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**〈Review Article〉****Critical appraisal of multidrug therapy in the ambulatory management of patients with COVID-19 and hypoxemia  
Part I. Evidence supporting the strength of association**

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(Received for publication December 17, 2024)

This critical appraisal is focused on three published case series of 119 COVID-19 patients with hypoxemia who were successfully treated in the United States, Zimbabwe, and Nigeria with similar off-label ivermectin-based multidrug treatments that may include ivermectin, nebulized nanosilver, doxycycline, zinc, Vitamins C, and Vitamin D, resulting in rapid recovery of oxygen levels. We used a simplified self-controlled case series method to investigate the association between treatment and the existence of hospitalization rate reduction. External controls of hospitalized patients were compared against the subgroup of patients with baseline room air SpO<sub>2</sub> ≤ 90% to investigate the association between treatment and the existence of mortality rate reduction. No deaths were reported in any of the three case series. One case series reported 5 hospitalization equivalent events (2 ventilations and 3 uses of supplemental oxygen). Combined, the three case series comprised 119 patients of which 61 patients presented with baseline room air SpO<sub>2</sub> ≤ 90%. All appropriate external controls were lower-bounded by 12% case fatality rate for hospitalized patients. The existence of hospitalization rate reduction was statistically significant and resilient against both random and systemic selection bias for two out of three

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[https://doi.org/10.11553/antibiotics.78.1\\_2](https://doi.org/10.11553/antibiotics.78.1_2)



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case series with the most aggressive treatments. The existence of mortality rate reduction was statistically significant when at least the two case series with the most aggressive treatments were combined. It is more likely than not that random selection bias alone cannot explain this reduction in mortality. These results established an association between the two most aggressive ivermectin-based multidrug treatment protocols and reduction in hospitalization and mortality for hypoxemic COVID-19 patients.

## 1. Introduction

On March 11, 2020, Coronavirus Disease 2019 (COVID-19), the disease caused by the Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2), was declared a pandemic by the World Health Organization (WHO)<sup>1</sup>. During 2020, while several governments and public health agencies were focused on contagion control and in-hospital patient care, several medical doctors from all around the world innovated and discovered early outpatient multidrug treatments using several repurposed medications in combination<sup>2–17</sup>. The present study is focused on previously proposed ivermectin-based multidrug protocols that can rescue patients with hypoxemia and result in the rapid recovery of peripheral oxygen saturation levels (SpO<sub>2</sub>), upon initiation of treatment<sup>18–22</sup>. Thus, the focus is on COVID-19 patients whose condition has deteriorated, due to lack of early treatment or due to insufficient response to some initial attempt at an early treatment.

The available empirical evidence consists of case series that were reported by Hazan and colleagues<sup>19</sup>, Stone and colleagues<sup>18</sup>, and Babalola and colleagues<sup>20</sup>. Hazan's baseline protocol, used on United States COVID-19 patients, was a 10-day treatment with ivermectin, doxycycline, zinc, Vitamin C, Vitamin D<sup>19</sup>, which was administered via telemedicine. The Stone/Gill multidrug protocol<sup>23, 24</sup>, which was used in Zimbabwe patients reported on by Stone *et al.*<sup>18</sup>, is a more aggressive 10-day multidrug protocol that consisted of nebulized nanosilver, ivermectin, doxycycline, zinc, Vitamin, C, and Vitamin D, with additional corticosteroids and anticoagulants added based on the bloodwork results. The Stone/Gill multidrug protocol<sup>24, 25</sup> was used at several urgent care centers in both Zimbabwe and South Africa, and it was designed under the assumption that some patients will be treated in an urgent care setting, while other patients will complete their treatment at home, as opposed to the telemedicine approach that was used in the United States. Babalola's protocol was less aggressive, with a baseline protocol consisting of a 5-day treatment of ivermectin, zinc, and Vitamin C, with some adjunct use of low-dose hydroxychloroquine and azithromycin on some patients.

All three protocols demonstrated rapid recovery of SpO<sub>2</sub> levels in hypoxemic patients upon the onset of treatment<sup>18, 19, 22</sup>. In particular, the Hazan and Stone case series showed the most rapid recovery pattern with statistically significant normalization trend of SpO<sub>2</sub> within 24 hr<sup>18, 26</sup>.

From an ethical perspective, this is sufficient to satisfy article 37 of the 2013 Helsinki declaration which allows the use of an unproven treatment with informed consent when it “offers hope of saving life, reestablishing health or alleviating suffering”<sup>27)</sup>. A causality argument in favor of the Hazan<sup>19)</sup> and Stone/Gill<sup>18, 25)</sup> protocols, that is based on the Bradford Hill criteria<sup>28–30)</sup>, will be presented in a sequel to this study.

The scope of this study is limited to establishing the Bradford Hill criterion of *strength of association* between treatment and reduction in mortality and hospitalizations. We identified appropriate historical/external control groups for the case fatality rate (CFR) of hospitalized patients in the United States, Zimbabwe, and Nigeria and compare them against the Hazan, Stone, and Babalola case series in order to establish the existence of some mortality rate reduction benefit. We used a risk-stratification scheme to make these case series comparable to the CFR of hospitalized patients and we also considered comparisons between the combined case series and the external controls in order to increase the statistical power. The external controls were sourced from the research literature<sup>31–37)</sup>, however, we also conducted a detailed independent analysis of a Center for Disease Control and Prevention (CDC) case surveillance public database<sup>38)</sup> to construct an appropriate external control for the United States patients. To investigate the existence of some hospitalization rate reduction efficacy, we used a self-controlled approach, which we think is self-evident, but was not explicitly attempted previously<sup>18–22)</sup>. Both comparisons are susceptible to bias towards the null hypothesis, so they cannot be used to obtain unbiased effect sizes. On the other hand, the decision on whether these protocols should be used is a binary choice, and a positive finding that can overcome the expected bias towards the null hypothesis is positive evidence in favor of these protocols.

## 2. Materials and Methods

### 2.1. Description of case series

The Hazan case series consisted of 26 patients who were treated in the United States, via telemedicine, between August 2020 and February 2021 by Hazan and colleagues<sup>19)</sup>. These patients were enrolled to participate in a clinical trial, however, they did not satisfy the inclusion criteria because their presentation with baseline room air SpO<sub>2</sub> ≤ 90% warranted in-hospital care, and they also declined hospitalization for a variety of personal reasons. We excluded 2 patients that died because they did not consent to treatment (patients 10 and 26 in Table 1 of Hazan *et al.*<sup>19)</sup>). One of the two excluded patients received only an initial dose of 36 mg ivermectin, with reported room air SpO<sub>2</sub> increase from baseline 73% to 87% within 24 hr, but declined further treatment (Patient 10 in Table 1 of Hazan *et al.*<sup>19)</sup>). The remaining 24 patients consented to treatment, of which 23 patients presented with baseline room air SpO<sub>2</sub> ≤ 90%. The treatment period overlapped with the first and second pre-delta periods, following the epidemic wave breakdown

**Table 1. Treatment protocols used for the Hazan case series<sup>19)</sup>, Stone case series<sup>18, 24, 25)</sup>, and Babalola case series<sup>20)</sup>**

Case Series	Treatment
Hazan	<ul style="list-style-type: none"> <li>• <i>Baseline protocol</i>: doxycycline (100 mg twice a day for 10 days), ivermectin (12 mg minimal dose on day 1, day 4, and day 8), zinc (25 mg elemental zinc twice a day for 10 days), Vitamin D3 (1,500 IU twice a day for 10 days), and Vitamin C (1,500 mg twice a day for 10 days).</li> <li>• <i>Additional medications</i>: two patients who presented with baseline room air SpO<sub>2</sub> at 72% and 73% received 36 mg of ivermectin on day 1.</li> </ul>
Stone	<ul style="list-style-type: none"> <li>• <i>Criteria for using the salvage protocol</i>: at least one of the following: <b>(a)</b> Patient is not ambulant; <b>(b)</b> tachypneic with rate over 22 per minute or slow respiratory rate from exhaustion; <b>(c)</b> confusion or decreased/loss of consciousness; <b>(d)</b> symptomatic for longer than 10 days and elevated pulse rate and/or above-mentioned symptoms. Patients that satisfied the above criteria were often significantly hypoxic with baseline room air SpO<sub>2</sub> ≤ 80%.</li> <li>• <i>Salvage protocol</i>: if initial assessment indicates poor prognosis and likely need for hospital referral, the following protocol is attempted at an urgent care setting: <b>(a)</b> ivermectin 0.6 mg/kg stat dose, may titrate to effect up to 1–2 mg/kg if SpO<sub>2</sub> does not increase, maintain at 0.3–0.6 mg/kg for up to 10 days until symptom free for 48 hr. <b>(b)</b> Continuous nanosilver nebulizations, until room air SpO<sub>2</sub> ≥ 90%, then reduce to at least three nebulizations per day. <b>(c)</b> 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. <b>(d)</b> Zinc sulfate 20–40 mg three times daily orally. <b>(e)</b> Aspirin 300 mg daily. <b>(f)</b> Prednisone 1 mg/kg or dexamethasone 8 mg IV stat, followed by prednisolone 40–80 mg once daily, if CRP &gt; 20 or room air SpO<sub>2</sub> ≤ 80%. <b>(g)</b> Enoxaparin 80 mg subcutaneously once daily transitioning to rivaroxaban 20 mg once daily for at least 30 days, if the D Dimer is raised, or longer if D Dimer has not come down. <b>(h)</b> 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.</li> <li>• <i>Initial treatment by trained nurses</i>: administered, if baseline room air SpO<sub>2</sub> &gt; 80%, not tachypneic, tachycardic, or confused (otherwise the <i>salvage protocol</i> is used). Initial administration of nanosilver nebulization 5–8 mL. Patient was then canulated. During canulation: <b>(a)</b> draw blood for bloodwork; <b>(b)</b> administer ivermectin at minimum dose 0.2 mg/kg (increased to 0.6 mg/kg during Delta); <b>(c)</b> if patient is hypoxic, febrile, or systemically unwell: IV ceftriaxone 1 g and either dexamethasone 8 mg stat or hydrocortisone 100–200 mg stat, as clinically indicated; <b>(d)</b> diabetes management, if needed.</li> <li>• <i>Doctor administered individualized treatment</i>: if patient presented with mild disease and was covid positive on PCR or antigen test, then <i>baseline protocol for mild disease</i> was used. Clinical diagnosis based on symptoms: hypoxia, raised LDH, low lymphocytes, raised monocytes, raised D dimer, suggestive radiology. <i>Baseline protocol for severe disease</i> or <i>salvage protocol</i> are used, if needed.</li> <li>• <i>Baseline protocol for mild disease</i>: ivermectin at 0.1–0.2 mg/kg on day 0, day 4, day 8; nanosilver nebulizations 5–8 mL three times daily for 5–7 days or for 48 hr after resolution of symptoms; doxycycline 100 mg twice a day for 10 days, zinc 20 mg three times daily for 10 days; Vitamin C 1 g three times daily and Vitamin D 5,000–10,000 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 hr after resolution of symptoms.</li> <li>• <i>Baseline protocol for severe disease</i>: ivermectin 0.2 mg to 0.3 mg/kg daily for 5 days, during the Beta wave and 0.4–0.6 mg/kg during the delta wave for 10 days; silver nebulizations 5–8 mL at least three times per day and continuously as needed when room air SpO<sub>2</sub> ≤ 90%; doxycycline 100 mg twice daily for 10 days; zinc 20 mg twice daily for 10 days; vitamin C 1 g three times daily and vitamin D 5,000–10,000 IU daily for 10 days.</li> <li>• <i>Criteria for baseline protocol for severe disease</i>: if any of the following were present: <b>(a)</b> the Lymphocyte to LDH ratio was over 210; <b>(b)</b> the D-Dimer was raised; <b>(c)</b> the CRP was raised; <b>(d)</b> the patient was in stage 3 (thrombosis) of the disease as per McCullough's definitions<sup>12)</sup>.</li> <li>• <i>Additional medications</i>: <b>(a)</b> If patient is hypoxic and CRP &gt; 20, then prednisone 40–80 mg daily is added. <b>(b)</b> If D-Dimer is raised, subcutaneous Enoxaparin at 80 mg–100 mg is administered followed by Rivaroxaban/Xarelto at 20 mg daily for 30 days. <b>(c)</b> If neutrophils are raised and the patient is canulated, ceftriaxone at 1 g 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.</li> </ul>
Babalola	<ul style="list-style-type: none"> <li>• <i>Baseline protocol</i>: ivermectin 0.2 mg/kg daily for 5 days, zinc sulfate (50–100 mg daily for 7 days), vitamin C (1,000 mg daily for 7 days)</li> <li>• <i>Additional medications</i>: hydroxychloroquine 200 mg per day for 3 days and azithromycin 500 mg per day for 3 days (given to 31 of 61 patients).</li> </ul>

by Adjei *et al.*<sup>32)</sup>.

