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Original Contribution

Choice of Outcome in COVID-19 Studies and Implications for Policy: Mortality and Fatality

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In this brief communication, we discuss the confusion of mortality with fatality in the interpretation of evidence in the coronavirus disease 2019 (COVID-19) pandemic, and how this confusion affects the translation of science into policy and practice. We discuss how this confusion has influenced COVID-19 policy in France, Sweden, and the United Kingdom and discuss the implications for decision-making about COVID-19 vaccine distribution. We also discuss how this confusion is an example of a more general statistical fallacy we term the "Missing Link Fallacy."

COVID-19; fatality; methods; Missing Link Fallacy; mortality; policy

Abbreviations: COVID-19, coronavirus disease 2019; HR, hazard ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

In this brief communication, we discuss the confusion of mortality with fatality in the interpretation of evidence amid the coronavirus disease 2019 (COVID-19) pandemic, and how this confusion affects the translation of science into policy and practice. We discuss how this confusion has influenced COVID-19 policy in France, Sweden, and the United Kingdom and discuss the implications for decision-making about COVID-19 vaccine distribution. We also discuss how this confusion represents an example of a more general statistical fallacy we term the "Missing Link Fallacy."

POLICY CONTEXT

France

French workers deemed vulnerable to death from COVID-19 were afforded extra legal protections—including a right to claim furlough if their job requires face-to-face activity. On August 29, 2020, the French government modified their definition of "vulnerable" to exclude various groups of people, including those with hypertension, chronic respiratory disease, and chronic cardiovascular disease (1). In support, the French government cited a single study: Williamson et al. (2), in which the authors took the primary care records of over 17 million adults in the United Kingdom and linked those records to 10,926 "COVID-19-related deaths." The authors then fitted a Cox proportional hazards model to the data, with covariates including age, sex, obesity, smoking, ethnicity, hypertension, chronic respiratory disease, chronic cardiovascular disease, and cancer; they reported the results of that Cox model in text, Table 2, and Figure 3. Citing Figure 3 specifically (1), the French government decided that all conditions with an adjusted hazard ratio (HR) below approximately 2 or 3 were not sufficiently vulnerable to warrant continued protection. This decision was overturned after an appeal to the French Supreme Court (3), supported by testimony from several epidemiologists worldwide. (Authors D.W., M.vS., and P.W.G.T. contributed testimony.)

Sweden

Similar judgments and modifications appear to have occurred in Sweden, with the Swedish Health Agency recently declaring "Some groups may have more severe symptoms if they become infected with COVID-19 . . . . High blood pressure alone does not appear to increase the risk at all according to the British study mentioned above [(2)], and

is therefore no longer on the list." (4, 5) (Note that the specific remark on high blood pressure (4) was subsequently changed in the most recently updated version (5); however, the overall reliance on Williamson et al. (2) remains.)

United Kingdom

In the United Kingdom, the Association of Local Authority Medical Advisors (https://alama.org.uk/, "an association of like-minded doctors with a special interest in occupational medicine who work in the public sector") reports a similar interest in identifying "vulnerability", which they define as, "the risk that, once infected with Covid-19, [an individual] . . . will develop serious illness and die . . . ." ALAMA stated that, "The best evidence on vulnerability to Covid-19 comes from epidemiological research . . . [and] the main data source has been the OpenSAFELY paper published in *Nature* [(2)], cross-referenced against other publications and sources." (6).

EVIDENTIARY CONTEXT

The OpenSAFELY study (2) remains unprecedented in its scope and visibility, including its publication in a prominent journal (*Nature*). It is therefore not surprising that it has received significant attention from policy makers. This makes it well suited to illustrating this issue. However, other than the size of this study and the attention it has received, the study is fairly typical of most "risk factor" epidemiologic studies. Much of the discussion that follows therefore applies to other published studies as well.

We and others have expressed serious concerns about the validity of using the individual HRs from the OpenSAFELY study to inform policy decisions (7, 8), and the authors have responded (9). These previous discussions have centered on the problems of drawing policy-relevant (i.e., causal) conclusions from "risk factor" analyses, where there is a high risk of committing the Table 2 Fallacy (10). Here, we focus on a different issue: misinterpretations of their work due to confusion between fatality and mortality.

The OpenSAFELY authors describe their outcome as "COVID-19-related death," which we could more properly refer to as COVID-19-related mortality (11, 12). This definition, and its implications, are worth clarifying. First, every one of the 10,926 individuals who experienced the outcome must have both 1) acquired the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, and subsequently 2) died from COVID-19. Second, the great majority of the 17 million adults examined by the OpenSAFELY authors never acquired the SARS-CoV-2 virus. The HRs for each "risk factor" reported in their paper therefore represent a combination of the association with the risk of infection and the association with the risk of death after infection.

