Data and materials: Critical appraisal of multi-drug therapy in the ambulatory management of patients with COVID-19 and hypoxemia

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Abstract

This document contains the data and materials for our research publication titled: "Critical appraisal of multi-drug therapy in the ambulatory management of patients with COVID-19 and hypoxemia". The document includes a brief explanation of the mathematical technique used for case series analysis, in general, the threshold calculations for the case series analyzed in the manuscript, and the threshold calculations for the treatment arm of the I-TECH study. Also included is the computer code that we have used to analyze the CDC database "COVID-19 case surveillance public use data with geography" and several tables displaying our calculations of the hospitalized and ICU CFR, using the January 20, 2023 snapshot of the database. Finally, we attach copies of the Parirenyatwa hospitals redzone statistics report, and the Stone/Gill protocol document.

Contents

1. Introduction

This document contains the data and materials for our research publication titled: "Critical appraisal of multi-drug therapy in the ambulatory management of patients with COVID-19 and hypoxemia". The document is organized as follows. Section 2 describes the details of the mathematical techniques used to calculate the efficacy thresholds and the random selection bias thresholds for case series, based on the case series threshold analysis method [**1**] method. Section 3 shows the threshold calculations for the Hazan case series [**2**]. Section 4 shows the threshold calculations for the Stone case series [**3**]. Section 5 shows the threshold calculations for the Babalola case series [**4–6**]. Section 6 shows the threshold calculations for the combined Stone + Hazan case series. Section 7 shows the threshold calculations for the combined Stone + Hazan + Babalola case series. Section 8 shows the threshold calculations for the treatment arm of the I-Tech trial [**7**]. Section 9 shows the computer code, written in R, used to process the January 20, 2023 snapshot of the CDC database [**8**]. Section 10 shows all the tables that we have calculated from the CDC database on the CFR for hospitalized and ICU patients in the United States over a variety of time periods, as well as on a month-to-month basis and cumulatively. Section 11 includes a copy of the unpublished report [**9**] on the mortality rate of hospitalized patients in the Parirenyatwa hospitals in Harare, Zimbabwe, which we have used in our paper as an external control group. Section 12 includes an updated copy of the Stone/Gill protocol [**10**], which was used to treat the patients in the Stone case series [**2**].

2. Methods

We analyze the case series by Stone [**3**], Hazan [**2**], and Babalola [**4–6**], following the case series threshold analysis method [**1**], which is briefly summarized in the following. We compare the treated patients with baseline room air SpO2 $\leq$ 90% against the hospitalized CFR from external controls to investigate efficacy with respect to mortality rate reduction. For investigating hospitalization rate reduction we use a self-controlled method in which the counterfactual hospitalizations without treatment are assumed to be at least all patients with SpO2 $\leq$ 90%.

2.1. Efficacy threshold calculation

Let N be the number of treated patients, a the number of treated patients with an adverse outcome (hospitalization or death). Let x be the probability of adverse outcome if the patient is untreated. We wish to reject the null hypothesis that the treatment is ineffective and that the event (N, a) just happened by chance. The p-value for rejecting the null hypothesis, as a function of x, is given by

$$p(N, a, x) = \sum_{n=0}^{N} \text{pr}(N, n|x)\ H(\text{pr}(N, a|x) - \text{pr}(N, n|x)), \tag{1}$$

with $\mathrm{pr}(N,a|x)$ the probability of the specific outcome (N,a) given by

$$\mathrm{pr}(N,a|x) = \binom{N}{a} x^a (1-x)^{N-a}. \tag{2}$$

We calculate the efficacy threshold x_0 via the equation

$$x_0(N,a,p_0) = \inf\{x \in [a/N,1] \mid p(N,a,x) \leq p_0\}, \tag{3}$$

with $p_0 = 0.05$ for 95% confidence. The threshold corresponds to the upper endpoint of the Sterne interval **[11]**.

This calculation has been implemented using the following Maxima code:

```
heaviside(x) := if x >= 0 then 1 else 0;
distr(N,a,x) := 100*binomial(N,a)*((x/100)^a)*(1-x/100)^(N-a);
pdistr(N,a,x) := float(sum(distr(N,n,x)*heaviside(distr(N,a,x)-distr(N,n,x)), n, 0, N));
```

2.2. Bayesian factor adjustment of the efficacy threshold

Let N be the number of treated patients, a the number of treated patients with an adverse outcome (hospitalization or death). Let x be the probability of adverse outcome if the patient is untreated. To calculate the adjusted efficacy threshold y_0, we consider the null hypothesis $H_0 : y_0 < x < 1$ and the alternative hypothesis $H_1 : 0 < x \leq y_0$, using the following prior probability distributions:

$$\mathrm{pr}(x|H_0(y_0,p_2)) = \begin{cases} 1/(p_2-y_0), & \text{if } x \in [y_0,p_2] \\ 0, & \text{if } x \in (p_2,1], \end{cases} \tag{4}$$

$$\mathrm{pr}(x|H_1(y_0,t)) = \begin{cases} 1/t, & \text{if } x \in [0,t] \\ 0, & \text{if } x \in (t,y_0]. \end{cases} \tag{5}$$

As explained by Gkioulekas and colleagues **[1]**, we calculate the Bayesian factor $B(N,a,y_0,p_2)$ given by the equations

$$B(N,a,y_0,p_2) = \max_{t\in(0,y_0]} \frac{\mathrm{pr}(N,a|H_1(y_0,t))}{\mathrm{pr}(N,a|H_0(y_0,p_2))}, \tag{6}$$

$$\mathrm{pr}(N,a|H_0(y_0,p_2)) = \frac{1}{p_2-y_0}\binom{N}{a}\int_{y_0}^{p_2} x^a(1-x)^{N-a}\,\mathrm{d}x, \tag{7}$$

$$\mathrm{pr}(N,a|H_1(y_0,t)) = \frac{1}{t}\binom{N}{a}\int_0^t x^a(1-x)^{N-a}\,\mathrm{d}x. \tag{8}$$

For confidence p_0, we use the empirical thresholds given by

$$B(N,a,y_0,p_2) \geq \frac{5(1-p_0)}{p_0}. \tag{9}$$

In particular we will identify the following thresholds:

$$p_0 = 0.05 \text{ requires } \log_{10} B(N,a,y_0,p_2) > 2, \tag{10}$$

$$p_0 = 0.01 \text{ requires } \log_{10} B(N,a,y_0,p_2) > 2.7, \tag{11}$$

$$p_0 = 0.001 \text{ requires } \log_{10} B(N,a,y_0,p_2) > 3.7. \tag{12}$$

If necessary, we increase the efficacy threshold x_0, from the original calculation, to y_0, such that the corresponding Bayesian Factor $B(N,a,y_0,p_2)$ satisfies Eq. (9).

We use the following Maxima code to implement the calculation of the Bayesian factor with exact symbolic integration:

```
bayesint(N,a,p,q) := integrate(((x/100)^a)*(1-(x/100))^(N-a),x,p,q);
bayes(N,a,q,p1,p2) := float(((p2-p1)/q)*bayesint(N,a,0,q)/bayesint(N,a,p1,p2));
lbayes(N,a,q,p1,p2) := float(log(bayes(N,a,q,p1,p2))/log(10));
lbayesmax(N,a,q,p2) := lmax(makelist(lbayes(N,a,t,q,p2),t,q/100,q,q/100));
```

To use numerical instead of symbolic integration, one can instead use:

```
bayesint(N,a,p,q) := first(quad_qags(((x/100)^a)*(1-(x/100))^(N-a),x,p,q));
```

For the calculations reported in this document, we have used symbolic integration.

2.3. Random selection bias threshold

Given an efficacy threshold y_0, after an optional adjustment with the Bayesian technique, it was previously shown [1] that the random selection bias threshold can be calculated via the equation:

$$x_1(N, y_0, p_0) = \inf\{x \in [y_0, 1] \mid p(N, \lceil y_0 N \rceil, x) < p_0\}. \tag{13}$$

To overcome systemic selection bias, where it is more likely to select healthy patients rather than unhealthy patients by a factor of f, the corresponding systemic selection bias threshold, as a function of f, is given by

$$x_1(f|N, y_0, p_0) = \frac{f x_1(N, y_0, p_0)}{1 + (f-1)x_1(N, y_0, p_0)}. \tag{14}$$

Suppose that we are able to bound the probability x of an adverse outcome without treatment in the interval $p_1 < x < p_2$, by use of the historical control. Then, if p_1 exceeds the random selection bias threshold x_1 (for $f = 1$), then the evidence of some treatment efficacy is clear and convincing. The corresponding selection bias tolerance F is obtained by solving the equation $x_1(f|N, y_0, p_0) = p_1$ with respect to f. The solution $f = F$ is given by

$$F = \frac{p_1[1 - x_1(N, y_0, p_0)]}{x_1(N, y_0, p_0)(1 - p_1)}. \tag{15}$$

We have not automated the calculation of the random selection bias threshold. The random selection bias tolerance is calculated using the following Maxima code:

```
fmax(p,x) := float((p*(100-x))/(x*(100-p)));
```

with the probabilities given as percentages.

3. Thresholds for Hazan case series

Hazan [2] treated 24 high-risk patients. One patient was not hypoxic but had difficulty breathing. The other 23 patients had baseline SpO2 $\leq$ 90%. The outcome of treatment was 0 hospitalizations and 0 deaths. Without treatment, we expected 23 out of 24 counterfactual hospitalizations, corresponding to 95.8% counterfactual hospitalization rate. So, we used $(N, a) = (23, 0)$ to calculate the mortality rate reduction thresholds and $(N, a) = (24, 0)$ to calculate the hospitalization rate reduction thresholds.

For Bayesian analysis of the mortality rate reduction thresholds, we used $p_2 = 23.48\%$, which was the upper endpoint of the estimated hospitalized CFR interval under the age restriction age ≥ 50, averaged over the treatment period between all goes 2020 and February 2021, based on the CDC database [8]. For Bayesian analysis of the hospitalization rate reduction thresholds we used the counterfactual hospitalization rate $p_2 = 23/24 = 95.8\%$.

3.1. Mortality rate reduction thresholds

- Mortality rate reduction efficacy threshold with $(N, a) = (23, 0)$

```
g(t) := pdistr(23, 0, t);
xlist: makelist(t, t, 13, 16, 1/10);
for t in xlist do print("x = ", float(t), "p-value % = ", g(t));

x =  13.0 p-value % =  6.370726659996516
x =  13.1 p-value % =  6.355112213995081
x =  13.2 p-value % =  6.344662108927906
x =  13.3 p-value % =  6.339347567701442
x =  13.4 p-value % =  6.339140809840622
x =  13.5 p-value % =  6.344014998908825
x =  13.6 p-value % =  6.353944190853153
x =  13.7 p-value % =  6.368903283277366
x =  13.8 p-value % =  6.388867965644667
x =  13.9 p-value % =  6.413814670412283
x =  14.0 p-value % =  6.44372052509959
x =  14.1 p-value % =  6.478563305291277
x =  14.2 p-value % =  6.518321388576821
```

```
x =  14.3 p-value % =  6.562973709427303
x =  14.4 p-value % =  6.612499715010316
x =  14.5 p-value % =  6.666879321943492
x =  14.6 p-value % =  3.951238348454439
=====[ 95% threshold ]=======================
x =  14.7 p-value % =  3.933516441873242
x =  14.8 p-value % =  3.91919898112144
x =  14.9 p-value % =  3.90827216479694
x =  15.0 p-value % =  3.900723212577591
x =  15.1 p-value % =  3.896540328686702
x =  15.2 p-value % =  3.895712665727943
x =  15.3 p-value % =  3.89823028889033
x =  15.4 p-value % =  3.904084140524169
x =  15.5 p-value % =  3.913266005089048
x =  15.6 p-value % =  3.925768474475144
x =  15.7 p-value % =  3.941584913699275
x =  15.8 p-value % =  3.960709426977291
x =  15.9 p-value % =  3.983136824174536
x =  16.0 p-value % =  4.008862587636258
```

- Efficacy threshold $x_0 = 14.6\%$
- Bayesian factor analysis with $(N, a) = (23, 0)$ and $p_2 = 23.48\%$

```
f(t) := lbayesmax(23, 0, t, 2348/100);
g(t) := pdistr(23, 0, t);
xlist: makelist(t, t, 13, 15, 1/10);
for t in xlist do print("x = ", float(t), "log bayes = ", f(t),
"p-value % = ", g(t));
```

```
x =  13.0 log bayes =  1.866052855134787 p-value % =  6.370726659996516
x =  13.1 log bayes =  1.874412195374929 p-value % =  6.355112213995081
x =  13.2 log bayes =  1.882762946580697 p-value % =  6.344662108927906
x =  13.3 log bayes =  1.891104947372761 p-value % =  6.339347567701442
x =  13.4 log bayes =  1.899438035155501 p-value % =  6.339140809840622
x =  13.5 log bayes =  1.907762046125405 p-value % =  6.344014998908825
x =  13.6 log bayes =  1.916076815280075 p-value % =  6.353944190853153
x =  13.7 log bayes =  1.92438217642783 p-value % =  6.368903283277366
x =  13.8 log bayes =  1.932677962197942 p-value % =  6.388867965644667
x =  13.9 log bayes =  1.940964004051497 p-value % =  6.413814670412283
x =  14.0 log bayes =  1.949240132292905 p-value % =  6.44372052509959
x =  14.1 log bayes =  1.957506176082063 p-value % =  6.478563305291277
x =  14.2 log bayes =  1.965761963447187 p-value % =  6.518321388576821
x =  14.3 log bayes =  1.974007321298327 p-value % =  6.562973709427303
x =  14.4 log bayes =  1.982242075441558 p-value % =  6.612499715010316
x =  14.5 log bayes =  1.99046605059389 p-value % =  6.666879321943492
x =  14.6 log bayes =  1.998679070398874 p-value % =  3.951238348454439
=====[ unadjusted 95% threshold ]=======================
x =  14.7 log bayes =  2.006880957442937 p-value % =  3.933516441873242
=====[ 95% threshold ]=======================
x =  14.8 log bayes =  2.015071533272447 p-value % =  3.91919898112144
x =  14.9 log bayes =  2.02325061841152 p-value % =  3.90827216479694
x =  15.0 log bayes =  2.031418032380574 p-value % =  3.900723212577591
```

- Log Bayes factor at the unadjusted efficacy threshold x_0 is: $\log_{10} B = 1.99$
- Adjusted mortality efficacy threshold to $y_0 = 14.7\%$
- Mortality random selection bias threshold with $N = 23$ and $y_0 = 14.7\%$

```
g(t) := pdistr(23, ceiling(23*14.7/100), t);
```

```
xlist: makelist(t, t, 38, 40, 1/10);
for t in xlist do print("x = ", float(t), "p-value % = ", g(t));

x =  38.0 p-value % =  5.162313431248752
x =  38.1 p-value % =  5.152499195489504
x =  38.2 p-value % =  5.144922967254469
x =  38.3 p-value % =  5.139582480741168
x =  38.4 p-value % =  5.136475680412595
x =  38.5 p-value % =  5.135600719441355
x =  38.6 p-value % =  5.136955958019471
x =  38.7 p-value % =  5.140539961535318
x =  38.8 p-value % =  5.146351498619123
x =  38.9 p-value % =  3.392460739983917
=====[ 95% selection bias threshold ]=========
x =  39.0 p-value % =  3.364970074677966
x =  39.1 p-value % =  3.339109101790096
x =  39.2 p-value % =  3.314872970522662
x =  39.3 p-value % =  3.292257100396688
x =  39.4 p-value % =  3.27125718138486
x =  39.5 p-value % =  3.251869173938292
x =  39.6 p-value % =  3.234089308907631
x =  39.7 p-value % =  3.217914087359112
x =  39.8 p-value % =  3.20334028028616
x =  39.9 p-value % =  3.190364928217144
x =  40.0 p-value % =  3.178985340719878
```

- Mortality random selection bias threshold $x_1 = 38.9\%$

3.2. Hospitalization rate reduction thresholds

- Hospitalization rate reduction efficacy threshold with $(N, a) = (24, 0)$

```
g(t) := pdistr(24, 0, t);
xlist: makelist(t, t, 13, 16, 1/10);
for t in xlist do print("x = ", float(t), "p-value % = ", g(t));

x =  13.0 p-value % =  6.436061302146697
x =  13.1 p-value % =  6.450865896328138
x =  13.2 p-value % =  6.471137269923191
x =  13.3 p-value % =  6.496847792945433
x =  13.4 p-value % =  6.52797064591623
x =  13.5 p-value % =  6.564479762081401
x =  13.6 p-value % =  6.606349770866244
x =  13.7 p-value % =  6.653555942569358
x =  13.8 p-value % =  6.706074134295353
x =  13.9 p-value % =  6.763880737126098
x =  14.0 p-value % =  4.017792212908554
=====[ 95% threshold ]=======================
x =  14.1 p-value % =  4.000429586034545
x =  14.2 p-value % =  3.98679304469207
x =  14.3 p-value % =  3.97686698402817
x =  14.4 p-value % =  3.970636974222325
x =  14.5 p-value % =  3.968089715297872
x =  14.6 p-value % =  3.969212992434967
x =  14.7 p-value % =  3.973995631786214
x =  14.8 p-value % =  3.982427456796332
x =  14.9 p-value % =  3.994499245027498
x =  15.0 p-value % =  4.010202685492207
x =  15.1 p-value % =  4.029530336495696
x =  15.2 p-value % =  4.052475583990176
x =  15.3 p-value % =  4.079032600443295
```

```
x =  15.4 p-value % =  4.109196304223374
x =  15.5 p-value % =  4.142962319504168
x =  15.6 p-value % =  2.470148265326641
x =  15.7 p-value % =  2.455233124189664
x =  15.8 p-value % =  2.4427183166123
x =  15.9 p-value % =  2.432596001710507
x =  16.0 p-value % =  2.424859354877966
```

- Hospitalization efficacy threshold $x_0 = 14.0\%$
- Bayesian factor analysis with $(N, a) = (24, 0)$ and $p_2 = 95.8\%$

```
f(t) := lbayesmax(24, 0, t, 958/10);
g(t) := pdistr(24, 0, t);
xlist: makelist(t, t, 13, 15, 1/10);
for t in xlist do print("x = ", float(t), "log bayes = ", f(t),
"p-value % = ", g(t));

x =  13.0 log bayes =  2.821228736075641 p-value % =  6.436061302146697
x =  13.1 log bayes =  2.833138924939699 p-value % =  6.450865896328138
x =  13.2 log bayes =  2.845062858104075 p-value % =  6.471137269923191
x =  13.3 log bayes =  2.857000567177474 p-value % =  6.496847792945433
x =  13.4 log bayes =  2.868952083877768 p-value % =  6.52797064591623
x =  13.5 log bayes =  2.880917440032496 p-value % =  6.564479762081401
x =  13.6 log bayes =  2.892896667579371 p-value % =  6.606349770866244
x =  13.7 log bayes =  2.904889798566788 p-value % =  6.653555942569358
x =  13.8 log bayes =  2.916896865154337 p-value % =  6.706074134295353
x =  13.9 log bayes =  2.928917899613318 p-value % =  6.763880737126098
x =  14.0 log bayes =  2.940952934327256 p-value % =  4.017792212908554
=====[ 95% threshold ]=======================
x =  14.1 log bayes =  2.953002001792428 p-value % =  4.000429586034545
x =  14.2 log bayes =  2.965065134618381 p-value % =  3.98679304469207
x =  14.3 log bayes =  2.977142365528461 p-value % =  3.97686698402817
x =  14.4 log bayes =  2.989233727360344 p-value % =  3.970636974222325
x =  14.5 log bayes =  3.001339253066568 p-value % =  3.968089715297872
x =  14.6 log bayes =  3.013458975715072 p-value % =  3.969212992434967
x =  14.7 log bayes =  3.02559292848973 p-value % =  3.973995631786214
x =  14.8 log bayes =  3.037741144690899 p-value % =  3.982427456796332
x =  14.9 log bayes =  3.04990365773596 p-value % =  3.994499245027498
x =  15.0 log bayes =  3.06208050115987 p-value % =  4.010202685492207
```

- Log Bayes factor at the unadjusted efficacy threshold x_0 is: $\log_{10} B = 2.94$
- Adjusted hospitalization efficacy threshold to $y_0 = 14.0\%$
- Hospitalization random selection bias threshold with $N = 24$ and $y_0 = 14.0\%$

```
g(t) := pdistr(24, ceiling(24*14.0/100), t);
xlist: makelist(t, t, 36, 38, 1/10);
for t in xlist do print("x = ", float(t),
"p-value % = ", g(t));

x =  36.0 p-value % =  5.531933511716902
x =  36.1 p-value % =  5.513038654981464
x =  36.2 p-value % =  5.496623435955988
x =  36.3 p-value % =  5.482684270639469
x =  36.4 p-value % =  5.471217802955343
x =  36.5 p-value % =  5.462220903255081
x =  36.6 p-value % =  5.45569066665253
x =  36.7 p-value % =  5.45162441119102
x =  36.8 p-value % =  5.450019675845222
```

```
x =  36.9 p-value % =  5.45087421835987
x =  37.0 p-value % =  5.454186012927404
x =  37.1 p-value % =  5.459953247706708
x =  37.2 p-value % =  5.468174322185096
x =  37.3 p-value % =  3.620472911089973
=====[ 95% selection bias threshold ]=========
x =  37.4 p-value % =  3.593169020533193
x =  37.5 p-value % =  3.567679564481506
x =  37.6 p-value % =  3.543999539700091
x =  37.7 p-value % =  3.52212424350221
x =  37.8 p-value % =  3.502049273501927
x =  37.9 p-value % =  3.483770527232644
x =  38.0 p-value % =  3.467284201632379
```

- Hospitalization random selection bias threshold $x_1 = 37.3\%$

4. Thresholds for Stone case series

Stone **[3]** treated 34 hypoxic patients with baseline SpO2 $\leq 93\%$ of which 28 patients presented with baseline SpO2 $\leq 90\%$ using the SID protocol **[10]**. The outcome of treatment was 1 deterioration/hospitalization and 0 deaths. Without treatment, we expected 28 out of 34 counterfactual hospitalizations, corresponding to 82.3% counterfactual hospitalization rate. So, we used $(N, a) = (28, 0)$ to calculate the mortality rate reduction thresholds and $(N, a) = (34, 1)$ to calculate the hospitalization rate reduction thresholds.

For Bayesian analysis of the mortality rate reduction thresholds, we used $p_2 = 23.3\%$, which was the Zimbabwe hospitalized CFR in Mashonaland **[12]**. For Bayesian analysis of the hospitalization rate reduction thresholds we used the counterfactual hospitalization rate $p_2 = 28/34 = 82.3\%$.