The Stone case series consisted of 34 COVID-19 patients who presented with baseline room air SpO<sub>2</sub> ≤ 93% and were treated in Harare, Zimbabwe between August 2020 and May 2021 in Stone's clinic by Stone and colleagues<sup>18)</sup>. The patients were treated in an outpatient clinic setting or at home, via visiting nurses, due to limited access to hospital resources and very limited access to supplemental oxygen. During the treatment period the dominant strains in Zimbabwe were the B.1.351 (Beta variant), which peaked in January 2021, and the B.1.617.1 (Delta variant), which peaked in July 2021<sup>39)</sup>. Furthermore, the Beta variant accounted for 95% of the sequenced cases since March 2021 and during most of the treatment period; the Delta variant was detected in Zimbabwe during May 2021, at the tail end of the treatment period<sup>40)</sup>.

The Babalola case series consisted of 61 patients who were treated in Nigeria with ivermectin-based multidrug protocols, of which 21 patients presented with hypoxemia and baseline room air SpO<sub>2</sub> ≤ 93%, and 10 of the 21 patients presented with baseline room air SpO<sub>2</sub> ≤ 90%<sup>20, 41)</sup>. Patients were treated in the Abuja Federal Capital Territory between April 2021 and June 2021. The treatment period corresponds to the interregnum between the second wave (Beta variant) and the third wave (Delta variant) in Nigeria<sup>21, Fig. 1)</sup>.

## 2.2. Treatment protocols

Table 1 summarizes the details of the treatment protocols used in the Hazan, Stone, and Babalola case series. The details of the treatment protocols used in the Hazan and Babalola case series are given in the respective publications<sup>19, 20)</sup>. The details of the Stone/Gill protocol were originally reported online<sup>23)</sup> and briefly summarized by Stone *et al.*<sup>18)</sup>. During the Summer of 2024, an updated version of the online document was provided to us by Stone<sup>25, 42)</sup>.

The multidrug treatment protocol used for the Hazan case series consisted of doxycycline (100mg twice a day for 10 days), ivermectin (12 mg minimal dose on day 1, day 4, and day 8), zinc (25 mg elemental zinc twice a day for 10 days), Vitamin D3 (1,500 IU twice a day for 10 days), and Vitamin C (1,500 mg twice a day for 10 days)<sup>19)</sup>. The ivermectin dosage was spread out to allow an approximately constant level of the medication in the plasma. Two patients who presented with very low baseline room air SpO<sub>2</sub> at 72% and 73% received an increased dose of 36 mg of ivermectin on day 1. Hazan and colleagues used customized vitamins C, D, and zinc which were tested in her laboratory for consistency and quality<sup>43)</sup>. All patients treated in this case series had pre-delta SARS-CoV-2 variants; Hazan later found it necessary to increase ivermectin dosage during the Delta variant<sup>43)</sup>. Finally, 7 out of 24 patients received additional medications prior to or during the 10-day treatment period: one patient received remdesivir, 3 patients received hydroxychloroquine, and 4 patients were enrolled in a clinical trial where they may have received placebo or a combination of hydroxychloroquine, azithromycin, Vitamin D, and zinc. Hazan observed that for the highest-risk patients, although the combination of ivermectin, doxy-

cycline, and Vitamin D was effective in restoring room air SpO<sub>2</sub> levels in hypoxemic patients, it was not always sufficient to eradicate the virus, and in those cases it was also necessary to add hydroxychloroquine and azithromycin<sup>43</sup>).

The baseline multidrug treatment protocol used in the Stone case series combined nebulized nanosilver, ivermectin, doxycycline, zinc, Vitamin C, and Vitamin D. Stone treated her patients in an urgent care setting, which allowed the treatment to be customized to the needs of the individual patient. As shown on Table 1, patients were initially treated and assessed by trained nurses. Most patients were then treated using either a baseline protocol for mild disease or the more aggressive baseline protocol for severe disease, based on symptomatic presentation and results from bloodwork. The baseline protocol for severe disease mirrored the one for mild disease but intensified the use of ivermectin, based on the safety data from Guzzo *et al.*<sup>44</sup>), and increased nanosilver nebulizations when oxygen saturation fell below 90%. Although doxycycline, zinc, vitamins C and D were consistently given for 10 days in the baseline protocols for both mild and severe disease, ivermectin and nanosilver nebulizations were generally continued up to 48 hr after the resolution of symptoms. Depending on bloodwork results, prednisone, enoxaparin, Xarelto, ceftriaxone were added to the respective baseline protocols when needed for some patients. For patients with very poor prognosis (typically with baseline room air SpO<sub>2</sub> ≤ 80%), a salvage protocol was attempted to prevent hospitalization, as shown on Table 1. Although Stone and colleagues did not use hydroxychloroquine in this particular case series, the adoption of nebulized nanosilver was intended to also function as a fast-acting antiviral that could eradicate viral multiplication in the lungs, analogously to Hazan's adjunct use of hydroxychloroquine and azithromycin in her highest-risk patients<sup>43</sup>).

For the Babalola case series, the treatment protocol consisted of ivermectin 0.2 mg/kg daily for 5 days in addition to zinc sulfate (50–100 mg daily for 7 days) and Vitamin C (1,000 mg daily for 7 days)<sup>20–22</sup>). However, 31 of 61 patients also received hydroxychloroquine 200 mg per day for 3 days and azithromycin 500 mg per day for 3 days. Supplemental oxygen was only administered when the oxygen level dipped below a certain threshold, or when the patient manifested evidence of respiratory distress<sup>41</sup>). Due to the treatment provided, supplemental oxygen was not necessary for most patients.

In all three case series, all patients survived, however, in the Babalola case series, 2 of the 61 hypoxemic patients had to use a ventilator and 3 additional patients needed supplemental oxygen, despite the provided treatment<sup>21</sup>).

### 2.3. Endpoints

The relevant and decisive endpoints for evaluating any COVID-19 treatment protocols are the hard endpoints of mortality rate reduction and hospitalization rate reduction. Consequently, we investigate both endpoints.

#### 2.4. Self-controlled case series method for establishing hospitalization rate reduction

We assume that, under the conventional standard of care, all patients with baseline  $\text{SpO}_2 \leq 90\%$  will be hospitalized, given the immediate need for supplemental oxygen and the high likelihood of further deterioration, as the disease progresses. Consequently, we can use a simplified self-controlled case series method to establish the existence of a hospitalization rate reduction benefit, as follows: Each case series can be viewed as a control in which the number of patients with baseline room air  $\text{SpO}_2 \leq 90\%$  are counted as counterfactual hospitalizations that would have taken place if standard guidelines had been followed instead of ivermectin-based multidrug treatment. This number of counterfactual hospitalizations can be then compared with the corresponding number of factual hospitalization and/or equivalent deterioration events with ivermectin-based multidrug treatment, as reported in the Results section.

Although hospitalization is a highly subjective endpoint, with possible regional variability in the criteria used to decide whether a patient should be admitted as an inpatient<sup>45)</sup>, using the baseline room air threshold  $\text{SpO}_2 \leq 90\%$  as a sufficient condition for counterfactual hospitalization events is nevertheless consistent with an early finding<sup>46)</sup> that the partial pressure of oxygen ( $\text{PaO}_2$ ) and  $\text{SpO}_2$  are both perceived as the most important factors for COVID-19 inpatient admission. It is also consistent with the National Institute of Health (NIH) COVID-19 treatment guidelines<sup>47)</sup> recommending that oxygen supplementation target an  $\text{SpO}_2$  level between 92% and 96%, as well as guidelines from medical centers recommending that hospitalization should be considered when room air  $\text{SpO}_2$  falls below 94%<sup>48)</sup> or 92%<sup>49)</sup>. Furthermore, studies from Serbia<sup>50)</sup> and Peru<sup>51)</sup> showed a substantial increase in the mortality rate of hospitalized patients as the baseline room air  $\text{SpO}_2$ , at the time of hospital admission, decreased from 90% to 80%. This provides an objective rationale for using the baseline room air  $\text{SpO}_2 \leq 90\%$  threshold as a sufficient condition for hospitalization, in the context of standard guidelines that preclude a pre-hospital intervention.

It is worth noting that some of the patients with higher levels of  $\text{SpO}_2$  could have also been hospitalized, given the high likelihood that some of those patients could deteriorate under the conventional standard of care. Thus, this approach provides a lower bound for the control's counterfactual hospitalization rate, and an odds ratio calculation can be expected to be biased towards the null hypothesis. Nevertheless, a positive finding that overcomes this bias is sufficient for establishing the existence of some hospitalization rate reduction efficacy.

#### 2.5. External controls for establishing mortality rate reduction

To establish the existence of a mortality rate reduction benefit, we risk-stratified the three case series under the constraint of baseline room air  $\text{SpO}_2 \leq 90\%$  and compared the observed mortality rate in the risk stratified case series against the CFR of hospitalized patients in appropriate external control groups. We relied on several external control groups in the United States<sup>32, 38)</sup>,

Zimbabwe<sup>33, 34</sup>), Nigeria<sup>35, 36</sup>), South Africa<sup>31</sup>), and globally<sup>37</sup>) to determine a reasonable lower-bound estimate for the mortality rate of hypoxemic patients without the use of any of the proposed ivermectin-based multidrug treatment protocols. The rationale for this comparison is a consequence of the underlying premise that if standard hospitalization guidelines had been followed instead of ivermectin-based treatment, then all patients with baseline room air SpO<sub>2</sub> ≤ 90% would have been referred to the hospital, where they would have been confronted with an averaged CFR greater than or equal to the average CFR of hospitalized patients.

This comparison also has a bias towards the null hypothesis, because in the external controls, the CFR for hospitalized patients includes both patients with and without hypoxemia. Indeed, Poskurica *et al.*<sup>50</sup>) showed that among the patients hospitalized in Serbia the average room air baseline oxygen level upon admission was 89% (with 7% IQR), indicating that some of the admitted patients came in with room air oxygen above 90%. The particular choice of risk stratification can be employed because no deaths were observed among the patients excluded by the risk stratification.

For all external controls, except for the CDC case surveillance public database<sup>38</sup>), we simply gathered and organized the CFRs for hospitalized patients, as reported in the respective publications. We independently analyzed the CDC case surveillance public database<sup>38</sup>) in this study as follows: For each case, the available information that is potentially relevant to our analysis includes the case's month/year, age group (broken down categorically to the age brackets 0–17, 18–49, 50–64, 65+), whether the case is symptomatic or asymptomatic, whether the case has been laboratory-confirmed, whether certain unspecified comorbidities exist, and whether the final outcome was hospitalization, ICU admission, or death. We filtered the database for all cases that were symptomatic, lab confirmed, resulting in hospitalization, and with known month/year.

