



The Totality of the Evidence¹

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A person suddenly collapses on the floor — what do you do? Given the choice between acting or not acting, surely every reasonable person will say we need to act without hesitation.

But how? We first quickly collect the available data: We check whether the collapsed person has a pulse, whether he’s breathing, whether he responds to verbal cues. If not, we suspect cardiac arrest and immediately start CPR — but still we try to collect both new and better data as we go along. If a blood pressure monitor becomes available and we find the patient’s pressure is fine and his pulse is regular — though we didn’t even feel one at first — everything changes; the situation is not as dire as we had thought. Perhaps he begins talking, though

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still his breathing is labored: Our chest compressions have broken his ribs. If we don't stop CPR, the bone may pierce his lungs, causing a tension pneumothorax — a life-threatening condition that must be treated right away. Despite our best intentions, we can kill the patient if we do not change our course of action.

The main challenge in epidemiology is how to translate what we know—and what we know about what we know — into the best course of action.

The first question in emergencies, this example teaches, is not *whether* to act. It is rather *how* to act to ensure our actions do more good than harm. Populations are not individual patients, of course, but the lesson is important for thinking about the debate over the right response to the COVID-19 crisis. In his recent essay² in these pages, the philosopher of medicine Jonathan Fuller sheds light on this debate by describing two opposing traditions in epidemiology: one, public health epidemiology, that relies on modeling and a diversity of data, and another, clinical epidemiology, that prizes high-quality evidence from randomized studies. In an equally thoughtful response,³ the epidemiologist Marc Lipsitch elaborates on what that opposition gets wrong.

Both Fuller and Lipsitch have eloquently expressed the simultaneously competing and coexisting worlds of models and evidence. I hope that we would all agree that we need both. Science is difficult; we cannot afford to look away from useful data, disciplines, approaches, and methods. I love science because most of the time I feel profoundly ignorant, in need of continuous education; I am grateful to all my colleagues — no matter their discipline — who help reduce my ignorance. At the same time, we should study the strengths, weaknesses, and complementarity of various approaches. The main challenge in epidemiology, in particular, is how to translate what we know — and what we know about what we know — into the best course of action.

² Fuller, Jonathan. 2020. "Models v. Evidence." Text. Boston Review. May 1, 2020. <https://bostonreview.net/science-nature/jonathan-fuller-models-v-evidence>.

³ Lipsitch, Marc. 2020. "Good Science Is Good Science." Text. Boston Review. May 12, 2020. <http://bostonreview.net/science-nature/marc-lipsitch-good-science-good-science>.

As Lipsitch wisely suggests, infectious disease epidemiology and clinical epidemiology are not necessarily two opposing stereotypes; almost always they are intermingled. And as Fuller acknowledges in passing, they can coexist in the same research agenda, in the same institution, even in the same person. Most scientists cannot be slotted in one bin or the other; they struggle to make their brains work in different paradigms. Both essays classify me under the evidence-based medicine (EBM) umbrella, but while it is true that I have written papers with “evidence-based medicine” in the title, I have no official degree in EBM. When I trained in the field with the late Tom Chalmers and Joseph Lau, there were no degrees of that sort. The term “evidence-based medicine” itself wasn’t coined until 1992 by clinical epidemiologists at McMaster University in Canada. Even now, almost thirty years later, in most places most scientists and physicians still have no clue what EBM really is. My official fellowship training, in fact, was in infectious diseases.

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Regardless of the difficulty of classifying scientists in bins, however, science does work eventually, as researchers share knowledge and correct misconceptions. And even if we take the stereotypes of the two traditions for granted, their features ought to be reversed in one respect. In a certain sense, it is clinical epidemiology that tends to be more pragmatic, and thus more action-oriented, than its foil. Traditional epidemiology — including research programs on mechanisms of disease — can be far removed from questions of action, for good reason: Basic science has great value in itself for learning about nature and modeling its mysteries. By contrast, EBM, in particular, argues for less theory and more real-world results, less speculation and more focus on the outcomes that matter most. To put it crudely but sharply, the EBM sensibility is that theories don’t count for much when they don’t save lives. That process of saving lives focuses on decisions of action. Practitioners of EBM know full well that failing to act has consequences; a central lesson that it teaches is that you’d better choose wisely what you do — and what you don’t.