4.1. Mortality rate reduction thresholds

- Mortality rate reduction efficacy threshold with $(N, a) = (28, 0)$

```
g(t) := pdistr(28, 0, t);
xlist: makelist(t, t, 11, 14, 1/10);
for t in xlist do print("x = ", float(t),
"p-value % = ", g(t));

x =  11.0 p-value % =  6.701895012998688
x =  11.1 p-value % =  6.712322748482844
x =  11.2 p-value % =  6.730285704024768
x =  11.3 p-value % =  6.755734944353593
x =  11.4 p-value % =  6.788623017184222
x =  11.5 p-value % =  6.828903829530939
x =  11.6 p-value % =  6.87653252737576
x =  11.7 p-value % =  6.931465378683845
x =  11.8 p-value % =  6.993659659756864
x =  11.9 p-value % =  7.063073544913754
x =  12.0 p-value % =  4.243848343294743
=====[ 95% threshold ]======================
x =  12.1 p-value % =  4.226785858175059
x =  12.2 p-value % =  4.214880092966865
x =  12.3 p-value % =  4.208105972162699
x =  12.4 p-value % =  4.206440403689749
x =  12.5 p-value % =  4.209862181680984
x =  12.6 p-value % =  4.218351890714577
x =  12.7 p-value % =  4.231891811525468
x =  12.8 p-value % =  4.250465828193516
x =  12.9 p-value % =  4.27405933681309
x =  13.0 p-value % =  4.302659155649479
x =  13.1 p-value % =  4.336253436787792
x =  13.2 p-value % =  4.374831579280323
```

```
x =  13.3 p-value % =  4.418384143798639
x =  13.4 p-value % =  2.648492357570753
x =  13.5 p-value % =  2.634613315192364
x =  13.6 p-value % =  2.624102064044084
x =  13.7 p-value % =  2.61694753218802
x =  13.8 p-value % =  2.613140375647659
x =  13.9 p-value % =  2.612672916563436
x =  14.0 p-value % =  2.615539081961856
```

- Mortality efficacy threshold $x_0 = 12.0\%$
- Bayesian factor analysis with $(N, a) = (28, 0)$ and $p_2 = 23.3\%$

```
f(t) := lbayesmax(28, 0, t, 233/10);
g(t) := pdistr(28, 0, t);
xlist: makelist(t, t, 11, 13, 1/10);
for t in xlist do print("x = ", float(t), "log bayes = ", f(t),
"p-value % = ", g(t));

x =  11.0 log bayes =  2.019173657669253 p-value % =  6.701895012998688
x =  11.1 log bayes =  2.029922332492758 p-value % =  6.712322748482844
x =  11.2 log bayes =  2.040664563855259 p-value % =  6.730285704024768
x =  11.3 log bayes =  2.051400151163906 p-value % =  6.755734944353593
x =  11.4 log bayes =  2.06212889134283 p-value % =  6.788623017184222
x =  11.5 log bayes =  2.072850578819108 p-value % =  6.828903829530939
x =  11.6 log bayes =  2.083565005509318 p-value % =  6.87653252737576
x =  11.7 log bayes =  2.094271960806692 p-value % =  6.931465378683845
x =  11.8 log bayes =  2.10497123156892 p-value % =  6.993659659756864
x =  11.9 log bayes =  2.115662602106617 p-value % =  7.063073544913754
x =  12.0 log bayes =  2.126345854172491 p-value % =  4.243848343294743
=====[ 95% threshold ]=======================
x =  12.1 log bayes =  2.137020766951259 p-value % =  4.226785858175059
x =  12.2 log bayes =  2.147687117050318 p-value % =  4.214880092966865
x =  12.3 log bayes =  2.158344678491229 p-value % =  4.208105972162699
x =  12.4 log bayes =  2.168993222702031 p-value % =  4.206440403689749
x =  12.5 log bayes =  2.179632518510437 p-value % =  4.209862181680984
x =  12.6 log bayes =  2.190262332137931 p-value % =  4.218351890714577
x =  12.7 log bayes =  2.20088242719482 p-value % =  4.231891811525468
x =  12.8 log bayes =  2.21149256467626 p-value % =  4.250465828193516
x =  12.9 log bayes =  2.222092502959311 p-value % =  4.27405933681309
x =  13.0 log bayes =  2.232681997801051 p-value % =  4.302659155649479
```

- Log Bayes factor at the unadjusted efficacy threshold x_0 is: $\log_{10} B = 2.13$
- Adjusted mortality efficacy threshold to $y_0 = 12.0\%$
- Mortality random selection bias threshold with $N = 28$ and $y_0 = 12.0\%$

```
g(t) := pdistr(28, ceiling(28*12/100), t);
xlist: makelist(t, t, 31, 33, 1/10);
for t in xlist do print("x = ", float(t),
"p-value percent = ", g(t));

x =  31.0 p-value percent =  6.512761162082442
x =  31.1 p-value percent =  6.501324803185581
x =  31.2 p-value percent =  6.493350986878416
x =  31.3 p-value percent =  6.488834013407967
x =  31.4 p-value percent =  6.487768449326759
x =  31.5 p-value percent =  6.490149122474641
x =  31.6 p-value percent =  6.49597111664557
x =  31.7 p-value percent =  6.505229765946677
```

```
x =  31.8 p-value percent =  6.517920648857059
x =  31.9 p-value percent =  6.534039581993788
x =  32.0 p-value percent =  4.412918184589109
=====[ 95% selection bias threshold ]=========
x =  32.1 p-value percent =  4.385904007332987
x =  32.2 p-value percent =  4.361512510189887
x =  32.3 p-value percent =  4.339737335671241
x =  32.4 p-value percent =  4.320572561162193
x =  32.5 p-value percent =  4.304012696197599
x =  32.6 p-value percent =  4.290052679443636
x =  32.7 p-value percent =  4.278687875389139
x =  32.8 p-value percent =  4.269914070750822
x =  32.9 p-value percent =  4.263727470596567
x =  33.0 p-value percent =  4.260124694191027
```

- Mortality random selection bias threshold $x_1 = 32.0\%$

4.2. Hospitalization rate reduction thresholds

- Hospitalization rate reduction efficacy threshold with $(N, a) = (34, 1)$

```
g(t) := pdistr(34, 1, t);
xlist: makelist(t, t, 14, 16, 1/10);
for t in xlist do print("x = ", float(t), "p-value % = ", g(t));

x =  14.0 p-value % =  7.901183194935921
x =  14.1 p-value % =  7.939911367023774
x =  14.2 p-value % =  7.986885157168945
x =  14.3 p-value % =  8.042059216959677
x =  14.4 p-value % =  8.10538879506308
x =  14.5 p-value % =  5.217313048586425
x =  14.6 p-value % =  5.198754218855221
x =  14.7 p-value % =  5.186411533832342
x =  14.8 p-value % =  5.18025698280401
x =  14.9 p-value % =  5.180264344213818
x =  15.0 p-value % =  5.186409103849488
x =  15.1 p-value % =  5.198668372670864
x =  15.2 p-value % =  5.217020804379902
x =  15.3 p-value % =  5.241446512830916
x =  15.4 p-value % =  5.271926989376776
x =  15.5 p-value % =  5.308445020244301
x =  15.6 p-value % =  5.350984604029628
x =  15.7 p-value % =  3.420036749361644
=====[ 95% threshold ]=======================
x =  15.8 p-value % =  3.404055334440826
x =  15.9 p-value % =  3.392463719334299
x =  16.0 p-value % =  3.385246886435124
```

- Hospitalization efficacy threshold $x_0 = 15.7\%$
- Bayesian factor analysis with $(N, a) = (34, 1)$ and $p_2 = 82.3\%$

```
f(t) := lbayesmax(34, 1, t, 823/10);
g(t) := pdistr(34, 1, t);
xlist: makelist(t, t, 14, 16, 1/10);
for t in xlist do print("x = ", float(t), "log bayes = ", f(t),
"p-value % = ", g(t));

x =  14.0 log bayes =  2.325041084050565 p-value % =  7.901183194935921
x =  14.1 log bayes =  2.339045133397037 p-value % =  7.939911367023774
x =  14.2 log bayes =  2.353065230407916 p-value % =  7.986885157168945
```

```
x =  14.3 log bayes =  2.367101558010572 p-value % =  8.042059216959677
x =  14.4 log bayes =  2.381197179300913 p-value % =  8.10538879506308
x =  14.5 log bayes =  2.395334474186899 p-value % =  5.217313048586425
x =  14.6 log bayes =  2.40948829856924 p-value % =  5.198754218855221
x =  14.7 log bayes =  2.423658822545062 p-value % =  5.186411533832342
x =  14.8 log bayes =  2.43788642397505 p-value % =  5.18025698280401
x =  14.9 log bayes =  2.452158832165929 p-value % =  5.180264344213818
x =  15.0 log bayes =  2.466448209141431 p-value % =  5.186409103849488
x =  15.1 log bayes =  2.480754713759246 p-value % =  5.198668372670864
x =  15.2 log bayes =  2.495100080799916 p-value % =  5.217020804379902
x =  15.3 log bayes =  2.509509359683704 p-value % =  5.241446512830916
x =  15.4 log bayes =  2.523936010184566 p-value % =  5.271926989376776
x =  15.5 log bayes =  2.538380181292583 p-value % =  5.308445020244301
x =  15.6 log bayes =  2.552842019791282 p-value % =  5.350984604029628
x =  15.7 log bayes =  2.567375351393483 p-value % =  3.420036749361644
=====[ 95% threshold ]=======================
x =  15.8 log bayes =  2.58194091425128 p-value % =  3.404055334440826
x =  15.9 log bayes =  2.596524360674598 p-value % =  3.392463719334299
x =  16.0 log bayes =  2.611125829035513 p-value % =  3.385246886435124
```

- Log Bayes factor at the unadjusted efficacy threshold x_0 is: $\log_{10} B = 2.57$
- Adjusted hospitalization efficacy threshold to $y_0 = 15.7\%$
- Hospitalization random selection bias threshold with $N = 34$ and $y_0 = 15.7\%$

```
g(t) := pdistr(34, ceiling(34*15.7/100), t);
xlist: makelist(t, t, 33, 36, 1/10);
for t in xlist do print("x = ", float(t), "p-value % = ", g(t));
```

```
x =  33.0 p-value % =  6.731956967889433
x =  33.1 p-value % =  6.722792862740215
x =  33.2 p-value % =  6.717792246593796
x =  33.3 p-value % =  6.716949263024116
x =  33.4 p-value % =  6.720258367250127
x =  33.5 p-value % =  6.727714319947253
x =  33.6 p-value % =  6.739312180497969
x =  33.7 p-value % =  4.743798159814899
=====[ 95% selection bias threshold ]=========
x =  33.8 p-value % =  4.713349047017783
x =  33.9 p-value % =  4.686166290865744
x =  34.0 p-value % =  4.662242451864523
x =  34.1 p-value % =  4.641570648786374
x =  34.2 p-value % =  4.624144556322762
x =  34.3 p-value % =  4.609958402186201
x =  34.4 p-value % =  4.599006963667827
x =  34.5 p-value % =  4.591285563657537
x =  34.6 p-value % =  4.586790066133632
x =  34.7 p-value % =  4.585516871129186
x =  34.8 p-value % =  4.587462909182459
x =  34.9 p-value % =  4.59262563527893
x =  35.0 p-value % =  4.601003022292633
x =  35.1 p-value % =  3.18485977341443
x =  35.2 p-value % =  3.161267749502046
x =  35.3 p-value % =  3.140130888695676
x =  35.4 p-value % =  3.121442421466504
x =  35.5 p-value % =  3.105196227893159
x =  35.6 p-value % =  3.091386835523116
x =  35.7 p-value % =  3.080009416817869
x =  35.8 p-value % =  3.071059786185822
x =  35.9 p-value % =  3.064534396606854
```

```
x =  36.0 p-value % =  3.060430335852606
```

- Hospitalization random selection bias threshold $x_1 = 33.7\%$

5. Thresholds for Babalola case series

The Babalola case series **[4–6]** consisted of a combination of 61 low-risk and high-risk patients. Of these patients 21 patients were hypoxic with baseline SpO2 $\leq$ 93%, and 10 patients presented with baseline room air SpO2 $\leq$ 90%. The outcome was 0 deaths, 2 patients using the ventilator, and 3 patients using supplemental oxygen. Consequently, without treatment we expected at least 10 out of 61 counterfactual hospitalizations, corresponding to 16.4% counterfactual hospitalization rate. With treatment, we counted the 5 patients that used supplemental oxygen or the ventilator as failures to prevent hospitalization, thus we counted 5 hospitalizations with treatment. We did not calculate the mortality rate reduction thresholds because using $(N, a) = (10, 0)$ involves a very small sample. However, we calculated hospitalization rate reduction thresholds using $(N, a) = (61, 5)$.

The counterfactual hospitalization rate was $10/61 = 16.4\%$ and it was exceeded by the unadjusted efficacy threshold x_0, so there was a failure to establish hospitalization rate reduction by the preponderance of evidence, which can be explained by the low-risk status of the patient cohort as well as the use of a less aggressive treatment protocol. For the purpose of adjusting the efficacy of threshold we set p_2 equal to the percentage of patients that were hypoxic with baseline room air SpO2 $\leq$ 93%, which was given by $p_2 = 21/61 = 34.4\%$.

Including both low-risk and high-risk patients biases towards the null hypothesis of no efficacy, so it is the most conservative approach, but nevertheless we will still obtain positive results when the Babalola case series **[4–6]** is combined with the Stone case series **[3]** and the Hazan case series **[2]**.

5.1. Hospitalization rate reduction thresholds

- Hospitalization rate reduction efficacy threshold with $(N, a) = (61, 5)$

```
g(t) := pdistr(61, 5, t);
xlist: makelist(t, t, 17, 19, 1/10);
for t in xlist do print("x = ", float(t), "p-value % = ", g(t));

x =  17.0 p-value % =  8.577592758890098
x =  17.1 p-value % =  8.628763401964067
x =  17.2 p-value % =  6.256046174954141
x =  17.3 p-value % =  6.238462964683035
x =  17.4 p-value % =  6.231928327268813
x =  17.5 p-value % =  6.236398999584731
x =  17.6 p-value % =  6.251834552355776
x =  17.7 p-value % =  6.278197235484284
x =  17.8 p-value % =  6.315451814591766
x =  17.9 p-value % =  4.546220895915466
=====[ 95% threshold ]=======================
x =  18.0 p-value % =  4.528947951007036
x =  18.1 p-value % =  4.520442264471574
x =  18.2 p-value % =  4.520675595512871
x =  18.3 p-value % =  4.529623719082893
x =  18.4 p-value % =  4.547266277870809
x =  18.5 p-value % =  4.573586626386231
x =  18.6 p-value % =  3.271670201849207
x =  18.7 p-value % =  3.255652414027116
x =  18.8 p-value % =  3.246466537168128
x =  18.9 p-value % =  3.244093880197336
x =  19.0 p-value % =  3.248520267608783
```

- Hospitalization efficacy threshold $x_0 = 17.9\%$
- Bayesian factor analysis with $(N, a) = (61, 5)$ and $p_2 = 34.4\%$

```
f(t) := lbayesmax(61, 5, t, 344/10);
g(t) := pdistr(61, 5, t);
xlist: makelist(t, t, 17, 203/10, 1/10);
for t in xlist do print("x = ", float(t), "log bayes = ", f(t),
"p-value % = ", g(t));

x =  17.0 log bayes =  1.493569671903531 p-value % =  8.577592758890098
x =  17.1 log bayes =  1.509761322040076 p-value % =  8.628763401964067
x =  17.2 log bayes =  1.525996013424686 p-value % =  6.256046174954141
x =  17.3 log bayes =  1.542354417542521 p-value % =  6.238462964683035
x =  17.4 log bayes =  1.558744247943838 p-value % =  6.231928327268813
x =  17.5 log bayes =  1.575238651895112 p-value % =  6.236398999584731
x =  17.6 log bayes =  1.591794735043633 p-value % =  6.251834552355776
x =  17.7 log bayes =  1.608406348064751 p-value % =  6.278197235484284
x =  17.8 log bayes =  1.62512847212959 p-value % =  6.315451814591766
x =  17.9 log bayes =  1.641881657430528 p-value % =  4.546220895915466
=====[ unadjusted 95% threshold ]======================
x =  18.0 log bayes =  1.658737347616338 p-value % =  4.528947951007036
x =  18.1 log bayes =  1.675655917193962 p-value % =  4.520442264471574
x =  18.2 log bayes =  1.692612798504069 p-value % =  4.520675595512871
x =  18.3 log bayes =  1.709696494843493 p-value % =  4.529623719082893
x =  18.4 log bayes =  1.726810635829636 p-value % =  4.547266277870809
x =  18.5 log bayes =  1.743994343757742 p-value % =  4.573586626386231
x =  18.6 log bayes =  1.761272828371064 p-value % =  3.271670201849207
x =  18.7 log bayes =  1.778581488022416 p-value % =  3.255652414027116
x =  18.8 log bayes =  1.795982443367796 p-value % =  3.246466537168128
x =  18.9 log bayes =  1.813454582444873 p-value % =  3.244093880197336
x =  19.0 log bayes =  1.830956540492798 p-value % =  3.248520267608783
x =  19.1 log bayes =  1.848564676395269 p-value % =  3.259735911654664
x =  19.2 log bayes =  1.866229174767201 p-value % =  3.27773527812893
x =  19.3 log bayes =  1.88392305230745 p-value % =  3.302516946043264
x =  19.4 log bayes =  1.901727775816162 p-value % =  2.317749419651901
x =  19.5 log bayes =  1.919583184427015 p-value % =  2.308747847953821
x =  19.6 log bayes =  1.937467450700344 p-value % =  2.304968896124012
x =  19.7 log bayes =  1.955457598596345 p-value % =  2.306404230112428
x =  19.8 log bayes =  1.973502319929769 p-value % =  2.313049937721306
x =  19.9 log bayes =  1.991575297084583 p-value % =  2.324906421006494
x =  20.0 log bayes =  2.009739085688532 p-value % =  2.341978284154277
=====[ 95% threshold ]=================
x =  20.1 log bayes =  2.027971377224883 p-value % =  1.63432904074377
x =  20.2 log bayes =  2.046231243130915 p-value % =  1.626039115979122
x =  20.3 log bayes =  2.064556211765087 p-value % =  1.621689755496815
```

- Log Bayes factor at the unadjusted efficacy threshold x_0 is: $\log_{10} B = 1.64$
- Adjusted hospitalization efficacy threshold to $y_0 = 20.0\%$
- Hospitalization random selection bias threshold with $N = 61$ and $y_0 = 20.0\%$

```
g(t) := pdistr(61, ceiling(61*20.0/100), t);
xlist: makelist(t, t, 32, 34, 1/10);
for t in xlist do print("x = ", float(t), "p-value % = ", g(t));

x =  32.0 p-value % =  7.561031077996428
x =  32.1 p-value % =  7.526174606304557
x =  32.2 p-value % =  7.499413925380816
x =  32.3 p-value % =  7.480734995445467
x =  32.4 p-value % =  7.470124390005045
x =  32.5 p-value % =  7.467569285404589
x =  32.6 p-value % =  7.473057446529427
x =  32.7 p-value % =  7.48657720873394
```

```
x =  32.8 p-value % =  5.69883507724718
x =  32.9 p-value % =  5.670375667963246
x =  33.0 p-value % =  5.648682288205065
x =  33.1 p-value % =  5.633742715222928
x =  33.2 p-value % =  5.625546086321589
x =  33.3 p-value % =  5.624082885249134
x =  33.4 p-value % =  5.629344924840239
x =  33.5 p-value % =  5.64132532597835
x =  33.6 p-value % =  4.241860682401031
=====[ 95% selection bias threshold ]=======================
x =  33.7 p-value % =  4.21898839654968
x =  33.8 p-value % =  4.201665794519958
x =  33.9 p-value % =  4.189882394330747
x =  34.0 p-value % =  4.183629549706375
```

- Hospitalization random selection bias threshold $x_1 = 33.6\%$

6. Thresholds for combined Stone+Hazan case series

To calculate the mortality rate reduction and hospitalization rate reduction thresholds for the combined Stone + Hazan case series, we used $(N, a) = (23, 0) + (28, 0) = (51, 0)$ for the calculation of the mortality rate reduction thresholds. For the corresponding Bayesian factor analysis, we used the very conservative estimate $p_2 = 10\%$, which is unrealistically small, because for any choice $p_2 \geq 10\%$ the Bayesian analysis does not necessitate any upward adjustment of the mortality rate reduction efficacy threshold x_0.

For the hospitalization rate reduction thresholds, we used $(N, a) = (24, 0) + (34, 1) = (58, 1)$. In combination, we anticipated $23 + 28 = 51$ counterfactual hospitalizations out of 58 patients without treatment, consequently for the corresponding Bayesian factor analysis we used the conservative choice $p_2 = 51/58 = 87.9\%$.

6.1. Mortality rate reduction thresholds

- Mortality rate reduction efficacy threshold with $(N, a) = (51, 0)$

```
g(t) := pdistr(51, 0, t);
xlist: makelist(t, t, 6, 8, 1/10);
for t in xlist do print("x = ", float(t), "p-value % = ", g(t));

x =  6.0 p-value % =  7.445796708555233
x =  6.1 p-value % =  7.475760450815867
x =  6.2 p-value % =  7.530881124810194
x =  6.3 p-value % =  7.610815022915339
x =  6.4 p-value % =  7.715229693517513
x =  6.5 p-value % =  7.843801842723696
x =  6.6 p-value % =  4.865199511422497
x =  6.7 p-value % =  4.853741415975144
x =  6.8 p-value % =  4.85994841174693
x =  6.9 p-value % =  4.883662721899324
x =  7.0 p-value % =  4.924742069286689
x =  7.1 p-value % =  4.983057879167961
x =  7.2 p-value % =  5.058493553617015
x =  7.3 p-value % =  5.150942817413303
x =  7.4 p-value % =  3.160865369922855
=====[ 95% threshold ]======================
x =  7.5 p-value % =  3.155176060025685
x =  7.6 p-value % =  3.161433359538339
x =  7.7 p-value % =  3.17958499389143
x =  7.8 p-value % =  3.20959252333895
x =  7.9 p-value % =  3.251430114005208
x =  8.0 p-value % =  3.305083342121804
```

- Mortality efficacy threshold $x_0 = 7.4\%$

- Bayesian factor analysis with $(N, a) = (51, 0)$ and $p_2 = 10\%$

```
f(t) := lbayesmax(51, 0, t, 10);
g(t) := pdistr(51, 0, t);
xlist: makelist(t, t, 6, 8, 1/10);
for t in xlist do print("x = ", float(t), "log bayes = ", f(t),
"p-value % = ", g(t));

x =  6.0 log bayes =  1.756585789002033 p-value % =  7.445796708555233
x =  6.1 log bayes =  1.772402927913403 p-value % =  7.475760450815867
x =  6.2 log bayes =  1.788148607187059 p-value % =  7.530881124810194
x =  6.3 log bayes =  1.803821638593064 p-value % =  7.610815022915339
x =  6.4 log bayes =  1.819420835225593 p-value % =  7.715229693517513
x =  6.5 log bayes =  1.834945012432848 p-value % =  7.843801842723696
x =  6.6 log bayes =  1.850392988774016 p-value % =  4.865199511422497
x =  6.7 log bayes =  1.86576358700224 p-value % =  4.853741415975144
x =  6.8 log bayes =  1.88105563507243 p-value % =  4.85994841174693
x =  6.9 log bayes =  1.896267967172648 p-value % =  4.883662721899324
x =  7.0 log bayes =  1.911399424777631 p-value % =  4.924742069286689
x =  7.1 log bayes =  1.926448857722906 p-value % =  4.983057879167961
x =  7.2 log bayes =  1.941415125297824 p-value % =  5.058493553617015
x =  7.3 log bayes =  1.956297097355705 p-value % =  5.150942817413303
x =  7.4 log bayes =  1.97109365543914 p-value % =  3.160865369922855
=====[ unadjusted 95% threshold ]=======================
x =  7.5 log bayes =  1.985803693918421 p-value % =  3.155176060025685
x =  7.6 log bayes =  2.000426121140884 p-value % =  3.161433359538339
=====[ 95% threshold ]==================
x =  7.7 log bayes =  2.014959860588899 p-value % =  3.17958499389143
x =  7.8 log bayes =  2.029403852044061 p-value % =  3.20959252333895
x =  7.9 log bayes =  2.043757052755112 p-value % =  3.251430114005208
x =  8.0 log bayes =  2.058018438606929 p-value % =  3.305083342121804
```

- Log Bayes factor at the unadjusted efficacy threshold x_0 is: $\log_{10} B = 1.97$
- Adjusted mortality efficacy threshold to $y_0 = 7.6\%$
- Mortality random selection bias threshold with $N = 51$ and $y_0 = 7.6\%$

```
g(t) := pdistr(51, ceiling(51*7.6/100), t);
xlist: makelist(t, t, 18, 20, 1/10);
for t in xlist do print("x = ", float(t), "p-value % = ", g(t));

x =  18.0 p-value % =  6.680110293763493
x =  18.1 p-value % =  6.692506724319102
x =  18.2 p-value % =  6.714195744946394
x =  18.3 p-value % =  6.745145465047911
x =  18.4 p-value % =  6.785325398068853
x =  18.5 p-value % =  4.779477781380148
=====[ 95% selection bias threshold ]=========
x =  18.6 p-value % =  4.761280812186526
x =  18.7 p-value % =  4.750442528641691
x =  18.8 p-value % =  4.746938851611675
x =  18.9 p-value % =  4.750748329514685
x =  19.0 p-value % =  4.761852047390708
x =  19.1 p-value % =  4.780233531880517
x =  19.2 p-value % =  4.805878652353918
x =  19.3 p-value % =  3.37564366324245
x =  19.4 p-value % =  3.357151626376817
x =  19.5 p-value % =  3.344302343768622
x =  19.6 p-value % =  3.337078908279209
x =  19.7 p-value % =  3.33546743002784
```

```
x =  19.8 p-value % =  3.339456959747061
x =  19.9 p-value % =  3.349039408811036
x =  20.0 p-value % =  3.364209466081411
```

- Mortality random selection bias threshold $x_1 = 18.5\%$

6.2. Hospitalization rate reduction thresholds

- Hospitalization rate reduction efficacy threshold with $(N, a) = (58, 1)$

```
g(t) := pdistr(58, 1, t);
xlist: makelist(t, t, 9, 10, 1/10);
for t in xlist do print("x = ", float(t), "p-value % = ", g(t));

x =  9.0 p-value % =  6.148263061736219
x =  9.1 p-value % =  6.224523857103195
x =  9.2 p-value % =  4.113167177337123
=====[ 95% threshold ]=======================
x =  9.3 p-value % =  4.099791735948565
x =  9.4 p-value % =  4.099914808295677
x =  9.5 p-value % =  4.113461601436069
x =  9.6 p-value % =  4.14036903954292
x =  9.7 p-value % =  4.180584846365599
x =  9.8 p-value % =  4.234066631556312
x =  9.9 p-value % =  2.782330495910057
x =  10.0 p-value % =  2.770997680483859
```

- Hospitalization efficacy threshold $x_0 = 9.2\%$
- Bayesian factor analysis with $(N, a) = (58, 1)$ and $p_2 = 87.9\%$

```
f(t) := lbayesmax(58, 1, t, 879/10);
g(t) := pdistr(58, 1, t);
xlist: makelist(t, t, 9, 10, 1/10);
for t in xlist do print("x = ", float(t), "log bayes = ", f(t),
"p-value % = ", g(t));

x =  9.0 log bayes =  2.727551125064538 p-value % =  6.148263061736219
x =  9.1 log bayes =  2.750665728347839 p-value % =  6.224523857103195
x =  9.2 log bayes =  2.773818903753588 p-value % =  4.113167177337123
=====[ 95% threshold ]=======================
x =  9.3 log bayes =  2.79709692344844 p-value % =  4.099791735948565
x =  9.4 log bayes =  2.820399867202918 p-value % =  4.099914808295677
x =  9.5 log bayes =  2.843762010682013 p-value % =  4.113461601436069
x =  9.6 log bayes =  2.867230100834091 p-value % =  4.14036903954292
x =  9.7 log bayes =  2.890723969421827 p-value % =  4.180584846365599
x =  9.8 log bayes =  2.914277034270081 p-value % =  4.234066631556312
x =  9.9 log bayes =  2.937937636550101 p-value % =  2.782330495910057
x =  10.0 log bayes =  2.961624754621575 p-value % =  2.770997680483859
```

- Log Bayes factor at the unadjusted efficacy threshold x_0 is: $\log_{10} B = 2.77$
- Adjusted hospitalization efficacy threshold to $y_0 = 9.2\%$
- Hospitalization random selection bias threshold with $N = 58$ and $y_0 = 9.2\%$

```
g(t) := pdistr(58, ceiling(58*9.2/100), t);
xlist: makelist(t, t, 21, 23, 1/10);
for t in xlist do print("x = ", float(t), "p-value % = ", g(t));

x =  21.0 p-value % =  5.171319586941431
x =  21.1 p-value % =  5.182370944821603
```

```
x =  21.2 p-value % =  5.201508791500397
x =  21.3 p-value % =  5.228718016821197
x =  21.4 p-value % =  3.764877902947141
=====[ 95% selection bias threshold ]=========
x =  21.5 p-value % =  3.74868487613011
x =  21.6 p-value % =  3.738937140779549
x =  21.7 p-value % =  3.735618403805992
x =  21.8 p-value % =  3.738715512404047
x =  21.9 p-value % =  3.748218376853068
x =  22.0 p-value % =  3.764119888469991
x =  22.1 p-value % =  3.786415832903905
x =  22.2 p-value % =  2.690989974190407
x =  22.3 p-value % =  2.679011241957028
x =  22.4 p-value % =  2.672027860611287
x =  22.5 p-value % =  2.670029851010766
x =  22.6 p-value % =  2.673010512013183
x =  22.7 p-value % =  2.680966354216368
x =  22.8 p-value % =  2.693897030034177
x =  22.9 p-value % =  1.914457241173169
x =  23.0 p-value % =  1.901913106525191
```

- Hospitalization random selection bias threshold $x_1 = 21.4\%$

7. Thresholds for combined Stone+Hazan+Babalola case series

To calculate the mortality rate reduction and hospitalization rate reduction thresholds for the combined Stone + Hazan + Babalola case series, we used

$$(N, a) = (23, 0) + (28, 0) + (10, 0) = (61, 0), \tag{16}$$

for the calculation of the mortality rate reduction thresholds. For the corresponding Bayesian factor analysis, we used the very conservative estimate $p_2 = 10\%$, which is unrealistically small, because for any choice $p_2 \geq 10\%$ the Bayesian analysis does not necessitate any upward adjustment of the mortality rate reduction efficacy threshold x_0.

