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Northside Baptist Church,
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**Secondary Sources**
**TAB**

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|---|---|
| **1.** | Alberta Government spends 2.5M on unusual covid-19 ad campaign: https://calgary.ctvnews.ca/alberta-government-spends-2-5m-on-unusual-covid-19-ad-campaign-1.5362851 |
| **2.** | Covid Lockdown Cost/Benefits: A Critical Assessment of the Literature"- Douglas Allen ; https://www.sfu.ca/~allen/LockdownReport.pdf |
| **3.** | Review of the Emerging Evidence Demonstrating the Efficacy of Ivermectin in the Prophylaxis and Treatment of Covid-19- American Journal of Therapeutics https://journals.lww.com/americantherapeutics/fulltext/2021/06000/review_of_the_emerging_evidence_demonstrating_the.4.aspx |
| **4.** | City Journal- Do Masks Work? A Review of the Evidence 11 August 2021 https://www.city-journal.org/do-masks-work-a-review-of-the-evidence |
| **5.** | Universal Declaration of Human Rights, December 10, 1948 |

BREAKING

Justin Trudeau's Liberals win minority government



CALGARY | News

# Alberta government spends $2.5M on unusual COVID-19 ad campaign

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Published Thursday, March 25, 2021 5:39PM MDT

The Alberta government says its COVID-19 ad campaigns "exceeded the scope" of all other government campaigns. (Supplied/YouTube)



CALGARY -- COVID Loves, a highly unusual ad featuring a character coined by many as 'Uncle COVID', had a total budget of $2.5 million, Alberta Health said Thursday.

The ad campaign, aimed at Albertans aged 40 and below, was intended to teach lessons about how easily COVID-19 could be spread in everyday situations.

The initiative included a series of videos featuring an individual wearing a COVID-virus mask complete with freakish grimace attending holiday gatherings, dancing and hugging it out with friends and loved ones.

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Alberta Health hasn't said if COVID Loves has been the most expensive ad campaign during



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the pandemic but the initiative also included a website that showed off all the places "Uncle COVID" loved to go, including birthday parties, baby showers and even wine tastings.


*(Supplied/COVIDLoves.ca)*

In all, the province says it spent $15.4 million on all of its COVID-19 education, testing promotions and support literature for various demographics.

"This includes six phases of a comprehensive campaign designed to inform Albertans of the latest information about public health measures throughout the pandemic," said Tom McMillan, assistant director of communications for Alberta Health, in a release.

"These campaigns have made extensive use of online display, social media, television, radio, billboards, and other print collateral."

However, McMillan says that even with the cost, the campaigns have had a considerable effect on sharing the appropriate messaging.

"The campaigns have exceeded the scope and reach of any previous Alberta government advertising campaigns."



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# Covid Lockdown Cost/Benefits: A Critical Assessment of the Literature

Douglas W. Allen*

April 2021

## ABSTRACT

An examination of over 80 Covid-19 studies reveals that many relied on assumptions that were false, and which tended to over-estimate the benefits and underestimate the costs of lockdown. As a result, most of the early cost/benefit studies arrived at conclusions that were refuted later by data, and which rendered their cost/benefit findings incorrect. Research done over the past six months has shown that lockdowns have had, at best, a marginal effect on the number of Covid-19 deaths. Generally speaking, the ineffectiveness of lockdown stems from voluntary changes in behavior. Lockdown jurisdictions were not able to prevent noncompliance, and non-lockdown jurisdictions benefited from voluntary changes in behavior that mimicked lockdowns. The limited effectiveness of lockdowns explains why, after one year, the unconditional cumulative deaths per million, and the pattern of daily deaths per million, is not negatively correlated with the stringency of lockdown across countries. Using a cost/benefit method proposed by Professor Bryan Caplan, and using two extreme assumptions of lockdown effectiveness, the cost/benefit ratio of lockdowns in Canada, in terms of life-years saved, is between 3.6–282. That is, it is possible that lockdown will go down as one of the greatest peacetime policy failures in Canada's history.

