Frequentist and Bayesian analysis methods for case series data for the early outpatient treatment of COVID-19

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November 2, 2021

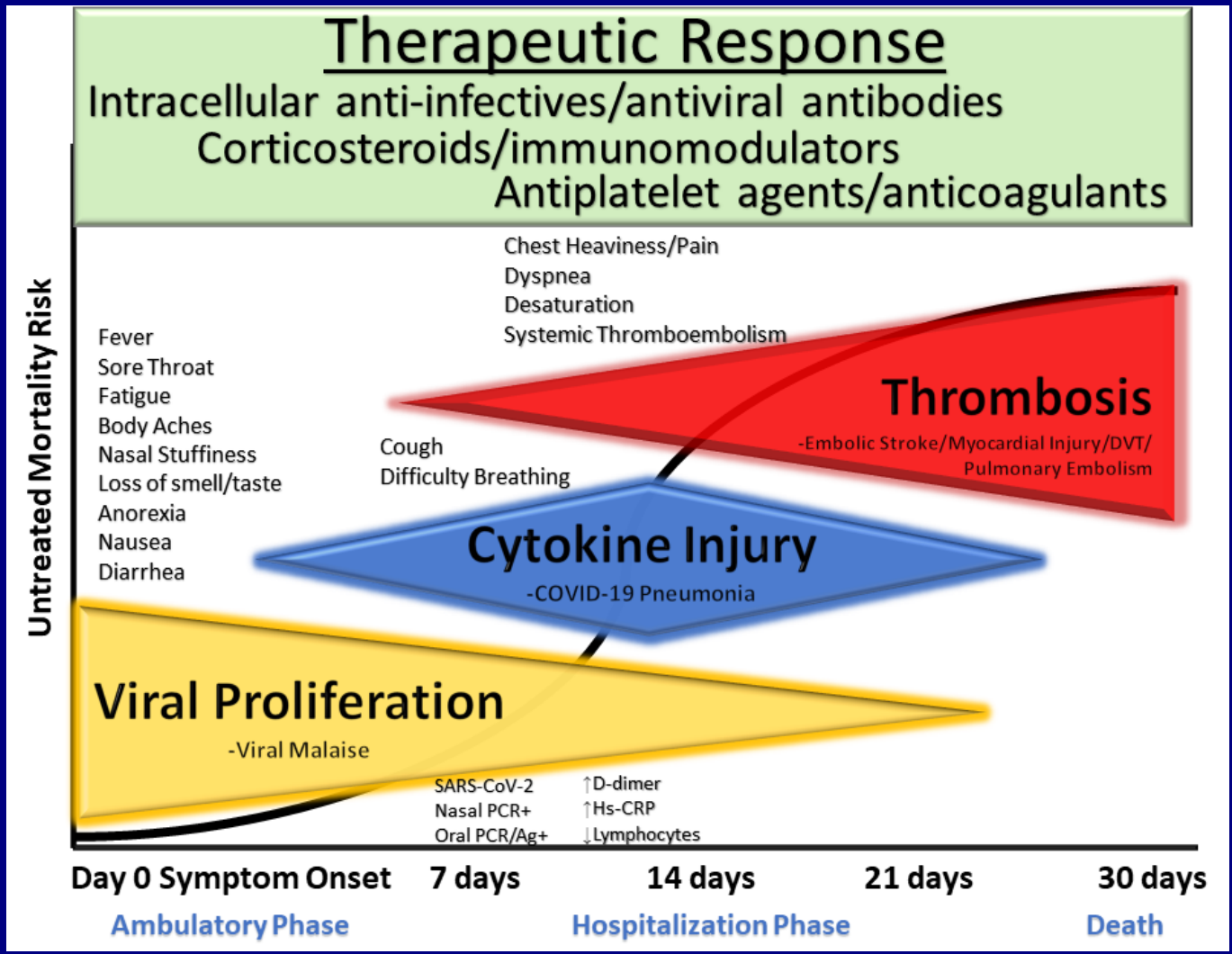
Early treatment – The Zelenko protocol

- The goal of early treatment of COVID-19 is to **prevent hospitalization and death.**
- Dr. Zelenko announced his treatment protocol via an March 23 2020 open letter addressed to ”all medical professionals around the world”.
  - **Risk stratify** patients as high risk vs low risk. High risk includes:
    1. Patients older than 60
    2. Patients that are immunocompromised or have comorbidities
    3. Patients not satisfying previous criteria that develop shortness of breath
  - **Treat** high risk patients with triple drug therapy: HCQ, Azithromycin, Zinc.
  - **Supportive care** and close monitoring of low risk patients.
- Mechanisms of action:
  - HCQ prevents to some extent the virus from entering the cell
  - HCQ opens a channel for Zinc to enter the cell
  - Zinc inside the cell blocks the virus from replicating
  - Azithromycin has antiviral properties and more importantly prevents a secondary bacterial infection.
- Zelenko concept: **Treat early to stop viral replication.**
- Outcomes were reported in a follow-up letter dated April 28, 2020:
  - 1450 patients were seen
  - 405 were risk-stratified in the high risk category and treated with the triple-drug therapy
  - 6 hospitalizations and 2 deaths.
- Emergency decision: **To do or not to do?**