For the hospitalization rate reduction thresholds, we used

$$(N, a) = (24, 0) + (34, 1) + (61, 5) = (119, 6). \tag{17}$$

In combination, we are anticipating $23 + 28 + 10 = 61$ counterfactual hospitalizations out of 119 patients without treatment, consequently for the corresponding Bayesian factor analysis we used the conservative choice $p_2 = 61/119 = 51.3\%$.

7.1. Mortality rate reduction thresholds

- Mortality rate reduction efficacy threshold with $(N, a) = (61, 0)$

```
g(t) := pdistr(61, 0, t);
xlist: makelist(t, t, 6, 7, 1/10);
for t in xlist do print("x = ", float(t), "p-value % = ", g(t));

x =  6.0 p-value % =  5.182366036586255
x =  6.1 p-value % =  5.293940569595473
x =  6.2 p-value % =  3.267368612733312
=====[ 95% threshold ]=======================
x =  6.3 p-value % =  3.267152475363462
x =  6.4 p-value % =  3.284203151289845
x =  6.5 p-value % =  3.318437284718317
x =  6.6 p-value % =  3.36979710255226
x =  6.7 p-value % =  3.438247472138885
x =  6.8 p-value % =  2.139247699308205
x =  6.9 p-value % =  2.133173871601978
x =  7.0 p-value % =  2.13880089605102
```

- Mortality efficacy threshold $x_0 = 6.2\%$
- Bayesian factor analysis with $(N, a) = (61, 0)$ and $p_2 = 10\%$

```
f(t) := lbayesmax(61, 0, t, 10);
g(t) := pdistr(61, 0, t);
xlist: makelist(t, t, 6, 7, 1/10);
for t in xlist do print("x = ", float(t), "log bayes = ", f(t),
"p-value % = ", g(t));

x =  6.0 log bayes =  2.082936872661563 p-value % =  5.182366036586255
x =  6.1 log bayes =  2.102618851892067 p-value % =  5.293940569595473
x =  6.2 log bayes =  2.122206701977779 p-value % =  3.267368612733312
=====[ 95% threshold ]=======================
x =  6.3 log bayes =  2.14169844223232 p-value % =  3.267152475363462
x =  6.4 log bayes =  2.161092084702625 p-value % =  3.284203151289845
x =  6.5 log bayes =  2.180385635968436 p-value % =  3.318437284718317
x =  6.6 log bayes =  2.199577099029407 p-value % =  3.36979710255226
x =  6.7 log bayes =  2.21866447527868 p-value % =  3.438247472138885
x =  6.8 log bayes =  2.237645766561334 p-value % =  2.139247699308205
x =  6.9 log bayes =  2.256518977315634 p-value % =  2.133173871601978
x =  7.0 log bayes =  2.275282116794584 p-value % =  2.13880089605102
```

- Log Bayes factor at the unadjusted efficacy threshold x_0 is: $\log_{10} B = 2.12$
- Adjusted mortality efficacy threshold to $y_0 = 6.2\%$
- Mortality random selection bias threshold with $N = 61$ and $y_0 = 6.2\%$

```
g(t) := pdistr(61, ceiling(61*6.2/100), t);
xlist: makelist(t, t, 16, 17, 1/10);
for t in xlist do print("x = ", float(t), "p-value % = ", g(t));

x =  16.0 p-value % =  5.226364839963209
x =  16.1 p-value % =  5.265959183289894
x =  16.2 p-value % =  3.711749044963744
=====[ 95% selection bias threshold ]=========
x =  16.3 p-value % =  3.698985317348112
x =  16.4 p-value % =  3.694520502259757
x =  16.5 p-value % =  3.698330201030001
x =  16.6 p-value % =  3.710395271231324
x =  16.7 p-value % =  3.730701624394571
x =  16.8 p-value % =  3.759240015866537
x =  16.9 p-value % =  2.63092555987208
x =  17.0 p-value % =  2.619467682532934
```

- Mortality random selection bias threshold $x_1 = 16.2\%$

7.2. Hospitalization rate reduction thresholds

- Hospitalization rate reduction efficacy threshold with $(N, a) = (119, 6)$

```
g(t) := pdistr(119, 6, t);
xlist: makelist(t, t, 10, 12, 1/10);
for t in xlist do print("x = ", float(t), "p-value % = ", g(t));

x =  10.0 p-value % =  9.016594681202983
x =  10.1 p-value % =  6.780001612929171
x =  10.2 p-value % =  6.787353650504302
x =  10.3 p-value % =  6.830171534926849
x =  10.4 p-value % =  6.90820375785284
x =  10.5 p-value % =  5.133161000855982
```

```
x =  10.6 p-value % =  5.147467702434201
x =  10.7 p-value % =  5.190815377736056
x =  10.8 p-value % =  3.867731843929945
=====[ 95% threshold ]=======================
x =  10.9 p-value % =  3.862695137462995
x =  11.0 p-value % =  3.88123205032672
x =  11.1 p-value % =  3.923265031744631
x =  11.2 p-value % =  2.88835495627442
x =  11.3 p-value % =  2.890104338883779
x =  11.4 p-value % =  2.91067599119662
x =  11.5 p-value % =  2.950055287145476
x =  11.6 p-value % =  2.144790771427504
x =  11.7 p-value % =  2.150856698552416
x =  11.8 p-value % =  2.171804204067943
x =  11.9 p-value % =  1.587344117242583
x =  12.0 p-value % =  1.584198410425766
```

- Hospitalization efficacy threshold $x_0 = 10.8\%$
- Bayesian factor analysis with $(N, a) = (119, 6)$ and $p_2 = 51.3\%$

```
f(t) := lbayesmax(119, 6, t, 513/10);
g(t) := pdistr(119, 6, t);
xlist: makelist(t, t, 10, 11, 1/10);
for t in xlist do print("x = ", float(t), "log bayes = ", f(t),
 "p-value % = ", g(t));
```

```
x =  10.0 log bayes =  2.063634426446877 p-value % =  9.016594681202983
x =  10.1 log bayes =  2.094649649929876 p-value % =  6.780001612929171
x =  10.2 log bayes =  2.125897418043964 p-value % =  6.787353650504302
x =  10.3 log bayes =  2.157380890956134 p-value % =  6.830171534926849
x =  10.4 log bayes =  2.189151356902623 p-value % =  6.90820375785284
x =  10.5 log bayes =  2.221140210735713 p-value % =  5.133161000855982
x =  10.6 log bayes =  2.253339657297835 p-value % =  5.147467702434201
x =  10.7 log bayes =  2.285824160916021 p-value % =  5.190815377736056
x =  10.8 log bayes =  2.318523177835909 p-value % =  3.867731843929945
=====[ 95% threshold ]=======================
x =  10.9 log bayes =  2.351416446113127 p-value % =  3.862695137462995
x =  11.0 log bayes =  2.384603439200212 p-value % =  3.88123205032672
```

- Log Bayes factor at the unadjusted efficacy threshold x_0 is: $\log_{10} B = 2.32$
- Adjusted hospitalization efficacy threshold to $y_0 = 10.8\%$
- Hospitalization random selection bias threshold with $N = 119$ and $y_0 = 10.8\%$

```
g(t) := pdistr(119, ceiling(119*10.8/100), t);
xlist: makelist(t, t, 17, 19, 1/10);
for t in xlist do print("x = ", float(t), "p-value % = ", g(t));
```

```
x =  17.0 p-value % =  8.685781973789256
x =  17.1 p-value % =  8.711007893644217
x =  17.2 p-value % =  6.914827296610692
x =  17.3 p-value % =  6.893378272699522
x =  17.4 p-value % =  6.894907876671976
x =  17.5 p-value % =  6.919323189322935
x =  17.6 p-value % =  5.449297788118877
x =  17.7 p-value % =  5.433420327449616
x =  17.8 p-value % =  5.437127420366989
x =  17.9 p-value % =  5.460355491196594
x =  18.0 p-value % =  4.26577476188551
```

```
=====[ 95% selection bias threshold ]=========
x =  18.1 p-value % =  4.254537161120481
x =  18.2 p-value % =  4.259802165705982
x =  18.3 p-value % =  4.28153050954027
x =  18.4 p-value % =  3.317452398008927
x =  18.5 p-value % =  3.309952708311219
x =  18.6 p-value % =  3.316210370696707
x =  18.7 p-value % =  3.336205607714175
x =  18.8 p-value % =  2.563357874769676
x =  18.9 p-value % =  2.558769183836605
x =  19.0 p-value % =  2.565533582810724
```

- Hospitalization random selection bias threshold $x_1 = 18.0\%$

8. Thresholds for Hazan + Babalola case series

To calculate the mortality rate reduction and hospitalization rate reduction thresholds for the combined Hazan + Babalola case series, we used $(N, a) = (23, 0) + (10, 0) = (33, 0)$ for the calculation of the mortality rate reduction thresholds. For the corresponding Bayesian factor analysis, we used the conservative estimate $p_2 = 18.18\%$, which was the mortality rate for symptomatic hospitalized patients in Kano State, Nigeria [**13**]. This is the most conservative choice when compared against the 19.48% case fatality rate for hospitalized patients for LMIC countries by the World Heart Federation study [**14**] and our choice of p_2 used for the Hazan case series alone.

For the hospitalization rate reduction thresholds, we used $(N, a) = (24, 0) + (61, 5) = (85, 5)$.In combination, we anticipated $23 + 10 = 33$ counterfactual hospitalizations out of 85 patients without treatment, consequently for the corresponding Bayesian factor analysis we used the conservative choice $p_2 = 33/85 = 38.8\%$.

8.1. Mortality rate reduction thresholds

- Mortality rate reduction efficacy threshold with $(N, a) = (33, 0)$

```
g(t) := pdistr(33, 0, t);
xlist: makelist(t, t, 10, 12, 1/10);
for t in xlist do print("x = ", float(t), "p-value percentage = ", g(t));

x =  10.0 p-value percentage =  7.260700222045903
x =  10.1 p-value percentage =  7.345610743704556
x =  10.2 p-value percentage =  4.448071309582566
=====[ 95% threshold ]=======================
x =  10.3 p-value percentage =  4.432825609296142
x =  10.4 p-value percentage =  4.424829698258415
x =  10.5 p-value percentage =  4.424042478322564
x =  10.6 p-value percentage =  4.430426295464651
x =  10.7 p-value percentage =  4.443946722482782
x =  10.8 p-value percentage =  4.464572346114712
x =  10.9 p-value percentage =  4.492274558583056
x =  11.0 p-value percentage =  4.527027353578275
x =  11.1 p-value percentage =  4.56880712669023
x =  11.2 p-value percentage =  4.617592480299571
x =  11.3 p-value percentage =  4.673364032940272
x =  11.4 p-value percentage =  2.814776982268185
x =  11.5 p-value percentage =  2.802783223124834
x =  11.6 p-value percentage =  2.795584248405036
x =  11.7 p-value percentage =  2.793163780625574
x =  11.8 p-value percentage =  2.795508579286136
x =  11.9 p-value percentage =  2.802608298984901
x =  12.0 p-value percentage =  2.81445534942549
```

- Mortality efficacy threshold $x_0 = 10.2\%$

- Bayesian factor analysis with $(N, a) = (33, 0)$ and $p_2 = 18.18\%$

```
f(t) := lbayesmax(33, 0, t, 1818/100);
g(t) := pdistr(33, 0, t);
xlist: makelist(t, t, 10, 12, 1/10);
for t in xlist do print("x = ", float(t), "log bayes = ", f(t), "p-value percent = ", g(t));

x =  10.0 log bayes =  2.01019277044629 p-value percent =  7.260700222045903
x =  10.1 log bayes =  2.021877922842493 p-value percent =  7.345610743704556
x =  10.2 log bayes =  2.033543061286889 p-value percent =  4.448071309582566
=====[ 95% threshold ]=======================
x =  10.3 log bayes =  2.045187798102073 p-value percent =  4.432825609296142
x =  10.4 log bayes =  2.056811742248747 p-value percent =  4.424829698258415
x =  10.5 log bayes =  2.068414499374527 p-value percent =  4.424042478322564
x =  10.6 log bayes =  2.079995671866219 p-value percent =  4.430426295464651
x =  10.7 log bayes =  2.091554858905627 p-value percent =  4.443946722482782
x =  10.8 log bayes =  2.103091656528984 p-value percent =  4.464572346114712
x =  10.9 log bayes =  2.114605657690063 p-value percent =  4.492274558583056
x =  11.0 log bayes =  2.126096452327054 p-value percent =  4.527027353578275
x =  11.1 log bayes =  2.137563627433261 p-value percent =  4.56880712669023
x =  11.2 log bayes =  2.149006767131697 p-value percent =  4.617592480299571
x =  11.3 log bayes =  2.160425452753637 p-value percent =  4.673364032940272
x =  11.4 log bayes =  2.171819262921192 p-value percent =  2.814776982268185
x =  11.5 log bayes =  2.183187773633944 p-value percent =  2.802783223124834
x =  11.6 log bayes =  2.194530558359734 p-value percent =  2.795584248405036
x =  11.7 log bayes =  2.205847188129608 p-value percent =  2.793163780625574
x =  11.8 log bayes =  2.217137231637007 p-value percent =  2.795508579286136
x =  11.9 log bayes =  2.228400255341211 p-value percent =  2.802608298984901
x =  12.0 log bayes =  2.239635823575095 p-value percent =  2.81445534942549
```

- Log Bayes factor at the unadjusted efficacy threshold x_0 is: $\log_{10} B = 2.03$
- Adjusted mortality efficacy threshold to $y_0 = 10.2\%$
- Mortality random selection bias threshold with $N = 33$ and $y_0 = 10.2\%$

```
g(t) := pdistr(33, ceiling(33*10.2/100), t);
xlist: makelist(t, t, 27, 29, 1/10);
for t in xlist do print("x = ", float(t), "p-value percent = ", g(t));

x =  27.0 p-value percent =  7.489516238877567
x =  27.1 p-value percent =  5.189703371255282
x =  27.2 p-value percent =  5.160477009717431
x =  27.3 p-value percent =  5.135044491187038
x =  27.4 p-value percent =  5.113395799363984
x =  27.5 p-value percent =  5.095521563041702
x =  27.6 p-value percent =  5.081413047706611
x =  27.7 p-value percent =  5.071062146483376
x =  27.8 p-value percent =  5.064461370441544
x =  27.9 p-value percent =  5.061603838279225
x =  28.0 p-value percent =  5.06248326539965
x =  28.1 p-value percent =  5.067093952396539
x =  28.2 p-value percent =  5.075430772964356
x =  28.3 p-value percent =  5.087489161249626
x =  28.4 p-value percent =  5.103265098659616
x =  28.5 p-value percent =  3.478282248707961
=====[ 95% selection bias threshold ]=========
x =  28.6 p-value percent =  3.455891369042793
x =  28.7 p-value percent =  3.436324927446423
x =  28.8 p-value percent =  3.419575143290656
x =  28.9 p-value percent =  3.405634996437667
x =  29.0 p-value percent =  3.394498219792121
```

- Mortality random selection bias threshold $x_1 = 28.5\%$

8.2. Hospitalization rate reduction thresholds

- Hospitalization rate reduction efficacy threshold with $(N, a) = (85, 5)$

```
g(t) := pdistr(85, 5, t);
xlist: makelist(t, t, 13, 14, 1/10);
for t in xlist do print("x = ", float(t), "p-value percentage = ", g(t));

x =  13.0 p-value percentage =  5.200316069593562
x =  13.1 p-value percentage =  5.213157232787764
x =  13.2 p-value percentage =  5.243381789375664
x =  13.3 p-value percentage =  5.290924898260976
x =  13.4 p-value percentage =  3.83133476166948
=====[ 95% threshold ]=======================
x =  13.5 p-value percentage =  3.824883589332865
x =  13.6 p-value percentage =  3.832314139925473
x =  13.7 p-value percentage =  3.853585547510585
x =  13.8 p-value percentage =  3.888669959175982
x =  13.9 p-value percentage =  2.799077350419765
x =  14.0 p-value percentage =  2.791955456375795
```

- Hospitalization efficacy threshold $x_0 = 13.4\%$
- Bayesian factor analysis with $(N, a) = (85, 5)$ and $p_2 = 38.8\%$

```
f(t) := lbayesmax(85, 5, t, 388/10);
g(t) := pdistr(85, 5, t);
xlist: makelist(t, t, 13, 14, 1/10);
for t in xlist do print("x = ", float(t), "log bayes = ", f(t), "p-value percent = ", g(t));

x =  13.0 log bayes =  1.948302931438409 p-value percent =  5.200316069593562
x =  13.1 log bayes =  1.97231508591244 p-value percent =  5.213157232787764
x =  13.2 log bayes =  1.996505561824193 p-value percent =  5.243381789375664
x =  13.3 log bayes =  2.020781373052973 p-value percent =  5.290924898260976
x =  13.4 log bayes =  2.045243414252174 p-value percent =  3.83133476166948
=====[ 95% threshold ]=======================
x =  13.5 log bayes =  2.069782883652019 p-value percent =  3.824883589332865
x =  13.6 log bayes =  2.094508323162728 p-value percent =  3.832314139925473
x =  13.7 log bayes =  2.119311405754379 p-value percent =  3.853585547510585
x =  13.8 log bayes =  2.144291662444207 p-value percent =  3.888669959175982
x =  13.9 log bayes =  2.169358282464374 p-value percent =  2.799077350419765
x =  14.0 log bayes =  2.194584330608476 p-value percent =  2.791955456375795
```

- Log Bayes factor at the unadjusted efficacy threshold x_0 is: $\log_{10} B = 2.05$
- Adjusted hospitalization efficacy threshold to $y_0 = 13.4\%$
- Hospitalization random selection bias threshold with $N = 85$ and $y_0 = 13.4\%$

```
g(t) := pdistr(85, ceiling(85*13.4/100), t);
xlist: makelist(t, t, 23, 24, 1/10);
for t in xlist do print("x = ", float(t), "p-value percent = ", g(t));

x =  23.0 p-value percent =  5.312095593876648
x =  23.1 p-value percent =  5.302711582929327
x =  23.2 p-value percent =  5.304625206042688
x =  23.3 p-value percent =  5.317811733743278
x =  23.4 p-value percent =  5.342250683122105
x =  23.5 p-value percent =  4.0701886090662
=====[ 95% selection bias threshold ]=========
```

```
x =  23.6 p-value percent =  4.057800625142685
x =  23.7 p-value percent =  4.054797384886225
x =  23.8 p-value percent =  4.061160930551213
x =  23.9 p-value percent =  4.076878746277712
x =  24.0 p-value percent =  3.094820608765865
```

- Hospitalization random selection bias threshold $x_1 = 23.5\%$

9. Thresholds for Stone + Babalola case series

To calculate the mortality rate reduction and hospitalization rate reduction thresholds for the combined Stone + Babalola case series, we used $(N, a) = (28, 0) + (10, 0) = (38, 0)$ for the calculation of the mortality rate reduction thresholds. For the corresponding Bayesian factor analysis, we used the conservative estimate $p_2 = 18.18\%$, which was the mortality rate for symptomatic hospitalized patients in Kano State, Nigeria **[13]**. This is the most conservative choice when compared against the 19.48% case fatality rate for hospitalized patients for LMIC countries by the World Heart Federation study **[14]** and our choice of p_2 used for the Hazan case series alone.

For the hospitalization rate reduction thresholds, we used $(N, a) = (34, 1) + (61, 5) = (95, 6)$. In combination, we anticipated $28 + 10 = 38$ counterfactual hospitalizations out of 95 patients without treatment, consequently for the corresponding Bayesian factor analysis we used the conservative choice $p_2 = 38/95 = 40\%$.

9.1. Mortality rate reduction thresholds

- Mortality rate reduction efficacy threshold with $(N, a) = (38, 0)$

```
g(t) := pdistr(38, 0, t);
xlist: makelist(t, t, 8, 10, 1/10);
for t in xlist do print("x = ", float(t), "p-value percentage = ", g(t));

x =  8.0 p-value percentage =  7.132511262207779
x =  8.1 p-value percentage =  7.140468380092227
x =  8.2 p-value percentage =  7.162484108461848
x =  8.3 p-value percentage =  7.198420655939588
x =  8.4 p-value percentage =  7.248144789797857
x =  8.5 p-value percentage =  7.311527293951062
x =  8.6 p-value percentage =  7.388442449819975
x =  8.7 p-value percentage =  7.478767539856878
x =  8.8 p-value percentage =  7.582382373502532
x =  8.9 p-value percentage =  4.595553441601854
=====[ 95% threshold ]=======================
x =  9.0 p-value percentage =  4.585249121361384
x =  9.1 p-value percentage =  4.584611887297948
x =  9.2 p-value percentage =  4.593580420982255
x =  9.3 p-value percentage =  4.61209882142149
x =  9.4 p-value percentage =  4.640116177232235
x =  9.5 p-value percentage =  4.677586149902834
x =  9.6 p-value percentage =  4.724466568156111
x =  9.7 p-value percentage =  4.780719033423462
x =  9.8 p-value percentage =  4.846308536440676
x =  9.9 p-value percentage =  2.943481481279717
x =  10.0 p-value percentage =  2.932297673102516
```

- Mortality efficacy threshold $x_0 = 8.9\%$
- Bayesian factor analysis with $(N, a) = (38, 0)$ and $p_2 = 18.18\%$

```
f(t) := lbayesmax(38, 0, t, 1818/100);
g(t) := pdistr(38, 0, t);
xlist: makelist(t, t, 8, 10, 1/10);
for t in xlist do print("x = ", float(t), "log bayes = ", f(t), "p-value percent = ", g(t));
```

```
x =  8.0 log bayes =  2.009007218793523 p-value percent =  7.132511262207779
x =  8.1 log bayes =  2.023254464597145 p-value percent =  7.140468380092227
x =  8.2 log bayes =  2.037487852884889 p-value percent =  7.162484108461848
x =  8.3 log bayes =  2.051706978039515 p-value percent =  7.198420655939588
x =  8.4 log bayes =  2.06591142838006 p-value percent =  7.248144789797857
x =  8.5 log bayes =  2.080100786120987 p-value percent =  7.311527293951062
x =  8.6 log bayes =  2.094274627333675 p-value percent =  7.388442449819975
x =  8.7 log bayes =  2.1084325219104 p-value percent =  7.478767539856878
x =  8.8 log bayes =  2.122574033530968 p-value percent =  7.582382373502532
x =  8.9 log bayes =  2.136698719632149 p-value percent =  4.595553441601854
=====[ 95% threshold ]=======================
x =  9.0 log bayes =  2.15080613138008 p-value percent =  4.585249121361384
x =  9.1 log bayes =  2.164895813645801 p-value percent =  4.584611887297948
x =  9.2 log bayes =  2.178967304984089 p-value percent =  4.593580420982255
x =  9.3 log bayes =  2.193020137615778 p-value percent =  4.61209882142149
x =  9.4 log bayes =  2.20705383741373 p-value percent =  4.640116177232235
x =  9.5 log bayes =  2.221067923892647 p-value percent =  4.677586149902834
x =  9.6 log bayes =  2.235061910202913 p-value percent =  4.724466568156111
x =  9.7 log bayes =  2.249035303128645 p-value percent =  4.780719033423462
x =  9.8 log bayes =  2.262987603090155 p-value percent =  4.846308536440676
x =  9.9 log bayes =  2.276918304151025 p-value percent =  2.943481481279717
x =  10.0 log bayes =  2.29082689402998 p-value percent =  2.932297673102516
```

- Log Bayes factor at the unadjusted efficacy threshold x_0 is: $\log_{10} B = 2.14$
- Adjusted mortality efficacy threshold to $y_0 = 8.9\%$
- Mortality random selection bias threshold with $N = 38$ and $y_0 = 8.9\%$

```
g(t) := pdistr(38, ceiling(38*8.9/100), t);
xlist: makelist(t, t, 24, 26, 1/10);
for t in xlist do print("x = ", float(t), "p-value percent = ", g(t));

x =  24.0 p-value percent =  5.667875980842995
x =  24.1 p-value percent =  5.661864583178787
x =  24.2 p-value percent =  5.660925800935665
x =  24.3 p-value percent =  5.66504838936484
x =  24.4 p-value percent =  5.67422190847807
x =  24.5 p-value percent =  5.688436698416538
x =  24.6 p-value percent =  5.70768385376081
x =  24.7 p-value percent =  5.731955196827189
x =  24.8 p-value percent =  3.944422939716608
=====[ 95% selection bias threshold ]=========
x =  24.9 p-value percent =  3.923845743515776
x =  25.0 p-value percent =  3.907159899941171
x =  25.1 p-value percent =  3.89435508994496
x =  25.2 p-value percent =  3.885422122625962
x =  25.3 p-value percent =  3.880352916833457
x =  25.4 p-value percent =  3.879140481779015
x =  25.5 p-value percent =  3.881778896684022
x =  25.6 p-value percent =  3.888263289490593
x =  25.7 p-value percent =  3.898589814663738
x =  25.8 p-value percent =  3.91275563011266
x =  25.9 p-value percent =  2.683573283062992
x =  26.0 p-value percent =  2.664925352461775
```

- Mortality random selection bias threshold $x_1 = 24.8\%$

9.2. Hospitalization rate reduction thresholds

- Hospitalization rate reduction efficacy threshold with $(N, a) = (95, 6)$

```
g(t) := pdistr(95, 6, t);
xlist: makelist(t, t, 13, 14, 1/10);
for t in xlist do print("x = ", float(t), "p-value percentage = ", g(t));

x =  13.0 p-value percentage =  6.48624358978905
x =  13.1 p-value percentage =  4.796240885642601
=====[ 95% threshold ]=======================
x =  13.2 p-value percentage =  4.791763086211255
x =  13.3 p-value percentage =  4.805607362293195
x =  13.4 p-value percentage =  4.837703949789989
x =  13.5 p-value percentage =  3.58108460009836
x =  13.6 p-value percentage =  3.567540942666549
x =  13.7 p-value percentage =  3.56871981837955
x =  13.8 p-value percentage =  3.584575842506316
x =  13.9 p-value percentage =  3.615080499726839
x =  14.0 p-value percentage =  2.642147642146036
```

- Hospitalization efficacy threshold $x_0 = 13.1\%$
- Bayesian factor analysis with $(N, a) = (95, 6)$ and $p_2 = 40\%$

```
f(t) := lbayesmax(95, 6, t, 40);
g(t) := pdistr(95, 6, t);
xlist: makelist(t, t, 13, 14, 1/10);
for t in xlist do print("x = ", float(t), "log bayes = ", f(t), "p-value percent = ", g(t));

x =  13.0 log bayes =  1.938681774927073 p-value percent =  6.48624358978905
x =  13.1 log bayes =  1.964226325119174 p-value percent =  4.796240885642601
=====[ unadjusted 95% threshold ]=======================
x =  13.2 log bayes =  1.989931864008947 p-value percent =  4.791763086211255
x =  13.3 log bayes =  2.015808300698729 p-value percent =  4.805607362293195
=====[ 95% threshold ]=======================
x =  13.4 log bayes =  2.041819289973925 p-value percent =  4.837703949789989
x =  13.5 log bayes =  2.06801956124984 p-value percent =  3.58108460009836
x =  13.6 log bayes =  2.094335805323458 p-value percent =  3.567540942666549
x =  13.7 log bayes =  2.120851496974787 p-value percent =  3.56871981837955
x =  13.8 log bayes =  2.147472737559239 p-value percent =  3.584575842506316
x =  13.9 log bayes =  2.174295051734609 p-value percent =  3.615080499726839
x =  14.0 log bayes =  2.201220987146271 p-value percent =  2.642147642146036
```

- Log Bayes factor at the unadjusted efficacy threshold x_0 is: $\log_{10} B = 1.96$
- Adjusted hospitalization efficacy threshold to $y_0 = 13.3\%$
- Hospitalization random selection bias threshold with $N = 95$ and $y_0 = 13.3\%$

```
g(t) := pdistr(95, ceiling(95*13.3/100), t);
xlist: makelist(t, t, 21, 23, 1/10);
for t in xlist do print("x = ", float(t), "p-value percent = ", g(t));

x =  21.0 p-value percent =  10.02330543767563
x =  21.1 p-value percent =  7.89143086511755
x =  21.2 p-value percent =  7.871734833329662
x =  21.3 p-value percent =  7.868976611893528
x =  21.4 p-value percent =  7.883099858640374
x =  21.5 p-value percent =  7.914049825740371
x =  21.6 p-value percent =  6.175734600746852
x =  21.7 p-value percent =  6.160180955590315
x =  21.8 p-value percent =  6.159086061029877
x =  21.9 p-value percent =  6.172409776585346
x =  22.0 p-value percent =  6.200116390514182
```

```
x =  22.1 p-value percent =  4.794954422536784
=====[ 95% selection bias threshold ]=========
x =  22.2 p-value percent =  4.782986062851871
x =  22.3 p-value percent =  4.783196280788996
x =  22.4 p-value percent =  4.795558318175432
x =  22.5 p-value percent =  3.712930252791989
x =  22.6 p-value percent =  3.693809697377733
x =  22.7 p-value percent =  3.684842128385763
x =  22.8 p-value percent =  3.686003776868267
x =  22.9 p-value percent =  3.697278577755372
x =  23.0 p-value percent =  2.838359244059413
```

- Hospitalization random selection bias threshold $x_1 = 22.1\%$

10. Thresholds for treatment arm of I-Tech trial

The treatment arm of the I-TECH trial [**7**] consisted of 241 high-risk patients with age ≥ 50 and at least one comorbidity. They were treated with a 5-day course of ivermectin at 0.4mg/kg between May 2021 and October 2021, and a substantial percentage of patients also received corticosteroids (26.9%), antibiotics (23.1%), and systemic anticoagulation (28.6%). Treatment was initiated within a 7-day window from the onset of symptoms. The resulting outcome was 3 deaths (1.2% mortality rate). Following the case series threshold analysis method [**1**], we use $p_2 = 10\%$ for the Bayesian adjustment of the efficacy threshold. The resulting efficacy threshold and random selection bias threshold calculations for mortality rate reduction are given in the following.

