. If D-Dimer is raised, subcutaneous Enoxaparin at 80mg-100mg is administered followed by Rivaroxaban/Xarelto at 20mg daily for 30 days.
  3. If neutrophils are raised and the patient is canulated, ceftriaxone at 1g daily is given until oral treatment is considered adequate. Oral treatment replaces ceftriaxone with either doxycycline 100 mg twice a day for 10 days or azithromycin 500 mg twice a day and then 500 mg once a day for 5 days. Both are used, when coinfection with mycoplasma cannot be excluded.

Stone/Gill protocol: salvage protocol

- *Criteria for using the salvage protocol:* At least one of the following:
  1. Patient is not ambulant
  2. Tachypneic with rate over 22 per minute or slow respiratory rate from exhaustion
  3. Confusion or decreased/loss of consciousness
  4. Symptomatic for longer than 10 days and elevated pulse rate and/or above-mentioned symptoms.
  5. Significantly hypoxic with baseline room air SpO2 $\leq$ 80%.
- *Salvage protocol:* If initial assessment indicates poor prognosis and likely need for hospital referral, the following protocol is attempted:
  1. ivermectin 0.6mg/kg stat dose, may titrate to effect up to 1-2mg/kg if SpO2 does not increase, maintain at 0.3-0.6 mg/kg for up to 10 days until symptom free for 48 hours.
  2. continuous nanosilver nebulizations, until room air SpO2 $\geq$ 90%, then reduce to three nebulizations per day.
  3. doxycycline 200 mg stat, then 100 mg for a minimum of 5 days (increased to 10 days during Delta) OR IV ceftriaxone 1-2 gr daily if unable to take oral meds.
  4. zinc sulfate 20-40 mg three times daily orally.
  5. aspirin 300 mg daily.
  6. prednisone 1mg/kg or dexamethasone 8mg IV stat, followed by prednisolone 40-80mg once daily, if CRP $>$ 20 or room air SpO2 $\leq$ 80%.
  7. enoxaparin 80mg subcutaneously once daily transitioning to rivaroxaban 20 mg once daily if the D Dimer is raised for at least 30 days or longer if D Dimer has not come down.
  8. Midazolam (only if confused and pulling out lines or pulling off oxygen).
- If the patient responds to treatment, regular protocol follows. If the patient does not respond to treatment, referral to hospital is arranged, or palliative support is provided at home, if hospital beds not available, as a last resort.

Temporality, Biological gradient, Consistency,



- Mean change to room air SpO2 levels from initial value at Day 0 for the Stone case series and for other patients treated similarly in the United States and Nigeria with baseline room air SpO2 $\leq$ 93%.
- *Direct Evidence–Temporality:* Rapid response to treatment
- *Direct Evidence–Biological gradient:* Strongest response observed with the most aggressive protocols (Stone and Hazan). Slower response with Babalola (no doxycycline, no variable ivermectin dose, 5-day instead of 10-day protocol)
- *Parallel Evidence–Consistency/Replicability:* Similar effect in patients from Zimbabwe, United States, and Nigeria.

Case series threshold analysis method.


COVID

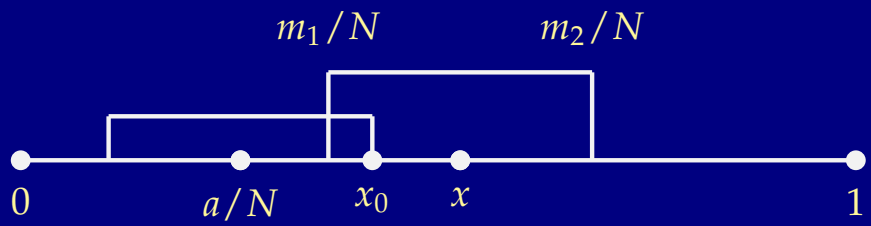
MDPI

Article

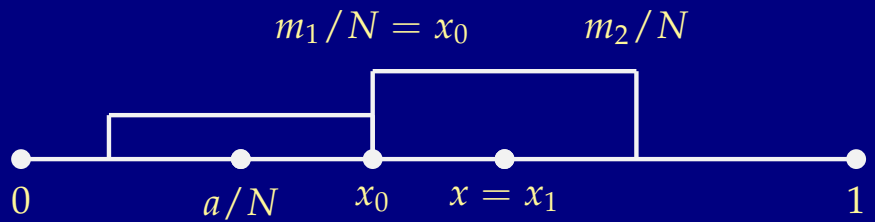
Statistical Analysis Methods Applied to Early Outpatient COVID-19 Treatment Case Series Data

Eleftherios Gkioulekas [1,*], Peter A. McCullough [2] and Vladimir Zelenko [3,†]

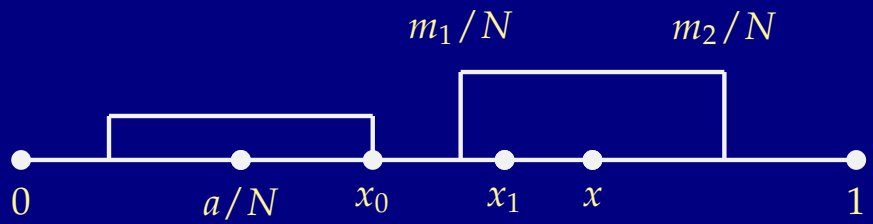
- **Preponderance of the evidence**



- **Crossover to clear and convincing**



- **Clear and convincing**



- Efficacy threshold x_0 may be increased to adjusted efficacy threshold y_0 to control a Bayesian factor. Then y_0 is used to obtain x_1.