This combined outcome is not unique to OpenSAFELY (e.g., Holman et al. (13)), and our concern here is in no way criticism of this choice of outcome per se. Used and interpreted appropriately, cause-specific mortality is a reasonable outcome, especially under present emergency conditions. However, even disregarding other methodological issues (7, 8), the OpenSAFELY results (and other studies of cause-specific mortality) do not distinguish between 1) a covariate associated with the risk of acquiring SARS-CoV-2 but unassociated with risk of death following infection, and 2) a covariate unassociated with risk of acquiring SARS-CoV-2 but associated with risk of death following infection. This is concerning, because all 3 policy recommendations reported above appear to rely on interpreting the findings to indicate associations with risk of death after acquiring SARS-CoV-2 (that is, SARS-CoV-2 fatality (11, 12)). (Here, we elide discussion of differences between the infection fatality—the outcome of death given infection with SARS-CoV-2—and case fatality—outcome of death given being a confirmed case of COVID-19. An overall similar discussion applies regardless of which we are discussing).

THE CORE ISSUE WITH THE EVIDENCE FOR THE POLICY

More formally, the outcome in OpenSAFELY can be described as the probability of A & B, where A is infection with SARS-CoV-2, and B is death from COVID-19. Probability calculus reminds us that

$$\Pr(A\&B) = \Pr(A) \times \Pr(B|A),$$

where $\Pr(A \& B)$ is the (cumulative) cause-specific mortality risk, $\Pr(A)$ is the (cumulative) incidence risk, and $\Pr(B|A)$ is the infection fatality risk. Unfortunately, the statements from France, Sweden, and the United Kingdom suggest they are all interested in only the latter half of that probability: $\Pr(B|A)$, the probability of death given infection. Indeed, the United Kingdom statement is explicit; they are interested in the risk that persons, once infected with COVID-19, will develop serious illness and die (6). Excepting any errors in translation, the French and Swedish statements appear equally clear.

In all 3 examples, the determinants of $\Pr(A\&B)$ (cause-specific mortality), as studied in OpenSAFELY, are therefore being misinterpreted as a proxy for the determinants of $\Pr(B|A)$ (infection fatality). At best, this may be somewhat uninformative for the desired and stated policy goal of identifying people at the greatest risk of fatality. At worst, this conflation may be dangerously misleading. To see why this is a problem, consider the following example.

Suppose that—in the OpenSAFELY cohort—people with chronic respiratory disease were better at social distancing and/or self-isolating because of an enhanced fear of respiratory infection, and as a result were less likely to acquire SARS-CoV-2 and subsequently COVID-19 than others. Suppose this translated to an incidence risk 0.5 times the risk in those without chronic respiratory disease. Table 1 shows data consistent with this hypothetical. Now suppose this fear were justified, and that those infected with SARS-CoV-2 who had chronic respiratory disease were substantially more likely to die, specifically that these people had a risk of death 4 times the risk of death in those without chronic respiratory disease. Table 2 shows data consistent with this aspect of the scenario, concentrating only on those 95,000 individuals from Table 1 who became infected. Assuming no deaths (or only trivial numbers) among the uninfected, in this situation

Table 1. Hypothetical Data on Infection Alone[a]

Infection	Infection = 1	Infection = 0	Total	Risk	RR
Exposed = 1	5,000	95,000	100,000	0.05	0.50
Exposed = 0	90,000	810,000	900,000	0.1	
Total	95,000	905,000	1,000,000		

Abbreviation: RR, risk ratio.
[a] The 95,000 people shown to be infected in this table are the only people who are in Table 2.

we would observe only a modest overall association—a risk ratio of approximately $0.5 \times 4.0 = 2.0$—between chronic respiratory disease and COVID-19-related death, broadly consistent with the HR reported in OpenSAFELY (2): This situation is shown in Table 3 (again assuming trivial/ignorable numbers of deaths among the uninfected). As we discuss in Web Appendix 1 (available at https://doi.org/10.1093/aje/kwab244), if these individuals had sheltered even more effectively (reducing their incidence risk ratio to 0.25) and had a more modest fatality risk ratio (of 3.0), then we might even observe a protective mortality risk ratio of $0.25 \times 3.0 = 0.75$, suggesting that their condition was overall protective.

An elevated cause-specific mortality risk ratio (or HR)—such as those reported in Williamson et al. (2) for many "risk factors"—may therefore arise due to an increased risk of infection, an increased risk of death given infection (fatality risk), or both, due to compound nature of the outcome. Again, while there is no inherent issue with examining mortality risk per se, the results of such analyses must be interpreted carefully to avoid inappropriate or harmful policy recommendations. For example, if people with chronic respiratory disease experience lower risks of infection due to enhanced social distancing but higher risks of death once infected, then they may experience genuine harm from policies that reduce their protections based on a modest mortality risk.