Furthermore, we calculated the hospitalized CFR of hospitalized patients both with and without the age ≥ 50 years restriction because it is a reasonable proxy for baseline room air SpO<sub>2</sub> < 92%, noting that both are being scored equivalently in the 4C mortality score for in hospital mortality of COVID-19 patients<sup>52</sup>). The 4C mortality score was rated as one of the top two predictive models for in-hospital mortality probability in terms of accuracy and a low risk of bias in a systematic review of several predictive models<sup>53</sup>). After filtering, we counted the number of cases in which it was known that the patient survived and the number of cases in which it was known that the patient died. Because of the substantial number of cases in which the mortality endpoint is unknown or unavailable, we conservatively estimated a range for the CFR of hospitalized patients as follows: (a) to obtain a reliable CFR lower bound, we assumed that all cases with unknown mortality status have survived; (b) to obtain a conservative CFR upper bound, we assumed that for all cases with unknown mortality status the probability of death is the same as within cases where the mortality status is known. This approach assumes that deaths are less likely to be unreported than survivals.

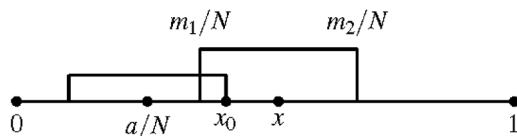
## 2.6. Statistical analysis

External controls<sup>32–38, 54)</sup> were used to establish the existence of mortality rate reduction and a simplified self-controlled case series methodology<sup>55)</sup> was used to establish the existence of hospitalization rate reduction. For the corresponding comparisons of the case series by Hazan<sup>19)</sup>, Stone<sup>18)</sup>, and Babalola<sup>20–22)</sup> against the corresponding controls, as a preliminary step, we used the two-sided exact Fisher test to calculate the  $p$ -value. The threshold  $p < 0.05$  was used for statistical significance. We calculated the corresponding odd ratios and odd ratio confidence intervals, with 95% confidence. To increase the statistical power, we also analyzed the combined Hazan + Stone and Hazan + Stone + Babalola case series. For the purpose of sensitivity analysis, we also analyzed the combined Hazan + Babalola and Stone + Babalola case series.

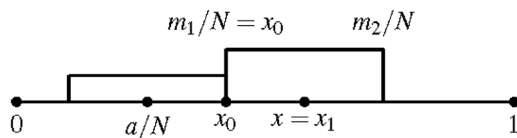
Because case series are susceptible to selection bias, establishing statistical significance using the exact Fisher test is necessary but not sufficient. To better ascertain the potential impact of selection bias, we further analyzed the case series using a recently introduced case series

**Fig. 1** Comparison of a case series ( $N, a$ ) of  $N$  treated patients, with  $a$  patients having an adverse outcome, against the population level probability  $x$  of an adverse outcome without treatment. The figure shows the relative position of the confidence interval for the probability of an adverse outcome with treatment (with upper endpoint  $x_0$ ) and the confidence interval  $[m_1/N, m_2/N]$  for the probability of an adverse outcome without treatment, which in turn determines whether the existence of some treatment efficacy has been shown by the *preponderance of evidence* and whether it is *clear and convincing*. Here,  $x_0$  is the *efficacy threshold* for establishing existence of efficacy by the *preponderance of evidence* and  $x_1$  is the *random selection bias threshold* for establishing existence of efficacy by the *clear and convincing* standard. This figure is adapted from the graphical abstract of Gkioulekas *et al.*<sup>56)</sup> under the terms of the CC-BY-4.0 license.

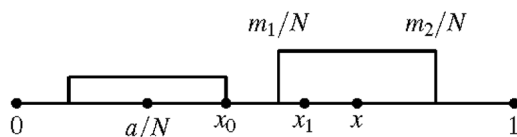
### Preponderance of the evidence



### Crossover to clear and convincing



### Clear and convincing



threshold analysis statistical technique<sup>56</sup>), which is based on the Sterne interval solution<sup>57</sup>) of the binomial proportion confidence interval problem and the Bayes factor<sup>58–62</sup>). Given a case series  $(N, a)$  of  $N$  treated patients with  $a$  adverse events (hospitalizations or deaths), and external controls that bound the population-level probability  $x$  of an adverse event without treatment into an interval  $p_1 < x < p_2$ , the method allows us to determine whether the contrast between the case series data  $(N, a)$  and the probability interval  $[p_1, p_2]$  is sufficiently large to be statistically significant, and to quantify how much selection bias is required to overturn a positive finding. An assumption that underlies this method is that all adverse events counted in  $a$  can be attributed to the disease rather than the treatment, which limits the applicability of the method only to treatments that use repurposed medications with known acceptable safety. This assumption was satisfied by the respective multidrug protocols.

An intuitive conceptualization of the case series threshold analysis<sup>56</sup>) statistical method is shown on Fig. 1, where we schematically display the *treatment interval*, appearing on the left, which is the confidence interval for the probability of an adverse event with treatment, and the *control interval*, appearing on the right, which is the confidence interval for the probability of an adverse event without treatment or under the current standard of care, for a patient group equivalent to the case series of treated patients. The treatment interval is the Sterne interval<sup>57</sup>) corresponding to a binomial trial  $(N, a)$  of  $N$  attempts with  $a$  failures. The control interval quantifies the extent of potential selection bias by expanding any given point-wise population-level probability  $x$  of adverse events without treatment into a confidence interval for the true value of that probability that is specific to our case series of  $N$  patients, if they have been selected randomly from the general population. For comparison purposes, we use conservative lower bounds for the population-level probability  $x$ .

The *efficacy threshold*  $x_0$  is the upper end point of the treatment interval using  $1 - p_0$  confidence (we use  $p_0 = 0.05$  as the threshold for statistical significance for all calculations). The *random selection bias threshold*  $x_1$  is the minimum value of  $x$  at which the two intervals do not intersect. Before calculating the random selection bias threshold  $x_1$ , we used a Bayesian technique to adjust the efficacy threshold  $x_0$  in the upwards direction to  $y_0 \geq x_0$  to ensure that the Bayes factor  $B$  comparing the null hypothesis  $H_0$  against the alternate hypothesis  $H_1$  satisfies  $\log_{10} B \geq 2$ . The computer code required to reproduce the threshold calculations reported in this paper is available on Figshare<sup>24</sup>). All relevant mathematical details on the case series threshold analysis method are provided in the original paper<sup>56</sup>) and Figshare<sup>24</sup>).

We say that the comparison shows the existence of efficacy by the *preponderance of evidence* when  $x$  is above the treatment interval, that is when  $x \geq y_0$ . A preponderance of evidence finding means that it is more likely than not that random selection bias does not overturn the existence of some treatment effect, so there is compelling evidence for emergency adoption. We say that the comparison shows *clear and convincing* existence of efficacy when the two intervals do

not intersect, that is when  $x \geq x_1$ . A clear and convincing finding means that we can have  $1 - p_0$  confidence that random selection bias does not overturn the existence of some treatment effect, at which point there is no longer equipoise between treatment and doing nothing.

If additional information is available that the probability  $x$  of an adverse event without treatment satisfies a lower bound  $x > p_1$  with  $p_1 > x_1$ , then we can calculate the *selection bias tolerance*  $F = [p_1(1 - x_1)]/[x_1(1 - p_1)]$  which measures the magnitude of systemic selection bias needed to overturn a clear and convincing finding of efficacy. Systemic selection bias with magnitude  $f$  means that the patients in the case series have not been randomly selected from the population, and, instead, it is  $f$  times more likely to select the healthier patients (i.e., those that would have done well without treatment) than it would have been, if the selection was truly random. The interpretation of  $F$  is that any systemic selection bias must have magnitude  $f$  with  $f > F$  to downgrade a clear and convincing finding into a preponderance of evidence finding.

## 2.7. Software

The efficacy threshold and random selection bias threshold for the respective case series were calculated using the computer algebra program Maxima 5.46.0<sup>63</sup>). Our independent analysis of the CDC database<sup>38</sup>) as well as the preparation of the tables reporting on the external controls were conducted using R 4.1.3<sup>64</sup>), in conjunction with the `dplyr` and `magrittr` packages. For our calculations, we used the January 20, 2023 snapshot of the CDC database<sup>38</sup>). The exact Fisher test calculations were also conducted using R 4.1.3<sup>64</sup>), in conjunction with the `stats` package. The computer code used for all calculations is available on Figshare<sup>24</sup>).

## 2.8. Availability of data and materials

The January 20, 2023 snapshot of the CDC database used for our calculations is available from the corresponding author upon request, because of the large size of the data file (0.9 GB with compression). The current version of the database can be downloaded from the CDC website<sup>38</sup>). The baseline room air SpO<sub>2</sub> data for the Hazan and Stone case series are available from the respective publications<sup>18, 19</sup>). We have made the following data and materials available on Figshare<sup>24</sup>): (1) the computer code and the details of the calculations of the efficacy thresholds and random selection bias thresholds for all case series discussed in this paper; (2) the computer code used to generate the LaTeX code for typesetting Table 2, Table 4, Table 5, Table 6, Table 8, and Table 9 directly from the data; (3) the baseline room air SpO<sub>2</sub>, age, and sex data for the Babalola case series, with permission from Olufemi Babalola; (4) the unpublished Parirenyatwa hospitals redzone statistics document<sup>33</sup>) and an updated version of the Stone/Gill protocol document<sup>25</sup>), provided to us by Jackie Stone.

### 2.9. Ethics approval and consent to participate

Not applicable. The study is an analysis of previously published data.

## 3. Results

### 3.1. Description of the case series

Table 2 shows the distribution of the demographic characteristics of the Hazan, Stone, and Babalola case series in terms of gender, age brackets and baseline SpO<sub>2</sub> at room air. The demographic characteristics for the combined case series Hazan + Stone, Hazan + Babalola, Stone + Babalola, and Hazan + Stone + Babalola are also shown. Furthermore, Table 2 shows the sex and age demographic characteristics for the risk stratified case series under the restriction of baseline room air SpO<sub>2</sub> ≤ 90%. To apply this restriction, we excluded one patient from the Babalola case series for whom the baseline room air SpO<sub>2</sub> was not available.

Males were consistently more prevalent than females in all three case series, and this pattern persists after introducing risk stratification with baseline room air SpO<sub>2</sub> ≤ 90%. Furthermore, the Hazan and Stone case series showed similar patient distributions by age brackets. With the high-risk age brackets corresponding to patients older than 40 years, we observed that with both the Hazan and Stone case series, under risk stratification with the constraint of baseline room air SpO<sub>2</sub> ≤ 90%, the corresponding age bracket percentages were perturbed by no more than 2%. For the lower risk age brackets of patients younger than 40 years, we observed that the Hazan case series had no patients with baseline room air SpO<sub>2</sub> ≤ 90%, however, the Stone case series had 4 patients (14.3%) with baseline room air SpO<sub>2</sub> ≤ 90%. The Babalola case series had a higher prevalence of younger patients compared to the Hazan and Stone case series. After risk stratification with baseline room air SpO<sub>2</sub> ≤ 90%, there was still a higher prevalence of younger patients in the Babalola case series (7 patients younger than 40 years and 3 patients older than 40 years). The increased prevalence of younger patients in the risk-stratified Stone and Babalola case series could be attributed to lower socioeconomic status of the African patients, relative to the United States patients treated in the Hazan case series. Qualitatively, we observed that risk stratification did not change the shape of the patient distribution across age brackets.

In terms of baseline room air SpO<sub>2</sub>, the majority of patients in both the Hazan and Stone case series were concentrated in the 85% to 90% bracket. The majority of patients in the Babalola case series were in the 93% to 100% bracket, but they are also concentrated in the 85% to 90% bracket after risk-stratification. A comparison of the Hazan case series against the Stone case series shows that in the Stone case series there was a higher prevalence of patients in the 80% to 85% bracket and the 75% to 80% bracket. This indicates that the African patients in Zimbabwe, on average, presented with more severe illness than the American patients.