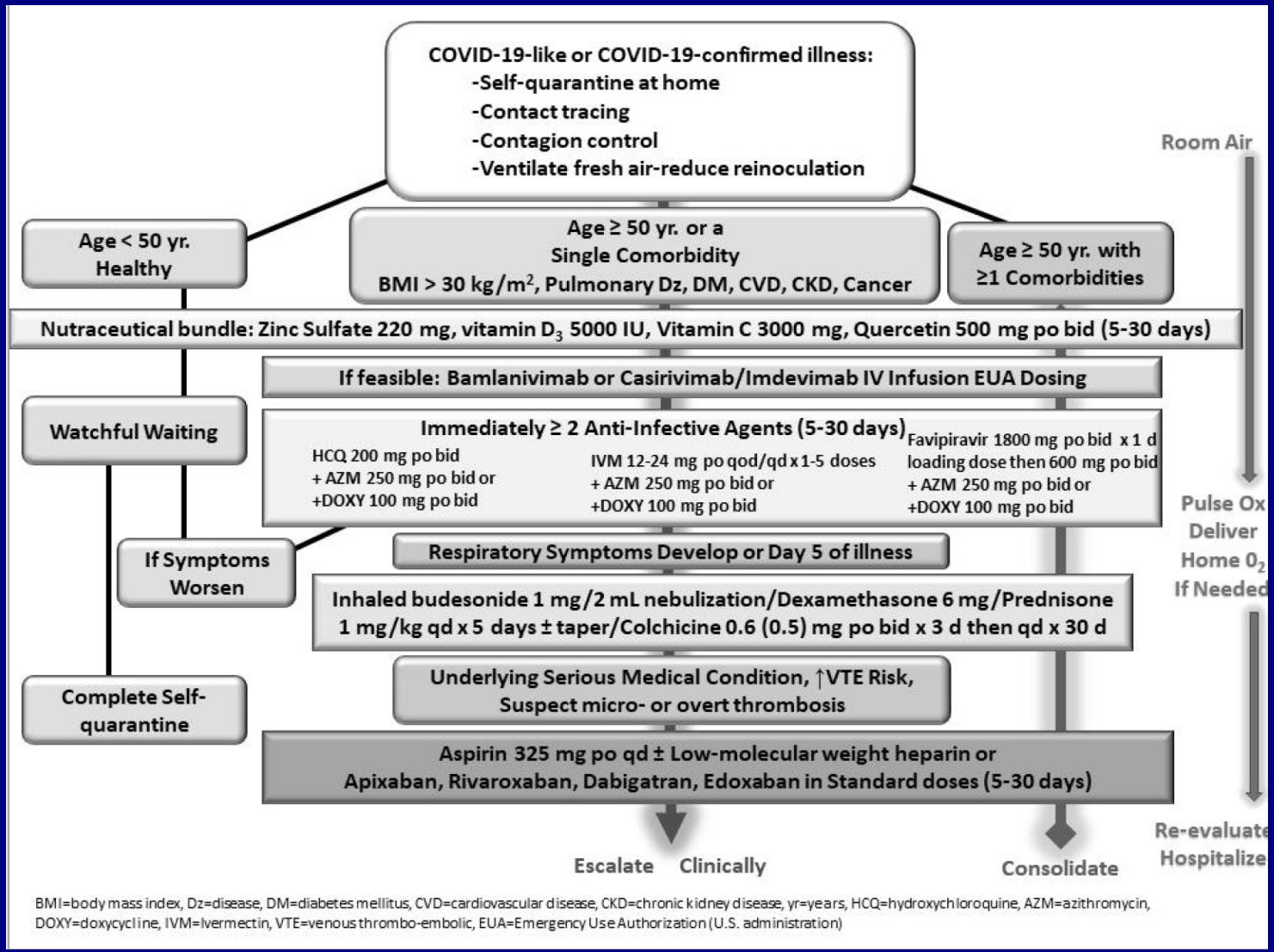
Early treatment – Improved protocols

- Between May 2020 and August 2020, Zelenko incrementally improved his treatment protocol as follows:
  - Quercetin protocol for low-risk patients to reduce severity of symptoms.
  - For more difficult cases, added: ivermectin, Anti-coagulants, steroids: budesonide, prednisone, home oxygen.
  - To prevent long covid, age threshold for high-risk classification was lowered to 45 years.
- McCullough's protocol.
  - P.A. McCullough, P.E. Alexander, R. Armstrong, C. Arvinte, A.F. Bain, R.P. Bartlett, R.L. Berkowitz, A.C. Berry, T.J. Borody, J.H. Brewer, A.M. Brufsky, T. Clarke, R. Derwand, A. Eck, J. Eck, R.A. Eisner, G.C. Fareed, A. Farella, S.N.S. Fonseca, C.E. Geyer, Jr., R.S. Gonnering, K.E. Graves, K.B.V. Gross, S. Hazan, K.S. Held, H. Thomas Hight, S. Immanuel, M.M. Jacobs, J.A. Ladapo, L.H. Lee, J. Littell, I. Lozano, H.S. Mangat, B. Marble, J.E. McKinnon, L.D. Merritt, J.M. Orient, R. Oskoui, D.C. Pompan, B.C. Procter, C. Prodromos, J.C. Rajter, J-J. Rajter, C. V.S. Ram, S.S. Rios, H.A. Risch, M.J.A. Robb, M. Rutherford, M. Scholz, M.M. Singleton, J.A. Tumlin, B.M. Tyson, R.G. Urso, K. Victory, E.L. Vliet, C.M. Wax, A.G. Wolkoff, V. Wooll, V. Zelenko. "Multifaceted highly targeted sequential multidrug treatment of early ambulatory high-risk SARS-CoV-2 infection (COVID-19)", *Reviews in Cardiovascular Medicine* **21 (4)** (2020), 517-530

Peter McCullough's protocol. I



Peter McCullough's protocol. II



Hospitalization risk without early treatment

- Early estimate of 10% to 18% hospitalization risk for patients older than 60
  - R. Verity and L.C. Okell and I. Dorigatti and P. Winskill and C. Whittaker and N. Imai and G. Cuomo-Dannenburg and H. Thompson and P.G.T. Walker and H. Fu and A. Dighe and J.T. Griffin and M. Baguelin and S. Bhatia and A. Boonyasiri and A. Cori and Z. Cucunuba and R. FitzJohn and K. Gaythorpe and W. Green and A. Hamlet and W. Hinsley and D. Laydon and G. Nedjati-Gilani and S. Riley and S. van Elsland and E. Volz and H. Wang and Y. Wang and X. Xi and C.A. Donnelly and A.C. Ghani and N.M. Ferguson. *Lancet Infect Dis* **20** (2020), 669-677