What does all this mean in the case of COVID-19? On March 3 the World Health Organization (WHO) director-general introduced a media briefing with these

distressing words: “Globally, about 3.4 percent of reported COVID-19 cases have died. By comparison, seasonal flu generally kills far fewer than 1 percent of those infected.”⁴ Others spoke of a very high reproduction number,⁵ of almost no asymptomatic infections,⁶ and of the high likelihood that the virus would infect most of the global population. Many, including the team led by Neil Ferguson at Imperial College London, drew comparisons to the 1918 pandemic, which cost at least 50 million lives.⁷ These claims had a dramatic and arguably dangerous impact on public perception. Moreover, if these claims had been true, any EBM practitioner would call for swift and thoroughgoing lockdown measures. EBM is dead clear in such situations: If the risk is 50 million deaths, shutting the world for a month or two is nothing.

But it was my infectious disease side that had questions. A virus that spreads like wildfire, killing one out of thirty and infecting almost everyone in the absence of a vaccine, should have killed far more people in China and should have spread widely worldwide, perhaps with millions of fatalities, by mid-March. Hence, as I wrote in an op-ed in Stat News,⁸ I began to plead that we seek to obtain better data as quickly as possible to best inform our actions. I think lockdown was justified as an initial response, given what little we knew about this new virus, but I also think we needed better data to decide on next steps. And given what we know now, it is reasonable to consider alternatives to population-wide lockdown, even as we

⁴ “WHO Director-General’s Opening Remarks at the Media Briefing on COVID-19 – 3 March 2020.” 2020. Accessed June 24, 2020. <https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19--3-march-2020>.

⁵ Tang, Biao, Nicola Luigi Bragazzi, Qian Li, Sanyi Tang, Yanni Xiao, and Jianhong Wu. 2020. “An Updated Estimation of the Risk of Transmission of the Novel Coronavirus (2019-NCov).” *Infectious Disease Modelling* 5: 248–55. <https://doi.org/10.1016/j.idm.2020.02.001>.

⁶ Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19).” 2020. Accessed June 24, 2020. [https://www.who.int/publications-detail-redirect/report-of-the-who-china-joint-mission-on-coronavirus-disease-2019-\(covid-19\)](https://www.who.int/publications-detail-redirect/report-of-the-who-china-joint-mission-on-coronavirus-disease-2019-(covid-19)).

⁷ “Report 9 - Impact of Non-Pharmaceutical Interventions (NPIs) to Reduce COVID-19 Mortality and Healthcare Demand.” 2020. Imperial College London. Accessed June 24, 2020. <http://www.imperial.ac.uk/medicine/departments/school-public-health/infectious-disease-epidemiology/mrc-global-infectious-disease-analysis/covid-19/report-9-impact-of-npis-on-covid-19/>.

⁸ Ioannidis, John P. A. 2020. “In the Coronavirus Pandemic, We’re Making Decisions without Reliable Data.” *STAT* (blog). March 17, 2020. <https://www.statnews.com/2020/03/17/a-fiasco-in-the-making-as-the-coronavirus-pandemic-takes-hold-we-are-making-decisions-without-reliable-data/>.

continue preventive hygiene measures, exercise local infection controls, focus on protecting those most at risk, and support healthcare systems to care for patients who are sick.

(Four) and a half months after COVID-19 was officially declared a pandemic, we lament a great and acute loss of life, especially in places like Lombardy and New York. Since the outbreak was detected in Wuhan in December 2019, the global death toll is estimated to be 346,000 as of this writing. But because our interventions can harm as well as help, it is not unreasonable to put this number in context.

We now know that the death toll is not comparable to that of the 1918 pandemic. We also now know that the virus has spread widely, but for the vast majority of people it is far less lethal than we thought: It kills far fewer than 3.4 percent of those who develop symptoms. (Just two months ago), the CDC adopted an estimated death rate of 0.4 percent for those who develop symptoms and acknowledged that there are many other infected people who develop no symptoms at all.⁹ These estimates will continue to improve as time goes on, but it is clear that the numbers are much lower than first feared. The exact infection fatality rate varies across populations and settings, but it appears that in most situations outside nursing homes and hospitals, it tends to be very low.¹⁰

We have learned that COVID-19 is yet another disease that unfortunately and disproportionately affects the elderly, the disadvantaged, and those with multiple underlying medical conditions. Besides massacring nursing homes, and having the potential to infect many vulnerable patients and providers in hospitals, it painfully emerges as yet another disease of inequality. The poor, the homeless, people in prisons, and low-wage workers in meat-processing plants and other essential jobs are among the hardest hit, while privileged people like me are videoconferencing in safety. That is a tragic disparity.