Table 3 displays the following information about the Hazan, Stone, and Babalola case series,

**Table 2. Demographic characteristics of the Hazan *et al.*<sup>19)</sup>, Stone *et al.*<sup>18)</sup>, and Babalola *et al.*<sup>20)</sup> case series**

Characteristic	Hazan		Stone		Babalola		H+B		S+B		H+S		H+S+B	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Baseline SpO <sub>2</sub> at room air														
93% < SpO <sub>2</sub> ≤ 100%	1	4.2	0	0.0	39	63.9	40	47.1	39	41.1	1	1.7	40	33.6
90% < SpO <sub>2</sub> ≤ 93%	0	0.0	6	17.6	11	18	11	12.9	17	17.9	6	10.3	17	14.3
85% < SpO <sub>2</sub> ≤ 90%	19	79.2	16	47.1	7	11.5	26	30.6	23	24.2	35	60.3	42	35.3
80% < SpO <sub>2</sub> ≤ 85%	2	8.3	7	20.6	0	0.0	2	2.4	7	7.4	9	15.5	9	7.6
75% < SpO <sub>2</sub> ≤ 80%	1	4.2	4	11.8	3	4.9	4	4.7	7	7.4	5	8.6	8	6.7
70% < SpO <sub>2</sub> ≤ 75%	1	4.2	0	0.0	0	0.0	1	1.2	0	0.0	1	1.7	1	0.8
65% < SpO <sub>2</sub> ≤ 70%	0	0.0	1	2.9	0	0.0	0	0.0	1	1.1	1	1.7	1	0.8
Missing SpO <sub>2</sub>	0	0.0	0	0.0	1	1.6	1	1.2	1	1.1	0	0.0	1	0.8
Demographics without risk stratification														
Sex														
Male	14	58.3	20	58.8	39	63.9	53	62.4	59	62.1	34	58.6	73	61.3
Female	10	41.7	14	41.2	22	36.1	32	37.6	36	37.9	24	41.4	46	38.7
Age brackets														
18 to 20 years	0	0.0	0	0.0	4	6.6	4	4.7	4	4.2	0	0.0	4	3.4
21 to 30 years	0	0.0	1	2.9	12	19.7	12	14.1	13	13.7	1	1.7	13	10.9
31 to 40 years	0	0.0	5	14.7	19	31.1	19	22.4	24	25.3	5	8.6	24	20.2
41 to 50 years	4	16.7	7	20.6	10	16.4	14	16.5	17	17.9	11	19	21	17.6
51 to 60 years	4	16.7	9	26.5	7	11.5	11	12.9	16	16.8	13	22.4	20	16.8
61 to 70 years	10	41.7	8	23.5	8	13.1	18	21.2	16	16.8	18	31	26	21.8
71 to 80 years	2	8.3	3	8.8	0	0.0	2	2.4	3	3.2	5	8.6	5	4.2
81 to 90 years	2	8.3	1	2.9	1	1.6	3	3.5	2	2.1	3	5.2	4	3.4
91 years or older	2	8.3	0	0.0	0	0.0	2	2.4	0	0.0	2	3.4	2	1.7
Demographics with baseline room air SpO <sub>2</sub> ≤ 90%														
Sex														
Male	14	60.9	16	57.1	6	60	20	60.6	22	57.9	30	58.8	36	59
Female	9	39.1	12	42.9	4	40	13	39.4	16	42.1	21	41.2	25	41
Age brackets														
18 to 20 years	0	0.0	0	0.0	1	10	1	3	1	2.6	0	0.0	1	1.6
21 to 30 years	0	0.0	1	3.6	2	20	2	6.1	3	7.9	1	2	3	4.9
31 to 40 years	0	0.0	3	10.7	4	40	4	12.1	7	18.4	3	5.9	7	11.5
41 to 50 years	4	17.4	6	21.4	1	10	5	15.2	7	18.4	10	19.6	11	18
51 to 60 years	4	17.4	8	28.6	1	10	5	15.2	9	23.7	12	23.5	13	21.3
61 to 70 years	9	39.1	6	21.4	1	10	10	30.3	7	18.4	15	29.4	16	26.2
71 to 80 years	2	8.7	3	10.7	0	0.0	2	6.1	3	7.9	5	9.8	5	8.2
81 to 90 years	2	8.7	1	3.6	0	0.0	2	6.1	1	2.6	3	5.9	3	4.9
91 years or older	2	8.7	0	0.0	0	0.0	2	6.1	0	0.0	2	3.9	2	3.3

Hazan = the Hazan case series by Hazan *et al.*<sup>19)</sup>; Stone = the Stone case series by Stone *et al.*<sup>18)</sup>; Babalola = the Babalola case series by Babalola *et al.*<sup>20)</sup>; H+B = the combined Hazan + Babalola case series; S+B = the combined Stone + Babalola case series; H+S = the combined Hazan + Stone case series; H+S+B = the combined Hazan + Stone + Babalola case series.

as well as the combined case series: total number of patients treated, number of patients treated with baseline room air SpO<sub>2</sub> ≤ 93%, number of patients treated with baseline room air SpO<sub>2</sub> ≤ 90%, number of deaths, number of patients that deteriorated, and the corresponding time period of treatment. We also display the percentage  $p_1$  of patients with baseline room air SpO<sub>2</sub> ≤ 90% among all treated patients. As explained in Section 2, we used a simplified self-controlled case se-

**Table 3. Case series of hypoxemic patients by Hazan *et al.*<sup>19)</sup>, Stone *et al.*<sup>18)</sup>, and Babalola *et al.*<sup>20)</sup>, and case series combinations**

Case series	Patients with baseline SpO <sub>2</sub>			Deaths	Deterioration	Period
	≤ 100%	≤ 93%	≤ 90% ( $p_1$ )			
Hazan	24	23	23 (95.8%)	0	0	2020-08 to 2021-02
Stone	34	34	28 (82.3%)	0	1	2020-08 to 2021-05
Babalola	61	21	10 (16.4%)	0	5	2021-04 to 2021-06
Hazan + Babalola	85	44	33 (38.8%)	0	5	2020-08 to 2021-06
Stone + Babalola	95	55	38 (40.0%)	0	6	2020-08 to 2021-06
Hazan + Stone	58	57	51 (87.9%)	0	1	2020-08 to 2021-05
Hazan + Stone + Babalola	119	78	61 (51.3%)	0	6	2020-08 to 2021-06

SpO<sub>2</sub> = baseline room air peripheral oxygen saturation; deterioration = number of events where use of supplemental oxygen or use of the ventilator was required;  $p_1$  = percentage of patients with baseline room air SpO<sub>2</sub> ≤ 90%, which is also a lower bound of the expected number of hospitalizations that would have taken place, if standard guidelines had been followed.

ries method to demonstrate the existence of hospitalization rate reduction efficacy, in which this percentage represents a lower bound of the expected counterfactual hospitalization rate that would have taken place under the conventional standard of care, specifically for the selected patients in the respective case series. We note that there were no deaths in any of the case series<sup>18–21)</sup>. In the Hazan case series, we counted 0 deteriorations, because it was explicitly reported that no patients were hospitalized<sup>19)</sup>. In the Stone case series, we counted 1 deterioration event corresponding to a 66 year old male patient whose room air SpO<sub>2</sub> declined from 85% baseline to 84% within 24hr and remained at 84% at 48hr, and who may have been briefly hospitalized<sup>65)</sup>, Table S1,S2); all other 33 patients showed immediate increase in SpO<sub>2</sub> within 48hr<sup>18, Table S1)</sup>. In the Babalola case series, we counted 5 deterioration events consisting of 2 patients that had to use a ventilator and 3 other patients who required the use of supplemental oxygen<sup>20, 41)</sup>.

### 3.2. Description of external controls for the United States

The following external controls were used to investigate the mortality rate reduction endpoint. Table 4 shows the United States CFR of hospitalized patients at the national level throughout the years of 2020, 2021, and 2022, calculated via the CDC's COVID-19 case surveillance public database<sup>38)</sup>. The selection criteria for constructing the subgroup of hospitalized cases is described in the methods section. Table 4 shows the CFR of hospitalized patients both over all age brackets as well as for the age ≥ 50 years age brackets. The CFR of hospitalized patients is reported as an interval: the calculation of the lower bound assumes survival for all cases with missing mortality data; the calculation of the upper bound assumes that for all cases with missing mortality data the likelihood of death is the same as in the cases with known data. A close examination of the monthly CFR of hospitalized patients shows that it had a dependence on the strain placed on the hospital system, as indicated by the total number of cases per month. A similar finding was observed by Jassat *et al.*<sup>31)</sup> with the month-to-month CFR of hospitalized patients re-

**Table 4. Monthly case fatality rate for symptomatic lab-confirmed COVID-19 patients that have been hospitalized in the United States, during 2020, 2021, and 2022**

Period	all ages				age $\geq$ 50 years			
	Cases	Died	Lived	CFR	Cases	Died	Lived	CFR
2020-01	116	1	40	0.86% to 2.44%	5	0	3	0% to 0%
2020-02	675	32	158	4.74% to 16.84%	213	30	2	14.08% to 93.75%
2020-03	57,703	8,842	28,437	15.32% to 23.72%	40,115	8,179	17,344	20.39% to 32.05%
2020-04	72,381	14,518	34,419	20.06% to 29.67%	53,379	14,299	21,789	26.79% to 39.62%
2020-05	39,618	4,011	18,999	10.12% to 17.43%	26,388	3,952	10,862	14.98% to 26.68%
2020-06	44,871	2,890	20,431	6.44% to 12.39%	28,294	2,816	11,522	9.95% to 19.64%
2020-07	68,853	6,265	30,435	9.1% to 17.07%	47,177	6,096	19,003	12.92% to 24.29%
2020-08	45,017	2,871	18,907	6.38% to 13.18%	31,685	2,823	12,186	8.91% to 18.81%
2020-09	35,309	1,362	15,313	3.86% to 8.17%	25,422	1,352	10,201	5.32% to 11.7%
2020-10	57,586	3,322	26,318	5.77% to 11.21%	43,464	3,305	18,964	7.6% to 14.84%
2020-11	100,089	10,093	42,949	10.08% to 19.03%	76,327	10,009	31,164	13.11% to 24.31%
2020-12	114,978	15,288	43,773	13.3% to 25.89%	89,545	14,966	32,387	16.71% to 31.61%
2021-01	94,337	10,861	38,448	11.51% to 22.03%	73,653	10,699	28,894	14.53% to 27.02%
2021-02	43,836	2,071	18,912	4.72% to 9.87%	32,732	2,060	13,591	6.29% to 13.16%
2021-03	40,133	947	19,824	2.36% to 4.56%	27,244	947	12,830	3.48% to 6.87%
2021-04	40,967	934	20,506	2.28% to 4.36%	25,778	907	12,054	3.52% to 7%
2021-05	24,688	279	11,007	1.13% to 2.47%	15,043	268	6,027	1.78% to 4.26%
2021-06	15,473	170	5,643	1.1% to 2.92%	8,542	169	2,714	1.98% to 5.86%
2021-07	39,648	2,317	15,427	5.84% to 13.06%	23,885	2,125	8,457	8.9% to 20.08%
2021-08	73,527	6,515	29,620	8.86% to 18.03%	47,668	6,147	17,409	12.9% to 26.1%
2021-09	59,634	4,011	24,769	6.73% to 13.94%	40,547	3,928	15,395	9.69% to 20.33%
2021-10	43,956	2,146	18,536	4.88% to 10.38%	31,163	2,112	12,201	6.78% to 14.76%
2021-11	45,134	2,980	19,892	6.6% to 13.03%	32,053	2,926	13,034	9.13% to 18.33%
2021-12	66,184	5,095	33,474	7.7% to 13.21%	43,197	4,998	19,144	11.57% to 20.7%
2022-01	85,570	10,295	32,695	12.03% to 23.95%	62,477	10,164	22,269	16.27% to 31.34%
2022-02	26,227	1,292	9,546	4.93% to 11.92%	19,930	1,287	7,048	6.46% to 15.44%
2022-03	8,837	103	3,338	1.17% to 2.99%	6,163	103	2,186	1.67% to 4.5%
2022-04	9,862	92	4,350	0.93% to 2.07%	7,160	91	3,074	1.27% to 2.88%
2022-05	20,395	384	8,812	1.88% to 4.18%	14,497	384	6,278	2.65% to 5.76%
2022-06	20,881	527	9,021	2.52% to 5.52%	15,797	527	6,649	3.34% to 7.34%
2022-07	25,504	748	11,067	2.93% to 6.33%	19,396	742	8,219	3.83% to 8.28%
2022-08	20,540	467	9,106	2.27% to 4.88%	15,703	467	6,804	2.97% to 6.42%
2022-09	14,671	254	6,618	1.73% to 3.7%	11,250	254	4,910	2.26% to 4.92%
2022-10	13,704	182	6,773	1.33% to 2.62%	10,988	182	5,291	1.66% to 3.33%
2022-11	15,120	345	7,088	2.28% to 4.64%	11,987	345	5,350	2.88% to 6.06%
2022-12	12,305	105	5,495	0.85% to 1.88%	9,724	105	4,171	1.08% to 2.46%

Calculations used a CDC database<sup>38)</sup>, accessed January 20, 2023.