- DSZ study – 15.4% hospitalization rate
  - M. Scholz, R. Derwand, V. Zelenko. *International Journal of Antimicrobial Agents* **56** (2020), 106214
- Cleveland study – 26% hospitalization rate
  - L. Jehi, X. Ji, A. Milinovich, S. Erzurum, A. Merlino, S. Gordon, J.B. Young, M.W. Kattan. *PLoS ONE* **15(8)** (2020), e0237419.
- MGB study – 27% hospitalization rate
  - H. Dashti, E.C. Roche, D.W. Bates, S. Mora, and O. Demler. *Scientific Reports* **11** (2021), 4945
- Without early treatment: **10%-25% risk of hospitalization for low+high risk demographic.**

Mortality risk without early treatment by age bracket. I

- R. Verity and L.C. Okell and I. Dorigatti and P. Winskill and C. Whittaker and N. Imai and G. Cuomo-Dannenburg and H. Thompson and P.G.T. Walker and H. Fu and A. Dighe and J.T. Griffin and M. Baguelin and S. Bhatia and A. Boonyasiri and A. Cori and Z. Cucunuba and R. FitzJohn and K. Gaythorpe and W. Green and A. Hamlet and W. Hinsley and D. Laydon and G. Nedjati-Gilani and S. Riley and S. van Elsland and E. Volz and H. Wang and Y. Wang and X. Xi and C.A. Donnelly and A.C. Ghani and N.M. Ferguson. *Lancet Infect Dis* **20** (2020), 669-677
  - Published in March 30, 2020. CFR based on data from China as of February 11, 2020.
  - From Table 1, the crude case fatality rates *in the absence of early treatment* are:

Age	Deaths	Cases	CFR
10-19	0	416	0%
20-29	7	3619	0.193%
30-39	18	7600	0.237%
40-49	38	8571	0.4%
50-59	130	10008	1.3%
60-69	309	8583	3.6%
70-79	312	3918	7.96%
≥ 80	208	1408	14.8%
≥ 60	829	13909	5.96%

Mortality risk without early treatment by age bracket. II

- Graziano Onder, Giovanni Rezza, Silvio Brusaferro. *JAMA* **323** (2020), 1775-1776
  - Published on March 23, 2020. Data as of March 17, 2020.
  - The mortality rates *in the absence of early treatment* in Italy, as a function of age bracket, are consistent with the mortality rates in China

Age	Italy CFR	China CFR
0-9	0%	0%
10-19	0%	0.2%
20-29	0%	0.2%
30-39	0.3%	0.2%
40-49	0.4%	0.4%
50-59	1.0%	1.3%
60-69	3.5%	3.6%
70-79	12.8%	8.0%
$\geq$ 80	20.2%	14.8%

- Without early treatment: Mortality rate risk for high-risk demographic due to age ranges from 3.5% to 20%.