- Mortality rate reduction efficacy threshold with $(N, a) = (241, 3)$

```
g(t) := pdistr(241,3, t);
xlist: makelist(t, t,3, 5, 1/10);
for t in xlist do print("x = ", float(t), "p-value % = ", g(t));

x =  3.0 p-value % =  12.91367717494094
x =  3.1 p-value % =  13.18941808611639
x =  3.2 p-value % =  9.689295438437387
x =  3.3 p-value % =  9.973202865890421
x =  3.4 p-value % =  7.247238694981315
x =  3.5 p-value % =  5.310642438483113
x =  3.6 p-value % =  5.408694358063727
x =  3.7 p-value % =  3.920620013937095
=====[ 95% threshold ]======================
x =  3.8 p-value % =  4.031037682690225
x =  3.9 p-value % =  2.889711748420044
x =  4.0 p-value % =  2.098519602252398
x =  4.1 p-value % =  2.128117271691881
x =  4.2 p-value % =  1.527924679076605
x =  4.3 p-value % =  1.567089773495854
x =  4.4 p-value % =  1.112029974757598
x =  4.5 p-value % =  1.15459498600343
x =  4.6 p-value % =  0.8095942850933938
x =  4.7 p-value % =  0.5769132368351253
x =  4.8 p-value % =  0.5899749422036711
x =  4.9 p-value % =  0.4152245745488685
x =  5.0 p-value % =  0.4305842540597258
```

- Efficacy threshold $x_0 = 3.7\%$

- Bayesian factor analysis with $(N, a) = (241, 3)$ and $p_2 = 10\%$

```
f(t) := lbayesmax(241, 3, t, 10);
g(t) := pdistr(241, 3, t);
xlist: makelist(t, t, 3, 5, 1/10);
```

```
for t in xlist do print("x = ", float(t), "log bayes = ", f(t),
"p-value % = ", g(t));

x =  3.0 log bayes =  1.57657346488918 p-value % =  12.91367717494094
x =  3.1 log bayes =  1.640955158927616 p-value % =  13.18941808611639
x =  3.2 log bayes =  1.70630851105895 p-value % =  9.689295438437387
x =  3.3 log bayes =  1.772586090283419 p-value % =  9.973202865890421
x =  3.4 log bayes =  1.839733766118152 p-value % =  7.247238694981315
x =  3.5 log bayes =  1.907744353601214 p-value % =  5.310642438483113
x =  3.6 log bayes =  1.976550175943291 p-value % =  5.408694358063727
x =  3.7 log bayes =  2.046084340987405 p-value % =  3.920620013937095
=====[ 95% threshold ]=======================
x =  3.8 log bayes =  2.116379676279575 p-value % =  4.031037682690225
x =  3.9 log bayes =  2.187339631385025 p-value % =  2.889711748420044
x =  4.0 log bayes =  2.258922175732297 p-value % =  2.098519602252398
x =  4.1 log bayes =  2.33118837036731 p-value % =  2.128117271691881
x =  4.2 log bayes =  2.404029748142579 p-value % =  1.527924679076605
x =  4.3 log bayes =  2.477425665857898 p-value % =  1.567089773495854
x =  4.4 log bayes =  2.551354931178933 p-value % =  1.112029974757598
x =  4.5 log bayes =  2.625794922918382 p-value % =  1.15459498600343
x =  4.6 log bayes =  2.700721537219321 p-value % =  0.8095942850933938
x =  4.7 log bayes =  2.776109100679504 p-value % =  0.5769132368351253
x =  4.8 log bayes =  2.851930249859604 p-value % =  0.5899749422036711
x =  4.9 log bayes =  2.928155775851881 p-value % =  0.4152245745488685
x =  5.0 log bayes =  3.004754431793562 p-value % =  0.4305842540597258
```

- Log Bayes factor at the unadjusted efficacy threshold x_0 is: $\log_{10} B = 2.05$
- Adjusted mortality efficacy threshold to $y_0 = 3.7\%$
- Mortality random selection bias threshold with $N = 241$ and $y_0 = 3.7\%$

```
g(t) := pdistr(241, ceiling(241*3.7/100), t);
xlist: makelist(t, t, 6, 8, 1/10);
for t in xlist do print("x = ", float(t), "p-value % = ", g(t));

x =  6.0 p-value % =  17.29059793204141
x =  6.1 p-value % =  13.86140851578023
x =  6.2 p-value % =  13.95888654813357
x =  6.3 p-value % =  11.10506262557341
x =  6.4 p-value % =  11.20978884439709
x =  6.5 p-value % =  8.849682969208095
x =  6.6 p-value % =  8.958070670867947
x =  6.7 p-value % =  7.017499168083293
x =  6.8 p-value % =  7.126243131495146
x =  6.9 p-value % =  5.539061722402249
x =  7.0 p-value % =  4.328214718834599
=====[ 95% selection bias threshold ]=========
x =  7.1 p-value % =  4.353480980262685
x =  7.2 p-value % =  3.376547214757037
x =  7.3 p-value % =  3.408216398799754
x =  7.4 p-value % =  2.623398809979779
x =  7.5 p-value % =  2.658562790864758
x =  7.6 p-value % =  2.03057996123678
x =  7.7 p-value % =  2.066952484216985
x =  7.8 p-value % =  1.566296413433803
x =  7.9 p-value % =  1.198096708452611
x =  8.0 p-value % =  1.204359762697581
```

- Mortality random selection bias threshold $x_1 = 7.0\%$

11. Computer code for analysis of CDC database and demographic tables

This is the computer code that we used to analyze the January 20, 2023 snapshot of the CDC database [8] and extract the case fatality rates for hospitalized patients, over several time periods. Also included is the computer code used to calculate the demographic tables and the tables with the exact Fisher test calculations that were reported in our main manuscript. A brief explanation of the files is as follows:

11.1. build-cfr-database.r

This file loads the entire database, filters cases that are lab confirmed, symptomatic, and hospitalized, and removes all entries with unknown date. The reduced dataset is then used to calculate the hospitalized case fatality rate as well as the case fatality rate for patients that have been admitted to the ICU. The results of these calculations are being saved in several data frames that are then used to generate the corresponding LaTeX tables. This includes month by month data frames, cumulative month by month data frames, as well as data frames over specific time periods of interest. In total, 6 data frames are calculated and saved as csv files.

```
#######################
# build-crf-database.r
#######################

# Database link
#
    https://data.cdc.gov/Case-Surveillance/COVID-19-Case-Surveillance-Public-Use-Data-with-Ge/n8mc-b4w4
# Downloaded excel version of csv

# provides select, mutate, filter, etc
library (dplyr)

# Needed for %>% operator
library (magrittr)

# Load data. Filter cases that are lab confirmed, symptomatic, and hospitalized.
# Remove entries with unknown date.
# Add an artificial day number to fix the yyyy-mm format used in database into new column "date"
a <- read.csv ("cdc-data-retrieved-01-20-2023.csv") %>%
  select (case_month, age_group, race, current_status, symptom_status, underlying_conditions_yn,
      hosp_yn,icu_yn, death_yn) %>%
  filter (hosp_yn == "Yes") %>%
  filter (current_status == "Laboratory-confirmed case", symptom_status == "Symptomatic") %>%
  filter (!is.na(case_month)) %>%
  mutate (date = as.Date (sprintf ("%s-01", case_month)))

# Filter icu admissions
filter_icu <- function (data) { data %>% filter (icu_yn == "Yes") }

# Filter rows by yyyy-mm intervals
filter_date_interval <- function (data, begin_year, begin_month, end_year, end_month) {
  begin_date_edit <- as.Date (ISOdate (year = begin_year, month = begin_month, day = 1))
  end_date_edit <- as.Date (ISOdate (year = end_year, month = end_month, day = 1))
  data %>% filter (begin_date_edit <= date, date <= end_date_edit)
}

# Create row with results for specific interval
calculate_cfr_dataframe <- function (data, when) {
 data.frame (timing = when,
  yes_all = data %>% filter (death_yn == "Yes") %>% nrow(),
  no_all = data %>% filter (death_yn == "No") %>% nrow(),
  everyone_all = data %>% nrow(),
  yes_older_than_50 = data %>% filter (death_yn == "Yes") %>% filter (age_group == "50 to 64
      years" | age_group == "65+ years") %>% nrow(),
  no_older_than_50 = data %>% filter (death_yn == "No") %>% filter (age_group == "50 to 64 years"
      | age_group == "65+ years") %>% nrow(),
  everyone_older_than_50 = data %>% filter (age_group == "50 to 64 years" | age_group == "65+
      years") %>% nrow(),
```

```
  yes_older_than_65 = data %>% filter (death_yn == "Yes") %>% filter (age_group == "65+ years")
      %>% nrow(),
  no_older_than_65 = data %>% filter (death_yn == "No") %>% filter (age_group == "65+ years") %>%
      nrow(),
  everyone_older_than_65 = data %>% filter (age_group == "65+ years") %>% nrow()) %>%
  mutate (
   cfr_all = yes_all/(no_all + yes_all),
   cfr_lower_bound_all = yes_all/everyone_all,
   cfr_older_than_50 = yes_older_than_50/(yes_older_than_50 + no_older_than_50),
   cfr_lower_bound_older_than_50 = yes_older_than_50/everyone_older_than_50,
   cfr_older_than_65 = yes_older_than_65/(yes_older_than_65 + no_older_than_65),
   cfr_lower_bound_older_than_65 = yes_older_than_65/everyone_older_than_65)
}

# Convert year, month to yyyy-mm format
get_yyyy_mm <- function (theyear, themonth) {
  format (as.Date (ISOdate (year = theyear, month = themonth, day = 1)) , "%Y-%m")
}

# Build month by month CFR database for hospitalized patients
monthly <- data.frame()
cumulative <- data.frame()
for (year in 2020:2022) for (month in 1:12) monthly <- monthly %>%
   rbind (a %>% filter_date_interval (year, month, year, month) %>% calculate_cfr_dataframe
       (get_yyyy_mm (year, month)))
for (year in 2020:2022) for (month in 1:12) cumulative <- cumulative %>%
   rbind (a %>% filter_date_interval (2020, 1, year, month) %>% calculate_cfr_dataframe
       (get_yyyy_mm (year, month)))

# Build month by month CFR database for hospitalized patients admitted to icu
monthly_icu <- data.frame()
cumulative_icu <- data.frame()
for (year in 2020:2022) for (month in 1:12) monthly_icu <- monthly_icu %>%
   rbind (a %>% filter_date_interval (year, month, year, month) %>% filter_icu () %>%
       calculate_cfr_dataframe (get_yyyy_mm (year, month)))
for (year in 2020:2022) for (month in 1:12) cumulative_icu <- cumulative_icu %>%
   rbind (a %>% filter_date_interval (2020, 1, year, month) %>% filter_icu () %>%
       calculate_cfr_dataframe (get_yyyy_mm (year, month)))

# Build cumulative hospitalized CFR for waves
waves <- data.frame()
waves <- waves %>% rbind (a %>% filter_date_interval (2020, 1, 2020, 9) %>%
    calculate_cfr_dataframe ("First pre-delta period: 2020-01 to 2020-09"))
waves <- waves %>% rbind (a %>% filter_date_interval (2020, 10, 2021, 2) %>%
    calculate_cfr_dataframe ("Second pre-delta period: 2020-10 to 2021-02"))
waves <- waves %>% rbind (a %>% filter_date_interval (2021, 3, 2021, 6) %>%
    calculate_cfr_dataframe ("Third pre-delta period: 2021-03 to 2021-06"))
waves <- waves %>% rbind (a %>% filter_date_interval (2021, 07, 2021, 12) %>%
    calculate_cfr_dataframe ("Delta: 2021-07 to 2021-12"))
waves <- waves %>% rbind (a %>% filter_date_interval (2022, 01, 2022, 03) %>%
    calculate_cfr_dataframe ("Early Omicron: 2022-01 to 2022-03"))
waves <- waves %>% rbind (a %>% filter_date_interval (2022, 4, 2022, 12) %>%
    calculate_cfr_dataframe ("Late Omicron: 2022-04 to 2022-12"))

# Cumulative during periods used in Hazan and Stone paper
waves <- waves %>% rbind (a %>% filter_date_interval (2020, 8, 2021, 2) %>%
    calculate_cfr_dataframe ("Hazan (treatment interval): 2020-08 to 2021-02"))
waves <- waves %>% rbind (a %>% filter_date_interval (2020, 1, 2021, 2) %>%
    calculate_cfr_dataframe ("Hazan (cumulative): 2020-01 to 2021-02"))


# Build cumulative icu admitted CFR for waves
waves_icu <- data.frame()
waves_icu <- waves_icu %>% rbind (a %>% filter_date_interval (2020, 1, 2020, 9) %>% filter_icu()
    %>% calculate_cfr_dataframe ("First pre-delta period: 2020-01 to 2020-09"))
```

```
waves_icu <- waves_icu %>% rbind (a %>% filter_date_interval (2020, 10, 2021, 2) %>% filter_icu()
    %>% calculate_cfr_dataframe ("Second pre-delta period: 2020-10 to 2021-02"))
waves_icu <- waves_icu %>% rbind (a %>% filter_date_interval (2021, 3, 2021, 6) %>% filter_icu()
    %>% calculate_cfr_dataframe ("Third pre-delta period: 2021-03 to 2021-06"))
waves_icu <- waves_icu %>% rbind (a %>% filter_date_interval (2021, 07, 2021, 12) %>% filter_icu()
    %>% calculate_cfr_dataframe ("Delta: 2021-07 to 2021-12"))
waves_icu <- waves_icu %>% rbind (a %>% filter_date_interval (2022, 01, 2022, 03) %>% filter_icu()
    %>% calculate_cfr_dataframe ("Early Omicron: 2022-01 to 2022-03"))
waves_icu <- waves_icu %>% rbind (a %>% filter_date_interval (2022, 4, 2022, 12) %>% filter_icu()
    %>% calculate_cfr_dataframe ("Late Omicron: 2022-04 to 2022-12"))


# Cumulative during periods used in Hazan and Stone paper
waves_icu <- waves_icu %>% rbind (a %>% filter_date_interval (2020, 8, 2021, 2) %>% filter_icu()
    %>% calculate_cfr_dataframe ("Hazan (treatment interval): 2020-08 to 2021-02"))
waves_icu <- waves_icu %>% rbind (a %>% filter_date_interval (2020, 1, 2021, 2) %>% filter_icu()
    %>% calculate_cfr_dataframe ("Hazan (cumulative): 2020-01 to 2021-02"))


# Save the CFR results
write.csv (monthly, file="cfr-monthly.csv")
write.csv (cumulative, file="cfr-cumulative.csv")
write.csv (waves, file="cfr-waves.csv")
write.csv (monthly_icu, file="cfr-icu-monthly.csv")
write.csv (cumulative_icu, file="cfr-icu-cumulative.csv")
write.csv (waves_icu, file="cfr-icu-waves.csv")
```

11.2. tables-cfr-database.r

Loads the data frames generated by the previous file and generates the corresponding LaTeX tables. For each data frame, it is possible to calculate three tables using no age restriction, or age ≥ 50, or age ≥ 65. The LaTeX code for each table is saved in a separate text file. The resulting tables are included in the next section of this document.

```
#########################
# tables-cfr-database.r
#########################

# provides select, mutate, filter, etc
library(dplyr)

# Needed for %>% operator
library(magrittr)

# LaTeX tables
source ("tables.r")

################################################
# Load data

# Round the CFR
round_cfr <- function(data, n) {
 data %>% mutate(
cfr_all = round(100*cfr_all, digits=n),
cfr_lower_bound_all = round(100*cfr_lower_bound_all, digits=n),
cfr_older_than_50 = round(100*cfr_older_than_50, digits=n),
cfr_lower_bound_older_than_50 = round(100*cfr_lower_bound_older_than_50, digits=n),
cfr_older_than_65 = round(100*cfr_older_than_65, digits=n),
cfr_lower_bound_older_than_65 = round(100*cfr_lower_bound_older_than_65, digits=n)
)
}

# Load data and round the CFR
monthly <- read.csv("cfr-monthly.csv") %>% round_cfr (2)
cumulative <- read.csv("cfr-cumulative.csv") %>% round_cfr (2)
waves <- read.csv("cfr-waves.csv") %>% round_cfr (2)
monthly_icu <- read.csv("cfr-icu-monthly.csv") %>% round_cfr (2)
cumulative_icu <- read.csv("cfr-icu-cumulative.csv") %>% round_cfr (2)
waves_icu <- read.csv("cfr-icu-waves.csv") %>% round_cfr (2)

################################################
# Table settings

# Settings for table with one age group
table_format_cfr <- "ccccc"

# Setting for large side by side tables
table_format_cfr_large <- "ccccccccc"

# Heading for any small table
table_header_cfr <- function () sprintf ("%s & %s & %s & %s & %s \\\\", textbf ("Period"), textbf
    ("Cases"), textbf ("Died"), textbf ("Lived"), textbf ("CFR"))

# Heading for table displaying all ages and age> 50
# For table is included in the paper
table_header_cfr_large <- function () list (sprintf ("%s & %s & %s \\\\", textbf ("Period"),
    multicol (4, textbf ("all ages")), multicol (4, "\\textbf{age} $\\geq 50$ \\textbf{years}")),
 paste (cline (2, 5), cline (6, 9), sep=""),
 sprintf ("%s \\\\", paste ("", textbf ("Cases"), textbf ("Died"), textbf ("Lived"), textbf
     ("CFR"), textbf ("Cases"), textbf ("Died"), textbf ("Lived"), textbf ("CFR"), sep=" & ")))

# Header for tables combining monthly and cumulative statistics together
```

```
# For tables in supplamentary document
table_header_cfr_combined <- function () list (sprintf ("%s & %s & %s \\\\", textbf ("Period"),
    multicol (4, textbf ("Monthly")), multicol (4, textbf ("Cumulative"))),
 paste (cline (2, 5), cline (6, 9), sep=""),
 sprintf ("%s \\\\", paste ("", textbf ("Cases"), textbf ("Died"), textbf ("Lived"), textbf
     ("CFR"), textbf ("Cases"), textbf ("Died"), textbf ("Lived"), textbf ("CFR"), sep=" & ")))

# Bottom caption for CFR tables for waves
table_waves_bottomcaption <- "Calculations used a CDC database \\cite{article:cdc:cfrdata},
    accessed January 20, 2023. The timing for the virus waves who reported in the table is
    consistent with Adjei \\etal \\cite{article:Boehmer:2022}.
\\par 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."

# Bottom caption for monthly CFR tables
table_bottomcaption <- "Calculations used a CDC database \\cite{article:cdc:cfrdata}, 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."


################################################
# Print the table cells

# print (cases, died, lived, cfr) for all ages
print_all_ages <- function (d, i) sprintf ("%i & %i & %i & %s\\%% to %s\\%%", d$everyone_all[i],
    d$yes_all[i], d$no_all[i], as.character (d$cfr_lower_bound_all[i]), as.character
    (d$cfr_all[i]))

# print (cases, died, lived, cfr) for age > 50
print_older_than_50 <- function (d, i) sprintf ("%i & %i & %i & %s\\%% to %s\\%%",
    d$everyone_older_than_50[i], d$yes_older_than_50[i], d$no_older_than_50[i], as.character
    (d$cfr_lower_bound_older_than_50[i]), as.character (d$cfr_older_than_50[i]))

# print (cases, died, lived, cfr) for age > 65
print_older_than_65 <- function (d, i) sprintf ("%i & %i & %i & %s\\%% to %s\\%%",
    d$everyone_older_than_65[i], d$yes_older_than_65[i], d$no_older_than_65[i], as.character
    (d$cfr_lower_bound_older_than_65[i]), as.character (d$cfr_older_than_65[i]))

################################################
# Print the table rows

# Print rows for table with all ages
print_latex_table_all <- function (d) for (i in 1:nrow(d)) cat (sprintf ("%s & %s \\\\",
    d$timing[i], print_all_ages (d, i)), "\n")

# Print rows for table for age > 50
print_latex_table_older_than_50 <- function (d) for (i in 1:nrow(d)) cat (sprintf ("%s & %s \\\\",
    d$timing[i], print_older_than_50 (d, i)), "\n")

# Print rows for table for age > 65
print_latex_table_older_than_65 <- function (d) for (i in 1:nrow(d)) cat (sprintf ("%s & %s \\\\",
    d$timing[i], print_older_than_65 (d, i)), "\n")

# Print rows for all ages and for age > 50 for large table
# This is for table included in the paper
print_latex_table_large <- function (d) for (i in 1:nrow(d)) cat (sprintf ("%s & %s & %s \\\\",
    d$timing[i], print_all_ages (d, i), print_older_than_50 (d, i)), "\n")

# Print rows for table combining monthly and cumulative data
# The first argument is one of:
# print_all_ages, print_older_than_50, print_older_than_65
```

```
# dm = data frame with monthly data
# dc = data frame with cumulative data
print_latex_table_combined <- function (print_method, dm, dc) for (i in 1:nrow(dm)) cat (sprintf
    ("%s & %s & %s \\\\", dm$timing[i], print_method (dm, i), print_method (dc, i)), "\n")

############################################################
############################################################
############################################################

#####################################################
# Make table for hospitalized CFR over distinct waves
#####################################################

cfr_waves_caption <- "Cumulative case fatality rate for symptomatic lab confirmed COVID-19
    patients that have been hospitalized in the United States over specific time periods."
sink ("latex-table-cfr-waves.txt")
use_latex_table (5)
begin_latex_table ("cfr-waves", cfr_waves_caption, table_format_cfr, table_header_cfr ())
category ("CFR for confirmed hospitalizations over all age groups")
hline ()
waves %>% print_latex_table_all ()
hline ()
category ("CFR for confirmed hospitalizations for $\\text{age}\\geq 50$")
hline ()
waves %>% print_latex_table_older_than_50 ()
hline ()
category ("CFR for confirmed hospitalizations for $\\text{age}\\geq 65$")
hline ()
waves %>% print_latex_table_older_than_65 ()
end_latex_table_with_caption (table_waves_bottomcaption)
sink ()

#####################################################
# Make monthly CFR table for all ages and age > 50
# This table is included in the paper
#####################################################

cfr_monthly_all_caption <- "Monthly case fatality rate for symptomatic lab-confirmed COVID-19
    patients that have been hospitalized in the United States, during 2020, 2021, and 2022."
sink ("latex-table-cfr-monthly-all.txt")
use_latex_table (9)
begin_latex_table ("cfr-monthly-all", cfr_monthly_all_caption, table_format_cfr_large,
    table_header_cfr_large ())
monthly %>% print_latex_table_large ()
end_latex_table_with_caption (table_bottomcaption)
sink ()

# Create a longtable version for doublespaced manuscript
sink ("latex-table-cfr-monthly-all-long.txt")
use_latex_longtable (9)
begin_latex_longtable ("cfr-monthly-all", cfr_monthly_all_caption, table_format_cfr_large,
    table_header_cfr_large ())
monthly %>% print_latex_table_large ()
end_latex_longtable_with_caption (table_bottomcaption)
sink ()

#####################################################
# Make combined table for hospitalized CFR for all ages
# This table is included in the supplamentary document
#####################################################

cfr_combined_all_caption <- "Monthly and cumulative case fatality rate for symptomatic
    lab-confirmed COVID-19 patients of all ages that have been hospitalized in the United States
    during 2020-2021 and 2022"
sink ("latex-table-cfr-combined-all.txt")
```

```
use_latex_table (9)
begin_latex_table ("cfr-combined-all", cfr_combined_all_caption, table_format_cfr_large,
    table_header_cfr_combined ())
print_all_ages %>% print_latex_table_combined (monthly, cumulative)
end_latex_table_with_caption (table_bottomcaption)
sink ()

#####################################################
# Make combined table for hospitalized CFR for age > 50
# This table is included in the supplamentary document
#####################################################

cfr_combined_older_than_50_caption <- "Monthly and cumulative case fatality rate for
    $\\text{age}\\geq 50\\;\\text{years}$ symptomatic lab-confirmed COVID-19 patients with that
    have been hospitalized in the United States during 2020-2021 and 2022"
sink ("latex-table-cfr-combined-older-than-50.txt")
use_latex_table (9)
begin_latex_table ("cfr-combined-older-than-50", cfr_combined_older_than_50_caption,
    table_format_cfr_large, table_header_cfr_combined ())
print_older_than_50 %>% print_latex_table_combined (monthly, cumulative)
end_latex_table_with_caption (table_bottomcaption)
sink ()

#####################################################
# Make combined table for hospitalized CFR for age > 65
# This table is included in the supplamentary document
#####################################################

cfr_combined_older_than_65_caption <- "Monthly and cumulative case fatality rate for
    $\\text{age}\\geq 65\\;\\text{years}$ symptomatic lab-confirmed COVID-19 patients with that
    have been hospitalized in the United States during 2020-2021 and 2022"
sink ("latex-table-cfr-combined-older-than-65.txt")
use_latex_table (9)
begin_latex_table ("cfr-combined-older-than-65", cfr_combined_older_than_65_caption,
    table_format_cfr_large, table_header_cfr_combined ())
print_older_than_65 %>% print_latex_table_combined (monthly, cumulative)
end_latex_table_with_caption (table_bottomcaption)
sink ()

#############################################################
#############################################################
#############################################################

#####################################################
# Make table for cumulative icu CFR over distinct waves
#####################################################

cfr_icu_waves_caption <- "Cumulative case fatality rate for symptomatic lab-confirmed COVID-19
    patients that have been admitted in the ICU in the United States, over specific time periods
    including the distinct SARS-CoV-2 variant waves and the case series treatment periods."
sink ("latex-table-icu-cfr-waves.txt")
use_latex_table (5)
begin_latex_table ("cfr-icu-waves", cfr_icu_waves_caption, table_format_cfr, table_header_cfr ())
category ("CFR for confirmed icu patients over all age groups")
hline ()
waves_icu %>% print_latex_table_all ()
hline ()
category ("CFR for confirmed icu patients for $\\text{age}\\geq 50$")
hline ()
waves_icu %>% print_latex_table_older_than_50 ()
hline ()
category ("CFR for confirmed icu patients for $\\text{age}\\geq 65$")
hline ()
waves_icu %>% print_latex_table_older_than_65 ()
end_latex_table_with_caption (table_waves_bottomcaption)
```

```
sink ()

#####################################################
# Make combined table for ICU CFR for all ages
# This table is included in the supplamentary document
#####################################################

cfr_icu_combined_all_caption <- "Monthly and cumulative case fatality rate for symptomatic
    lab-confirmed COVID-19 patients of all ages that have been admitted to the ICU in the United
    States during 2020-2021 and 2022"
sink ("latex-table-cfr-icu-combined-all.txt")
use_latex_table (9)
begin_latex_table ("cfr-icu-combined-all", cfr_icu_combined_all_caption, table_format_cfr_large,
    table_header_cfr_combined ())
print_all_ages %>% print_latex_table_combined (monthly_icu, cumulative_icu)
end_latex_table_with_caption (table_bottomcaption)
sink ()


#####################################################
# Make combined table for ICU CFR for age > 50
# This table is included in the supplamentary document
#####################################################

cfr_icu_combined_older_than_50_caption <- "Monthly and cumulative case fatality rate for
    $\\text{age}\\geq 50\\;\\text{years}$ symptomatic lab-confirmed COVID-19 patients with that
    have been admitted to the ICU in the United States during 2020-2021 and 2022"
sink ("latex-table-cfr-icu-combined-older-than-50.txt")
use_latex_table (9)
begin_latex_table ("cfr-icu-combined-older-than-50", cfr_icu_combined_older_than_50_caption,
    table_format_cfr_large, table_header_cfr_combined ())
print_older_than_50 %>% print_latex_table_combined (monthly_icu, cumulative_icu)
end_latex_table_with_caption (table_bottomcaption)
sink ()

#####################################################
# Make combined table for ICU CFR for age > 65
# This table is included in the supplamentary document
#####################################################

cfr_icu_combined_older_than_65_caption <- "Monthly and cumulative case fatality rate for
    $\\text{age}\\geq 65\\;\\text{years}$ symptomatic lab-confirmed COVID-19 patients with that
    have been admitted to the ICU in the United States during 2020-2021 and 2022"
sink ("latex-table-cfr-icu-combined-older-than-65.txt")
use_latex_table (9)
begin_latex_table ("cfr-icu-combined-older-than-65", cfr_icu_combined_older_than_65_caption,
    table_format_cfr_large, table_header_cfr_combined ())
print_older_than_65 %>% print_latex_table_combined (monthly_icu, cumulative_icu)
end_latex_table_with_caption (table_bottomcaption)
sink ()
```