* email: allen@sfu.ca. Department of Economics, Simon Fraser University, Burnaby, Canada. Thanks to various colleagues and friends for their comments.

## I. Introduction

In my forty years as an academic, I've never seen anything like the response and reaction to Covid-19. The research response has been immense, with estimates of over 40,000 papers related to the topic produced in one year. This research covers every imaginable aspect of Covid-19, and over the course of the past year knowledge about the virus, the human reactions to it, and the consequences of these reactions has exploded. In one word, the Covid-19 information cascade has been "overwhelming."

In contrast, the ubiquitous media, public health, and political response to the pandemic has been one-sided, incomplete, and almost unchanging over the past year. With respect to lockdown policies, many political jurisdictions have repeated the same spring 2020 programs in 2021, ignoring what has been learned in the meantime. Often public announcements were made that were inconsistent with basic Covid-19 facts that were easy to look up if you know where to look. Furthermore, when research results contrary to the official government response were shared on social media, they were often pulled from social media platforms. As a result, for average Canadians the public media and official public health news conferences have been the only source of Covid-19 information.

This review of a small segment of the literature is intended to give some guidance for those who would otherwise not have access to academic research. The focus is to only critically assess the cost/benefit studies that have been written over the past year on lockdown policies related to the Covid-19 pandemic.[1]

The report covers over 80 different academic studies and related Covid-19 data sites. I have sought out studies that i) dealt with matters of "lockdown" either directly or indirectly, and ii) were related directly or indirectly to issues relevant to the costs or benefits of lockdown.

[1] The studies referred to are listed in the Reference section. Many papers and data sites have links to webpages. Because these links often "ran off the page" I often had to break them up by inserting a space. Hence, if the link does not work, check to make sure there are no spaces.

The term "lockdown" is used to generically refer to state actions that imposed various forms of non-pharmaceutical interventions. That is, the term will be used to include mandatory state-enforced closing of non-essential business, education, recreation, and spiritual facilities; mask and social distancing orders; stay-in-place orders; and restrictions on private social gatherings.

"Lockdown" does not refer to cases of "isolation," where a country was able to engage in an early and sufficient border closure that prevented trans-border transmission, followed by a mandated lockdown that eliminated the virus in the domestic population, which was then followed by perpetual isolation until the population is fully vaccinated. This strategy was adopted by a number of island countries like New Zealand.[2] Here I will only consider lockdown as it took place in Canada and most of the world; that is, within a country where the virus became established.

This is a complicated report because it covers a wide range of studies, and deals with a wide range of issues. Table 1 outlines the substance of the report. Sections II: A and B, discuss four critical assumptions often made within the context of estimating benefits and costs. Understanding these assumptions explains why early studies claimed that the benefits of lockdown were so high, and also explains why the predictions of those models turned out to be false.

Section II: C, examines major cost/benefit studies completed over the first six months of the pandemic, and then focuses on what I believe to be the critical factor: distinguishing between mandated and voluntary changes in behavior. This section concludes with an interpretation of some unconditional death comparisons across countries that are typically reported in the media. Section II:D surveys the research done on the costs of lockdown. Finally, Section III. presents a simple alternative cost/benefit methodology to generate two cost/benefit ratios of lockdown.

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[2] Other island countries with this strategy include many Pacific island nations (like Samoa and Tonga), Caribbean islands (like Cuba and Jamaica), and Iceland. Some countries have been able to mimic being islands in border closings like South Korea, Finland, and Norway.