Mortality risk without early treatment from comorbidities

- N. Barda, D. Riesel, A. Akriv, J. Levy, U. Finkel, G. Yona, D. Greenfeld, S. Sheiba, J. Somer, E. Bachmat, G.N. Rothblum, U. Shalit, D. Netzer, R. Balicer, Noa Dagan. *Nature Communications* **11** (2020), 4439
- Epidemiology Group of Emergency Response Mechanism of New Coronavirus Pneumonia, Chinese Center for Disease Control and Prevention. *Chinese Journal of Epidemiology* **41** (2020), 145-151.
  - Case fatality rate based on early-stage analysis of COVID-19 outbreak in China in the period up to February 11, 2020 vs similar statistics from Israel published on September 7, 2020.

Comorbidity	Deaths	Cases	China CFR	Deaths	Cases	Israel CFR
Cardiovascular disease	92	873	10.5%	87	518	16.7%
Diabetes	80	1102	7.3%	71	531	13%
Respiratory disease	32	511	6.3%	23	361	6%
Hypertension	161	2683	6%	102	744	13.7%
Cancer	6	107	5.6%	37	264	10%

- Without early treatment: Mortality rate risk for high-risk demographic due to comorbidities ranges from 5% to 15%.

Mortality risk without early treatment from obesity and shortness of breath

- Previous papers do not provide a mortality rate risk due to obesity and shortness of breath.
- S.N.S. Fonseca, A. de Queiroz Sousa, A.G. Wolkoff, M.S. Moreira, B.C. Pinto, C.F.V. Takeda, E. Rebouas, A.P.V. Abdon, A.L.A. Nascimento, H.A. Risch. *Travel Medicine and Infectious Disease* **38** (2020), 101906
- Multivariate regression analysis for risk factors has calculated the following odds-ratios:

Comorbidity	Odds Ratio	p-value
Heart disease	1.67 (1.03–2.70)	0.037
Dyspnea at diagnosis	2.07 (1.33-3.26)	0.0017
Obesity	2.38 (1.24–4.58)	0.009

- Comparison of these 3 risk factors shows that both obesity and dyspnea are more dangerous than heart disease.
- Without early treatment: Mortality rate risk due to obesity and dyspnea $\geq 5\%$.

Case series evidence

- DSZ study – 141 high risk patients – lab confirmed only – Zelenko protocol
  - Scholz, M.; Derwand, R.; Zelenko, V. *International Journal of Antimicrobial Agents* **56** (2020), 106214
- Zelenko 04-28-2020 case series – 405 high risk patients – Zelenko protocol
  - H.A. Risch. *American Journal of Epidemiology* **189** (2020), 1218-1226
- Zelenko 06-14-2020 case series – 800 high risk patients – enhanced Zelenko protocol
  - H.A. Risch. *American Journal of Epidemiology* **189** (2020), 1444-1449
- Israeli control group – 4179 low and high risk patients – no early treatment
  - N. Barda, D. Riesel, A. Akriv, J. Levy, U. Finkel, G. Yona, D. Greenfeld, S. Sheiba, J. Somer, E. Bachmat, G.N. Rothblum, U. Shalit, D. Netzer, R. Balicer, Noa Dagan. *Nature Communications* **11** (2020), 4439
- Procter first case series – 320 high risk patients – McCullough protocol
  - B.C. Procter, C. Ross, V. Pickard, E. Smith, C. Hanson, P.A. McCullough. *Reviews in Cardiovascular Medicine* **21 (4)** (2020), 611-614
- Procter second case series – 869 high risk patients – McCullough protocol
  - B.C. Procter, C. Ross, V. Pickard, E. Smith, C. Hanson, P.A. McCullough. *International Journal of Innovative Research in Medical Science* **6** (2021), 219-221
- Raoult case series – 1495 high risk patients – McCullough protocol
  - M. Million, J-C. Lagier, H. Tissot-DuPont, I. Ravaux, C. Dhiver, C. Tomei, N Cassir, L. DeLorme, S. Cortaredona, S. Gentile, E. Jouve, A. Giraud-Gatineau, H. Chaudet, L. Camoin-Jau, P. Colson, P. Gautret, P-E. Fournier, B. Maille, J-C. Deharo, P. Habert, J-Y. Gaubert, A. Jacquier, S. Honore, K. Guillon-Lorvellec, Y. Obadia, P. Parola, P. Brouqui, D. Raoult, *Reviews in Cardiovascular Medicine* **22** (2021), 1063-1072