CFR = Case Fatality Rate; lower bound is (Died)/(Cases) and assumes survival for all cases with unknown outcome; upper bound is (Died)/(Lived+Died), and assumes that for all patient cases with an unknown outcome the proportion of fatalities is equal to the proportion of fatalities in the cases where the outcome is known.

ported in South Africa hospitals. Therefore, for external control purposes, it is important to consider the averaged CFR of hospitalized patients over the entire treatment time period.

Table 5 shows the average CFR of hospitalized patients for the time period during which patients were treated for the Hazan case series, between August 2020 and February 2021, and the cumulative CFR of hospitalized patients through the end of the Hazan case series treatment time period (January 2020 to February 2021). The CFR of hospitalized patients is reported over all age brackets and over the age  $\geq$  50 years age brackets. Using the age  $\geq$  50 restriction as a proxy for

**Table 5. Cumulative case fatality rate for symptomatic lab confirmed COVID-19 patients that have been hospitalized in the United States over specific time periods**

Period	Cases	Died	Lived	CFR
CFR for confirmed hospitalizations over all age groups				
First pre-delta period: 2020-01 to 2020-09	364,543	40,792	167,139	11.19% to 19.62%
Second pre-delta period: 2020-10 to 2021-02	410,826	41,635	170,400	10.13% to 19.64%
Third pre-delta period: 2021-03 to 2021-06	121,261	2,330	56,980	1.92% to 3.93%
Delta: 2021-07 to 2021-12	328,083	23,064	141,718	7.03% to 14%
Early Omicron: 2022-01 to 2022-03	120,634	11,690	45,579	9.69% to 20.41%
Late Omicron: 2022-04 to 2022-12	152,982	3,104	68,330	2.03% to 4.35%
Hazan (treatment interval): 2020-08 to 2021-02	491,152	45,868	204,620	9.34% to 18.31%
Hazan (cumulative): 2020-01 to 2021-02	775,369	82,427	337,539	10.63% to 19.63%
CFR for confirmed hospitalizations for age $\geq 50$				
First pre-delta period: 2020-01 to 2020-09	252,678	39,547	102,912	15.65% to 27.76%
Second pre-delta period: 2020-10 to 2021-02	315,721	41,039	125,000	13% to 24.72%
Third pre-delta period: 2021-03 to 2021-06	76,607	2,291	33,625	2.99% to 6.38%
Delta: 2021-07 to 2021-12	218,513	22,236	85,640	10.18% to 20.61%
Early Omicron: 2022-01 to 2022-03	88,570	11,554	31,503	13.05% to 26.83%
Late Omicron: 2022-04 to 2022-12	116,502	3,097	50,746	2.66% to 5.75%
Hazan (treatment interval): 2020-08 to 2021-02	372,828	45,214	147,387	12.13% to 23.48%
Hazan (cumulative): 2020-01 to 2021-02	568,399	80,586	227,912	14.18% to 26.12%

Calculations used a CDC database<sup>38</sup>, accessed January 20, 2023. The timing for the virus waves reported in this table is consistent with Adjei *et al.*<sup>32</sup>.

CFR = Case Fatality Rate; lower bound is (Died)/(Cases) and assumes survival for all cases with unknown outcome; upper bound is (Died)/(Lived+Died), and assumes that for all patient cases with an unknown outcome the proportion of fatalities is equal to the proportion of fatalities in the cases where the outcome is known.

hypoxemia, we obtained a conservative 12.13% lower-bound for the CFR of hospitalized patients over the treatment time period that the risk-stratified Hazan case series should be compared against. The cumulative CFR of hospitalized patients through February 2021 had a 14.18% lower bound, which is consistent with the external control used by Hazan *et al.*<sup>19</sup>). However, we believe that 12% is the most reliable lower bound for the CFR of hospitalized patients for United States patients during the treatment period of the Hazan case series.

Because of the substantial amount of missing data on mortality outcomes in the CDC database<sup>38</sup>, we also considered, as an alternate external control group, a CDC study<sup>32</sup>) of the in-hospital CFR for patients hospitalized across the United States obtained from the Premier Healthcare Database Special COVID-19 release<sup>66</sup>) (hereafter PHD-SR), in order to confirm consistency with the CFR intervals obtained from the CDC database<sup>38</sup>). The PHD-SR database reported data from several hundreds of hospitals across the United States. Table 6 shows the in-hospital CFR with or without the restriction age  $\geq 50$  years during the Delta wave (July 2021 to October 2021), early Omicron wave (January 2022 to March 2022), and late Omicron wave (April 2022 to June 2022), calculated from the data reported by the CDC report<sup>38</sup>) on the PHD-SR database. Table 5 shows the intervals for the CFR of hospitalized patients during the same waves, in addition to the pre-delta periods, as defined by Adjei *et al.*<sup>32</sup>), to compare them against the numbers reported from the PHD-SR database on Table 6. There was no consistent pattern over the available waves regarding

**Table 6. Case fatality rate for hospitalized patients, as reported in the United States, South Africa, Zimbabwe, Nigeria, and worldwide**

Location	Period	Cases	Died	CFR
CFR for confirmed hospitalizations over all age groups				
United States PHD-SR (Delta) <sup>32)</sup>	2021-07 to 2021-10	163,094	24,658	15.12%
United States PHD-SR (Early Omicron) <sup>32)</sup>	2022-01 to 2022-03	104,395	13,701	13.12%
United States PHD-SR (Late Omicron) <sup>32)</sup>	2022-04 to 2022-06	20,655	1,004	4.86%
South Africa (first wave) <sup>31)</sup>	2020-03 to 2020-08	83,742	17,042	20.35%
South Africa (beta) <sup>31)</sup>	2020-09 to 2021-03	135,472	33,999	25.1%
South Africa (combined) <sup>31)</sup>	2020-03 to 2021-03	219,214	51,041	23.28%
Zimbabwe (Parirenyatwa hospitals) <sup>33)</sup>	2020-06 to 2020-12	336	119	35.42%
Zimbabwe (Mashonaland West Province) <sup>34)</sup>	2020-04 to 2022-04	673	157	23.33%
Lagos, Nigeria (all patients) <sup>35)</sup>	2020-04 to 2020-10	266	37	13.91%
Lagos, Nigeria (only hypoxemic patients) <sup>35)</sup>	2020-04 to 2020-10	102	32	31.37%
Kano State, Nigeria (all patients) <sup>36)</sup>	2020-04 to 2021-03	195	21	10.77%
Kano State, Nigeria (without asymptomatic) <sup>36)</sup>	2020-04 to 2021-03	77	14	18.18%
World Heart Federation study (all patients) <sup>37)</sup>	2020-06 to 2021-09	5,313	801	15.08%
World Heart Federation study (LMIC) <sup>37)</sup>	2020-06 to 2021-09	2,526	492	19.48%
CFR for confirmed hospitalizations for age $\geq 50$				
United States PHD-SR (Delta) <sup>32)</sup>	2021-07 to 2021-10	114,336	20,943	18.32%
United States PHD-SR (Early Omicron) <sup>32)</sup>	2022-01 to 2022-03	88,639	12,914	14.57%
United States PHD-SR (Late Omicron) <sup>32)</sup>	2022-04 to 2022-06	17,675	961	5.44%

CFR = Case Fatality Rate; PHD-SR = Premier Healthcare Database Special COVID-19 Release<sup>66)</sup>

whether the actual CFR of hospitalized patients was more likely to be closer to the lower bound rather than the upper bound obtained from the CDC case surveillance database<sup>38)</sup>, except that it tended to be confined within the neighborhood of those bounds.

### 3.3. Description of external controls for Africa

Table 6 shows the estimated CFR for hospitalized patients from the African external control groups<sup>31, 33–37)</sup>, and the corresponding total number of cases and the time period for each of the external controls.

For Zimbabwe, the most relevant external control group is the unpublished statistics of the in-hospital CFR in the Parirenyatwa group of hospitals in Harare, Zimbabwe, between May 2020 and December 2020<sup>33)</sup>, reporting a 35.42% CFR for hospitalized patients. Because this period intersects, but does not entirely overlap, with the treatment time interval corresponding to the Stone case series<sup>18)</sup>, we also considered an alternative external control group from the nearby Mashonaland West Province, Zimbabwe<sup>34)</sup>, ranging between April 2020 and April 2022, reporting a 23.33% CFR for hospitalized patients. Since the predominant variant in the Stone case series was the Beta variant<sup>18, 40)</sup>, and because both external control groups had small sample size, we also considered, as an additional external control group the in-hospital CFR in South Africa, which was reported on a month-to-month basis between March 2020 and March 2021, with substantially larger sample sizes<sup>31)</sup>. The average CFR for hospitalized patients in South Africa over the

entire reported time period was 23.28%. During the time period between September 2020 and March 2021, during which the beta variant was dominant in South Africa, the reported hospitalized CFR for hospitalized patients was 25.1%, and in the pre-beta time period it was 20.35%.

For Nigeria, the availability of external control groups for estimating the CFR for hospitalized patients is very limited, however, we identified the following two studies: The first study<sup>35)</sup> consisted of 226 hospitalized COVID-19 patients in Lagos, Nigeria, who were treated between April 2020 and October 2020 in the Lagos University Teaching Hospital, and reported an overall 13.91% CFR. The facility served both as an isolation center for COVID-19 patients, for contagion control purposes, and as an inpatient treatment center for patients with moderate or severe COVID-19. As a result, the study underestimated the true CFR of in-patients, noting that 30.5% of the treated patients were initially asymptomatic. The study also explicitly reported 31.37% CFR for hypoxemic hospitalized patients, with hypoxemia defined by the authors as  $\text{SpO}_2 \leq 90\%$  for adults and  $\text{SpO}_2 \leq 92\%$  in children. Patients were treated with artemether-lumefantrine, ritonavir-boosted lopinavir, azithromycin, and Vitamin C between April 2020 and June 2020, however, further details of the treatment protocol were not given.

The second study<sup>36)</sup> consisted of 195 COVID-19 patients from Kano State, Nigeria, treated at the Kwanar Dawaki isolation center over a wider period between April 2020 and March 2021. Similarly to the preceding study, the facility operated both as an isolation center and an inpatient treatment center, thus including patients whose initial COVID-19 presentation was asymptomatic, mild to moderate, or severe to life-threatening. The authors reported the mortality outcomes for each of these three presentations, and for our statistical analysis we calculated the CFR, both including and excluding the patients in the initially asymptomatic category: over all patients, the average CFR was 10.77%, and excluding the asymptomatic patients the average CFR increased to 18.18%. We note that patients with mild or moderate COVID-19 were treated with Vitamin C, zinc sulfate, paracetamol, and loratadine. Between April 2020 and October 2020, patients with severe or life-threatening disease were also treated with azithromycin, hydroxychloroquine, oxygen, heparin, lopinavir, and corticosteroids. Between November 2020 and March 2021 hydroxychloroquine and lopinavir were replaced with calcium supplements and ivermectin. Further details of the respective treatment protocols were not provided.