IMPLICATIONS FOR VACCINE DISTRIBUTION

These concerns are acutely relevant to understanding and determining which individuals should be prioritized for the earliest receipt of SARS-CoV-2 vaccines. The US Centers for Disease Control and Prevention (CDC), for example, describes a framework for vaccine priority (14) that gives preference to (among other groups) "[p]eople with certain underlying medical conditions (who) are at increased risk for severe COVID-19 illness." The WHO framework for COVID-19 vaccine allocation similarly suggests prioritizing people "with comorbidities . . . determined to be at significantly higher risk of severe disease or death" (15, p. 10). The judgment of which medical conditions are recommended for prioritization by the CDC is influenced by several studies of mortality risk (16), including OpenSAFELY, when the focus should arguably be on the fatality risk of death (or the risk of serious illness) following infection.

DISCUSSION

Making policy amid a public health emergency, based on rapidly evolving evidence, is extremely challenging; we do not discount these challenges. Indeed we laud all policy makers who base their decisions on scientific evidence rather than on ideology. Nor must we let perfect be the enemy of good. When it comes to evidence, we can't always get what we want, but this is no excuse for complacency. Policy must be informed by appropriate evidence. Poor or inapplicable evidence may not just be distracting or misleading; it may be genuinely harmful. In particular, making policy based on confusing mortality with fatality could place the highest-risk individuals at substantially increased risk of death, and must be avoided.

More generally, we urge scientists to clarify the target populations to which their results apply and, where possible, to separate multistage outcomes such as mortality into distinct stages, such as incidence and fatality (17). Regardless, scientists should aim to communicate more clearly and modestly about the policy implications of their results, and take time to consider and address the ways that they may be misinterpreted.

Table 2. Hypothetical Data on Death Given Infection[a]

Death | Infection	Death = 1	Death = 0	Total	Risk	RR
Exposed = 1	200	4,800	5,000	0.04	4.00
Exposed = 0	900	89,100	90,000	0.01	
Total	1,100	93,900	95,000		

Abbreviation: RR, risk ratio.
[a] The 95,000 people shown to be infected in Table 1 are the only people who are in this table.

Table 3. Hypothetical Data on Combined Outcome of Infection and Death[a]

Combined Outcome	Death = 1	Death = 0	Total	Risk	RR
Exposed = 1	200	99,800	100,000	0.002	2.00
Exposed = 0	900	899,100	900,000	0.001	
Total	1,100	998,900	1,000,000		

Abbreviation: RR, risk ratio.

[a] The 1,100 deaths from Table 2 are the only deaths in this table because we assume trivial numbers of deaths from the uninfected (which we regard as reasonable over short time periods).

More broadly, we note that the confusion of $\Pr(A\&B)$ and represents a more general statistical fallacy, in the same way that that the assumption that $\Pr(B|A)$ is equal to $\Pr(A|B)$ (the Prosecutor's Fallacy (18)) is a more general statistical fallacy. We term the general case of the issue identified here the "Missing Link Fallacy"; because $\Pr(A\&B) = \Pr(B|A) \times \Pr(A)$, the assertion that $\Pr(A\&B) = \Pr(B|A)$ is incorrect in that it is missing the "link" of $\Pr(A)$. We see high potential for this confusion to arise in other settings, particularly interpretation of diagnostic test results, in which epidemiologists and policy makers may confuse the probability of an individual both having a disease (which would take the place of A in the equation above) and testing positive for that disease (which would take the place of B) with the positive predictive value, that is, the probability of that individual testing positive given they truly have the disease.

We emphasize that there is nothing wrong with mortality as an outcome per se; it may be precisely the right outcome to study when our goal is to prevent death overall or to target vaccination for the purpose of limiting transmission—rather than to target vaccinations to reduce the morbidity and mortality associated with infections specifically. Specifically, risk of infection may depend on behavior (as opposed to biology) to a greater extent than risk of death given infection, and thus may be more amenable to public health intervention (e.g., government financial support for staying at home). If the goal is reducing mortality in absence of vaccines, then it might be sensible to base policy on mortality.

Rather, we urge policy makers to look more carefully at the outcomes being examined in studies that they are using to inform policy (e.g., Centers for Disease Control and Prevention (16)), be alert for outcomes that inherently require one or more preconditions to be met, and consider the implications of the compound nature of those outcomes for the policies they are considering. Policy makers interested in factors that predispose to a higher risk of death in those infected with SARS-CoV-2, for example, should give preference to studies that focus on groups of infected individuals.

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