Given what we know now, it is reasonable to consider alternatives to population-wide lockdown, even as we focus on protecting those most at risk and support

⁹ CDC. 2020. "Coronavirus Disease 2019 (COVID-19)." Centers for Disease Control and Prevention. February 11, 2020. <https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html>.

¹⁰ Ioannidis, John. 2020. "The Infection Fatality Rate of COVID-19 Inferred from Seroprevalence Data | MedRxiv." Accessed June 24, 2020. <https://www.medrxiv.org/content/10.1101/2020.05.13.20101253v2>.

health care systems to care for patients who are sick.

At the same time, we should not look away from the real harms of the most drastic of our interventions, which also disproportionately affect the disadvantaged. We know that prolonged lockdown of the entire population has delayed cancer treatments¹¹ and has made people with serious disease like heart attacks avoid going to the hospital.¹² It is leading hospital systems to furlough and lay off personnel,¹³ it is devastating mental health,¹⁴ it is increasing domestic violence and child abuse,¹⁵ and it has added at least 36.5 million new people to the ranks of the unemployed in the United States alone. Many of these people will lose health insurance, putting them at further risk of declining health and economic distress. Prolonged unemployment is estimated to lead to an extra 75,000 deaths of despair in the United States alone over the coming decade.¹⁶ At a global level, disruption has increased the number of people at risk of starvation to more than a billion,¹⁷ suspension of mass vaccination campaigns is posing a threat of resurgence of

11 Sud, Amit, Michael E. Jones, John Broggio, Chey Loveday, Bethany Torr, Alice Garrett, David L. Nicol, et al. 2020. "Collateral Damage: The Impact on Cancer Outcomes of the COVID-19 Pandemic." *MedRxiv*.

12 Krumholz, Harlan M., and M.D. 2020. "Where Have All the Heart Attacks Gone?" *The New York Times*, April 6, 2020, sec. Well. <https://www.nytimes.com/2020/04/06/well/live/coronavirus-doctors-hospitals-emergency-care-heart-attack-stroke.html>.

13 Leila Fadel, Meg Anderson, and Robert Benincasa. 2020. "As Hospitals Lose Revenue, More Than A Million Health Care Workers Lose Jobs." NPR.Org. Accessed June 24, 2020. <https://www.npr.org/2020/05/08/852435761/as-hospitals-lose-revenue-thousands-of-health-care-workers-face-furloughs-layoff>.

14 Moser, Dominik Andreas, Jennifer Glaus, Sophia Frangou, and Daniel Scott Schechter. 2020. "Years of Life Lost Due to the Psychosocial Consequences of COVID19 Mitigation Strategies Based on Swiss Data." *MedRxiv*.

15 Stanley, Maclen. 2020. "Why the Increase in Domestic Violence During COVID-19?" *Psychology Today*. Accessed June 24, 2020. <https://www.psychologytoday.com/blog/making-sense-chaos/202005/why-the-increase-in-domestic-violence-during-covid-19>.

16 "Projected Deaths of Despair During COVID-19 · Well Being Trust." 2020. *Well Being Trust* (blog). Accessed June 24, 2020. <https://wellbeingtrust.org/areas-of-focus/policy-and-advocacy/reports/projected-deaths-of-despair-during-covid-19/>.

17 Picheta, Rob. 2020. "Global Famines of 'Biblical Proportions' Will Be Caused by Coronavirus Pandemic, UN Warns - CNN." Accessed June 24, 2020. <https://www.cnn.com/2020/04/22/africa/coronavirus-famine-un-warning-intl/index.html>.

infectious diseases that kill children,¹⁸ modeling suggests¹⁹ an excess of 1.4 million deaths from tuberculosis by 2025,²⁰ and a doubling of the death toll from malaria in 2020 is expected compared with 2018.²¹ I hope these modeling predictions turn out to be as wrong as several COVID-19 modeling predictions have, but they may not. All of these impacts matter, too. Policymakers must consider the harms of restrictive policies, not just their benefits.