11.3. other-hospitalized-cfr.r

This is the code needed to do the arithmetic for calculating the various estimates for hospitalized CFR in the United States using the Premier Healthcare Database [**15,16**], as well as the external control groups from South Africa [**17**], Zimbabwe [**9,12**], and Nigeria [**13,18**], and the World Heart Federation [**14**]. The code does the arithmetic and generates the LaTeX table included in our paper.

```
##########################
# other-hospitalized-cfr.r
##########################

library (dplyr)
library (magrittr)
source ("tables.r")

# Add entry to data frame
add_entry <- function (d, arg_location, arg_timing, arg_cases, arg_deaths) d %>% rbind (data.frame
    (location = arg_location, timing = arg_timing, cases = arg_cases, deaths = arg_deaths) %>%
mutate (cfr = round ((100*deaths)/cases, digits = 2)))

# Create data frames
cfr_any_age <- data.frame ()
cfr_age_50 <- data.frame ()


# Premier Healthcare Database
# Adjei MMWR
cfr_any_age <- cfr_any_age %>% add_entry ("United States PHD-SR (Delta)", "2021-07 to 2021-10",
    163094, 24658) %>%
add_entry ("United States PHD-SR (Early Omicron)", "2022-01 to 2022-03", 104395, 13701) %>%
add_entry ("United States PHD-SR (Late Omicron)", "2022-04 to 2022-06", 20655, 1004) %>%
add_entry ("United States PHD-SR (cumulative)", "2020-04 to 2022-06", 1072106, 128517)

cfr_age_50 <- cfr_age_50 %>% add_entry ("United States PHD-SR (Delta)", "2021-07 to 2021-10",
    51208+43708+19420, 7696+9044+4203) %>%
add_entry ("United States PHD-SR (Early Omicron)", "2022-01 to 2022-03", 26258+38648+23733,
    2842+5896+4176) %>%
add_entry ("United States PHD-SR (Late Omicron)", "2022-04 to 2022-06", 3691+7063+6921,
    139+371+451)

# South Africa
# Jassat
cfr_any_age <- cfr_any_age %>% add_entry ("South Africa (first wave)", "2020-03 to 2020-08",
    400+1449+5787+18209+38226+19671, 45+185+1072+3698+8335+3707) %>%
add_entry ("South Africa (beta)", "2020-09 to 2021-03", 8851+7735+11110+39582+52019+11940+4235,
    1314+1167+2506+10621+15274+2380+737) %>%
add_entry ("South Africa (combined)", "2020-03 to 2021-03",
    400+1449+5787+18209+38226+19671+8851+7735+11110+39582+52019+11940+4235,
    45+185+1072+3698+8335+3707+1314+1167+2506+10621+15274+2380+737)

# Zimbabwe
cfr_any_age <- cfr_any_age %>% add_entry ("Zimbabwe (Parirenyatwa hospitals)", "2020-06 to
    2020-12", 336, 119) %>%
add_entry ("Zimbabwe (Mashonaland West Province)", "2020-04 to 2022-04", 673, 157)

# Lagos, Nigeria
cfr_any_age <- cfr_any_age %>% add_entry ("Lagos, Nigeria (combined)", "2020-04 to 2020-10",
    222+37+7, 37) %>%
add_entry ("Lagos, Nigeria (only hypoxemic patients)", "2020-04 to 2020-10", 64+32+6, 32)

 # Kano State, Nigeria
cfr_any_age <- cfr_any_age %>% add_entry ("Kano State, Nigeria (combined)", "2020-04 to 2021-03",
    195, 21) %>%
add_entry ("Kano State, Nigeria (excluding the initially asymptomatic", "2020-04 to 2021-03",
    45+32, 8+6)
```

```
# World Heart Federation Study
cfr_any_age <- cfr_any_age %>% add_entry ("World Health Federation study (combined)", "2020-06 to
    2021-09", 5313, 683+118) %>%
add_entry ("World Health Federation study (LMIC)", "2020-06 to 2021-09", 2526, 403+89)


# settings for table
table_format_cfr <- "ccccc"
table_header_cfr <- function () list (sprintf ("%s & %s & %s & %s & %s \\\\", textbf ("Location"),
    textbf ("Period"), textbf ("Cases"), textbf ("Died"), textbf ("CFR")))

# Print rows for table
print_table_row <- function (d, i) sprintf ("%s & %s & %i & %i & %s\\%% \\\\", d$location[i],
    d$timing[i], d$cases[i], d$deaths[i], as.character (d$cfr[i]))

# Print table
print_table <- function (d) for (i in 1:nrow(d)) cat (print_table_row (d, i), "\n")

# Make the CFR table
other_cfr_caption <- "Case fatality rate for hospitalized patients, as reported in the United
    States, South Africa, Zimbabwe, Nigeria, and worldwide."
sink ("latex-table-other-cfr.txt")
use_latex_table (5)
begin_latex_table ("other-cfr", other_cfr_caption, table_format_cfr, table_header_cfr ())
category ("CFR for confirmed hospitalizations over all age groups")
hline ()
cfr_any_age %>% print_table ()
hline ()
category ("CFR for confirmed hospitalizations for $\\text{age}\\geq 50$")
hline ()
cfr_age_50 %>% print_table ()
end_latex_table_with_caption ("CFR = Case Fatality Rate; PHD-SR = Premier Healthcare Database
    Special COVID-19 Release \\cite{article:pincai:database}")
sink ()
```

11.4. fisher-tests.r

Calculates the exact Fisher test comparisons between the case series and the external control groups and generates the LaTeX code for the two tables included in our main manuscript that present the results of these comparisons. Also calculates the exact Fisher test comparing the PRINCIPLE trial against the population level CFR.

```
#################
# fisher-tests.r
#################

library (dplyr)
library (magrittr)
library (stats)
source ("tables.r")

#########################
# Fisher test calculation
#########################

# Fisher table configurations
table_format_fisher <- "ccccc"

# Round p to n decimals and return LaTeX string
simplify_number <- function (p, n) ifelse (log10 (p) >= -n, as.character (round (p, digits=n)),
    ifelse (is.finite (log10 (p)), sprintf ("$10^{%s}$", as.character(floor (log10 (p)))), "0"))

# Compare treatment group (N, a) against control group (M, b)
do_fisher_test <- function (N, a, M, b) {
  test <- fisher.test (data.frame ("cured" = c (M-b, N-a), "noncured" = c (b, a), row.names = c
      ("control", "treated")))
  data.frame (treated.N = N, treated.a = a, control.M = M, control.b = b, lowci =
      test$conf.int[1], highci = test$conf.int[2], or = test$estimate, p = test$p.value)
}

# Make Fisher row to table
make_fisher_row <- function (f, desc) sprintf ("%s & (%i, %i) & (%i, %i) & %s (%s -- %s) & %s
    \\\\", desc, f$treated.N, f$treated.a, f$control.M, f$control.b, simplify_number (f$or, 2),
    simplify_number (f$lowci, 2), simplify_number (f$highci, 2), simplify_number (f$p, 3))

# Add Fisher row to table
add_fisher_row <- function (desc, N, a, M, b) cat (do_fisher_test (N, a, M, b) %>% make_fisher_row
    (desc), "\n")

#################################################
# Fisher table for hospitalization rate reduction
#################################################

# Table configuration
table_header_fisher <- function () list (sprintf ("%s & %s & %s & %s & %s \\\\", textbf ("Case
    series"), "$(N, a)$", "$(N, b)$", textbf ("OR (95\\% CI)"), textbf ("$p$-value")))
fisher_hospitalizations_caption <- "Self-controlled exact Fisher test comparisons of factual vs
    counterfactual hospitalization events in the Hazan \\etal\\cite{article:Borody:2022}, Stone
    \\etal\\cite{article:Aldous:2022}, and Babalola \\etal\\cite{article:Omede:2021} case series
    and in the combined case series."

# Make table
sink ("table-fisher-hospitalizations.txt")
use_latex_table (5)
begin_latex_table ("fisher-hospitalizations", fisher_hospitalizations_caption,
    table_format_fisher, table_header_fisher ())
add_fisher_row ("Hazan", 24, 0, 24, 23)
add_fisher_row ("Stone", 34, 1, 34, 28)
add_fisher_row ("Babalola", 61, 5, 61, 10)
add_fisher_row ("Hazan + Babalola", 24+61, 5, 24+61, 23+10)
```

```
add_fisher_row ("Stone + Babalola", 34+61, 1+5, 34+61, 28+10)
add_fisher_row ("Hazan + Stone", 24+34, 1, 24+34, 23+28)
add_fisher_row ("Hazan + Stone + Babalola", 24+34+61, 1+5, 24+34+61, 23+28+10)
end_latex_table_with_caption ("$(N, a)$ = 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 $\\text{SpO2}\\leq 90\\%$; OR =
    odds ratio; CI = confidence interval.")
sink ()

##########################################
# Fisher table for mortality rate reduction
##########################################

# Table configuration
table_header_fisher <- function () list (sprintf ("%s & %s & %s & %s & %s \\\\", textbf ("External
    control"), "$(N, a)$", "$(M, b)$", textbf ("OR (95\\% CI)"), textbf ("$p$-value")))
fisher_mortality_caption <- "Exact Fisher test comparisons between the Hazan
    \\etal\\cite{article:Borody:2022}, Stone \\etal\\cite{article:Aldous:2022}, and Babalola
    \\etal\\cite{article:Omede:2021} case series and corresponding external control groups from
    Table~\\ref{fig:cfr-waves} and Table~\\ref{fig:other-cfr}, with respect to mortality rate
    reduction."
fisher_mortality_bottomcaption <- "$(N,a)$ = treatment case series with $N$ cases and $a$ deaths;
    $(M, b)$ = external control with $M$ cases and $b$ deaths with data shown on
    Table~\\ref{fig:cfr-waves} and Table~\\ref{fig:other-cfr}; OR = Odds Ratio; CI = Confidence
    Interval;
\\par The case series have been risk-stratified under the $\\text{SpO2}\\leq 90\\%$ 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."

# Table content
fisher_mortality_content <- function () {
  category ("Hazan case series compared with")
  hline ()
  add_fisher_row ("CDC (treatment interval, any age)", 23, 0, 491152 , 45868)
  add_fisher_row ("CDC (treatment interval, $\\text{age}\\geq 50$)", 23, 0, 372828, 45214)
  add_fisher_row ("CDC (cumulative, any age)", 23, 0, 775369, 82427)
  add_fisher_row ("CDC (cumulative, $\\text{age}\\geq 50$)", 23, 0, 568399, 80586)
  add_fisher_row ("World Heart Federation study (all patients)", 23, 0, 5313, 801)
  hline ()
  category ("Stone case series compared with")
  hline ()
  add_fisher_row ("Zimbabwe (Parirenyatwa hospitals)", 28, 0, 336, 119)
  add_fisher_row ("Zimbabwe (Mashonaland West Province)", 28, 0, 673, 157)
  add_fisher_row ("South Africa (beta)", 28, 0, 135472, 33999)
  add_fisher_row ("South Africa (combined)", 28, 0, 219214, 51041)
  add_fisher_row ("World Heart Federation study (LMIC)", 28, 0, 2526, 492)
  hline ()
  category ("Babalola case series compared with")
  hline ()
  add_fisher_row ("Lagos, Nigeria (only hypoxemic patients)", 10, 0, 102, 32)
  add_fisher_row ("Kano State, Nigeria (without asymptomatic)", 10, 0, 77, 14)
  add_fisher_row ("World Heart Federation study (LMIC)", 10, 0, 2526, 492)
  hline ()
  category ("Hazan + Babalola case series compared with")
  hline ()
  add_fisher_row ("CDC (treatment interval, any age)", 33, 0, 491152 , 45868)
  add_fisher_row ("CDC (treatment interval, $\\text{age}\\geq 50$)", 33, 0, 372828, 45214)
  add_fisher_row ("World Heart Federation study (all patients)", 33, 0, 5313, 801)
  hline ()
  category ("Stone + Babalola case series compared with")
  hline ()
  add_fisher_row ("CDC (treatment interval, any age)", 38, 0, 491152 , 45868)
  add_fisher_row ("CDC (treatment interval, $\\text{age}\\geq 50$)", 38, 0, 372828, 45214)
  add_fisher_row ("World Heart Federation study (all patients)", 38, 0, 5313, 801)
```

```
  hline ()
  category ("Hazan + Stone case series compared with")
  hline ()
  add_fisher_row ("CDC (treatment interval, any age)", 51, 0, 491152 , 45868)
  add_fisher_row ("CDC (treatment interval, $\\text{age}\\geq 50$)", 51, 0, 372828, 45214)
  add_fisher_row ("World Heart Federation study (all patients)", 51, 0, 5313, 801)
  hline ()
  category ("Hazan + Stone + Babalola case series compared with")
  hline ()
  add_fisher_row ("CDC (treatment interval, any age)", 61, 0, 491152 , 45868)
  add_fisher_row ("CDC (treatment interval, $\\text{age}\\geq 50$)", 61, 0, 372828, 45214)
  add_fisher_row ("World Heart Federation study (all patients)", 61, 0, 5313, 801)
}

# For single-spaced manuscript
sink ("table-fisher-mortality.txt")
use_latex_table (5)
begin_latex_table ("fisher-mortality", fisher_mortality_caption, table_format_fisher,
    table_header_fisher ())
fisher_mortality_content ()
end_latex_table_with_caption (fisher_mortality_bottomcaption)
sink ()

# For double-spaced manuscript
sink ("table-fisher-mortality-long.txt")
use_latex_longtable (5)
begin_latex_longtable ("fisher-mortality", fisher_mortality_caption, table_format_fisher,
    table_header_fisher ())
fisher_mortality_content ()
end_latex_longtable_with_caption (fisher_mortality_bottomcaption)
sink ()


################################################
# PRINCIPLE
################################################

sink ("table-fisher-principle.txt")
table_header_fisher <- function () list (sprintf ("%s & %s & %s & %s & %s \\\\", textbf ("Case
    series"), "$(N, a)$", "$(M, b)$", textbf ("OR (95\\% CI)"), textbf ("$p$-value")))
fisher_principle_caption <- "Comparison with two-tailed exact Fisher test between the 2157 patient
    treatment group from the PRINCIPLE trial \\cite{article:Principle:2024} and the United Kingdom
    population level CFR between June 23, 2021 and July 1, 2022."
fisher_principle_bottomcaption <- "$(N,a)$ = treatment case series with $N$ cases and $a$ deaths;
    $(M, b)$ = external control with $M$ cases and $b$ deaths with data obtained from the
    population level CFR data in the United Kingdom between June 23, 2021 and July 1, 2022
    \\cite{owidcoronavirus}; OR = Odds Ratio; CI = Confidence Interval"
use_latex_table (5)
begin_latex_table ("fisher-principle", fisher_principle_caption, table_format_fisher,
    table_header_fisher ())
category ("PRINCIPLE treatment arm compared against entire UK population")
add_fisher_row ("Principle", 2157, 3, 265355, 685)
hline ()
category ("Counterfactual comparisons with increased sample size")
add_fisher_row ("Principle $\\times$ 2", 2*2157, 2*3, 265355, 685)
add_fisher_row ("Principle $\\times$ 3", 3*2157, 3*3, 265355, 685)
add_fisher_row ("Principle $\\times$ 4", 4*2157, 4*3, 265355, 685)
add_fisher_row ("Principle $\\times$ 5", 5*2157, 5*3, 265355, 685)
end_latex_table_with_caption (fisher_principle_bottomcaption)
sink ()
```

11.5. demographics.r

Calculates the demographic tables included in our paper directly from the baseline room air SpO2 files for the Hazan, Stone, and Babalola case series.

```
################
# demographics.r
################

library (dplyr)
library (magrittr)
source ("tables.r")

# Load case series data
hazan <- read.csv ("series-hazan.csv")
stone <- read.csv ("series-stone.csv")
babalola <- read.csv ("series-babalola.csv")

#######################################################
# Return percent in string form (n out of N)
percentage <- function (n, N) ifelse (n == 0, paste ("$", "0.0", "\\", "%$", sep=""), ifelse
    (100*(n/N) >= 0.1, paste ("$", sprintf ("%s", round (100*(n/N), digits=1)), "\\", "%$",
    sep=""), sprintf ("$10^{%s}$", as.character (floor (log10 (n/N))))))
percentage_without_the_symbol <- function (n, N) ifelse (n == 0, paste ("$", "0.0", "$", sep=""),
    ifelse (100*(n/N) >= 0.1, paste ("$", sprintf ("%s", round (100*(n/N), digits=1)), "$",
    sep=""), "$< 0.1$"))

#######################################################
# Count yes and calculate percentage; save results in dataframe
# data = complete dataset
# filtered_data = filtered dataset for which N and % are needed
count_rows <- function (filtered_data, data) data.frame (all = data %>% nrow (), N = filtered_data
    %>% nrow ()) %>% mutate (percent = percentage_without_the_symbol (N, all))

# Convert the count dataframe to LaTeX code
write_latex <- function (result) sprintf (" $%s$ & %s ", as.character (result$N), as.character
    (result$percent))

#######################################################
# Counters -- return LaTeX code for table entry

count_male <- function (data) data %>% filter (sex == "Male") %>% count_rows (data) %>%
    write_latex ()
count_female <- function (data) data %>% filter (sex == "Female") %>% count_rows (data) %>%
    write_latex ()
count_age_bracket <- function (data, a, b) data %>% filter (a <= age, age <= b) %>% count_rows
    (data) %>% write_latex ()

# note: (a, b) = (0, 0) counts missing values
count_spo2 <- function (data, a, b) if (a > 0 & b > 0) data %>% filter (a < basespo2, basespo2 <=
    b) %>% count_rows (data) %>% write_latex () else data %>% filter (is.na (basespo2)) %>%
    count_rows (data) %>% write_latex ()

#######################################################
# Write LaTeX table rows

add_male <- function (desc) cat (sprintf ("%s & %s & %s & %s & %s & %s & %s & %s \\\\", desc,
  hazan %>% count_male (),
  stone %>% count_male (),
  babalola %>% count_male (),
  rbind (hazan, babalola) %>% count_male (),
  rbind (stone, babalola) %>% count_male (),
  rbind (hazan, stone) %>% count_male (),
  rbind (hazan, stone, babalola) %>% count_male ()), "\n")

add_female <- function (desc) cat (sprintf ("%s & %s & %s & %s & %s & %s & %s & %s \\\\", desc,
```

```
  hazan %>% count_female (),
  stone %>% count_female (),
  babalola %>% count_female (),
  rbind (hazan, babalola) %>% count_female (),
  rbind (stone, babalola) %>% count_female (),
  rbind (hazan, stone) %>% count_female (),
  rbind (hazan, stone, babalola) %>% count_female ()), "\n")

add_age <- function (desc, a, b) cat (sprintf ("%s & %s & %s & %s & %s & %s & %s & %s & %s \\\\", desc,
  hazan %>% count_age_bracket (a, b),
  stone %>% count_age_bracket (a, b),
  babalola %>% count_age_bracket (a, b),
  rbind (hazan, babalola) %>% count_age_bracket (a, b),
  rbind (stone, babalola) %>% count_age_bracket (a, b),
  rbind (hazan, stone) %>% count_age_bracket (a, b),
  rbind (hazan, stone, babalola) %>% count_age_bracket (a, b)), "\n")

# note: (a, b) = (0, 0) counts missing values
spo2_describe <- function (a, b) if (a > 0 & b > 0) paste ("$", a, "\\", "%", " < \\text{SpO2}
    \\leq ", b, "\\", "%$", sep="") else paste ("Missing SpO2", sep="")

add_spo2 <- function (a, b) cat (sprintf ("%s & %s & %s & %s & %s & %s & %s & %s & %s \\\\",
    spo2_describe (a, b),
  hazan %>% count_spo2 (a, b),
  stone %>% count_spo2 (a, b),
  babalola %>% count_spo2 (a, b),
  rbind (hazan, babalola) %>% count_spo2 (a, b),
  rbind (stone, babalola) %>% count_spo2 (a, b),
  rbind (hazan, stone) %>% count_spo2 (a, b),
  rbind (hazan, stone, babalola) %>% count_spo2 (a, b)), "\n")

#########################################################
# Configure LaTeX table

table_caption <- "Demographic characteristics of the Hazan \\etal\\cite{article:Borody:2022},
    Stone \\etal\\cite{article:Aldous:2022}, and Babalola \\etal\\cite{article:Omede:2021} case
    series"
table_bottomcaption <- "\\textbf{Hazan} = the Hazan case series by Hazan
    \\etal\\cite{article:Borody:2022}; \\textbf{Stone} = the Stone case series by Stone
    \\etal\\cite{article:Aldous:2022}; \\textbf{Babalola} = the Babalola case series by Babalola
    \\etal\\cite{article:Omede:2021}; \\textbf{H+B} = the combined Hazan + Babalola case series;
    \\textbf{S+B} = the combined Stone + Babalola case series; \\textbf{H+S} = the combined Hazan
    + Stone case series; \\textbf{H+S+B} = the combined Hazan + Stone + Babalola case series."
table_format <- "lccccccccccccccc"
table_header <- function () list (sprintf ("& %s & %s & %s & %s & %s & %s & %s \\\\",
   multicol (2, textbf ("Hazan")), multicol (2, textbf ("Stone")), multicol (2, textbf
       ("Babalola")),
   multicol (2, textbf ("H+B")), multicol (2, textbf ("S+B")), multicol (2, textbf ("H+S")),
   multicol (2, textbf ("H+S+B"))),
  sprintf ("%s%s%s%s%s%s%s", cline (2, 3), cline (4, 5), cline (6, 7), cline (8,9), cline (10,
      11),cline (12, 13), cline (14, 15)),
  "\\textbf{Characteristic} & N & \\% & N & \\% & N & \\% & N & \\% & N & \\% & N & \\% & N & \\%
      \\\\")

#########################################################
# Load data with risk stratification

load_data <- function (spo2_threshold)
{
# Load data
  hazan <<- read.csv ("series-hazan.csv")
  stone <<- read.csv ("series-stone.csv")
  babalola <<- read.csv ("series-babalola.csv")

# Risk stratify, if requested
```

```
  if (spo2_threshold < 100)
  {
     hazan <<- hazan %>% filter (basespo2 <= spo2_threshold)
     stone <<- stone %>% filter (basespo2 <= spo2_threshold)
     babalola <<- babalola %>% filter (basespo2 <= spo2_threshold)
  }
}

#######################################################
# Table contents

# Show the SpO2 brackets
table_baseline_oxygen <- function (spo2_threshold)
{
  category ("Baseline SpO2 at room air")
  if (spo2_threshold > 93) add_spo2 (93, 100)
  if (spo2_threshold > 90) add_spo2 (90, 93)
  if (spo2_threshold > 85) add_spo2 (85, 90)
  if (spo2_threshold > 80) add_spo2 (80, 85)
  if (spo2_threshold > 75) add_spo2 (75, 80)
  if (spo2_threshold > 70) add_spo2 (70, 75)
  if (spo2_threshold > 65) add_spo2 (65, 70)
  if (spo2_threshold == 100) add_spo2 (0, 0)
}

# Show the sex/age demographics
table_demographics <- function ()
{
  category ("Sex")
  add_male ("Male")
  add_female ("Female")
  hline ()
  category ("Age brackets")
  add_age ("18 to 20 years", 18, 20)
  add_age ("21 to 30 years", 21, 30)
  add_age ("31 to 40 years", 31, 40)
  add_age ("41 to 50 years", 41, 50)
  add_age ("51 to 60 years", 51, 60)
  add_age ("61 to 70 years", 61, 70)
  add_age ("71 to 80 years", 71, 80)
  add_age ("81 to 90 years", 81, 90)
  add_age ("91 years or older", 91, 100)
}

# Produce table content
table_content <- function ()
{
  load_data (100)
  table_baseline_oxygen (100)
  hline ()
  category ("Demographics without risk stratification")
  hline ()
  table_demographics ()
  hline ()
  category ("Demographics with baseline room air SpO2 $\\leq 90\\%$")
  hline ()
  load_data (90)
  table_demographics ()
}

#######################################################
# Make the demographic table

sink ("table-demographic.txt")
use_latex_table (15)
```

```
begin_latex_table ("demographic", table_caption, table_format, table_header ())
table_content ()
end_latex_table_with_caption (table_bottomcaption)
sink ()
```