Strength of association: Hospitalization rate reduction

	Patients with baseline SpO2					
Case series	$\leq 100\%$	$\leq 93\%$	$\leq 90\%$ (p_1)	**Deaths**	**Deterioration**	**Time Period**
Stone	34	34	28 (82.3%)	0	0	2020-08 to 2021-05

- To investigate the existence of some ***hospitalization rate reduction***:
  - Assume that at least all patients with SpO2 $\leq 90\%$ would have been hospitalized if one followed standard guidelines
  - Simplified self-control method: the same case series is used both as a treatment and control group
  - As treatment group: use of supplemental oxygen or ventilation are counted as hospitalization events
  - As self-control: all patients with SpO2 $\leq 90\%$ are counted as counterfactual hospitalization events
- **Self-controlled Exact Fisher test comparisons**

Case series	(N, a)	(N, b)	**OR (95% CI)**	p**-value**
Stone	(34, 0)	(34, 28)	0 (0 – 0.04)	10^{-13}

- **Hospitalization rate reduction thresholds using 95% confidence intervals**

Case series (SpO2 $\leq 100\%$)	(N, a)	x_0	$\log_{10} B$	p_2	y_0	x_1
Stone	(34, 0)	9.9%	2.98	82.3%	9.9%	27.7%

- $p_1 > x_1 \implies$ **clear and convincing** hospitalization rate reduction

External control for hospitalized CFR: World Heart Federation

Cardiovascular Risk Factors and Clinical Outcomes among Patients Hospitalized with COVID-19: Findings from the World Heart Federation COVID-19 Study

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DIMPLE KONDAL
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FAUSTO PINTO
PABLO PEREL
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ON BEHALF OF THE WHF COVID-19 STUDY COLLABORATORS

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- World Heart Federation: 5313 consecutive patients prospectively recruited between June 2020 and September 2021 from 40 hospitals across 23 different countries.
- 15.08% Global hospitalized CFR
- 19.48% LMIC hospitalized CFR

External controls for hospitalized CFR: Zimbabwe

- **External control: Mashonaland Province, Zimbabwe**


Factors associated with COVID-19 fatality among patients admitted in Mashonaland West Province, Zimbabwe 2020-2022: a secondary data analysis

Kudzai Madamombe, Gerald Shambira, Gift Masoja, Tapiwa Dhliwayo, Tsitsi Patience Juru, Notion Tafara Gombe, Addmore Chadambuka, Mujinga Karakadzai, Mufuta Tshimanga

- **External control: South Africa**


Difference in mortality among individuals admitted to hospital with COVID-19 during the first and second waves in South Africa: a cohort study

Waasila Jassat, Caroline Mudara, Lovelyn Ozougwu, Stefano Tempia, Lucille Blumberg, Mary-Ann Davies, Yogan Pillay, Terence Carter, Ramphelane Morewane, Milani Wolmarans, Anne von Gottberg, Jinal N Bhiman, Sibongile Walaza, Cheryl Cohen, DATCOV author group

Location	Timing	Cases	Died	CFR
CFR for confirmed hospitalizations over all age groups				
South Africa (first wave)	2020-03 to 2020-08	83742	17042	20.35%
South Africa (beta)	2020-09 to 2021-03	135472	33999	25.1%
South Africa (combined)	2020-03 to 2021-03	219214	51041	23.28%
Zimbabwe (Parirenyatwa hospitals)	2020-06 to 2020-12	336	119	35.42%
Zimbabwe (Mashonaland West Province)	2020-04 to 2022-04	673	157	23.33%
World Heart Federation study (LMIC)	2020-06 to 2021-09	2526	492	19.48%

Mortality rate reduction: Stone case series

- **Exact Fisher test comparisons with external controls**

External control	(N, a)	(M, b)	OR (95% CI)	p-value
Stone case series compared with				
Zimbabwe (Parirenyatwa hospitals)	(28, 0)	(336, 119)	0 (0 – 0.26)	10^{-5}
Zimbabwe (Masholand West Province)	(28, 0)	(673, 157)	0 (0 – 0.47)	10^{-4}
South Africa (beta)	(28, 0)	(135472, 33999)	0 (0 – 0.42)	10^{-4}
South Africa (combined)	(28, 0)	(219214, 51041)	0 (0 – 0.46)	0.001
World Heart Federation study (LMIC)	(28, 0)	(2526, 492)	0 (0 – 0.58)	0.003