Summary of high risk patient case series

Study	Total	High-risk	Hospitalizations & Deaths	
DSZ study	712	141	4 (2.8%)	1 (0.7%)
Zelenko April 2020	1450	405	6 (1.4%)	2 (0.4%)
Zelenko June 2020	2200	800	12 (1.5%)	2 (0.25%)
Procter I	922	320	6 (1.8%)	1 (0.3%)
Procter II	?	869	20 (2.3%)	2 (0.2%)
Raoult	10429	1495	106 (7.0%)	5 (0.3%)
DSZ control	377	< 377	58 ($>$15%)	13 ($>$3.4%)
Israeli control	4179	< 4179	N/A	143 ($>$3.4%)
Raoult control	2114	520	38 (7.3%)	11 (2%)

- Consistent high-risk mortality rates between Zelenko, Procter, and Raoult
- Consistent mortality rates between Zelenko control group (without demographic data) and Israeli control group (with demographic data; low+high risk)
- Raoult encouraged short hospitalization in his institution for close monitoring
- In the US, doctors tried to prevent hospitalizations due to poor NIH standard of care.
- Raoult control group did not receive the complete protocol (duration, medications).

Zelenko case series vs control groups

Study	odds ratio	95% CI	p-value
Exact Fisher tests on mortality rates			
DSZ study vs DSZ control	0.2	0.02–1.54	**0.12**
Zelenko April 2020 vs DSZ control	0.13	0.03–0.61	0.003
Zelenko June 2020 vs DSZ control	0.07	0.01–0.31	10^{-5}
DSZ vs Israeli control	0.2	0.03–1.45	**0.09**
Zelenko April 2020 vs Israeli control	0.14	0.03–0.57	0.0002
Zelenko June 2020 vs Israeli control	0.07	0.02–0.28	10^{-9}
Exact Fisher tests on hospitalization rates			
DSZ vs DSZ control	0.16	0.05–0.45	0.02
Zelenko April 2020 vs DSZ control	0.08	0.03–0.19	10^{-13}
Zelenko June 2020 vs DSZ control	0.08	0.04–0.16	10^{-19}

- No demographic data for Zelenko control group
- Demographic data available for Israeli control group: low+high risk
- Consistency between control groups.
- We are expecting more than 90% efficacy in mortality and hospitalization rate reduction against no early treatment.
- Question: **What if we want to determine that the treatment is effective against no treatment *without measuring the precise efficacy*?**

Methodology: Exact Fisher test

- Let N be the number of treated patients, a the number of treated patients with an adverse outcome (hospitalization or death), M the number of untreated patients in the control group, and b the number of untreated patients with an adverse outcome (hospitalization or death) in the control group.
- The odds ratio comparing the two groups is given by

$$\text{OR} = \frac{a(M-b)}{b(N-a)}, \tag{1}$$

and the corresponding p-value is given by

$$p(N,a,M,b) = \frac{\binom{a+b}{b}\binom{N+M-a-b}{N-a}}{\binom{N+M}{N}}, \tag{2}$$

$$\mathcal{P}(N,a,M,b) = \sum_{n=0}^{\min\{N,a+b\}} p(N,n,M,a+b-n)H(p(N,a,M,b)-p(N,n,M,a+b-n)), \tag{3}$$

with $H(x)$ being a modified Heavyside function given by

$$H(x) = \begin{cases} 1, & \text{if } x \geq 0 \\ 0, & \text{if } x < 0. \end{cases} \tag{4}$$

Methodology: Analysis of case series

- We can compare case series with known hospitalization/mortality rates for untreated high-risk patients, as follows:
  - 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 probably of adverse outcome if the patient is untreated.
  - We assume that the treatment itself is safe and causes no adverse events.
  - 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

$$\mathcal{P}(N, a, x) = \sum_{n=0}^{N} p(N, n|x) H(p(N, a|x) - p(N, n|x)) \tag{5}$$

  with $p(N, a|x)$ the probability of the specific outcome (N, a) given by

$$p(N, a|x) = \binom{N}{a} x^a (1 - x)^{N-a} \tag{6}$$

  - To establish statistical significance, we seek a threshold x_0 such that $x_0 < x \leq 1 \implies \mathcal{P}(N, a, x) < p_0$, and then we show that $x > x_0$.
  - Standard choice is to use $p_0 = 0.05$ for 95% confidence. Alternatively, we can also explore the x_0 thresholds for $p_0 = 0.01$ (99% confidence) and $p_0 = 0.001$ (99.9% confidence), to see how sensitive x_0 is to increasing demands in statistical confidence.