Finally, we cited a World Heart Federation study<sup>37)</sup> of 5,313 consecutive COVID-19 patients, prospectively recruited between June 2020 and September 2021 from 40 hospitals across 23 different countries, representing a geographically and economically diverse sampling of countries that included countries classified by the World Bank as lower income countries (LIC), lower or middle income countries (LMIC), middle income countries (MIC), and high income countries (HIC). The combined CFR for the entire sample of patients was 15.08%. Noting that both Zimbabwe and Nigeria are classified by the World Bank as LMIC<sup>67)</sup>, the CFR obtained from the subgroup of patients recruited from LMIC countries was 19.48%. In both calculations the CFR in-

**Table 7. Efficacy thresholds and random selection bias thresholds for the mortality endpoint and the hospitalization endpoint for the case series by Hazan *et al.*<sup>19)</sup>, Stone *et al.*<sup>18)</sup>, Babalola *et al.*<sup>20)</sup>, and the combined case series**

Mortality rate reduction thresholds using 95% confidence intervals						
Case series (SpO <sub>2</sub> ≤ 90%)	( <i>N</i> , <i>a</i> )	<i>x</i> <sub>0</sub>	log <sub>10</sub> <i>B</i>	<i>p</i> <sub>2</sub>	<i>y</i> <sub>0</sub>	<i>x</i> <sub>1</sub>
Hazan	(23, 0)	14.6%	1.99	23.48%	14.7%	38.9%
Stone	(28, 0)	12.0%	2.13	23.3%	12.0%	32.0%
Hazan + Babalola	(33, 0)	10.2%	2.03	18.18%	10.2%	28.5%
Stone + Babalola	(38, 0)	8.9%	2.14	18.18%	8.9%	24.8%
Hazan + Stone	(51, 0)	7.4%	1.97	10%	7.6%	18.5%
Hazan + Stone + Babalola	(61, 0)	6.2%	2.12	10%	6.2%	16.2%
Hospitalization rate reduction thresholds using 95% confidence intervals						
Case series (SpO <sub>2</sub> ≤ 100%)	( <i>N</i> , <i>a</i> )	<i>x</i> <sub>0</sub>	log <sub>10</sub> <i>B</i>	<i>p</i> <sub>2</sub>	<i>y</i> <sub>0</sub>	<i>x</i> <sub>1</sub>
Hazan	(24, 0)	14.0%	2.94	95.8%	14.0%	37.3%
Stone	(34, 1)	15.7%	2.57	82.3%	15.7%	33.7%
Babalola	(61, 5)	17.9%	1.64	34.4%	20.0%	33.6%
Hazan + Babalola	(85, 5)	13.4%	2.05	38.8%	13.4%	23.5%
Stone + Babalola	(95, 6)	13.1%	1.96	40%	13.3%	22.1%
Hazan + Stone	(58, 1)	9.2%	2.77	87.9%	9.2%	21.4%
Hazan + Stone + Babalola	(119, 6)	10.8%	2.32	51.3%	10.8%	18.0%

*N* = number of patients in the case series; *a* = number of adverse outcomes with treatment (hospitalizations or deaths respectively); *x*<sub>0</sub> = efficacy threshold controlling only the *p*-value requirement  $p(N, a, x) < 0.05$  for all  $x > x_0$ ; log<sub>10</sub> *B* = decimal logarithm of Bayes factor  $B(N, a, x_0, p_2)$  evaluated at the efficacy threshold *x*<sub>0</sub>, comparing the null hypothesis  $H_0: 0 \leq q \leq x_0$  against the alternate hypothesis  $H_1: x_0 \leq q \leq 1$ , with *q* the expected probability of an adverse event with treatment; *p*<sub>2</sub> = expected worst-case probability of an adverse event without treatment; *y*<sub>0</sub> = adjusted efficacy threshold controlling both the *p*-value and the requirement log<sub>10</sub>  $B(N, a, x, p_2) \geq 2$  for all  $x > y_0$ ; *x*<sub>1</sub> = random selection bias threshold.

cluded both in-hospital deaths and deaths within 30 days after discharge.

### 3.4. Case series threshold analysis

Table 7 shows the results of our calculation of the efficacy threshold and random selection bias threshold for the case series listed in Table 3, both with respect to the mortality rate reduction endpoint and the hospitalization rate reduction endpoint. Shown on the table are: the unadjusted efficacy threshold *x*<sub>0</sub> that controls the *p*-value; the corresponding Bayes factor log<sub>10</sub> *B* for the alternate hypothesis *H*<sub>1</sub> evaluated at the unadjusted efficacy threshold *x*<sub>0</sub>; the adjusted efficacy threshold *y*<sub>0</sub> which controls both the *p*-value and the Bayes factor; the random selection bias threshold *x*<sub>1</sub> calculated from *y*<sub>0</sub>. For the hospitalization rate reduction endpoint, we used the entire case series without risk stratification in the threshold calculations. Not excluding the lower risk patients results in a more conservative argument.

As explained in the methods section, the adjusted efficacy threshold *y*<sub>0</sub> is adjusted upwards from the efficacy threshold *x*<sub>0</sub> when log<sub>10</sub> *B* < 2, to control both the *p*-value and the Bayes factor. Except for the Babalola case series threshold for the hospitalization rate reduction endpoint, which was increased by 2.1%, all other adjustments to the efficacy threshold were less than 0.2%. The parameter *p*<sub>2</sub>, shown on Table 7, is the expected worst-case probability of an adverse out-

come in the control, and it is used to define the priors used in the calculation of the Bayes factor  $\log_{10} B$ . Decreasing  $p_2$  tends to decrease the contrast between the null hypothesis  $H_0$  and the alternate hypothesis  $H_1$  in the calculation of  $\log_{10} B$ , so the conservative approach is to use lower bounds for  $p_2$ .

For the mortality rate reduction endpoint, the  $p_2$  parameter was chosen as follows. For the Hazan case series, we considered measures of the United States CFR for hospitalized patients over the treatment period between August 2020 and February 2021 as shown on Table 4. The peak month by month CFR for hospitalized patients without any age restriction occurred on December 2020, ranging from 13.3% to 25.89%, suggesting 25.89% as a possible choice for  $p_2$ ; however, the CFR for hospitalized patients averaged over the entire treatment period with the age  $\geq 50$  years restriction is reported on Table 5 as ranging from 12.13% to 23.48%. Thus, we chose the smallest of the two upper bounds and set  $p_2 = 23.48\%$ . For the Stone case series we chose  $p_2 = 23.3\%$ , which was the smallest number between: (a) the 35.42% CFR for hospitalized patients reported in the Parirenyatwa hospitals in Harare, Zimbabwe; (b) the 23.33% CFR for hospitalized patients reported in the Mashonaland West Province, Zimbabwe (see Table 6). For the combined case series Hazan + Babalola and Stone + Babalola, we used  $p_2 = 18.18\%$ , which was the CFR for patients hospitalized in Kano State, Nigeria, excluding the asymptomatic patients, as shown on Table 6, noting that it is the more conservative choice given that higher values for  $p_2$  were chosen for the Hazan and Stone case series. For the combined case series Hazan + Stone and Hazan + Stone + Babalola, there was sufficient statistical power to ensure that any value  $p_2 \geq 10\%$  does not result in any non-negligible upward adjustment of the efficacy threshold  $x_0$ , so we chose  $p_2 = 10\%$ .

For the hospitalization reduction rate endpoint, we set  $p_2$  equal to the counterfactual hospitalization rate for the self-control, which was lower-bounded by the percentage of patients with baseline room air  $\text{SpO}_2 \leq 90\%$  shown on Table 3, for all case series except for the Babalola case series. This was the most conservative choice possible, and it did not result in any upwards adjustments of the efficacy thresholds larger than 0.2%. For the Babalola case series, this choice was mathematically inconsistent because the counterfactual hospitalization rate fails to exceed the unadjusted efficacy threshold, consequently we used the less conservative choice of setting  $p_2 = 34.4\%$  equal to the percentage of patients that were hypoxemic with room air baseline  $\text{SpO}_2 \leq 93\%$  (21 patients out of 61, as shown on Table 3).

### 3.5. Existence of hospitalization rate reduction efficacy

Table 8 shows the odds ratio, 95% confidence interval, and the exact Fisher test  $p$ -value obtained from the comparison between the complete case series ( $N, a$ ) and the corresponding self control series ( $N, b$ ). Here,  $N$  is the total number of patients,  $a$  is the factual number of hospitalization events that include the reported use of supplemental oxygen and the use of ventilators,

**Table 8. Self-controlled exact Fisher test comparisons of factual vs counterfactual hospitalization events in the Hazan *et al.*<sup>19)</sup>, Stone *et al.*<sup>18)</sup>, and Babalola *et al.*<sup>20)</sup> case series and in the combined case series**

Case series	( <i>N</i> , <i>a</i> )	( <i>N</i> , <i>b</i> )	OR (95% CI)	<i>p</i> -value
Hazan	(24, 0)	(24, 23)	0 (0–0.02)	10 <sup>−12</sup>
Stone	(34, 1)	(34, 28)	10 <sup>−3</sup> (10 <sup>−4</sup> –0.06)	10 <sup>−12</sup>
Babalola	(61, 5)	(61, 10)	0.46 (0.11–1.59)	0.27
Hazan + Babalola	(85, 5)	(85, 33)	0.1 (0.03–0.28)	10 <sup>−7</sup>
Stone + Babalola	(95, 6)	(95, 38)	0.1 (0.03–0.26)	10 <sup>−8</sup>
Hazan + Stone	(58, 1)	(58, 51)	10 <sup>−3</sup> (10 <sup>−5</sup> –0.02)	10 <sup>−23</sup>
Hazan + Stone + Babalola	(119, 6)	(119, 61)	0.05 (0.02–0.13)	10 <sup>−16</sup>

(*N*, *a*) = treatment case series with *N* patients and *a* factual hospitalization events (use of supplemental oxygen or ventilator); (*N*, *b*) = counterfactual control case series with *N* patients and at least *b* counterfactual hospitalizations, lower-bounded by the number of patients with baseline room air SpO<sub>2</sub> ≤ 90%; OR = odds ratio; CI = confidence interval.

and *b* is a lower bound of the counterfactual number of hospitalizations that would have occurred if one had followed standard hospitalization guidelines, obtained by counting the number of patients with baseline room air SpO<sub>2</sub> ≤ 90%. A statistically significant reduction in the hospitalization rate was inferred for the Hazan and Stone case series and for the combined Hazan + Stone, Hazan + Babalola, Stone + Babalola, and Hazan + Stone + Babalola case series. The Babalola case series, by itself, failed to achieve statistically significant hospitalization rate reduction. These comparisons are biased towards the null hypothesis of no efficacy because *b* underestimates the total number of counterfactual hospitalizations that would have occurred under the standard guidelines. Because of the self-controlled design, these comparisons are not susceptible to selection bias, however, hospitalization is not an entirely objective endpoint, therefore there is the possibility of some bias in the estimation of the counterfactual hospitalization rate lower bounds, which can mathematically be redefined as an equivalent selection bias in the treatment arm.

The selection bias tolerance *F* can be used to quantify the magnitude of the gap between the random selection bias threshold and the counterfactual hospitalization rate. For the combined Hazan + Stone case series, using *p*<sub>1</sub> = 87.9% and *x*<sub>1</sub> = 21.4%, gives a selection bias tolerance *F* = 26.7. Including the Babalola case series, for the combined Hazan + Stone + Babalola case series, this selection bias tolerance decreases to *F* = 4.8 (using *p*<sub>1</sub> = 51.3% and *x*<sub>1</sub> = 18.0%). In both cases the systemic selection bias tolerance is high enough for a clear and convincing finding for hospitalization rate reduction with excellent resilience. The combinations Hazan + Babalola and Stone + Babalola are relevant only for sensitivity analysis, and the corresponding selection bias tolerance is *F* = 2.06 (Hazan + Babalola, with *p*<sub>1</sub> = 38.8% and *x*<sub>1</sub> = 23.5%) and *F* = 2.35 (Stone + Babalola, with *p*<sub>1</sub> = 40% and *x*<sub>1</sub> = 22.1%). Both results give acceptable resilience.

