

On the Zelenko protocol: The road not taken

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The Zelenko protocol

- ▶ The SARS-CoV-2 pandemic has turned our world upside down, with initial reports of very high mortality rates in China, then Italy, and then several other nations generating much fear and uncertainty.
- ▶ Governments from around the world pursued very strict lockdown policies to curb the overwhelming of hospital resources, at the expense of our constitutional and civil liberties, resulting in severe damage to the world economy.
- ▶ On March 23, 2020 Dr. Vladimir Zev Zelenko circulated his first open letter to “*all medical professionals around the world*” where he first presented what has now come to be known as *the Zelenko protocol*:
 - ▶ Dr. Zelenko risk-stratified his patients into a high-risk and low risk group
 - ▶ The high risk group included all patients all patients older than 60, or immunocompromised, or with comorbidities.
 - ▶ Any patients initially assessed as low-risk were moved to the high-risk category, if they developed shortness of breath.
 - ▶ *Treated the high risk group with:* hydroxychloroquine (200mg twice a day for 5 days); azithromycin (500mg once a day for 5 days); and zinc sulfate 220mg (50mg elemental zinc) once a day for 5 days)
 - ▶ The *low-risk group* was treated with supportive care and was closely monitored.

Outcomes

- ▶ 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.
- ▶ The Zelenko concept: **Treat early to prevent the virus from spreading to the lungs and to other vital organs and stop the progression of the disease.**
- ▶ 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.
- ▶ Outcomes were reported in a follow-up letter dated June 14, 2020:
 - ▶ 2200 patients were seen
 - ▶ 800 were risk-stratified in the high risk category and treated with the triple-drug therapy and additional medications (steroids, anticoagulants, etc.)
 - ▶ 12 hospitalizations and 2 deaths
- ▶ A proliferation of "research" on HCQ was used to attack the Zelenko protocol:
 - ▶ Two studies published on NEJM and JAMA used faked data and were retracted
 - ▶ Studies on hospitalized patients showed no benefit (to be expected – with late treatment virus has already spread everywhere)
 - ▶ Studies using lethal dosage of HCQ showed negative effect (i.e. overdosing on medication is bad)
 - ▶ Studies on low-risk patients showed negligible benefit. (low risk patients generally recover on their own)

Research studies on the Zelenko protocol

- ▶ Zelenko's retrospective study:
 1. Scholz, M.; Derwand, R.; Zelenko, V. "COVID-19 outpatients - early risk-stratified treatment with zinc plus low dose hydroxychloroquine and azithromycin: a retrospective case series study", *International Journal of Antimicrobial Agents* 56 (2020), 106214
- ▶ This is an initial study where the April dataset was restricted only to patients with lab-test confirmation that they were infected
 - ▶ *Treatment group*: 141 high risk patients; 4 hospitalizations (2.8%); 1 death (0.7%)
 - ▶ *Control group*: 377 low and high risk patients; 58 hospitalizations (15%); 13 deaths (3.4%)
 - ▶ *Hospitalization reduction*: odd ratio 0.16 (CI: 0.05 to 0.45; p -value 2%) – **84% efficacy**
 - ▶ *Mortality reduction*: odd ratio 0.2 (CI 0.02 to 1.54; p -value 12%) – **80% efficacy**
- ▶ Improved results if the complete April dataset is used:
 - ▶ *Treatment group*: 405 high risk patients; 6 hospitalizations (1.4%); 2 deaths (0.4%)
 - ▶ *Control group*: 377 low and high risk patients; 58 hospitalizations (15%); 13 deaths (3.4%)
 - ▶ *Hospitalization reduction*: odd ratio 0.08 (CI: 0.03 to 0.19; p -value 10^{-11} %) – **92 % efficacy**
 - ▶ *Mortality reduction*: odd ratio 0.13 (CI 0.03 to 0.61; p -value 0.29%) – **87% efficacy**
- ▶ Further improved results if the complete June dataset is used:
 - ▶ *Treatment group*: 800 high risk patients; 12 hospitalizations (1.5%); 2 deaths (0.25%)
 - ▶ *Control group*: 377 low and high risk patients; 58 hospitalizations (15%); 13 deaths (3.4%)
 - ▶ *Hospitalization reduction*: odd ratio 0.08 (CI: 0.04 to 0.15; p -value 10^{-17} %) – **92 % efficacy**
 - ▶ *Mortality reduction*: odd ratio 0.07 (CI 0.01 to 0.31; p -value 0.001%) – **93% efficacy**
- ▶ Critique: Lack of demographic data with control group (most likely a combination of low risk and high risk patients).