11.6. tables.r

This is an auxiliary utility code that is being used for the creation of LaTeX tables.

```
####################
# tables.r
####################

####################
# Make LaTeX tables
####################

# Boldfont used for table headers
textbf <- function (s) paste ("\\textbf{", s, "}", sep="")

# Multicolumn
multicol <- function (n, description) sprintf ("\\multicolumn{%s}{c}{%s} ", as.character (n),
    description)
multicol_left <- function (n, description) sprintf ("\\multicolumn{%s}{l}{%s} ", as.character (n),
    description)

# Multicolumn category entry
category <- function (s) cat (multicol_left (table_columns, textbf (s)), "\\\\ \n")

#########################################################
# Tabularx tables

# Define table lines for tabularx
# N is number of columns
use_latex_table <- function (N) {
  hline <<- function () cat ("\\midrule", "\n")
  bottomrule <<- function () cat ("\\bottomrule", "\n")
  toprule <<- function () cat ("\\toprule", "\n")
  cline <<- function (a, b) sprintf ("\\cmidrule(lr){%s-%s}", as.character (a), as.character (b))
  table_columns <<- N
}

# The length \tablewidth is used to control horizontal size of table
# Add \newlength{\tablewidth} to preamble of your document
# To load table, one can use a macro like:
# \newcommand{\loadtable}[2]{\setlength{\tablewidth}{#1\textwidth}\input{#1}}

# Open table. Arguments: table label, table caption, table format, table header
begin_latex_table <- function (tablelabel, tablecaption, tableformat, tableheader) {
  cat ("\\begin{table}[htb!]\\begin{center}", "\n")
  cat (sprintf ("\\caption{\\label{fig:%s}\\small %s}", tablelabel, tablecaption), "\n")
  cat ("{\\small", "\n")
  cat (sprintf ("\\begin{tabularx}{\\tablewidth}{%s}", tableformat), "\n")
  toprule ()
  for (i in tableheader) cat (i, "\n")
  hline ()
}

# Close table
end_latex_table <- function () {
  bottomrule ()
  cat ("\\end{tabularx}", "\n")
  cat ("\\end{center}\\end{table}", "\n")
}

# Close table with bottom caption
# Definition of bottom caption command
# \newcommand{\bottomcaption}[3]{\multicolumn{#1}{l}{\parbox{#2}{\vspace{6pt}\small #3}} \\}
end_latex_table_with_caption <- function (desc) {
  bottomrule ()
  cat (sprintf ("\\bottomcaption{%i}{\\tablewidth}{%s} \\\\", table_columns, desc), "\n")
```

```
  cat ("\\end{tabularx}", "\n")
  cat ("}", "\n")
  cat ("\\end{center}\\end{table}", "\n")
}


#######################################################
# longtable for doublespaced version of manuscript

# Define table lines for longtable
# N is number of columns
use_latex_longtable <- function (N) {
  hline <<- function () cat ("\\hline", "\n")
  bottomrule <<- hline
  toprule <<- hline
  cline <<- function (a, b) sprintf ("\\cline{%s-%s}", as.character (a), as.character (b))
  table_columns <<- N
}

# Open LaTeX longtable for doublespaced versions
begin_latex_longtable <- function (tablelabel, tablecaption, tableformat, tableheader) {
  cat ("\\begin{center}", "\n")
  cat ("{\\small", "\n")
  cat (sprintf ("\\begin{longtable}{%s}", tableformat), "\n")
  cat (sprintf ("\\caption{\\small %s}", tablecaption), "\n")
  cat (sprintf ("\\label{fig:%s} \\\\", tablelabel), "\n")
  toprule ()
  for (i in tableheader) cat (i, "\n")
  hline ()
}

# Close longtable
end_latex_longtable <- function () {
  bottomrule ()
  cat ("\\end{longtable}", "\n")
  cat ("\\end{center}", "\n")
}

# Close longtable with bottom caption
end_latex_longtable_with_caption <- function (desc) {
  bottomrule ()
  cat (sprintf ("\\bottomcaption{%i}{\\tablewidth}{%s} \\\\", table_columns, desc), "\n")
  cat ("\\end{longtable}", "\n")
  cat ("}", "\n")
  cat ("\\end{center}", "\n")
}
```

11.7. cure-data-set.r

The July 7, 2023 snapshot of the CDC database **[8]** contained an error in the naming of the case_month field. This short script corrected that error.

```
##################
# cure-data-set.r
##################
a <- read.csv("cdc-data-retrieved-07-07-2023.csv")
a$case_month <- a$ï..case_month
write.csv (a, file="cdc-data-retrieved-07-07-2023-corrected.csv")
```

12. The baseline SpO2 raw data for the Hazan, Stone, and Babalola case series

The following spreadsheet CSV files are used by demographics.r to calculate the demographic details for the Hazan, Stone, and Babalola case series. The data for series-hazan.csv was obtained from Table 1 of Hazan *et al.* [**2**]. The data for series-stone.r was obtained from the supplementary material of Stone *et al.* [**3**]. The data from series-babalola.r was obtained from Babalola [**19**] via email correspondence.

The data fields for the csv files are organized as follows:

age	The age of the patient
sex	Whether the patient is male or female
basespo2	Baseline room air SpO2 of patient at the onset of treatment.

12.1. series-hazan.csv

```
age, sex, basespo2
66,Male,90
62,Male,77
75,Male,88
66,Female,97
66,Female,89
43,Female,88
62,Male,86.5
57,Male,88
94,Female,88
63,Female,90
47,Male,84
69,Female,88
69,Male,88
71,Male,88
67,Female,88
46,Female,87
86,Male,88
59,Female,90
54,Male,88
92,Male,85
63,Male,90
57,Male,73
46,Female,90
87,Male,90
```

12.2. series-stone.csv

```
age, sex, basespo2
25,Male,79
32,Female,88
35,Male,87
37,Male,92
38,Female,76
40,Female,93
42,Male,90
44,Female,89
44,Male,87
45,Male,83
49,Female,66
50,Female,89
50,Male,92
52,Female,90
55,Female,82
55,Male,81
56,Female,87
57,Female,84
58,Male,85
58,Male,89
```

```
59,Male,79
59,Male,92
61,Female,87
61,Female,92
62,Male,88
62,Male,91
66,Male,85
66,Male,88
68,Male,89
68,Male,90
71,Female,89
75,Male,80
80,Female,85
90,Male,88
```

12.3. series-babalola.csv

```
"age","sex","basespo2"
29,"Male",93
52,"Female",89
32,"Male",76
33,"Female",78
32,"Male",96
61,"Female",98
62,"Female",94
41,"Female",92
54,"Male",94
28,"Male",94
32,"Male",96
42,"Male",98
40,"Female",95
25,"Male",96
68,"Male",78
65,"Female",97
38,"Male",96
45,"Male",98
56,"Male",92
60,"Female",92
89,"Male",91
31,"Male",95
24,"Male",92
48,"Male",89
34,"Male",92
36,"Male",98
46,"Male",94
32,"Male",92
62,"Female",94
32,"Female",99
32,"Female",92
19,"Female",90
21,"Female",90
62,"Male",94
33,"Female",92
23,"Male",90
25,"Male",94
35,"Male",94
26,"Male",96
19,"Female",94
38,"Male",94
34,"Female",94
32,"Female",94
65,"Female",94
24,"Male",94
```

```
20,"Male",94
41,"Female",94
57,"Male",94
64,"Male",94
48,"Female",94
58,"Male",94
18,"Male",94
48,"Male",94
34,"Male",90
55,"Male",94
49,"Male",NA
30,"Female",94
32,"Male",90
43,"Male",92
30,"Female",95
21,"Male",94
```

---

13. CFR calculation for hospitalized and ICU patients in the United States

Table 1: 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	364543	40792	167139	11.19% to 19.62%
Second pre-delta period: 2020-10 to 2021-02	410826	41635	170400	10.13% to 19.64%
Third pre-delta period: 2021-03 to 2021-06	121261	2330	56980	1.92% to 3.93%
Delta: 2021-07 to 2021-12	328083	23064	141718	7.03% to 14%
Early Omicron: 2022-01 to 2022-03	120634	11690	45579	9.69% to 20.41%
Late Omicron: 2022-04 to 2022-12	152982	3104	68330	2.03% to 4.35%
Hazan (treatment interval): 2020-08 to 2021-02	491152	45868	204620	9.34% to 18.31%
Hazan (cumulative): 2020-01 to 2021-02	775369	82427	337539	10.63% to 19.63%
CFR for confirmed hospitalizations for age ≥ 50				
First pre-delta period: 2020-01 to 2020-09	252678	39547	102912	15.65% to 27.76%
Second pre-delta period: 2020-10 to 2021-02	315721	41039	125000	13% to 24.72%
Third pre-delta period: 2021-03 to 2021-06	76607	2291	33625	2.99% to 6.38%
Delta: 2021-07 to 2021-12	218513	22236	85640	10.18% to 20.61%
Early Omicron: 2022-01 to 2022-03	88570	11554	31503	13.05% to 26.83%
Late Omicron: 2022-04 to 2022-12	116502	3097	50746	2.66% to 5.75%
Hazan (treatment interval): 2020-08 to 2021-02	372828	45214	147387	12.13% to 23.48%
Hazan (cumulative): 2020-01 to 2021-02	568399	80586	227912	14.18% to 26.12%
CFR for confirmed hospitalizations for age ≥ 65				
First pre-delta period: 2020-01 to 2020-09	153283	34327	53197	22.39% to 39.22%
Second pre-delta period: 2020-10 to 2021-02	211089	37620	78913	17.82% to 32.28%
Third pre-delta period: 2021-03 to 2021-06	40543	1972	15935	4.86% to 11.01%
Delta: 2021-07 to 2021-12	132803	18688	49818	14.07% to 27.28%
Early Omicron: 2022-01 to 2022-03	63212	10561	21854	16.71% to 32.58%
Late Omicron: 2022-04 to 2022-12	92605	3054	40786	3.3% to 6.97%
Hazan (treatment interval): 2020-08 to 2021-02	247339	41487	91753	16.77% to 31.14%
Hazan (cumulative): 2020-01 to 2021-02	364372	71947	132110	19.75% to 35.26%

Calculations used a CDC database [**8**], accessed January 20, 2023. The timing for the virus waves who reported in the table is consistent with Adjei *et al.* [**15**].
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.

Table 2: Monthly and cumulative case fatality rate for symptomatic lab-confirmed COVID-19 patients of all ages that have been hospitalized in the United States during 2020-2021 and 2022

Period	Monthly				Cumulative			
	Cases	Died	Lived	CFR	Cases	Died	Lived	CFR
2020-01	116	1	40	0.86% to 2.44%	116	1	40	0.86% to 2.44%
2020-02	675	32	158	4.74% to 16.84%	791	33	198	4.17% to 14.29%
2020-03	57703	8842	28437	15.32% to 23.72%	58494	8875	28635	15.17% to 23.66%
2020-04	72381	14518	34419	20.06% to 29.67%	130875	23393	63054	17.87% to 27.06%
2020-05	39618	4011	18999	10.12% to 17.43%	170493	27404	82053	16.07% to 25.04%
2020-06	44871	2890	20431	6.44% to 12.39%	215364	30294	102484	14.07% to 22.82%
2020-07	68853	6265	30435	9.1% to 17.07%	284217	36559	132919	12.86% to 21.57%
2020-08	45017	2871	18907	6.38% to 13.18%	329234	39430	151826	11.98% to 20.62%
2020-09	35309	1362	15313	3.86% to 8.17%	364543	40792	167139	11.19% to 19.62%
2020-10	57586	3322	26318	5.77% to 11.21%	422129	44114	193457	10.45% to 18.57%
2020-11	100089	10093	42949	10.08% to 19.03%	522218	54207	236406	10.38% to 18.65%
2020-12	114978	15288	43773	13.3% to 25.89%	637196	69495	280179	10.91% to 19.87%
2021-01	94337	10861	38448	11.51% to 22.03%	731533	80356	318627	10.98% to 20.14%
2021-02	43836	2071	18912	4.72% to 9.87%	775369	82427	337539	10.63% to 19.63%
2021-03	40133	947	19824	2.36% to 4.56%	815502	83374	357363	10.22% to 18.92%
2021-04	40967	934	20506	2.28% to 4.36%	856469	84308	377869	9.84% to 18.24%
2021-05	24688	279	11007	1.13% to 2.47%	881157	84587	388876	9.6% to 17.87%
2021-06	15473	170	5643	1.1% to 2.92%	896630	84757	394519	9.45% to 17.68%
2021-07	39648	2317	15427	5.84% to 13.06%	936278	87074	409946	9.3% to 17.52%
2021-08	73527	6515	29620	8.86% to 18.03%	1009805	93589	439566	9.27% to 17.55%
2021-09	59634	4011	24769	6.73% to 13.94%	1069439	97600	464335	9.13% to 17.37%
2021-10	43956	2146	18536	4.88% to 10.38%	1113395	99746	482871	8.96% to 17.12%
2021-11	45134	2980	19892	6.6% to 13.03%	1158529	102726	502763	8.87% to 16.97%
2021-12	66184	5095	33474	7.7% to 13.21%	1224713	107821	536237	8.8% to 16.74%
2022-01	85570	10295	32695	12.03% to 23.95%	1310283	118116	568932	9.01% to 17.19%
2022-02	26227	1292	9546	4.93% to 11.92%	1336510	119408	578478	8.93% to 17.11%
2022-03	8837	103	3338	1.17% to 2.99%	1345347	119511	581816	8.88% to 17.04%
2022-04	9862	92	4350	0.93% to 2.07%	1355209	119603	586166	8.83% to 16.95%
2022-05	20395	384	8812	1.88% to 4.18%	1375604	119987	594978	8.72% to 16.78%
2022-06	20881	527	9021	2.52% to 5.52%	1396485	120514	603999	8.63% to 16.63%
2022-07	25504	748	11067	2.93% to 6.33%	1421989	121262	615066	8.53% to 16.47%
2022-08	20540	467	9106	2.27% to 4.88%	1442529	121729	624172	8.44% to 16.32%
2022-09	14671	254	6618	1.73% to 3.7%	1457200	121983	630790	8.37% to 16.2%
2022-10	13704	182	6773	1.33% to 2.62%	1470904	122165	637563	8.31% to 16.08%
2022-11	15120	345	7088	2.28% to 4.64%	1486024	122510	644651	8.24% to 15.97%
2022-12	12305	105	5495	0.85% to 1.88%	1498329	122615	650146	8.18% to 15.87%

Calculations used a CDC database **[8]**, 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.

Table 3: Monthly and cumulative case fatality rate for age $\geq$ 50 years symptomatic lab-confirmed COVID-19 patients with that have been hospitalized in the United States during 2020-2021 and 2022

Period	Monthly				Cumulative			
	Cases	Died	Lived	CFR	Cases	Died	Lived	CFR
2020-01	5	0	3	0% to 0%	5	0	3	0% to 0%
2020-02	213	30	2	14.08% to 93.75%	218	30	5	13.76% to 85.71%
2020-03	40115	8179	17344	20.39% to 32.05%	40333	8209	17349	20.35% to 32.12%
2020-04	53379	14299	21789	26.79% to 39.62%	93712	22508	39138	24.02% to 36.51%
2020-05	26388	3952	10862	14.98% to 26.68%	120100	26460	50000	22.03% to 34.61%
2020-06	28294	2816	11522	9.95% to 19.64%	148394	29276	61522	19.73% to 32.24%
2020-07	47177	6096	19003	12.92% to 24.29%	195571	35372	80525	18.09% to 30.52%
2020-08	31685	2823	12186	8.91% to 18.81%	227256	38195	92711	16.81% to 29.18%
2020-09	25422	1352	10201	5.32% to 11.7%	252678	39547	102912	15.65% to 27.76%
2020-10	43464	3305	18964	7.6% to 14.84%	296142	42852	121876	14.47% to 26.01%
2020-11	76327	10009	31164	13.11% to 24.31%	372469	52861	153040	14.19% to 25.67%
2020-12	89545	14966	32387	16.71% to 31.61%	462014	67827	185427	14.68% to 26.78%
2021-01	73653	10699	28894	14.53% to 27.02%	535667	78526	214321	14.66% to 26.81%
2021-02	32732	2060	13591	6.29% to 13.16%	568399	80586	227912	14.18% to 26.12%
2021-03	27244	947	12830	3.48% to 6.87%	595643	81533	240742	13.69% to 25.3%
2021-04	25778	907	12054	3.52% to 7%	621421	82440	252796	13.27% to 24.59%
2021-05	15043	268	6027	1.78% to 4.26%	636464	82708	258823	12.99% to 24.22%
2021-06	8542	169	2714	1.98% to 5.86%	645006	82877	261537	12.85% to 24.06%
2021-07	23885	2125	8457	8.9% to 20.08%	668891	85002	269994	12.71% to 23.94%
2021-08	47668	6147	17409	12.9% to 26.1%	716559	91149	287403	12.72% to 24.08%
2021-09	40547	3928	15395	9.69% to 20.33%	757106	95077	302798	12.56% to 23.9%
2021-10	31163	2112	12201	6.78% to 14.76%	788269	97189	314999	12.33% to 23.58%
2021-11	32053	2926	13034	9.13% to 18.33%	820322	100115	328033	12.2% to 23.38%
2021-12	43197	4998	19144	11.57% to 20.7%	863519	105113	347177	12.17% to 23.24%
2022-01	62477	10164	22269	16.27% to 31.34%	925996	115277	369446	12.45% to 23.78%
2022-02	19930	1287	7048	6.46% to 15.44%	945926	116564	376494	12.32% to 23.64%
2022-03	6163	103	2186	1.67% to 4.5%	952089	116667	378680	12.25% to 23.55%
2022-04	7160	91	3074	1.27% to 2.88%	959249	116758	381754	12.17% to 23.42%
2022-05	14497	384	6278	2.65% to 5.76%	973746	117142	388032	12.03% to 23.19%
2022-06	15797	527	6649	3.34% to 7.34%	989543	117669	394681	11.89% to 22.97%
2022-07	19396	742	8219	3.83% to 8.28%	1008939	118411	402900	11.74% to 22.71%
2022-08	15703	467	6804	2.97% to 6.42%	1024642	118878	409704	11.6% to 22.49%
2022-09	11250	254	4910	2.26% to 4.92%	1035892	119132	414614	11.5% to 22.32%
2022-10	10988	182	5291	1.66% to 3.33%	1046880	119314	419905	11.4% to 22.13%
2022-11	11987	345	5350	2.88% to 6.06%	1058867	119659	425255	11.3% to 21.96%
2022-12	9724	105	4171	1.08% to 2.46%	1068591	119764	429426	11.21% to 21.81%

Calculations used a CDC database **[8]**, 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.

Table 4: Monthly and cumulative case fatality rate for age $\geq$ 65 years symptomatic lab-confirmed COVID-19 patients with that have been hospitalized in the United States during 2020-2021 and 2022

Period	Monthly				Cumulative			
	Cases	Died	Lived	CFR	Cases	Died	Lived	CFR
2020-01	3	0	2	0% to 0%	3	0	2	0% to 0%
2020-02	111	28	2	25.23% to 93.33%	114	28	4	24.56% to 87.5%
2020-03	22203	6149	7628	27.69% to 44.63%	22317	6177	7632	27.68% to 44.73%
2020-04	34128	12792	11079	37.48% to 53.59%	56445	18969	18711	33.61% to 50.34%
2020-05	16049	3694	5484	23.02% to 40.25%	72494	22663	24195	31.26% to 48.37%
2020-06	15992	2459	5715	15.38% to 30.08%	88486	25122	29910	28.39% to 45.65%
2020-07	28547	5338	10447	18.7% to 33.82%	117033	30460	40357	26.03% to 43.01%
2020-08	19884	2581	6843	12.98% to 27.39%	136917	33041	47200	24.13% to 41.18%
2020-09	16366	1286	5997	7.86% to 17.66%	153283	34327	53197	22.39% to 39.22%
2020-10	28824	3190	11815	11.07% to 21.26%	182107	37517	65012	20.6% to 36.59%
2020-11	51163	9418	19642	18.41% to 32.41%	233270	46935	84654	20.12% to 35.67%
2020-12	60479	13448	20660	22.24% to 39.43%	293749	60383	105314	20.56% to 36.44%
2021-01	49771	9646	18557	19.38% to 34.2%	343520	70029	123871	20.39% to 36.12%
2021-02	20852	1918	8239	9.2% to 18.88%	364372	71947	132110	19.75% to 35.26%
2021-03	14803	833	6330	5.63% to 11.63%	379175	72780	138440	19.19% to 34.46%
2021-04	13286	769	5491	5.79% to 12.28%	392461	73549	143931	18.74% to 33.82%
2021-05	8003	241	2846	3.01% to 7.81%	400464	73790	146777	18.43% to 33.45%
2021-06	4451	129	1268	2.9% to 9.23%	404915	73919	148045	18.26% to 33.3%
2021-07	12944	1581	4283	12.21% to 26.96%	417859	75500	152328	18.07% to 33.14%
2021-08	27620	4738	9750	17.15% to 32.7%	445479	80238	162078	18.01% to 33.11%
2021-09	24632	3422	8923	13.89% to 27.72%	470111	83660	171001	17.8% to 32.85%
2021-10	19872	1951	7495	9.82% to 20.65%	489983	85611	178496	17.47% to 32.42%
2021-11	20268	2608	7844	12.87% to 24.95%	510251	88219	186340	17.29% to 32.13%
2021-12	27467	4388	11523	15.98% to 27.58%	537718	92607	197863	17.22% to 31.88%
2022-01	44091	9223	15246	20.92% to 37.69%	581809	101830	213109	17.5% to 32.33%
2022-02	14552	1235	5028	8.49% to 19.72%	596361	103065	218137	17.28% to 32.09%
2022-03	4569	103	1580	2.25% to 6.12%	600930	103168	219717	17.17% to 31.95%
2022-04	5530	91	2338	1.65% to 3.75%	606460	103259	222055	17.03% to 31.74%
2022-05	11359	384	4999	3.38% to 7.13%	617819	103643	227054	16.78% to 31.34%
2022-06	12412	527	5197	4.25% to 9.21%	630231	104170	232251	16.53% to 30.96%
2022-07	15247	705	6570	4.62% to 9.69%	645478	104875	238821	16.25% to 30.51%
2022-08	12389	461	5452	3.72% to 7.8%	657867	105336	244273	16.01% to 30.13%
2022-09	9091	254	4034	2.79% to 5.92%	666958	105590	248307	15.83% to 29.84%
2022-10	9044	182	4474	2.01% to 3.91%	676002	105772	252781	15.65% to 29.5%
2022-11	9728	345	4333	3.55% to 7.37%	685730	106117	257114	15.48% to 29.21%
2022-12	7805	105	3389	1.35% to 3.01%	693535	106222	260503	15.32% to 28.97%

Calculations used a CDC database **[8]**, 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.

Table 5: Cumulative case fatality rate for symptomatic lab-confirmed COVID-19 patients that have been admitted in the ICU in the United States, over specific time periods including the distinct SARS-CoV-2 variant waves and the case series treatment periods.