### 3.6. Mortality rate reduction efficacy for the Hazan, Stone, and Babalola case series

Table 9 shows exact Fisher test comparisons between the appropriate external control groups and the Hazan, Stone, Babalola case series, as well as the four combined case series. For the

**Table 9** Exact Fisher test comparisons between the Hazan *et al.*<sup>19)</sup>, Stone *et al.*<sup>18)</sup>, and Babalola *et al.*<sup>20)</sup> case series and corresponding external control groups from Table 5 and Table 6, with respect to mortality rate reduction

External control	( <i>N</i> , <i>a</i> )	( <i>M</i> , <i>b</i> )	OR (95% CI)	<i>p</i> -value
Hazan case series compared with				
CDC (treatment interval, any age)	(23, 0)	(491,152, 45,868)	0 (0–1.69)	0.267
CDC (treatment interval, age ≥ 50)	(23, 0)	(372,828, 45,214)	0 (0–1.26)	0.103
CDC (cumulative, any age)	(23, 0)	(775,369, 82,427)	0 (0–1.46)	0.165
CDC (cumulative, age ≥ 50)	(23, 0)	(568,399, 80,586)	0 (0–1.05)	0.065
World Heart Federation study (all patients)	(23, 0)	(5,313, 801)	0 (0–0.98)	0.039
Stone case series compared with				
Zimbabwe (Parirenyatwa hospitals)	(28, 0)	(336, 119)	0 (0–0.26)	10 <sup>-5</sup>
Zimbabwe (Mashonaland West Province)	(28, 0)	(673, 157)	0 (0–0.47)	10 <sup>-4</sup>
South Africa (beta)	(28, 0)	(135,472, 33,999)	0 (0–0.42)	10 <sup>-4</sup>
South Africa (combined)	(28, 0)	(219,214, 51,041)	0 (0–0.46)	0.001
World Heart Federation study (LMIC)	(28, 0)	(2,526, 492)	0 (0–0.58)	0.003
Babalola case series compared with				
Lagos, Nigeria (only hypoxemic patients)	(10, 0)	(102, 32)	0 (0–1.05)	0.06
Kano State, Nigeria (without asymptomatic)	(10, 0)	(77, 14)	0 (0–2.3)	0.355
World Heart Federation study (LMIC)	(10, 0)	(2,526, 492)	0 (0–1.85)	0.225
Hazan + Babalola case series compared with				
CDC (treatment interval, any age)	(33, 0)	(491,152, 45,868)	0 (0–1.15)	0.07
CDC (treatment interval, age ≥ 50)	(33, 0)	(372,828, 45,214)	0 (0–0.86)	0.028
World Heart Federation study (all patients)	(33, 0)	(5,313, 801)	0 (0–0.67)	0.011
Stone + Babalola case series compared with				
CDC (treatment interval, any age)	(38, 0)	(491,152, 45,868)	0 (0–0.99)	0.046
CDC (treatment interval, age ≥ 50)	(38, 0)	(372,828, 45,214)	0 (0–0.74)	0.012
World Heart Federation study (all patients)	(38, 0)	(5,313, 801)	0 (0–0.58)	0.005
Hazan + Stone case series compared with				
CDC (treatment interval, any age)	(51, 0)	(491,152, 45,868)	0 (0–0.73)	0.013
CDC (treatment interval, age ≥ 50)	(51, 0)	(372,828, 45,214)	0 (0–0.54)	0.002
World Heart Federation study (all patients)	(51, 0)	(5,313, 801)	0 (0–0.42)	10 <sup>-4</sup>
Hazan + Stone + Babalola case series compared with				
CDC (treatment interval, any age)	(61, 0)	(491,152, 45,868)	0 (0–0.61)	0.006
CDC (treatment interval, age ≥ 50)	(61, 0)	(372,828, 45,214)	0 (0–0.45)	10 <sup>-4</sup>
World Heart Federation study (all patients)	(61, 0)	(5,313, 801)	0 (0–0.35)	10 <sup>-5</sup>

(*N*, *a*) = treatment case series with *N* cases and *a* deaths; (*M*, *b*) = external control with *M* cases and *b* deaths with data shown on Table 5 and Table 6; OR = Odds Ratio; CI = Confidence Interval; The case series have been risk-stratified under the SpO<sub>2</sub> ≤ 90% constraint for the baseline room air oxygen saturation, to make them comparable with the CFR of hospitalized patients. Lower bounds are used for the CDC external control.

Hazan case series, exact Fisher test comparisons are shown between the risk-stratified Hazan case series with (*N*, *a*) = (23, 0) and the lower bounds of the CDC external controls and the CFR of hospitalized patients from the World Heart Federation study<sup>37)</sup>. Regardless of whether the treatment interval CFR or the cumulative CFR is used, and whether the age ≥ 50 years constraint is used for the definition of the external control group, all comparisons fail to demonstrate a statistically significant effect. Borderline statistical significance is obtained only when one compares the

Hazan risk-stratified case series against the World Heart Federation study<sup>37)</sup>, which provided a 15.08% global CFR for hospitalized patients. Similar results are obtained when the risk-stratified Hazan case series is analyzed using the case series threshold analysis method<sup>56)</sup>. Comparing the CFR for hospitalized patients from all CDC external controls, using either the treatment interval or the cumulative interval, and using either all ages or the age  $\geq 50$  years constraint, against the adjusted efficacy threshold  $y_0 = 14.7\%$ , we see that all lower bound estimates of the CFR are below  $y_0$  and all upper bound estimates of the CFR for hospitalized patients are above  $y_0$ . It is therefore unclear whether the existence of mortality rate reduction has been established by the preponderance of evidence. With the age  $\geq 50$  years restriction, the corresponding cumulative CFR lower bound for hospitalized patients is 14.18% which is very close to the adjusted efficacy threshold of  $y_0 = 14.7\%$ ; however, the CFR lower bound for hospitalized patients over the treatment time period is reduced to 12.13%. We conclude that, although there is a very compelling signal of benefit, there is insufficient statistical power for a decisive finding of preponderance of evidence in support of mortality rate reduction, if we use the Hazan case series by itself.

For the Stone case series, we used the external control groups from Zimbabwe<sup>33, 34)</sup> and South Africa<sup>31)</sup>, shown on Table 6, and the subgroup of 2526 hospitalized patients from LMIC countries reported by the World Heart Federation study<sup>37)</sup>. All comparisons shown on Table 9 give a statistically significant mortality rate reduction finding with  $p \leq 0.003$ . The Parirenyatwa group of hospitals in Harare, Zimbabwe reported 35.4% CFR for hospitalized COVID-19 patients admitted between May 2020 and December 2020, which overlaps but does not encompass the treatment time period of the Stone case series<sup>33)</sup>. A reduced CFR for hospitalized patients of 23.3% was reported<sup>34)</sup> for COVID-19 patients in Mashonaland West Province, Zimbabwe between April 2020 and April 2022. Both reports are presented in Table 6. Combined, these two reports account for a total of 1009 patients with 27.3% averaged CFR for hospitalized patients, and they are consistent with the 23.28% averaged CFR for hospitalized patients reported in South Africa between March 2020 and March 2021<sup>31)</sup>, with a substantially larger sample size of 219214 hospitalized patients. The predominant strain during the Stone case series treatment time interval was the Beta variant, with the Delta variant appearing at the tail end of the treatment time interval<sup>40)</sup>. In South Africa, the Beta variant was dominant between September 2020 and March 2021 (the published monthly CFR data for hospitalized patients did not go beyond March 2021), and an increased CFR of 25.1% for hospitalized patients was observed during that time, up from a 20.35% CFR for hospitalized patients during the preceding wave. The World Heart Federation measured 19.48% CFR for hospitalized patients in LMIC countries, such as Zimbabwe<sup>37)</sup>. These numbers can be compared against the mortality rate reduction endpoint thresholds calculated on Table 7, where we reported for the Stone case series  $y_0 = 12.0\%$  adjusted efficacy threshold and  $x_1 = 32.0\%$  random selection bias threshold. The adjusted efficacy threshold  $y_0 = 12.0\%$  is exceeded by the reported CFR for hospitalized patients from all of the above external controls,

therefore we can reliably claim a mortality rate reduction finding by the preponderance of evidence. Although, the 35.4% CFR for hospitalized patients reported for the Parirenyatwa hospitals in Harare, Zimbabwe<sup>33</sup>) exceeds the random selection bias threshold  $x_1 = 32.0\%$ , we hesitate to claim a clear and convincing finding, since this result is not sustained across the majority of the other external control groups.

For the Babalola case series, all comparisons shown on Table 9 between the risk-stratified case series  $(N, a) = (10, 0)$  and the external controls from Nigeria<sup>35, 36</sup>) and the World Heart Federation study<sup>37</sup>) failed to reach statistical significance. Nevertheless, the comparison with hospitalized hypoxemic patients in Lagos, Nigeria gives  $p = 0.06$  which is close to the threshold for statistical significance. There is insufficient statistical power to draw any reliable conclusions, consequently we did not calculate the adjusted efficacy threshold  $y_0$  or the random selection bias threshold  $x_1$ .

### 3.7. Mortality rate reduction efficacy for the combined case series

The combined Hazan + Stone case series includes 51 patients with baseline room air SpO<sub>2</sub>  $\leq 90\%$  and 0 deaths. In both case series, similar multidrug treatment protocols were used, with the overlapping medications being ivermectin, zinc sulfate, doxycycline, Vitamin C, and Vitamin D, resulting in similar rapid recovery rates of room air SpO<sub>2</sub> levels. The exact Fisher test comparisons, shown on Table 9, between the combined Hazan + Stone case series and the CDC database external controls over the treatment interval for the Hazan case series, both with and without the age  $\geq 50$  years restriction, as well as with the World Heart Federation study<sup>37</sup>) external control over all patients, consistently show a statistically significant reduction in mortality rate with  $p \leq 0.013$ . Furthermore, because the CFR lower bound for hospitalized patients in the United States external controls is substantially lower than the CFR for hospitalized patients in Zimbabwe and LMIC external controls, a positive finding using exclusively the United States external controls will be sustained if equivalent controls are used.

A comparison with an appropriate mixed external control is possible using the case series threshold analysis<sup>56</sup>) method. For the combined Hazan + Stone case series, as shown in Table 7, the adjusted efficacy threshold was  $y_0 = 7.6\%$  and the random selection bias threshold was  $x_1 = 18.5\%$ , both for mortality rate reduction. An estimated 12% lower bound for the CFR for hospitalized patients in the United States clearly exceeds the 7.6% adjusted efficacy threshold for the combined Hazan + Stone case series, so we can draw a decisive conclusion that mortality rate reduction can be claimed by the preponderance of evidence. If we use the 12% lower bound for 23 patients in the Hazan case series and the 20% lower bound for the 28 patients in the Stone case series, all with baseline room air SpO<sub>2</sub>  $\leq 90\%$ , the combined average CFR lower bound for hospitalized patients is 16.4%, which does not exceed the random selection bias threshold of 18.5%, so we can rule out a decisive clear and convincing claim.