Mortality reduction using alternate control group

- ▶ Alternate control group of low risk and high risk patients with known demographic data (4179 patients with 143 deaths)
 - ▶ Noam Barda, Dan Riesel, Amichay Akriv, Joseph Levy, Uriah Finkel, Gal Yona, Daniel Greenfeld, Shimon Sheiba, Jonathan Somer, Eitan Bachmat, Guy N. Rothblum, Uri Shalit, Doron Netzer, Ran Balicer & Noa Dagan. “Developing a COVID-19 mortality risk prediction model when individual-level data are not available”, *Nature Communications* 11 (2020), 4439
- ▶ Lab-confirmed restricted April data set
 - ▶ *Treatment group*: 141 high risk patients; 4 hospitalizations (2.8%); 1 death (0.7%)
 - ▶ *Control group*: 4179 low and high risk patients; 143 deaths (3.4%)
 - ▶ *Mortality reduction*: odd ratio 0.2 (CI 0.03 to 1.45; p -value 9%) – **80% efficacy**
- ▶ Complete April data set
 - ▶ *Treatment group*: 405 high risk patients; 6 hospitalizations (1.4%); 2 deaths (0.4%)
 - ▶ *Control group*: 4179 low and high risk patients; 143 deaths (3.4%)
 - ▶ *Mortality reduction*: odd ratio 0.14 (CI 0.03 to 0.57; p -value 0.02%) – **86% efficacy**
- ▶ Complete June data set
 - ▶ *Treatment group*: 800 high risk patients; 12 hospitalizations (1.5%); 2 deaths (0.25%)
 - ▶ *Control group*: 4179 low and high risk patients; 143 deaths (3.4%)
 - ▶ *Mortality reduction*: odd ratio 0.07 (CI 0.02 to 0.28; p -value 10^{-7} %) – **93% efficacy**
- ▶ Mortality reduction efficacy results are consistent with both control groups.

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

$$R = \frac{a(M - b)}{b(N - a)}, \quad (1)$$

and the corresponding p -value is given by

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

$$p = \sum_{n=0}^{a+b} f(N, n, M, a+b-n) H(f(N, a, M, b) - f(N, n, M, a+b-n)), \quad (3)$$

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

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

Methodology: Analysis of observational data

- ▶ We can use statistical analysis to compare real-world observational data 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

$$p(N, a, x) = \sum_{n=0}^N g(N, n, x) H(g(N, a, x) - g(N, n, x)) \quad (5)$$

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

$$g(N, a, x) = \binom{N}{a} x^a (1-x)^{N-a} \quad (6)$$

- ▶ To establish statistical significance, we seek a threshold x_0 such that $x_0 < x \leq 1 \implies p(N, a, x) < p_0$, 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.

Efficacy thresholds based on Zelenko's data.

- ▶ The meaning of the cross-over threshold x_0 : If the mortality rate x for high-risk patients without early outpatient treatment is greater than x_0 then the early treatment is effective.
- ▶ Current estimates place x between 5% and 10%
- ▶ Cross-over threshold for Zelenko study data.
 - ▶ *Treatment group*: 141 high risk patients; 4 hospitalizations (2.8%); 1 death (0.7%)
 - ▶ For 95% confidence: Requires $x > 3.9\%$
 - ▶ For 99% confidence: Requires $x > 5.4\%$
- ▶ Cross-over threshold for Zelenko April letter data
 - ▶ *Treatment group*: 405 high risk patients; 6 hospitalizations (1.4%); 2 deaths (0.4%)
 - ▶ For 95% confidence: Requires $x > 1.8\%$
 - ▶ For 99% confidence: Requires $x > 2.5\%$
 - ▶ For 99.9% confidence: Requires $x > 3\%$
- ▶ Cross-over threshold for Zelenko June letter data
 - ▶ *Treatment group*: 800 high risk patients; 12 hospitalizations (1.5%); 2 deaths (0.25%)
 - ▶ For 95% confidence: Requires $x > 1.0\%$
 - ▶ For 99% confidence: Requires $x > 1.3\%$
 - ▶ For 99.9% confidence: Requires $x > 1.6\%$

Efficacy thresholds based on Procter's data.

- ▶ Brian C. Procter, Casey Ross, Vanessa Pickard, Erica Smith, Cortney Hanson, Peter A. McCullough. "Clinical outcomes after early ambulatory multidrug therapy for high-risk SARS-CoV-2 (COVID-19) infection", *Reviews in Cardiovascular Medicine* **21 (4)** (2020), 611-614
- ▶ *Treatment group*: 320 high-risk patients treated; 6 patients hospitalized (1.8%); 1 patient died (0.3%)
- ▶ Cross-over threshold for mortality rate
 - ▶ For 95% confidence: Requires $x > 1.7\%$
 - ▶ For 99% confidence: Requires $x > 2.3\%$
 - ▶ For 99.9% confidence: Requires $x > 3.1\%$
- ▶ We note that for 95% statistical significance, this study shows that if the mortality rate for high risk patients exceeds 1.7%, then the treatment protocol is effective in terms of mortality reduction.
- ▶ High risk patients were defined as: older than 50 and/or presence of comorbidities.

Case fatality rate distribution by age in China

- ▶ 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: "Estimates of the severity of coronavirus disease 2019: a model-based analysis", *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%

- ▶ We note that the CFR for the 50-59 age group exceeds the efficacy threshold obtained from Dr. Zelenko's June letter data.
- ▶ We also note that the overall CFR for the age group older than age 60 exceeds all efficacy thresholds.