Period	Cases	Died	Lived	CFR
CFR for confirmed icu patients over all age groups				
First pre-delta period: 2020-01 to 2020-09	43668	8895	12521	20.37% to 41.53%
Second pre-delta period: 2020-10 to 2021-02	36223	10389	9428	28.68% to 52.42%
Third pre-delta period: 2021-03 to 2021-06	9931	531	2964	5.35% to 15.19%
Delta: 2021-07 to 2021-12	29369	5539	5907	18.86% to 48.39%
Early Omicron: 2022-01 to 2022-03	8943	3214	1465	35.94% to 68.69%
Late Omicron: 2022-04 to 2022-12	6885	770	1916	11.18% to 28.67%
Hazan (treatment interval): 2020-08 to 2021-02	44584	11345	12086	25.45% to 48.42%
Hazan (cumulative): 2020-01 to 2021-02	79891	19284	21949	24.14% to 46.77%
CFR for confirmed icu patients for age ≥ 50				
First pre-delta period: 2020-01 to 2020-09	32693	8285	7973	25.34% to 50.96%
Second pre-delta period: 2020-10 to 2021-02	30445	10041	7263	32.98% to 58.03%
Third pre-delta period: 2021-03 to 2021-06	6974	526	1815	7.54% to 22.47%
Delta: 2021-07 to 2021-12	21895	5225	3759	23.86% to 58.16%
Early Omicron: 2022-01 to 2022-03	7535	3115	1078	41.34% to 74.29%
Late Omicron: 2022-04 to 2022-12	5754	766	1521	13.31% to 33.49%
Hazan (treatment interval): 2020-08 to 2021-02	36984	10971	9105	29.66% to 54.65%
Hazan (cumulative): 2020-01 to 2021-02	63138	18326	15236	29.03% to 54.6%
CFR for confirmed icu patients for age ≥ 65				
First pre-delta period: 2020-01 to 2020-09	19614	6382	3803	32.54% to 62.66%
Second pre-delta period: 2020-10 to 2021-02	20739	8356	4510	40.29% to 64.95%
Third pre-delta period: 2021-03 to 2021-06	3808	418	844	10.98% to 33.12%
Delta: 2021-07 to 2021-12	12677	4025	2001	31.75% to 66.79%
Early Omicron: 2022-01 to 2022-03	5310	2554	683	48.1% to 78.9%
Late Omicron: 2022-04 to 2022-12	4365	728	1119	16.68% to 39.42%
Hazan (treatment interval): 2020-08 to 2021-02	25056	9172	5552	36.61% to 62.29%
Hazan (cumulative): 2020-01 to 2021-02	40353	14738	8313	36.52% to 63.94%

Calculations used a CDC database **[8]**, accessed January 20, 2023. The timing for the virus waves who reported in the table is consistent with Adjei *et al.* **[15]**.
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.

Table 6: Monthly and cumulative case fatality rate for symptomatic lab-confirmed COVID-19 patients of all ages that have been admitted to the ICU in the United States during 2020-2021 and 2022

Period	Monthly				Cumulative			
	Cases	Died	Lived	CFR	Cases	Died	Lived	CFR
2020-01	12	0	1	0% to 0%	12	0	1	0% to 0%
2020-02	194	22	22	11.34% to 50%	206	22	23	10.68% to 48.89%
2020-03	9032	2336	2456	25.86% to 48.75%	9238	2358	2479	25.53% to 48.75%
2020-04	8361	2474	2165	29.59% to 53.33%	17599	4832	4644	27.46% to 50.99%
2020-05	5114	980	1570	19.16% to 38.43%	22713	5812	6214	25.59% to 48.33%
2020-06	5369	838	1525	15.61% to 35.46%	28082	6650	7739	23.68% to 46.22%
2020-07	7225	1289	2124	17.84% to 37.77%	35307	7939	9863	22.49% to 44.6%
2020-08	4640	611	1406	13.17% to 30.29%	39947	8550	11269	21.4% to 43.14%
2020-09	3721	345	1252	9.27% to 21.6%	43668	8895	12521	20.37% to 41.53%
2020-10	5316	763	1891	14.35% to 28.75%	48984	9658	14412	19.72% to 40.12%
2020-11	9188	2450	2613	26.67% to 48.39%	58172	12108	17025	20.81% to 41.56%
2020-12	10556	4049	2252	38.36% to 64.26%	68728	16157	19277	23.51% to 45.6%
2021-01	7872	2668	1786	33.89% to 59.9%	76600	18825	21063	24.58% to 47.19%
2021-02	3291	459	886	13.95% to 34.13%	79891	19284	21949	24.14% to 46.77%
2021-03	2995	231	915	7.71% to 20.16%	82886	19515	22864	23.54% to 46.05%
2021-04	3398	220	1106	6.47% to 16.59%	86284	19735	23970	22.87% to 45.16%
2021-05	2120	42	624	1.98% to 6.31%	88404	19777	24594	22.37% to 44.57%
2021-06	1418	38	319	2.68% to 10.64%	89822	19815	24913	22.06% to 44.3%
2021-07	3904	446	766	11.42% to 36.8%	93726	20261	25679	21.62% to 44.1%
2021-08	6912	1378	1363	19.94% to 50.27%	100638	21639	27042	21.5% to 44.45%
2021-09	5311	923	1093	17.38% to 45.78%	105949	22562	28135	21.3% to 44.5%
2021-10	4003	566	865	14.14% to 39.55%	109952	23128	29000	21.03% to 44.37%
2021-11	4265	830	930	19.46% to 47.16%	114217	23958	29930	20.98% to 44.46%
2021-12	4974	1396	890	28.07% to 61.07%	119191	25354	30820	21.27% to 45.13%
2022-01	6474	2818	958	43.53% to 74.63%	125665	28172	31778	22.42% to 46.99%
2022-02	1855	356	355	19.19% to 50.07%	127520	28528	32133	22.37% to 47.03%
2022-03	614	40	152	6.51% to 20.83%	128134	28568	32285	22.3% to 46.95%
2022-04	439	20	98	4.56% to 16.95%	128573	28588	32383	22.23% to 46.89%
2022-05	824	70	237	8.5% to 22.8%	129397	28658	32620	22.15% to 46.77%
2022-06	984	98	239	9.96% to 29.08%	130381	28756	32859	22.06% to 46.67%
2022-07	1240	214	312	17.26% to 40.68%	131621	28970	33171	22.01% to 46.62%
2022-08	965	119	277	12.33% to 30.05%	132586	29089	33448	21.94% to 46.51%
2022-09	596	61	172	10.23% to 26.18%	133182	29150	33620	21.89% to 46.44%
2022-10	597	45	194	7.54% to 18.83%	133779	29195	33814	21.82% to 46.33%
2022-11	710	97	210	13.66% to 31.6%	134489	29292	34024	21.78% to 46.26%
2022-12	530	46	177	8.68% to 20.63%	135019	29338	34201	21.73% to 46.17%

Calculations used a CDC database **[8]**, 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.

Table 7: Monthly and cumulative case fatality rate for age $\geq$ 50 years symptomatic lab-confirmed COVID-19 patients with that have been admitted to the ICU in the United States during 2020-2021 and 2022

Period	Monthly				Cumulative			
	Cases	Died	Lived	CFR	Cases	Died	Lived	CFR
2020-01	0	0	0	NA% to NA%	0	0	0	NA% to NA%
2020-02	89	20	0	22.47% to 100%	89	20	0	22.47% to 100%
2020-03	6555	1976	1500	30.14% to 56.85%	6644	1996	1500	30.04% to 57.09%
2020-04	6516	2373	1398	36.42% to 62.93%	13160	4369	2898	33.2% to 60.12%
2020-05	3703	949	929	25.63% to 50.53%	16863	5318	3827	31.54% to 58.15%
2020-06	3770	795	886	21.09% to 47.29%	20633	6113	4713	29.63% to 56.47%
2020-07	5521	1242	1418	22.5% to 46.69%	26154	7355	6131	28.12% to 54.54%
2020-08	3605	587	951	16.28% to 38.17%	29759	7942	7082	26.69% to 52.86%
2020-09	2934	343	891	11.69% to 27.8%	32693	8285	7973	25.34% to 50.96%
2020-10	4395	756	1437	17.2% to 34.47%	37088	9041	9410	24.38% to 49%
2020-11	7689	2396	2018	31.16% to 54.28%	44777	11437	11428	25.54% to 50.02%
2020-12	9017	3854	1760	42.74% to 68.65%	53794	15291	13188	28.43% to 53.69%
2021-01	6700	2583	1392	38.55% to 64.98%	60494	17874	14580	29.55% to 55.07%
2021-02	2644	452	656	17.1% to 40.79%	63138	18326	15236	29.03% to 54.6%
2021-03	2270	231	623	10.18% to 27.05%	65408	18557	15859	28.37% to 53.92%
2021-04	2438	218	693	8.94% to 23.93%	67846	18775	16552	27.67% to 53.15%
2021-05	1436	39	366	2.72% to 9.63%	69282	18814	16918	27.16% to 52.65%
2021-06	830	38	133	4.58% to 22.22%	70112	18852	17051	26.89% to 52.51%
2021-07	2611	386	452	14.78% to 46.06%	72723	19238	17503	26.45% to 52.36%
2021-08	5001	1271	825	25.41% to 60.64%	77724	20509	18328	26.39% to 52.81%
2021-09	3920	884	658	22.55% to 57.33%	81644	21393	18986	26.2% to 52.98%
2021-10	3084	550	580	17.83% to 48.67%	84728	21943	19566	25.9% to 52.86%
2021-11	3305	802	623	24.27% to 56.28%	88033	22745	20189	25.84% to 52.98%
2021-12	3974	1332	621	33.52% to 68.2%	92007	24077	20810	26.17% to 53.64%
2022-01	5489	2723	692	49.61% to 79.74%	97496	26800	21502	27.49% to 55.48%
2022-02	1574	352	282	22.36% to 55.52%	99070	27152	21784	27.41% to 55.48%
2022-03	472	40	104	8.47% to 27.78%	99542	27192	21888	27.32% to 55.4%
2022-04	352	20	73	5.68% to 21.51%	99894	27212	21961	27.24% to 55.34%
2022-05	675	70	184	10.37% to 27.56%	100569	27282	22145	27.13% to 55.2%
2022-06	821	98	193	11.94% to 33.68%	101390	27380	22338	27% to 55.07%
2022-07	1037	210	243	20.25% to 46.36%	102427	27590	22581	26.94% to 54.99%
2022-08	802	119	214	14.84% to 35.74%	103229	27709	22795	26.84% to 54.86%
2022-09	501	61	139	12.18% to 30.5%	103730	27770	22934	26.77% to 54.77%
2022-10	511	45	162	8.81% to 21.74%	104241	27815	23096	26.68% to 54.63%
2022-11	605	97	166	16.03% to 36.88%	104846	27912	23262	26.62% to 54.54%
2022-12	450	46	147	10.22% to 23.83%	105296	27958	23409	26.55% to 54.43%

Calculations used a CDC database **[8]**, 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.

Table 8: Monthly and cumulative case fatality rate for age $\geq$ 65 years symptomatic lab-confirmed COVID-19 patients with that have been admitted to the ICU in the United States during 2020-2021 and 2022

Period	Monthly				Cumulative			
	Cases	Died	Lived	CFR	Cases	Died	Lived	CFR
2020-01	0	0	0	NA% to NA%	0	0	0	NA% to NA%
2020-02	47	20	0	42.55% to 100%	47	20	0	42.55% to 100%
2020-03	3555	1187	661	33.39% to 64.23%	3602	1207	661	33.51% to 64.61%
2020-04	3979	1934	608	48.61% to 76.08%	7581	3141	1269	41.43% to 71.22%
2020-05	2196	813	388	37.02% to 67.69%	9777	3954	1657	40.44% to 70.47%
2020-06	2194	639	377	29.12% to 62.89%	11971	4593	2034	38.37% to 69.31%
2020-07	3326	973	727	29.25% to 57.24%	15297	5566	2761	36.39% to 66.84%
2020-08	2341	497	519	21.23% to 48.92%	17638	6063	3280	34.37% to 64.89%
2020-09	1976	319	523	16.14% to 37.89%	19614	6382	3803	32.54% to 62.66%
2020-10	2966	703	849	23.7% to 45.3%	22580	7085	4652	31.38% to 60.36%
2020-11	5254	2091	1257	39.8% to 62.46%	27834	9176	5909	32.97% to 60.83%
2020-12	6222	3096	1144	49.76% to 73.02%	34056	12272	7053	36.03% to 63.5%
2021-01	4578	2082	858	45.48% to 70.82%	38634	14354	7911	37.15% to 64.47%
2021-02	1719	384	402	22.34% to 48.85%	40353	14738	8313	36.52% to 63.94%
2021-03	1301	173	309	13.3% to 35.89%	41654	14911	8622	35.8% to 63.36%
2021-04	1307	183	310	14% to 37.12%	42961	15094	8932	35.13% to 62.82%
2021-05	776	34	164	4.38% to 17.17%	43737	15128	9096	34.59% to 62.45%
2021-06	424	28	61	6.6% to 31.46%	44161	15156	9157	34.32% to 62.34%
2021-07	1364	241	213	17.67% to 53.08%	45525	15397	9370	33.82% to 62.17%
2021-08	2744	912	414	33.24% to 68.78%	48269	16309	9784	33.79% to 62.5%
2021-09	2229	688	364	30.87% to 65.4%	50498	16997	10148	33.66% to 62.62%
2021-10	1874	469	338	25.03% to 58.12%	52372	17466	10486	33.35% to 62.49%
2021-11	1980	648	338	32.73% to 65.72%	54352	18114	10824	33.33% to 62.6%
2021-12	2486	1067	334	42.92% to 76.16%	56838	19181	11158	33.75% to 63.22%
2022-01	3773	2182	423	57.83% to 83.76%	60611	21363	11581	35.25% to 64.85%
2022-02	1174	332	194	28.28% to 63.12%	61785	21695	11775	35.11% to 64.82%
2022-03	363	40	66	11.02% to 37.74%	62148	21735	11841	34.97% to 64.73%
2022-04	258	20	49	7.75% to 28.99%	62406	21755	11890	34.86% to 64.66%
2022-05	526	70	140	13.31% to 33.33%	62932	21825	12030	34.68% to 64.47%
2022-06	606	98	139	16.17% to 41.35%	63538	21923	12169	34.5% to 64.31%
2022-07	778	176	182	22.62% to 49.16%	64316	22099	12351	34.36% to 64.15%
2022-08	600	115	139	19.17% to 45.28%	64916	22214	12490	34.22% to 64.01%
2022-09	389	61	107	15.68% to 36.31%	65305	22275	12597	34.11% to 63.88%
2022-10	396	45	124	11.36% to 26.63%	65701	22320	12721	33.97% to 63.7%
2022-11	470	97	132	20.64% to 42.36%	66171	22417	12853	33.88% to 63.56%
2022-12	342	46	107	13.45% to 30.07%	66513	22463	12960	33.77% to 63.41%

Calculations used a CDC database **[8]**, 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.

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A. Parirenyatwa hospitals redzone statistics report

This section attaches a copy of the unpublished Parirenyatwa group of hospitals report [**9**] which was used as an external control group in our paper. We note that on page 5 of the report, we are told that out of 336 admissions 35.4% of the patients died from COVID-19. From this, we uniquely obtain a count of 119 deaths, noting that neither 118 deaths and 120 deaths gives a CFR that rounds to 35.4%.

The pie graph on Annex 5 is somewhat confusing and may lead one to think that the CFR is 26%, which would have corresponded to between 86 and 89 deaths, however from the comment after Annex 6, it is clear that there are 82 deaths reported solely on the months of August and December alone, and from the bar graph on Annex 6, it is clear that there are more than 89 deaths throughout the entire period.

PARIRENYATWA GROUP OF HOSPITALS REDZONE STATISTICS FOR THE PERIOD 5 MAY 2020 TO 31 DECEMBER 2020

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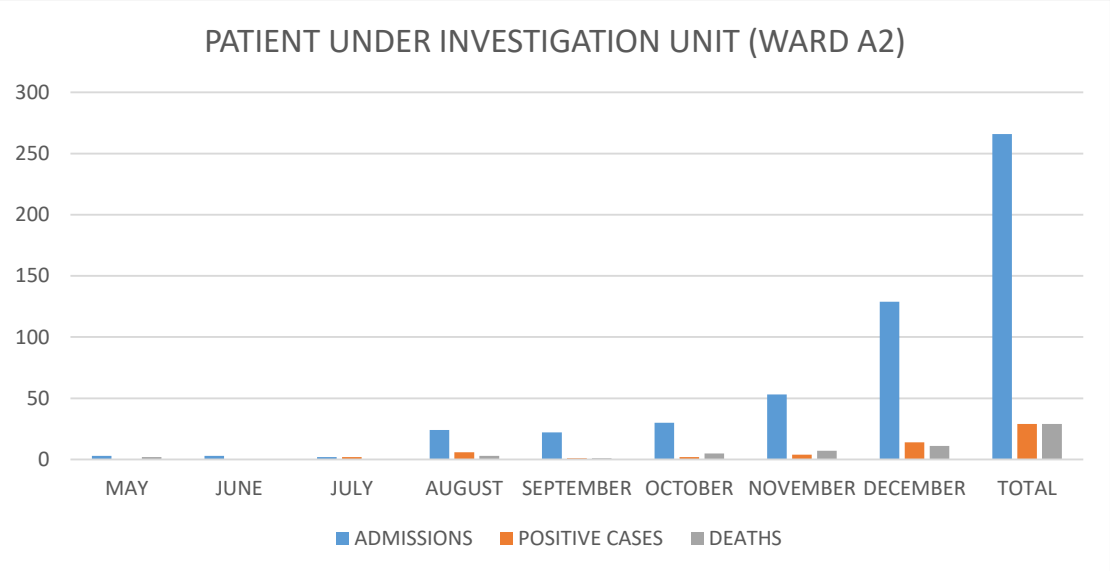
PARIRENYATWA GROUP OF HOSPITALS REDZONE STATISTICS FOR THE PERIOD 5 MAY 2020 TO 31 DECEMBER 2020

PATIENT UNDER INVESTIGATION WARD A2

ANNEX 1 MONTHLY STATISTICS FOR THE PUI WARD

MONTH	ADMISSIONS	POSITIVE CASES	DEATHS	T/F TO GREEN ZONE	DISCHARGES	MISSED OUTCOMES
MAY	3	0	2		1	0
JUNE	3	0	0	2		1
JULY	2	2	0			0
AUGUST	24	6	3		14	1
SEPTEMBER	22	1	1			20
OCTOBER	30	2	5	8		15
NOVEMBER	53	4	7	15	13	14
DECEMBER	129	14	11	20		84
TOTAL	**266**	**25**	**26**	**45**	**15**	**155**

ANNEX 2: ADMISSIONS, POSITIVE CASES AND DEATHS IN PUI



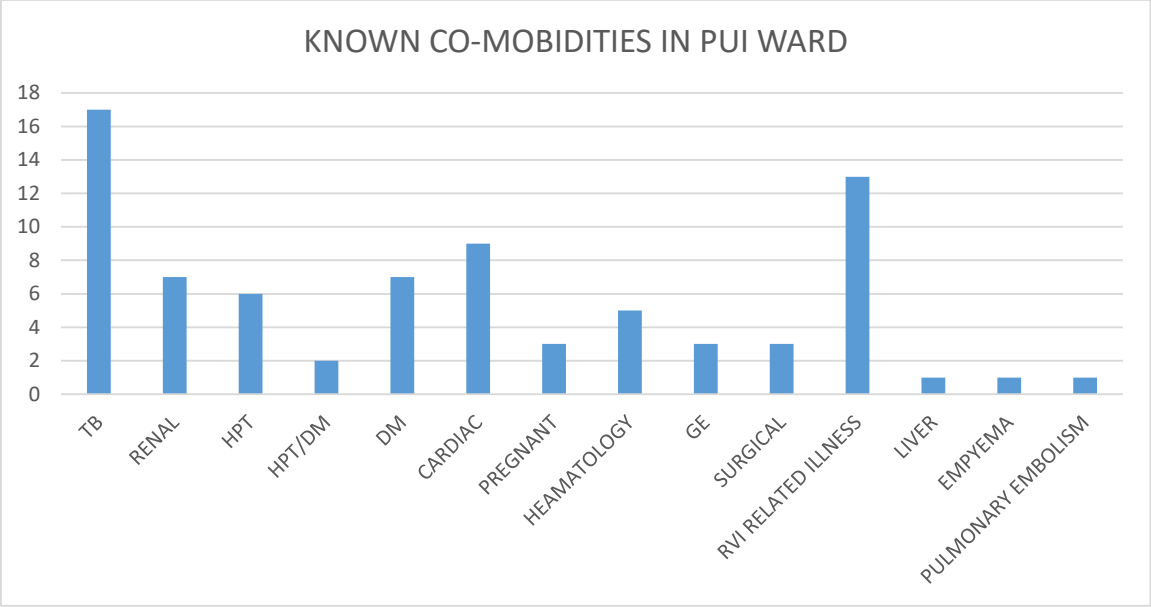
COMPILED BY IPC DEPARTMENT 10/01/2020

PARIRENYATWA GROUP OF HOSPITALS REDZONE STATISTICS FOR THE PERIOD 5 MAY 2020 TO 31 DECEMBER 2020

COMMENT: A TOTAL OF 266 PATIENTS PASSED THROUGH THE PUI WARD. Total deaths were 26, total positive cases transferred to the Red Zone were 25, a total of 45 patients were transferred to the green zone and a total of 155 had missed recorded outcomes.

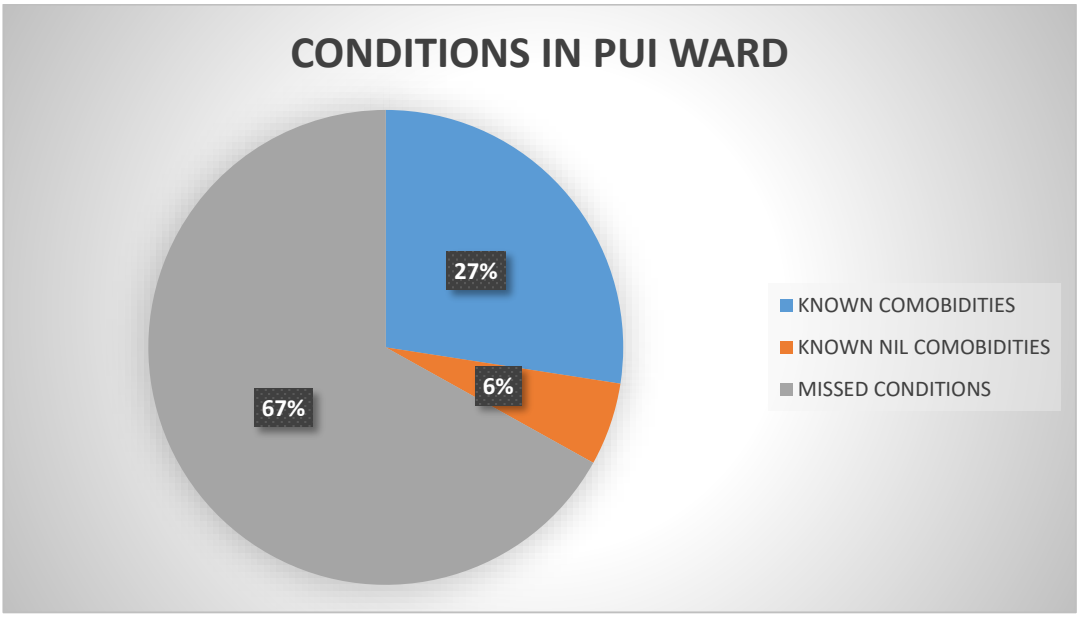
CASE FATALITY RATIO OF PUI IN 2020 WAS 9.7%

ANNEX 3 CO-MOBIDITIES IDENTIFIED IN THE PUI WARD



COMMENT: Out of the 266 patients admitted in the suspected patient ward. Only 73 had known comorbidities and 15 had no known co morbidities and a total of 178 had missed information regarding comorbidities.