Methodology: Calculating the efficacy threshold

- By definition, we calculate the efficacy threshold x_0 via the equation

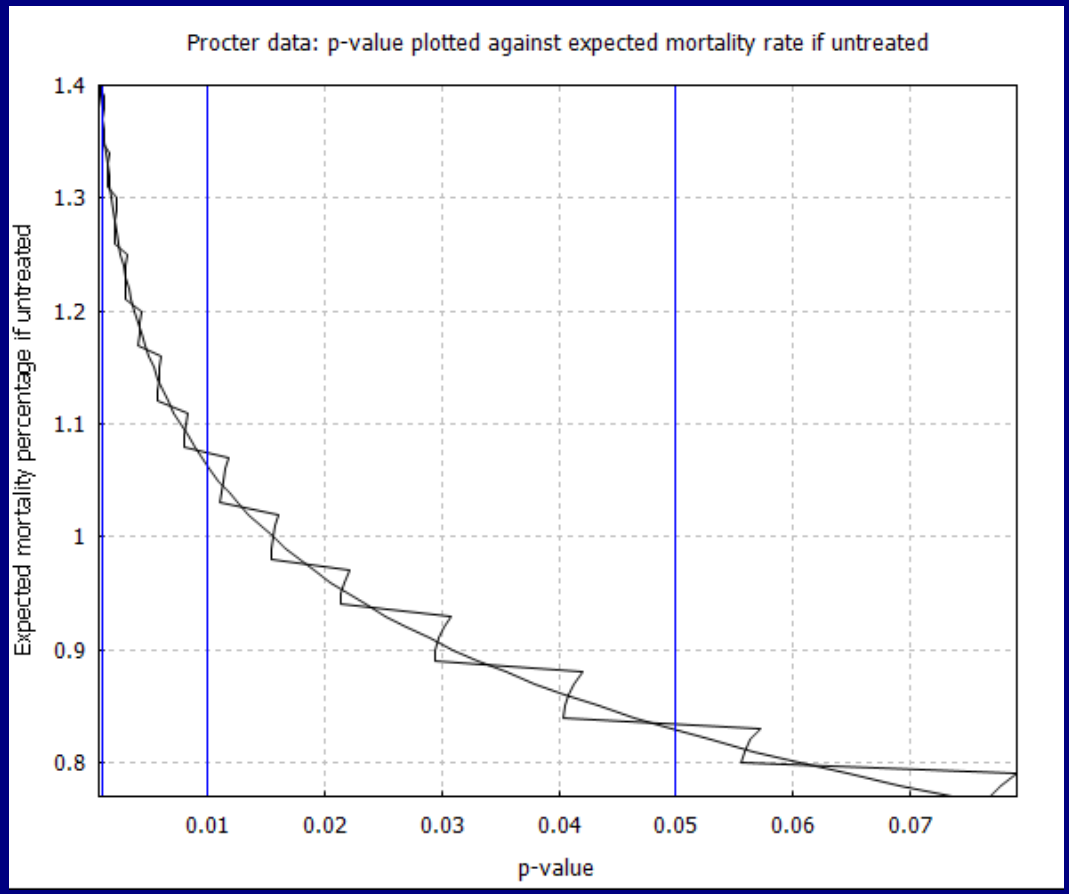
$$x_0(N, a, p_0) = \inf\{x \in [a/N, 1] \mid \mathcal{P}(N, a, x) \leq p_0\} \tag{7}$$

  with $p_0 = 0.05$ for 95% confidence, $p_0 = 0.01$ for 99% confidence and $p_0 = 0.001$ for 99.9% confidence.
- The threshold corresponds to the upper endpoint of the Sterne interval.
- An alternate ***approximation*** of x_0 can be obtained using the upper endpoint of the Clopper-Pearson interval:

$$x_0(N, a, p_0) = \inf\{x \in [a/N, 1] \mid \sum_{n=0}^{a} p(N, n|x) \leq p_0/2\} \tag{8}$$

- With the Clopper-Pearson interval the right tail of the distribution is assumed to be equal to the left tail. Thus, equivalent to a one-tail test.
- Binomial proportion confidence interval problem.
- For the math background see:
  1. C. Clopper and E.S. Pearson. *Biometrika* **26** (1934), 404-413
  2. T.E. Sterne. *Biometrika* **41** (1954), 275-278
  3. J. Reiczigel. *Statistics in Medicine* **22** (2003), 611-621
  4. L.D. Brown, T.T. Cai, A. DasGupta. *Statistical Science* **16 (2)** (2001), 101-133

Example: Proctor II case series (expected mortality without early treatment vs p-value)