Case fatality rate distribution by age in Italy

- ▶ Graziano Onder, Giovanni Rezza, Silvio Brusaferro: “Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy”, *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%
≥ 80	20.2%	14.8%

Case fatality rates by underlying health condition in China and Israel

- ▶ Noam Barda, Dan Riesel, Amichay Akriv, Joseph Levy, Uriah Finkel, Gal Yona, Daniel Greenfeld, Shimon Sheiba, Jonathan Somer, Eitan Bachmat, Guy N. Rothblum, Uri Shalit, Doron Netzer, Ran Balicer & Noa Dagan. “Developing a COVID-19 mortality risk prediction model when individual-level data are not available”, *Nature Communications* **11** (2020), 4439
- ▶ Epidemiology Group of Emergency Response Mechanism of New Coronavirus Pneumonia, Chinese Center for Disease Control and Prevention. “Analysis of Epidemiological Characteristics of New Coronavirus Pneumonia”, *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.
 - ▶ Overall we see the mortality rate risk due to comorbidities ranges from 4% to 13%.

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%

Mortality rate risk from obesity and shortness of breath

- ▶ Previous papers do not provide a mortality rate risk due to obesity and shortness of breath.
- ▶ Silvia Nunes Szente Fonseca, Anastasio de Queiroz Sousa, Alexandre Giandoni Wolkoff, Marcelo Sampaio Moreira, Bruno Castro Pinto, Christianne Fernandes Valente Takeda, Eduardo Rebouas, Ana Paula Vasconcellos Abdon, Anderson L.A. Nascimento, Harvey A. Risch. “Risk of hospitalization for Covid-19 outpatients treated with various drug regimens in Brazil: Comparative analysis”, *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.
- ▶ It follows that we can safely lower-bound obesity and dyspnea with 5% mortality rate, since heart disease itself presents a mortality rate risk exceeding 5%.

Conclusion

- ▶ In conclusion, we can argue that every risk factor (age, comorbidities, including obesity and shortness of breath) in untreated patients present a mortality rate risk greater than 5%.
- ▶ There is a big gap between 5% and our previous calculations of the cross-over threshold x_0 for 95% confidence.
 - ▶ $x_0 = 3.9\%$ for Zelenko study (lab-confirmed subset of Zelenko April dataset)
 - ▶ $x_0 = 1.8\%$ for complete Zelenko April dataset
 - ▶ $x_0 = 1.0\%$ for Zelenko July dataset
 - ▶ $x_0 = 1.7\%$ for Procter dataset
- ▶ This establishes that early treatment certainly reduces the mortality rate, leaving open the question of how much it is reduced.
- ▶ In terms of policy-making, by the end of April 2020 we had both Dr. Zelenko's data set and the mortality rate statistics for high-risk patients that do not receive early treatment.
- ▶ Thus, there was sufficient information to conclude at that time that the Zelenko protocol was effective in terms of saving lives.
- ▶ The only thing that a well-designed randomized control trial can add to this analysis is to determine the precise efficacy percentage.
- ▶ Is it ethical to validate the Zelenko protocol with a randomized control trial, when there is already clear and convincing evidence of efficacy?

Further reading

- ▶ Risch, Harvey A, “Early Outpatient Treatment of Symptomatic, High-Risk Covid-19 Patients that Should be Ramped-Up Immediately as Key to the Pandemic Crisis”, *American Journal of Epidemiology* **198** (2020), 1218-1226
- ▶ Peter A. McCullough, Paul E. Alexander, Robin Armstrong, Cristian Arvinte, Alan F. Bain, Richard P. Bartlett, Robert L. Berkowitz, Andrew C. Berry, Thomas J. Borody, Joseph H. Brewer, Adam M. Brufsky, Teryn Clarke, Roland Derwand, Alieta Eck, John Eck, Richard A. Eisner, George C. Fareed, Angelina Farella, Silvia N. S. Fonseca, Charles E. Geyer, Jr., Russell S. Gonnering, Karladine E. Graves, Kenneth B. V. Gross, Sabine Hazan, Kristin S. Held, H. Thomas Hight, Stella Immanuel, Michael M. Jacobs, Joseph A. Ladapo, Lionel H. Lee, John Littell, Ivette Lozano, Harpal S. Mangat, Ben Marble, John E. McKinnon, Lee D. Merritt, Jane M. Orient, Ramin Oskoui, Donald C. Pompan, Brian C. Procter, Chad Prodromos, Juliana Cepelowicz Rajter, Jean-Jacques Rajter, C. Venkata S. Ram, Salette S. Rios, Harvey A. Risch, Michael J. A. Robb, Molly Rutherford, Martin Scholz, Marilyn M. Singleton, James A. Tumlin, Brian M. Tyson, Richard G. Urso, Kelly Victory, Elizabeth Lee Vliet, Craig M. Wax, Alexandre G. Wolkoff, Vicki Wooll, Vladimir 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

Thank you!