- **Case series threshold analysis**

Mortality rate reduction thresholds using 95% confidence intervals						
Case series (SpO2 $\leq$ 90%)	(N, a)	x_0	$\log_{10} B$	p_2	y_0	x_1
Stone	(28, 0)	12.0%	2.13	23.3%	12.0%	32.0%

- Mortality rate reduction established by the **preponderance of evidence** because:
  1. External control hospitalized CFR $\geq$ 20%
  2. Adjusted efficacy threshold $y_0 = 12.0\%$
  3. Random selection bias threshold $x_1 = 32.0\%$

Mechanistic Evidence

- **Biological Plausibility**
  1. *ivermectin:* several anti-inflammatory mechanisms, prevents virus binding to cells, prevents entry of viral proteins to cell nucleus, reverses red blood cell microclotting.
  2. *nebulized nanosilver:* coat the virus and prevent viral entry to cells; have anticoagulant mechanisms and dissolve red cell blood microclots; prevent viral particles from forming new micro-clots
  3. *doxycycline:* several anti-inflammatory mechanisms, different antiviral mechanisms
  4. *ivermectin + zinc, doxycycline + zinc:* both ivermectin and doxycycline allow zinc ions to enter the cells, which then inhibit viral replication via the RDRP viral enzyme.
  5. *zinc:* by itself, anti-inflammatory mechanisms, enhances mucosal immunity
  6. *vitamin D:* anti-inflammatory mechanisms; prevents immune dysregulation
  7. *vitamin C:* enhances immune response to the virus while reducing inflammation; prevents depletion of vitamin C levels during illness.
- **Coherence**
  1. Scheim 2022: Oxygen desaturation caused by red blood cell microclots in the lungs mediated by glycan bindings between glycans on viral spike protein and sialoglycoproteins on the red blood cell surface. Common cold viruses express a protein that dissolves these bindings
  2. Boschi *et al.*2022: spike protein causes red cell microclots in vitro; ivermectin prevents the formation of microclots when added before spike protein and reverses the microclots when added afterwards
  3. Jeremiah 2020: In vitro experiment silver nanoparticles with size 2-15 nm prevent SARS-CoV-2 entry to cell at concentrations 10-fold less than what is toxic to the cells themselves. Nanosilver article size consistent with gaps between spike proteins on the virus.

Parallel evidence: analogy/similarity

- Procter case series: 869 high-risk patients treated early in Texas using combination therapy: ivermectin, hydroxychloroquine, zinc, azithromycin, doxycycline, budesonide, dexamethasone, IV vitamins: clear and convincing mortality rate reduction when compared against the United States population level CFR.
- RCTs of combination ivermectin + doxycycline by Mahmud 2021 and Hashim 2021 both show mortality rate reduction for outpatients and inpatients.
- Several negative RCTs used ivermectin monotherapy, or treated low-risk patients, or used low dose; details in paper.
- Ecological study in Peru: 14-fold the reduction in excess deaths when the use of ivermectin was introduced followed by 13 fold increase in excess deaths when the next government prohibited the use of ivermectin
- Wieler 2023: randomized case study; nanosilver injections who resulted in statistically significant mortality rate reduction
- Tabatabaeizadeh 2022, Rheingold 2023: meta-analyses confirming the association between zinc supplementation and mortality rate reduction
- Borche 2021: correlation between increased vitamin D3 levels and reduced mortality in hospitalized patients; recommended 25-hydroxyvitamin D3 levels above 50ng/ml
- Kow 2033, Qin 2024: meta-analyses confirming the association between vitamin C administration and mortality rate reduction in hospitalized COVID-19 patients.

Conclusion

- **Stone/Gill protocol**
  - The rapid recovery of SpO2 via the Stone/Gill protocol justifies use because, at minimum, this protocol can alleviate suffering.
  - Reduction of hospitalization is shown to be *clear and convincing*
  - Reduction of mortality is shown by the *preponderance of evidence*
  - In the paper we have presented stronger results by combining the three case series together. However, the Stone case series alone also provides a compelling argument.
  - The dosage of ivermectin should be tuned to severity of patient presentation for optimal outcomes.
  - More data exists from doctors in Zimbabwe and South Africa, however they are reluctant to go public due to fear of persecution by medical boards.
- **Bradford Hill criteria**
  - Using the Bradford Hill criteria to infer causality has seen as controversial because the underlying argument is neither deductive or inductive
  - Ward 2009: a causality argument via an RCT is *inductive*, whereas a causality argument is an *inference to the best explanation*.
  - Harman 1965: Inference to the best explanation is a logical inference that begins with an array of factual evidence and infers the truth of a specific hypothesis by arguing that this specific hypothesis, if true, provides the best explanation for the available evidence relative to any other alternative hypothesis.
  - We note that the inductive RCT causality argument is limited to the internal validity of the RCT.
  - To support the external validity of an RCT also requires an *inference to the best explanation* argument.

Thank you!

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