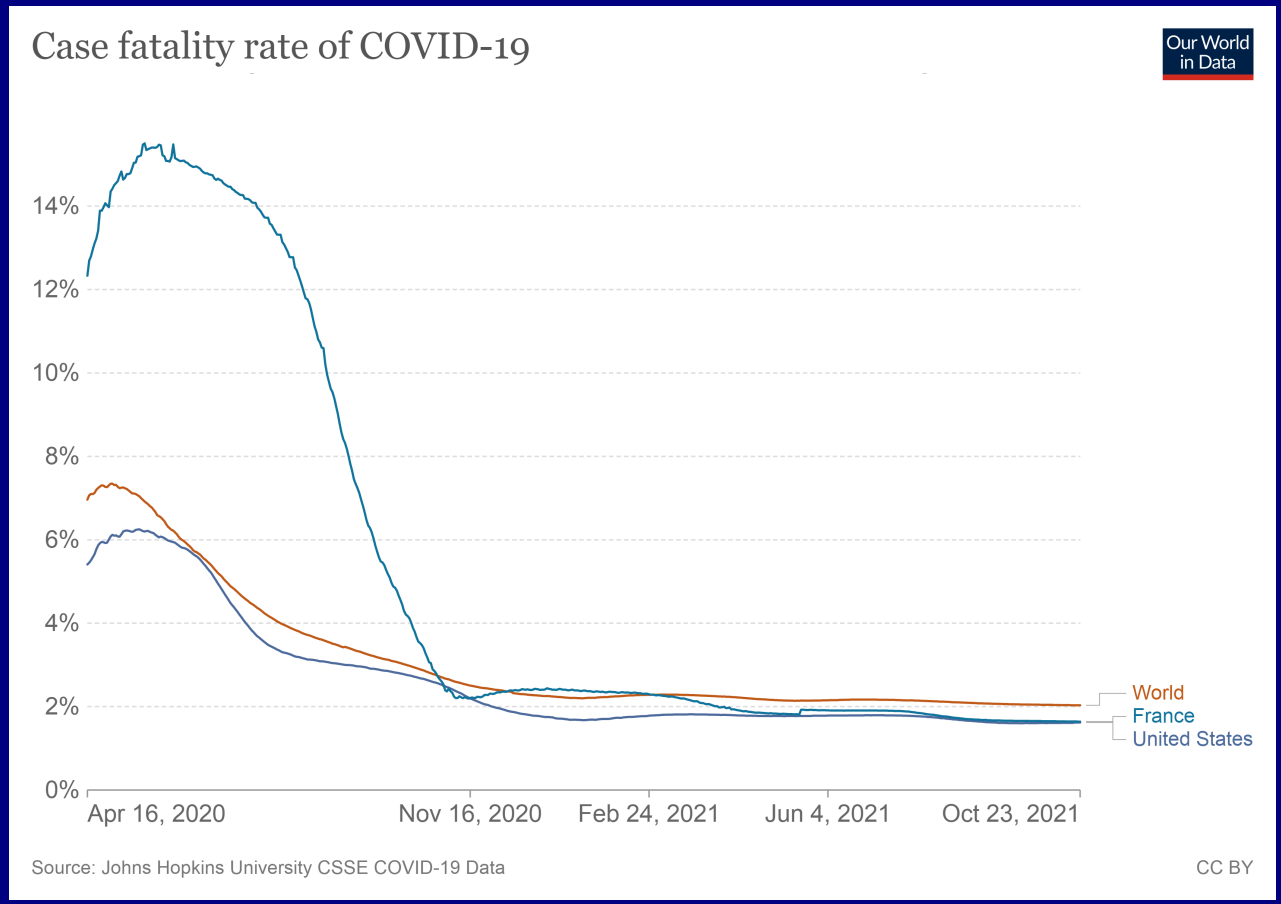
- Zigzag curve is the exact Sterne interval efficacy threshold
- Smooth curve is the Clopper-Pearson interval approximate efficacy threshold

Efficacy thresholds for mortality and hospitalization rates

Study	95% threshold	99% threshold	99.9% threshold
Mortality rate efficacy thresholds			
DSZ study	3.8% (3.9%)	5.4% (5.2%)	N/A
Zelenko April 2020	1.8%	2.5% (2.3%)	3%
Zelenko June 2020	1.0%	1.3% (1.2%)	1.6% (1.5%)
Procter I	1.7% (1.8%)	2.3%	3.1%
Procter II	0.84% (0.83%)	1.08% (1.07%)	1.4% (1.38%)
Raoult	0.79% (0.78%)	0.96% (0.95%)	1.16%
Hospitalization rate efficacy thresholds			
DSZ study	7.0% (7.2%)	8.8% (8.7%)	10.6% (10.7%)
Zelenko April 2020	3.2%	3.9%	4.7%
Zelenko June 2020	2.7%	3.0%	3.5%
Procter I	4.1%	4.9%	5.9%
Procter II	3.6%	4%	4.5%

- These are all case series with ***high-risk patients***
- Without early treatment: 10%–25% hospitalization risk
- Without early treatment: 3.5%–20% mortality risk
- Risk intervals without early treatment exceed efficacy thresholds above (except for DSZ study wrt mortality risk reduction)

Compare with Case Fatality Rate in US and France



- US CFR ranged from 2% to 6% in 2020 and converged to 1.7% in 2021
- France CFR ranged from 2% to 16% in 2020 and also converged to 1.7% in 2021
- CFR exceeds efficacy thresholds for Zelenko June 2020, Procter II, Raoult!!