Good science can come from public health epidemiology, from the study of infectious diseases, from evidence-based medicine, from clinical epidemiology, or from any discipline. I agree with Lipsitch that we need to respect the *totality* of the evidence — including, I would stress, evidence about the harms of prolonged lockdown — rather than rely too narrowly on the claims of any one disciplinary specialty. At the beginning, in the absence of high-quality data, we can do what seems most reasonable, following the precautionary principle and using common sense. But beyond this point, failing to correct our ignorance and adapt our actions as quickly as possible is not good science. Nor is politicizing scientific disagreement or looking away from the undeniable harms of our well-intentioned actions.

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¹⁸ Organization, World Health. 2020. “Guiding Principles for Immunization Activities during the COVID-19 Pandemic: Interim Guidance, 26 March 2020.” <https://apps.who.int/iris/handle/10665/331590>.

¹⁹ “Report 19 - The Potential Impact of the COVID-19 Epidemic on HIV, TB and Malaria in Low- and Middle-Income Countries.” 2020. Imperial College London. Accessed June 24, 2020. <http://www.imperial.ac.uk/medicine/departments/school-public-health/infectious-disease-epidemiology/mrc-global-infectious-disease-analysis/covid-19/report-19-hiv-tb-malaria/>.

²⁰ Stulpin, Caitlyn. 2020. “COVID-19 Will Set Fight against TB Back at Least 5 Years.” Accessed June 24, 2020. <https://www.healio.com/news/infectious-disease/20200506/covid19-will-set-fight-against-tb-back-at-least-5-years>.

²¹ World Health Organization. 2020. “The Potential Impact of Health Service Disruptions on the Burden of Malaria.” Accessed June 24, 2020. <https://www.who.int/publications-detail-redirect/the-potential-impact-of-health-service-disruptions-on-the-burden-of-malaria>.

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Born in New York City in 1965 and raised in Athens, Greece. Valedictorian (1984) at Athens College; National Award of the Greek Mathematical Society (1984); MD (top rank of medical school class) from the National University of Athens in 1990; also received DSc in biopathology from the same institution. Trained at Harvard and Tufts (internal medicine and infectious diseases), then held positions at NIH, Johns Hopkins and Tufts. Chaired the Department of Hygiene and Epidemiology, University of Ioannina Medical School in 1999–2010 while also holding adjunct professor positions at Harvard, Tufts, and Imperial College. Senior advisor on knowledge integration at NCI/NIH (2012–6). Served as president, Society for Research Synthesis Methodology, and editorial board member of many leading journals (including PLoS Medicine, Lancet, Annals of Internal Medicine, JNCI among others) and as editor-in-chief of the European Journal of Clinical Investigation (2010–2019). Delivered ~600 invited and honorary lectures. Recipient of many awards (e.g., European Award for Excellence in Clinical Science [2007]; Medal for Distinguished Service, Teachers College, Columbia University [2015]; Chanchlani Global Health Award [2017]; Epiphany Science Courage Award [2018]; Einstein fellow [2018]). Inducted in the Association of American Physicians (2009), European Academy of Cancer Sciences (2010) American Epidemiological Society (2015), European Academy of Sciences and Arts (2015), National Academy of Medicine (2018). Honorary titles from FORTH (2014) and Ioannina (2015); honorary doctorates from Rotterdam (2015), Athens (2017), Tilburg (2019), Edinburgh (2019). Multiple honorary lectureships/visiting professorships (Caltech, Oxford, LSHTM, Yale, University of Utah, University of Connecticut, University of California–Davis Davis, University of Pennsylvania, Washington University–St. Louis, NIH, among others). The PLoS Medicine paper on “Why most published research findings are false” has been the most-accessed article in the history of Public Library of Science (3 million hits). Author of seven literary books in Greek, three of which were shortlisted for best book of the year Anagnostis awards. Brave Thinker scientist for 2010; according to Atlantic, “may be one of the most influential scientists alive.” Highly Cited Researcher according to Thomson Reuters in both Clinical Medicine and in Social Sciences. Citation indices: h=199, m=8 per Google Scholar. Current citation rate: >4,500 new citations per month (among the 10

scientists worldwide who are currently the most commonly cited, perhaps also the currently most-cited physician). When contrasted against my vast ignorance, these values offer excellent proof that citation metrics can be horribly unreliable. I have no personal social media accounts — I admire people who can outpour their error-free wisdom in them, but I make a lot of errors, I need to revisit my writings multiple times before publishing, and I see no reason to make a fool of myself more frequently than is sadly unavoidable. I consider myself privileged to have learned and to continue to learn from interactions with students and young scientists (of all ages) from all over the world, and I love to be constantly reminded that I know next to nothing.