ANNEX 4: CO-MOBID CONDITIONS IDENTIFIED IN THE PUI WARD



COMMENT: ONLY 27% OF PATIENTS ADMITTED INTO THE PUI HAD KNOWN RECORDED COMOBIDITIES. 67% OF THE PATIENTS HAD MISSED CONDITIONS

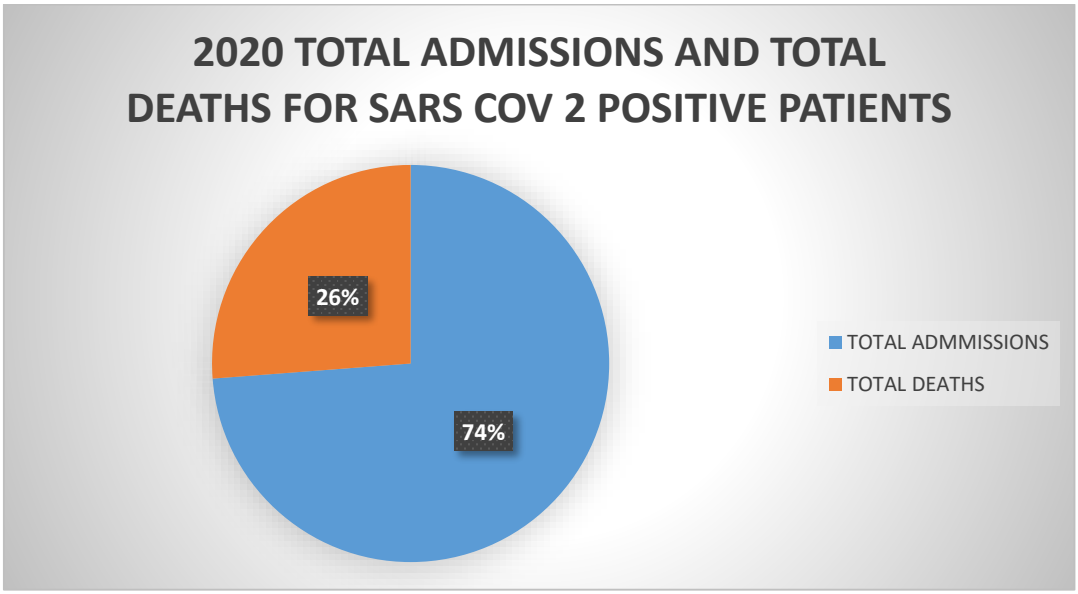
RED ZONE STATISTICS (POSITIVE CASES WARD)

RED ZONE ADMISSIONS

CATEGORY OF ADMISSIONS	**TOTAL**
DIRECT ADMISSIONS	178
TRANSFER INS FROM QUARANTINE CENTERS	45
TRANSFER INS FROM PRIVATE HOSPITALS	34
TRANSFER INS FROM OTHER GOVERNMENT INSTITUTIONS	23
TRANSFER IN FROM PUI WARD A2	24
PATIENTS RECEIVED FROM THE GREEN ZONE	32
TOTAL PATIENTS ADMITTED IN THE RED ZONE	**336**

PARIRENYATWA GROUP OF HOSPITALS REDZONE STATISTICS FOR THE PERIOD 5 MAY 2020 TO 31 DECEMBER 2020

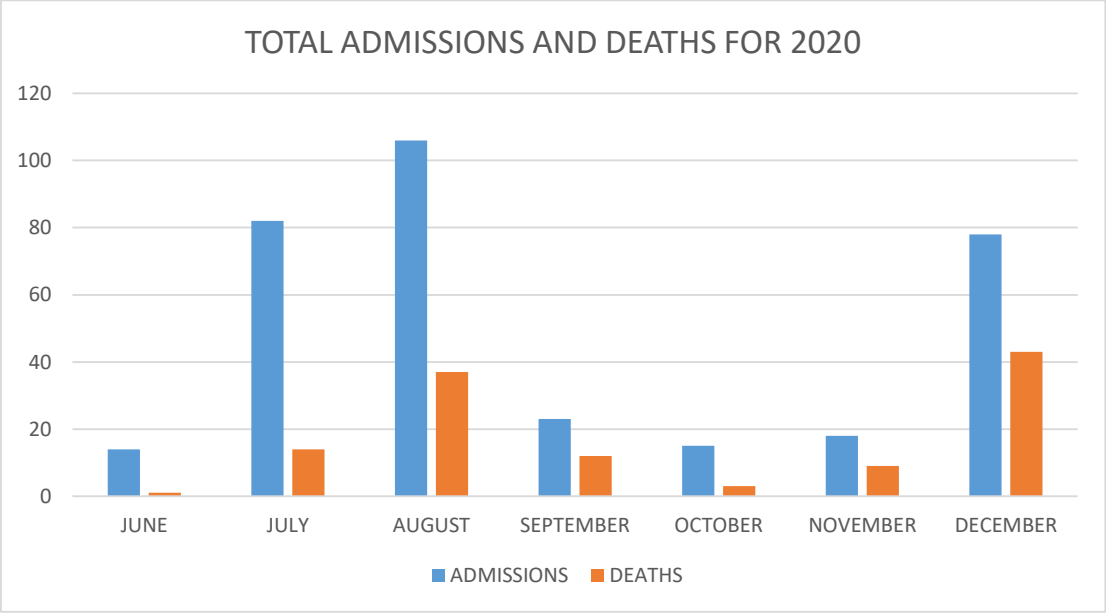
ANNEX 5: TOTAL ADMISSIONS AND DEATHS FROM JUNE TO DECEMBER 31



COMMENT: OF THE 336 ADMISSION WE LOST 26% OF THE PATIENTS THAT SUCCUMBED TO COVID-19 DISEASE.

CASE FATALITY RATIO OF PATIENTS ADMITTED IN THE RED ZONE WAS 35.4%

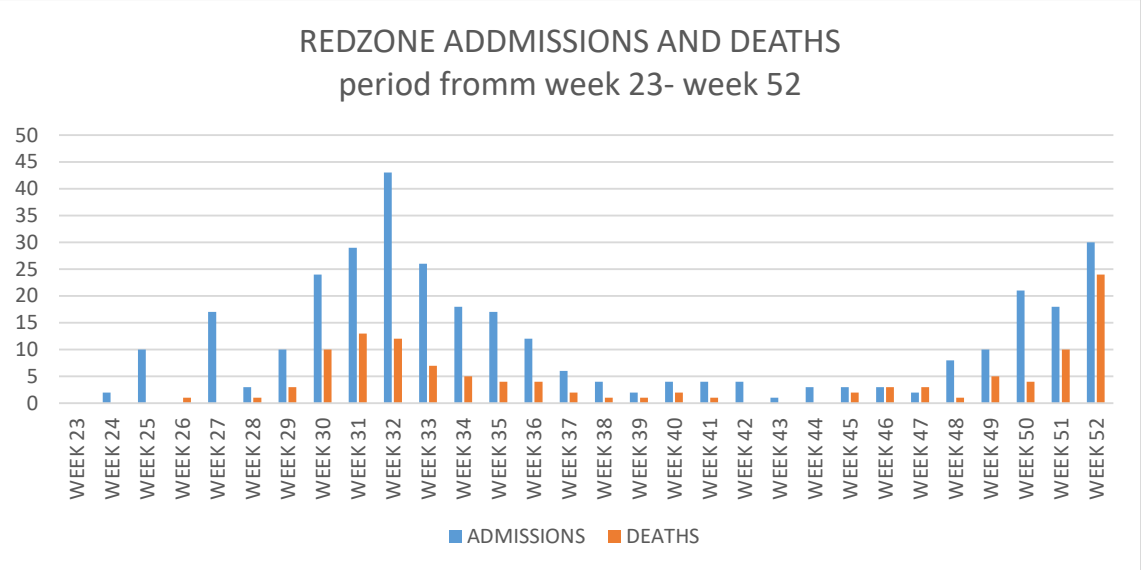
ANNEX 6: TOTAL ADMISSIONS AND DEATHS PER MONTH



COMPILED BY IPC DEPARTMENT 10/01/2020

COMMENT: the highest number of admissions was in August with a total of 106 patients followed by December with 78 patients. The patient in days(stay days) were however more pronounced in December which resulted in wards filling up to admitting a total of 60 patients due to the delayed turnaround time because of severity of disease. The months also experienced high death rates with a total of 37 deaths in august and 45 in December.

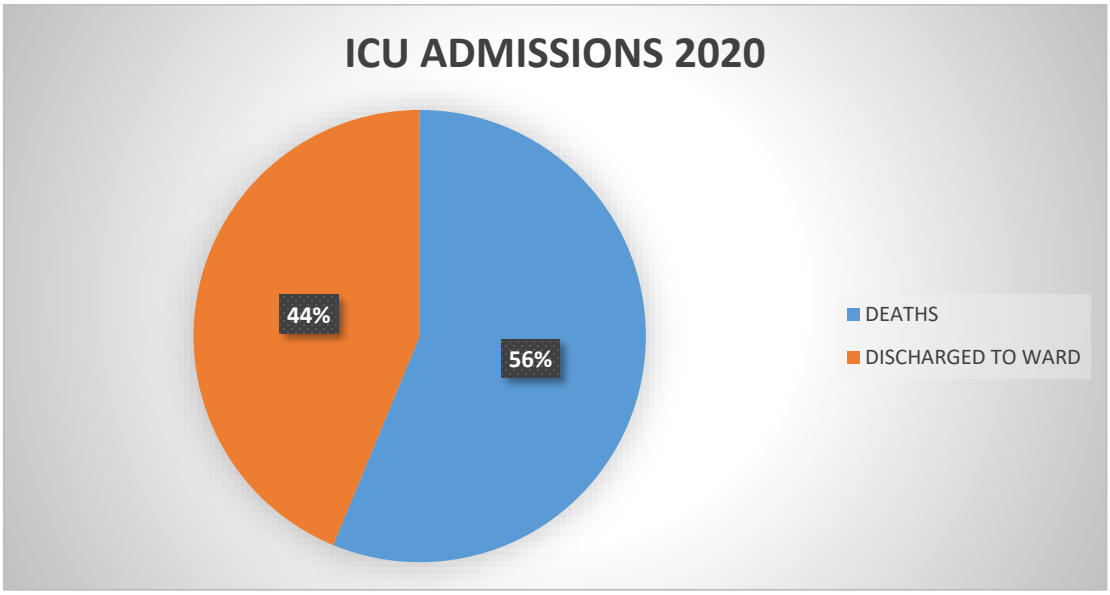
ANNEX 7: TOTAL WEEKLY ADMISSIONS AND DEATHS SINCE WEEK 23 TO WEEK 52



COMMENT: Weekly admissions for the year 2020, initial admission was on the 9th of June week 24 with 3 admissions there was a high turnover of patients between week 30 – 36 and a decline in patients between the period weeks 37 – week 48. Fromm week 48 there was a sudden rise in admissions of patients and deaths, this was the beginning of the second wave to date a rise in admissions is still experienced and severity of disease as well.

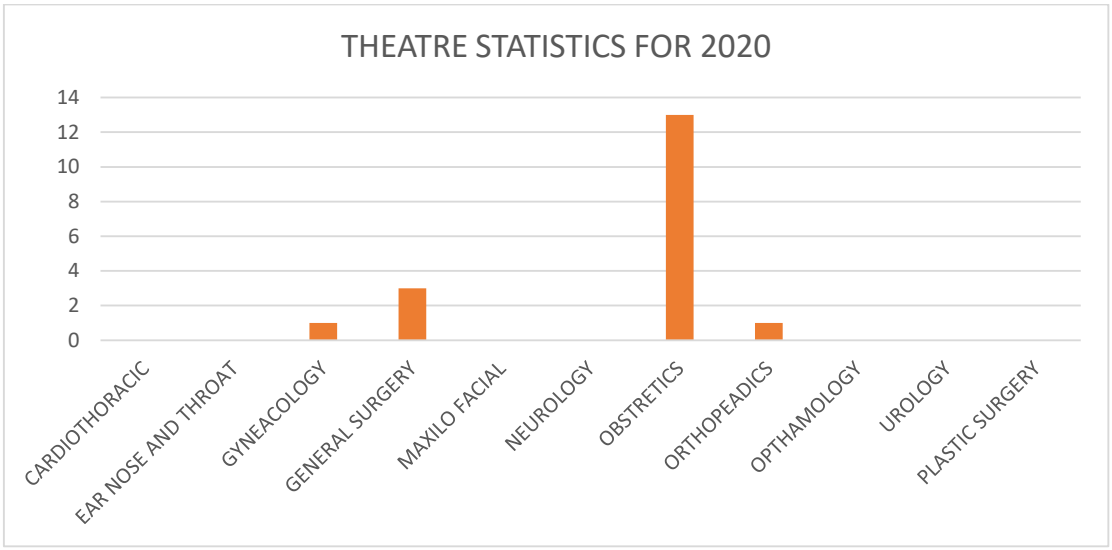
PARIRENYATWA GROUP OF HOSPITALS REDZONE STATISTICS FOR THE PERIOD 5 MAY 2020 TO 31 DECEMBER 2020

ANNEX 8: INTENSIVE CARE UNIT ADMISSIONS



COMMENT: A TOTAL OF 16 PATIENTS WERE ADMITTED IN THE ICU IN 2020 SINCE THE BEGINNING OF THE PANDEMIC. THE CASE FATALITY RATIO IN ICU WAS 0.56% (LOST 9 PATIENTS OUT OF THE 16)

ANNEX 9: THEATRE STATISTICS FOR 2020

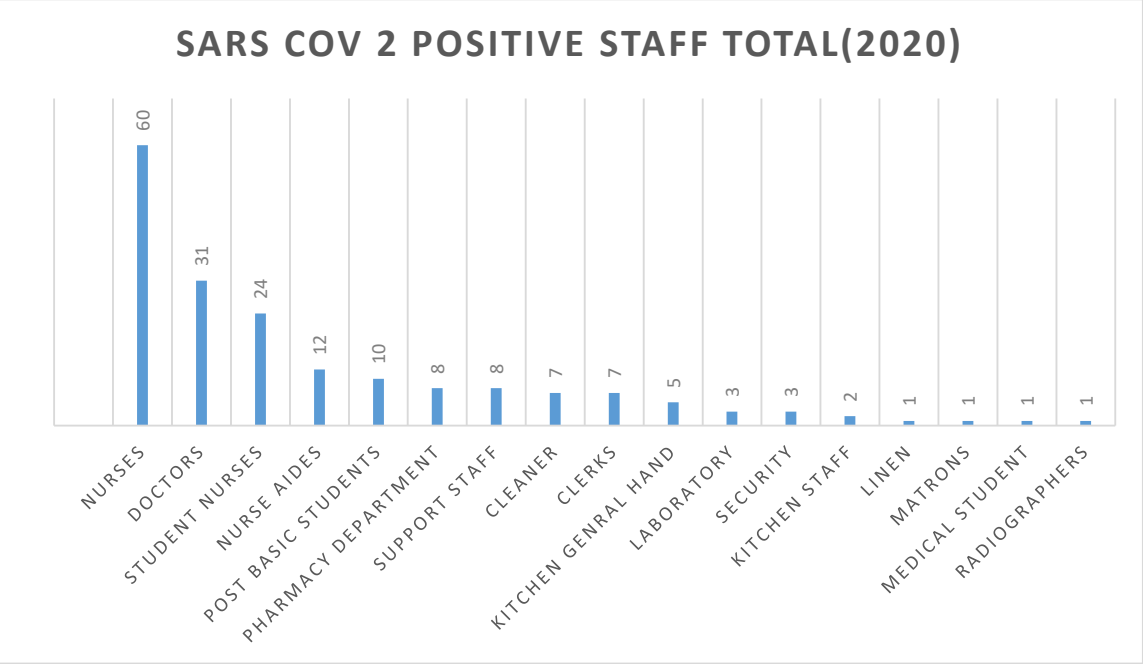


COMMENT: A TOTAL OF 18 THEATRE CASES WERE DONE. ONLY OBSTRETRICS,GENERAL SURGERY,GYNEACOLOGY AND ORTHOPEADIC CASES WERE DONE WITH THE HIGHEST NUMBER OF

COMPILED BY IPC DEPARTMENT 10/01/2020

CASES BEING DONE IN OBSTRETRICS A TOTAL OF 13 LOWER SEGMENT CEASERIAN SECTIONS WERE DONE DURING THE PERIOD OF JUNE TO DECEMBER 2020, THE FIRST CASE WAS DONE IN AUGUST.

ANNEX 10: SARS COV 2 POSITIVE STAFF SINCE JUNE TO 31 DECEMBER 2020



COMMENT: A TOTAL OF 184 MEMBERS OF STAFF AT PARIRENYATWA GROUP OF HOSPITALS WERE KNOWN TO BE INFECTED WITH SARS COV2 INFECTION, AMONGST THESE THE NURSES AND DOCTORS WERE THE MOST AFFECTED RESPECTIVELY.

B. The Stone/Gill protocol

This section includes an updated version of the Stone/Gill protocol document [**10**], describing the treatment protocol that was used in South Africa and Zimbabwe in certain urgent care treatment centers, aimed at preventing hospitalizations and deaths of COVID-19 patients. This is also the treatment protocol that was used in the Stone case series [**3**]. Dr. Stone provided us with an updated version of the document in response to several questions and email correspondence [**20**]. The updated document has included the protocols that were used during the delta variant.

Zimbabwe rollout of Silver and Ivermectin Protocol.

In early 2020, with a looming pandemic, it became obvious in Zimbabwe that the country's healthcare system was inadequate to deal with the upcoming infections.
With a shortage of general healthcare facilities, including ICU beds and a poor general population, it was imperative that any solution needed to be low-cost, but highly effective.
When Covid-19 infections began to escalate, it became clear that positive patients would have to be treated predominantly at home, as there were an inadequate number of ICU and hospital beds. Doctors were forced to come up with innovative methods of treating the pandemic.

The positive support received from the Zimbabwean government provided doctors with the freedom to try different treatment regimens, leading to an interesting protocol which is currently being used successfully today. This protocol allows doctors to treat patients who present with oxygen saturations even lower than 80% at home, rather than admitting them and burdening the healthcare system. As a consequence of successful treatment protocols, the Covid-19 mortality rate in Zimbabwe was lower than that seen in first world countries.

A Harare physician, Dr Jackie Stone, was making colloidal silver for her family and decided to use it on a patient with Covid-19, leading to exceptional results. As I was using Ivermectin at the time for my own family, we realised, through discussion, that the mode of action of the two treatments was such that they complemented each other and this prompted us to collaborate in putting a protocol together which included the use of both agents and Doxycycline.
This approach was validated in Zimbabwe through collaboration with Professor Thomas Borody who predicted that Ivermectin, Doxycycline and Zinc would be the optimal antiviral combination for COVID 19.

The outcome was better than expected. Patients, including those with oxygen saturations of below 80%, treated according to the combination protocol, would recover within 24 hours and did not require hospitalisation. The treatment was very cost-effective and patients could be treated at home.

Treatment at home was eventually extended to nursing patients at home, if they required oxygen. This protocol was associated with a mortality rate much lower than that experienced in more advanced, first world countries. The treatment was found to be reliable enough to send a patient home, if their condition showed signs of noticeable improvement and their oxygen saturation levels were rising. Even with initial saturation levels of well below 80%, patients were confidently sent home on this treatment. Any patient sent home with compromised oxygen saturation levels would be supervised by nursing staff. A small number of patients with severe disease were admitted to state hospitals, not always resulting in the best outcome, as these patients had invariably already reached a critical point of no return.

From August 2020, to the end of November 2020, there were only two deaths reported in a practice seeing an average of 20 patients a day and using the combined Silver/Ivermectin protocol. Both patients had unfortunately arrived too late, with saturation levels of below 50%.

With this positive outcome and the knowledge that the treatment was working successfully, the combination protocol is being extended to the rest of the country, with the support of the Zimbabwean government and some sponsors who are bringing in large amounts of Ivermectin

and silver, to assist with the rollout of this protocol.

The SID Protocol. Dr Jackie Stone and Dr Martin Gill

SID stands for Silver, Ivermectin and Doxycycline

An "A-B-C-D-E-F" approach to treating Covid-19-positive patients with the SID protocol:

Initial assessment to determine if admission to the unit is needed (A,B,C,D,E)

A = ASSESSMENT (A-B-C-D-E)

A: Ambulant - If on a stretcher or too exhausted to walk they should be admitted to the unit, and not discharged until improving.

B: Breathing - If tachypnoeic with a respiratory rate over 22 per minute or worsening / slow respiratory rate due to exhaustion, (often associated with hypoxia with an O2 saturation below 70%)(watch the exhausted patient carefully).

C: Consciousness/confusion - Confusion or decreased or loss of consciousness is a bad prognostic factor. Keep in for observation under ICU level nursing care if possible, rather than home nursing.

D: Duration - If the patient has been symptomatic for longer than 10 days and is displaying the above-mentioned symptoms and/or has an elevated pulse rate, then the prognosis may be poor. This patient must remain in the unit for aggressive care including continuous nebulisation IV steroids and antibiotics, and subcutaneous enoxaparin if available.

E: Elevated pulse rate

Patients fulfilling any of the above criteria were flagged, as they were generally distressed, confused and often significantly hypoxic (Sp02<80%) and needed immediate and continuous care.

They were immediately put on continuous nebulisation using oxygen, cannulated, anticoagulated and bloods were taken for prognostic as well as treatment reasons.

The following protocol was then followed:

Start patient on Ivermectin 0.6 mg/kg stat dose. Be prepared to titrate to effect up to 1-2mg/kg if saturations do not come up. Maintain on 0.3- 0.6mg per kg for up to 10 days. Rather err of the side of giving too much, than too little given the safety margins and therapeutic index of this drug. Warn the patient there is a 20% chance of visual side effects. Continue until symptom free for 48 hours.

Continuous nano particulate silver nebulisations - continue until saturations are above 90% then reduce to at least 3 times a day.

Doxycycline 200mg stat then 100 mg bd for a minimum of 5 days. 10 days of treatment was given in Delta. If patient unable to tolerate oral meds, IV Ceftriaxone 1-2g was given daily.

Zinc Sulphate 20-40 mg tds p.o.

Prednisone 1mg/kg or Dexamethasone 8 mg iv stat, followed by Prednisolone 40-80mg od for 5-10 days if CRP over 20 or if saturation less than 80%

Aspirin 300 mg daily

Clexane (enoxaparin) 80mg subcutaneously od transitioning to rivaroxaban 20mg od if the D Dimer is raised. Continue rivaroxaban for at least 30 days and longer if D Dimer has not come down.

Midazolam, ONLY if confused and pulling out lines/pulling off oxygen. Rarely more than 1 dose is needed.

Monitor O2

If the patient responds to treatment, continue as indicated below.

If the patient doesn't respond, counsel family.

Arrange referral to nearest hospital with ventilatory support as a last resort.

If not available, provide palliative support at home. (This was only needed in patients presenting with less than 50% saturation)

Patients not requiring admission to the unit:

A- Assessment: Sats >80%, not tachypnoeic, tachycardic or confused.

B = BREATHING

B = BLOODS

Breathing

All sick patients were given an initial nanoparticulate silver nebulization 5-8 ml.

Patients with a respiratory rate of over 22 to 25 per minute are flagged.

Respiratory distress is of concern: patients who are short of breath, grunting, or showing signs of shortness of breath and in particular tiredness, are flagged as high risk. Patients with saturations of <80% are commenced on oxygen.

Bloods

Bloods were drawn before silver nebulisation treatment was commenced. Blood was planned to be stored for cytokines and viral load studies for a clinical trial, which did not occur because of regulatory issues.

Nurses were instructed to draw yellow, purple and blue topped tubes. Initial bloods on all patients were: Full Blood Count, LDH, lymphocyte ratio, CRP and D-Dimer.

In the case of patients who had the funds, those who were diabetic, or dehydrated, a U&E and HbA1c were done, as clinically indicated.

Patients who presented with chest pain received a CKMB blood test.

C = CANNULATION – bloods to be drawn, meds to be given

In terms of OBSERVATIONS, pulse and saturations are important:

If the pulse rate was >120, or if the saturations were <80%, patients were considered high risk and were likely to need more time in the unit and to need home nursing and home oxygen, when they left.

Cannulation

Cannulation was the route by which bloods were taken. This often took place simultaneously with the other ABC's.

Patients who were hypoxic, febrile and systemically unwell were given Ceftriaxone 1g, intravenously and Dexamethazone 8mg, or Hydrocortisone 100 - 200mg, as a stat dose, as clinically indicated.

D = DRUGS

D = DIABETES

D = DOCTOR

Drugs

The first drug administered is Ivermectin at a minimum dose of 0.2mg/kg. During Delta the starting dose was 0.6mg/kg.

Diabetes

A glucose reading was taken for diabetic patients, if it had not been done already. Patients with uncontrolled diabetes were referred to a diabetic GP for an intravenous insulin infusion and diabetes management. This care was provided by a dedicated doctor, as part of this protocol, as bringing diabetes under strict control had been shown to improve survival rates in diabetic patients. Should the patient elect to have their treating doctor offer the patient this support, it was their choice.

Doctor

The above protocol was initiated by trained and experienced nurses in a very underresourced setting . At this stage, the doctor needed to have been called and the full blood count and LDH were usually available. From this point, the patient was provided with individualised treatment by the doctor.

If the patient was hypoxic and the CRP >20, treatment included Prednisone 40mg - 80mg daily. In cases where the D-Dimer was raised, subcutaneous Enoxaparin, at a dose of 80mg – 100mg (8000 – 10 000u) was administered, followed by Riveroxiban/Xarelto at a dose of 20mg per day, for 30 days.

If neutrophils were raised and the patient remained cannulated, a dose of Ceftriaxone at a dose of 1g daily was given, until oral treatment was considered adequate. When the switch was made to oral treatment, Doxycycline was used at a dose of 100mg BD for 10 days. The alternative was Azithromycin 500mg bd then 500mg od for 5 day. Both Doxy and Azithro can be used if coinfection with mycoplasma cannot be excluded.

If the patient presented with mild disease and was positive for Covid on PCR, or antigen testing,

a clinical diagnosis was made on the basis of symptoms such as: (a) Hypoxia; (b) Raised LDH; (c) Low lymphocytes; (d) Raised monocytes; (e) Raised D-Dimer; (f) Suggestive radiology.

Ivermectin was given at a dose of 0.1mg to 0.2mg per kilogram, on days zero, four and eight in 2020. By December 2020 this increased to 12mg once daily in December for 5-7 days and as we realised that higher doses led to more rapid recovery with no safety concerns, the dose progressively increased to 0.4-0.6mg/kg once daily for 5-7 days by July 2021, as knowledge regarding the need for and safety of higher doses became available, and was given for up to 48 hours after resolution of symptoms. This was used in conjunction with nanoparticulate silver nebulization 5-8 ml three times daily for 5-7 days (or for 48 hours post symptoms resolution), doxycycline 100mg twice daily for 10 days and Zinc 20mg three times a day for 10 days.

Vitamin D was given to all patients at 5000 – 10 000 IU per day as well, and Vitamin C was dosed at 1g three times a day, if available.

If any of the following were present:

(a) The Lymphocyte to LDH ratio was over 210;
(b) The D-Dimer was raised;
(c) The CRP was raised;
(d) The patient was in stage 3 of the disease as per the FLCCC/Dr. McCullough's definitions.

they were given all of the following:

Ivermectin. This was dosed at 0.2 to 0.3mg per kilogram daily, for 5 days during the beta wave and 0.4- 0.6mg/kg for 10 days during the delta wave

Silver nebulisation 5-8ml at least three times a day up to continuously if needed, if sats dropped below 90%

Doxycycline 100mg twice daily for 10 days

Zinc 20mg twice daily for 10 days

E = EXIT FROM THE UNIT

Exiting the unit needed to be well planned, as when the patient entered, they had 6 hours in the unit, which was a relay station between the patient and home nursing, or hospital.
Should a patient's condition be assessed as severe, and the patient was deemed unlikely to survive, palliative home nursing was required, with a palliative care protocol as per the University of Cape Town. This happened once.

Most patients were started on a treatment protocol, and the exit strategy was normally home on Ivermectin treatment, nebulisation with Nano Silver, as well as oral Doxycycline and Zinc.

Home nursing and home oxygen could be added to this treatment

Patients who were going to require intubation and ventilation and who were deteriorating, were transferred to hospital, with the knowledge that Ivermectin and Nano Silver nebulisation

treatments will be discontinued. This only occurred when we ran out of oxygen. This almost always led to the death of these patients.

Consequently, only palliative patients were transferred to hospital, or the patient was kept for just over 24 hours, during which time 2 doses of Ivermectin and continual Silver nebulisations were given.

In cases where additional respiratory support was required, patients were put on high flow oxygen with PEEP via an OxERA mask.

F = FAMILY

Patients' families were assessed for prophylaxis. Ivermectin at 0.1mg to 0.2mg per kilogram was used as a single dose for this purpose, as well as a single Silver nebulisation, which was repeated when they returned to see the family the next day and when they went home with their relative. In delta 0.2-0.4mg/kg was given od for 5 days as prevention