Bayesian factor analysis

- Calculates "distance" between efficacy and null hypothesis at the efficacy threshold x_0.
- We introduce the null hypothesis $H_0(p_1, p_2) : p_1 \leq x \leq p_2$ and the efficacy hypothesis $H_1(q) : x \leq q$.
- The Bayesian factor is given by

$$p(N, a|H_0(p_1, p_2)) = \frac{1}{p_2 - p_1} \binom{N}{a} \int_{p_1}^{p_2} x^a (1-x)^{N-a} \, \mathrm{d}x \tag{9}$$

$$p(N, a|H_1(q)) = \frac{1}{q} \binom{N}{a} \int_{0}^{q} x^a (1-x)^{N-a} \, \mathrm{d}x \tag{10}$$

$$B(N, a|H_1(q), H_0(p_1, p_2)) = \frac{p(N, a|H_1(q))}{p(N, a|H_0(p_1, p_2))} \tag{11}$$

- We assess the efficacy threshold x_0 by calculating

$$b(x_0, p_2) = \max_{t \in (0, x_0)} \log B(N, a|H_1(t), H_0(x_0, p_2)) \tag{12}$$

- We want $b(x_0, p_2) \geq 2$ (decisive), or at least $b(x_0, p_2) \geq 1.5$ (very strong)
- Note the dependence on p_2 (i.e. maximum risk of adverse outcome without treatment)

Bayes factor at efficacy thresholds

Bayes factors at the mortality rate efficacy thresholds				
Study	95% threshold	2% Bayes	5% Bayes	10% Bayes
DSZ study	3.8%	N/A	1.38	1.99
Zelenko April 2020	1.8%	1.17	2.04	2.45
Zelenko June 2020	1.0%	2.06	2.66	3.02
Procter I	1.7%	1.28	2.07	2.47
Procter II	0.84%	1.92	2.48	2.82
Raoult	0.79%	1.91	2.45	2.79
Bayes factors at the hospitalization rate efficacy thresholds				
Study	95% threshold	10% Bayes	15% Bayes	20% Bayes
DSZ study	7.0%	1.30	1.71	1.92
Zelenko April 2020	3.2%	2.00	2.24	2.39
Zelenko June 2020	2.7%	2.24	2.47	2.61
Procter I	4.1%	1.89	2.15	2.32
Procter II	3.6%	1.98	2.23	2.39

- With DSZ study, we are cautioned due to small sample size the efficacy thresholds may need to be increased.
- Other studies look ok.

Bayes corrected thresholds

Mortality rate Bayesian efficacy thresholds				
Study	95% threshold	log Bayes = 2 thresholds		
		$p_2 = 2\%$	$p_2 = 5\%$	$p_2 = 10\%$
DSZ study	3.8%	N/A	N/A	3.9%
Zelenko April 2020	1.8%	N/A	1.8%	1.5%
Zelenko June 2020	1.0%	1.0%	0.8%	0.6%
Procter I	1.7%	N/A	1.9%	1.3%
Procter II	0.84%	0.87%	0.7%	0.6%
Raoult	0.79%	0.82%	$< 0.7\%$	$< 0.7\%$
Hospitalization rate Bayesian efficacy thresholds				
Study	95% threshold	log Bayes = 2 thresholds		
		$p_2 = 10\%$	$p_2 = 15\%$	$p_2 = 20\%$
DSZ study	7.0%	9.5%	7.8%	7.2%
Zelenko April 2020	3.2%	3.2%	3.0%	2.9%
Zelenko June 2020	2.7%	2.6%	2.5%	2.4%
Procter I	4.1%	4.3%	4.0%	3.7%
Procter II	3.6%	3.7%	3.5%	3.4%

- All Bayes efficacy thresholds are also below what is necessary to establish in hospitalization and mortality rate reduction.

Concluding thoughts

- Because:
  1. Signal of benefit for early treatment is very strong;
  2. Early treatment uses repurposed drugs with known excellent safety record;
  3. The alternative is to do nothing;

  it is possible to establish efficacy by comparing case series of high risk patients against previously observed mortality/hospitalization risks without treatment.
- We presented the mathematical techniques for doing so.
- This approach proves existence of efficacy but does not precisely calculate efficacy.
- An RCT can measure the efficacy if both arms of the trial are sufficiently large.
- However, the decision to deploy early treatment is Boolean: yes or no
- Enough evidence to authorize early treatment was available by April 29, 2020.
- Early treatment has been and still is suppressed by public health officials.
  1. S.J. Hatfill. *Journal of the American Physicians and Surgeons* **26** (2021), 74-76
  2. L. Mucchielli. *Journal of Sociology* **56** (2020), 736-744
- Prophylactic protocols:
  1. R.B. Stricker and M.C. Fesler. *Journal of Infection and Public Health* **14** (2021), 1161-1163
  2. P. Behera, B.K. Patro, B.M. Padhy, P.R. Mohapatra, S.K. Bal, P.D. Chandanshive, R.R. Mohanty, SR Ravikumar, A. Singh, S.R. Singh, S.S.K. Pentapati, J. Nair, G. Batmanbane. *Cureus* **13(8)** (2021), e16897.

Thank you!