It is also interesting to consider the combined Hazan + Stone + Babalola case series, which includes 61 patients with baseline room air  $\text{SpO}_2 \leq 90\%$  and 0 deaths. The exact Fisher test comparisons, reported on Table 9, between the combined Hazan + Stone + Babalola case series and the same external controls used in the previous comparison for the combined Hazan + Stone case series show statistically significant reduction in the mortality rate with  $p \leq 0.006$ . Furthermore, Table 7 shows the adjusted efficacy threshold and the random selection bias threshold for the combined Hazan + Stone + Babalola case series, which were  $y_0 = 6.2\%$  and  $x_1 = 16.2\%$  respectively for the mortality rate reduction endpoint. If we use the very conservative lower bound of 12% for the CFR of hospitalized patients under conventional treatment for all patients in the combined case series, then the 6.2% efficacy threshold is exceeded by a wide margin, which establishes decisively the existence of a mortality rate reduction benefit by the preponderance of evidence but fails to do so by the clear and convincing standard. On the other hand, if we use the 12% lower bound for the CFR of hospitalized patients for the 23 patients in the United States, and use the 19.5% CFR for hospitalized patients in LMIC nations from the World Heart Federation Study<sup>37)</sup> for the 38 patients in Nigeria and Zimbabwe, then the average CFR lower bound is 16.7%, which exceeds the random selection bias threshold of  $x_1 = 16.2\%$ , but with a very tight margin, making the claim susceptible to any systemic selection bias that might exist. Finally, if we adopt the most aggressive conservative lower bound for hospitalized CFR from the CDC case surveillance database<sup>38)</sup>, by disregarding the restriction age  $\geq 50$  years and using the smallest CFR lower bound for hospitalized patients amongst the first two pre-Delta periods, the Delta wave, and the Early Omicron wave, which is 7.3%, noting that the Beta wave that was dominant in both Zimbabwe<sup>40)</sup> and Nigeria<sup>21)</sup> was generally more lethal than preceding waves<sup>31)</sup>, we are still showing a decisive finding of the existence of mortality rate reduction by the preponderance of evidence.

Lastly, we considered, strictly for the purpose of sensitivity analysis, the combined Hazan + Babalola and Stone + Babalola case series. Table 9 shows that all of the exact Fisher test comparisons between the combined Stone + Babalola case series and the external controls show statistically significant mortality rate reduction with  $p < 0.046$ . For the combined Hazan + Babalola case series, comparison with the United States external control group of hospitalized patients from the CDC database<sup>38)</sup> with no age restrictions fails to reach statistical significance with  $p = 0.07$ . The other two comparisons are statistically significant with  $p < 0.028$ . As noted earlier, the age  $\geq 50$  years is an appropriate proxy for the additional risk factor of hypoxemia upon hospital admission for hospitalized patients, so the statistically significant comparison with the United States external control group of hospitalized patients from the CDC database with the age  $\geq 50$  years restriction is more appropriate. Table 7 reports  $y_0 = 10.2\%$  for the adjusted efficacy threshold of the combined Hazan + Babalola case series and  $y_0 = 8.9\%$  for the adjusted efficacy threshold of the combined Stone + Babalola case series. Both thresholds are exceeded by the

12% lower bound for the hospitalized CFR of hospitalized patients of both United States and African external controls, thereby establishing a mortality rate reduction finding by the preponderance of evidence.

#### 4. Discussion

We analyzed the case series of hypoxemic patients reported by Hazan *et al.*<sup>19)</sup>, Stone *et al.*<sup>18)</sup>, and Babalola *et al.*<sup>20–22)</sup> using a self-controlled case series methodology combined with the recently introduced case series statistical analysis technique<sup>56)</sup>, and showed clear and convincing evidence of the existence of some hospitalization rate reduction. More importantly, we quantified the considerable resilience of this result with respect to systemic selection bias, which can threaten the validity of the result, if the selection of patients from the general population is not random. For the Stone case series alone, the existence of mortality rate reduction can be shown by the preponderance of evidence, when compared with the hospitalized CFR in Zimbabwe, or South Africa, or more broadly with the average hospitalized CFR of LMIC nations. Combining the Hazan and Stone case series establishes decisively the existence of mortality rate reduction by the preponderance of evidence, even when compared against the most conservative estimate of CFR for hospitalized patients in the United States, under the age  $\geq 50$  years restriction. Including the Babalola case series, to combine all three case series, decisively shows mortality rate reduction by the preponderance of evidence even without the age  $\geq 50$  years restriction.

Babalola *et al.*<sup>20)</sup> found that adding hydroxychloroquine and azithromycin to ivermectin did not appear to contribute to faster clearance of the virus. However, the dosage of hydroxychloroquine was 200 mg/day for 3 days and the dosage for azithromycin was 500 mg/day for 3 days. In the original Zelenko protocol<sup>5)</sup>, hydroxychloroquine was administered at 200 mg twice a day for 5 days and azithromycin was given at the same dosage for 5 days as opposed to 3 days. Thus, one cannot rule out the possibility that the lack of a positive effect could be attributed to underdosing, and the result does not necessarily extrapolate to the early treatment of COVID-19, initiated before the deterioration of SpO<sub>2</sub> levels. Hazan communicated to us that in her clinical experience adding hydroxychloroquine and azithromycin to her baseline protocol of ivermectin, doxycycline, zinc, and vitamins C and D was necessary to eradicate the virus for some of her patients<sup>43)</sup>.

Because for all three case series, patients were treated before the emergence of the omicron variants, natural immunity remained protective with respect to reinfections<sup>68)</sup>, so it is very likely that the results have not been confounded by prior immunity. Babalola and colleagues<sup>20)</sup> reported that their 61 patients, who were treated with the ivermectin-based multidrug protocols were not vaccinated. In the United States, the vaccine roll out started in mid-December 2020<sup>69)</sup>, and given the two-dose schedule we expect that patients in the Hazan case series were not fully vaccinated until the beginning of February 2021, which was the final month for the treatment time period of

the Hazan case series<sup>19)</sup>. Furthermore, the treatment time period for the Hazan case series does not intersect with the third pre-delta period<sup>19, 32)</sup> during which a substantial decline in the hospitalized CFR was observed in the CDC database<sup>38)</sup>. In Zimbabwe, vaccines were rolled out on February 2021<sup>70)</sup>, so they were available for 4 out of 10 months of the treatment time period for the Stone case series<sup>18)</sup>. Nevertheless, given that all patients in the Stone case series presented with baseline room air SpO<sub>2</sub> ≤ 93% and all but one of the patients in the Hazan case series presented with SpO<sub>2</sub> ≤ 90%, we can infer that there was insufficient antiviral immune response at the initial onset of the illness, specifically for any of the selected patients in these case series that may have been fully vaccinated.

With the emergence of the Omicron variants during 2022, the overall CFR in the United States decreased and the earlier Delta variants were displaced because natural immunity against Omicron variants also prevented infections with the Delta variant<sup>71)</sup>. The decreased lethality of the Omicron variants can be explained by their reduced efficiency in invading the lung parenchyma and, from there, the bloodstream<sup>72)</sup>. However, the *in vitro* study by Boschi *et al.*<sup>73)</sup> showed that the Omicron spike proteins induce red blood cell clumping even at approximately 10 times less minimum concentration than the spike proteins of the Wuhan, Alpha, and Delta variants, which can be explained, in part, by the increased electrostatic surface potential of the Omicron spike proteins<sup>73)</sup>. Boschi *et al.*<sup>73)</sup> also showed that the minimum ivermectin concentration needed to inhibit or release hemagglutination induced by the Omicron spike protein is equal to the minimum ivermectin concentration needed to result in the same effect against the Delta spike protein. Furthermore, Table 4 shows that, although COVID-19 hospitalizations decreased during the Late Omicron period in the United States, some patients still presented with severe life-threatening COVID-19 disease. Ivermectin-based multidrug protocols remain relevant for handling these severe cases.

Our statistical analysis has several limitations. The main weakness of our analysis is the small sample size of the case series, even when combining all three series, that prevents us from establishing a claim of clear and convincing mortality rate reduction with some modest amount of systemic selection bias tolerance. The reported results are applicable to the variants that were circulating at the time and other variants of comparable lethality. Using baseline room air SpO<sub>2</sub> ≤ 90% as a proxy for calculating a lower bound for the counterfactual hospitalization rate, under the conventional standard of care, is inevitably based on subjective hospitalization thresholds recommended by the official standard of care guidelines promulgated by the NIH<sup>47)</sup> and other government agencies worldwide. The CDC case surveillance database<sup>38)</sup> external control group has a considerable amount of missing data, forcing us to use lower bound estimates of the hospitalized CFR that are likely to underestimate its true magnitude, so neutral results should be interpreted with caution. Our analysis of the CDC case surveillance database<sup>38)</sup> used the snapshot downloaded on January 20, 2023. Subsequent updates of the database resulted in negligible fluctuations in the hospitalized CFR over the same periods. The available external control groups for Zimbabwe<sup>33, 34)</sup> and Nigeria<sup>36, 36)</sup>

also have small sample sizes and could thus have some biases. Hospitalized CFR is dependent not only on the virulence of the particular COVID-19 strains but also on the hospital resources available and the extent to which those resources are strained by case load.

## 5. Conclusion

This study has shown that the existence of some hospitalization rate reduction is clear and convincing when the Stone/Gill or Hazan multidrug protocol is employed in severely hypoxemic patients, and it is also very resilient to systemic selection bias. The existence of a mortality rate reduction effect is shown by the preponderance of evidence by combining the Hazan and Stone case series, and the threshold to clear and convincing can be crossed only when combining all three case series. These findings support the strength of association between the Hazan and Stone/Gill multidrug protocols and reduction in hospitalizations and deaths.

### Abbreviations

CDC, Center for Disease Control and Prevention; CFR, Case Fatality Rate; COVID-19, Coronavirus Disease 2019; LMIC, Low or middle income country; NIH, National Institute of Health; PaO<sub>2</sub>, Partial pressure of oxygen; PHD-SR, Premier Healthcare Database Special COVID-19 Release; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; SpO<sub>2</sub>, Peripheral oxygen saturation; WHO, World Health Organization.

### Acknowledgements

It is a pleasure to thank Olufemi Babalola for sharing the data from his case series with the authors. We also thank Marc Rendell for encouragement and helpful correspondence, Anthony M. Kyriakopoulos for helpful comments on the paper, David Scheim for sharing a copy of the Parirenyatwa document<sup>33)</sup> cited in our paper, Jacqueline Stone for email correspondence about her treatment protocol and for providing us with an updated version of her protocol description document<sup>24, 25)</sup>, and Sabine Hazan for email correspondence about her treatment protocol.

### Dedication

This paper is dedicated to the memory of Jacqueline Stone who passed away on October 3, 2024. Jacqueline Stone invented the idea of adding nebulized nanosilver into the ivermectin, doxycycline, zinc, Vitamin D, Vitamin C multidrug protocol for the treatment of COVID-19 patients. Furthermore, she instructed several other outpatient doctors in using her protocol, resulting in a nationwide reduction of COVID-19 mortality throughout the nation of Zimbabwe. An account of Dr. Stone's efforts and of the opposition against herself and colleagues, which contributed to her untimely passing, has been memorialized in a posthumously published book chapter<sup>74)</sup>.

## Funding

This work was not supported by external research funding.

## Conflict of Interest

Peter McCullough is the part-time Chief Scientific Officer for the Wellness Company, Boca Raton, Florida, United States of America, which had no role in the study or the writing of the manuscript. Eleftherios Gkioulekas is affiliated with the the School of Mathematical and Statistical Sciences at The University of Texas Rio Grande Valley, which regularly invites visiting scholars from other academic institutions and directly receives donations to fund scholarships, however he has not himself hosted any visiting scholars or received a scholarship. Colleen Aldous has no conflicts of interest.

## Note added to the article

After the acceptance of this article on January 7, 2025, the article by Hazan and colleagues<sup>19)</sup> was retracted by the journal *Future Microbiology* on January 9, 2025. A rewritten preprint<sup>75)</sup> of Hazan *et al.*<sup>19)</sup> has addressed the concerns raised in the retraction notice, including concerns about the patient enrollment process. Furthermore, the underlying patient data that this series of articles is dependent on remains unchanged. Finally, the data analysis of Hazan *et al.*<sup>19)</sup> regarding the CDC external control is superseded by the data analysis presented in this series of articles.

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