**Table 1: Outline of the Main Body of Report**

**II. Cost Benefit Studies**

A. Issues in Determining Lockdown Benefits
*The Counterfactual Number of Cases/Deaths*
*The Exogenous Behavior Assumption*
*The Assumed Value of Life*

B. An Issue in Lockdown Costs
*Comparing Apples to Oranges*
*Summary of Theoretical Issues*

C. Reviewing Lockdown Cost/Benefit Studies
*Early Theoretical Cost/Benefit Studies*
*April–June: Early Challenging Results*
*Four Stylized Facts About Covid-19*
*Voluntary versus Mandated Lockdown Channels*
*Unconditional Cross-Country Covid-19 Comparisons*

D. The Costs of Lockdown

**III. An Alternative Cost/Benefit Methodology**

The major conclusions of this report are:

a. A proper cost/benefit study of a specific policy must consider all costs and all benefits of that policy.

b. All estimates of costs and benefits depend on various assumptions of parameters and structural model forms, and many of the studies examined (especially the early ones) relied on assumptions that were false, and which tended to over-estimate the benefits and under-estimate the costs of lockdown.

c. As a result of (b) most of the early cost/benefit studies arrived at conclusions that were refuted later by data, and which rendered their cost/benefit findings incorrect.

d. Advances in models and data over the past six months have showed that lockdowns have had, at best, a marginal effect on the number of Covid-19

deaths. Generally speaking, the ineffectiveness of lockdown stems from voluntary changes in behavior. Lockdown jurisdictions were not able to prevent non-compliance, and non-lockdown jurisdictions benefited from voluntary changes in behavior that mimicked lockdowns.

e. The limited effectiveness of lockdowns explains why, after one year, the unconditional cumulative deaths per million, and the pattern of daily deaths per million, is not negatively correlated with the stringency of lockdown across countries.

f. Using a cost/benefit method proposed by Professor Bryan Caplan, and using two extreme assumptions of lockdown effectiveness, the cost/benefit ratio of lockdowns in terms of life-years saved is between 3.6–282.

## II. Cost Benefit Studies

When it comes to the question of choosing any type of public policy, the Nobel prize winner Ronald Coase put it best:

> It would clearly be desirable if the only actions performed were those in which what was gained was worth more than what was lost. But in choosing between social arrangements within the context of which individual decisions are made, we have to bear in mind that a change in the existing system which will lead to an improvement in some decisions may well lead to a worsening of others.... In devising and choosing between social arrangements we should have regard for the total effect.
>
> [Coase p. 44, 1960]

Coase was making two points. The first should be obvious: policy decisions should be made based on both costs and benefits. To focus on one side of the issue and consider only costs or only benefits will necessarily provide a misdirection. The second point is more subtle: an attempt to achieve a particular benefit through one mechanism might lead to an exacerbation of the costs. There are multiple methods to achieve a goal, but the cost consequences might be different for each method. At the end of the day, choosing the optimal policy requires a "regard for the total effect."

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Over the course of the Covid-19 pandemic, there has been no public evidence that either the federal or provincial governments of Canada have considered both the benefit and cost sides of their policy decisions. To my knowledge, no government has provided any formal cost/benefit analysis of their actions. Indeed, the steady press conferences and news releases almost entirely focus on one single feature of the disease. Although the focus of government announcements has changed over the year, from "flattening the curve", number of Covid-19 deaths, number of Covid19 cases, variant transmissions, etc., there has seldom been any mention of the costs of the actions taken to address these concerns.

Economists and other social scientists have naturally been attracted to the policy issues surrounding Covid-19. Economists in particular, given their training in modeling human behavior and testing those models with real world data, have written hundreds of papers that deal with both the costs and the benefits of lockdown. Here, aside from going through some of the theoretical issues, I provide a summary of the major findings.

## A. Issues in Determining Lockdown Benefits

Over the course of the first six months of the pandemic most of the "action" in cost/benefit studies came from the benefit side. That is, many studies reported enormous benefits to lockdown, and so little attention was given to the particulars of lockdown costs. Therefore, before going through a sequential review of studies to show the progression of understanding over the past year, I start by addressing some general theoretical and empirical issues of estimating Covid-19 lockdown benefits. Understanding these assumptions explains why the conclusions across studies are so different.

### *The Counterfactual Number of Cases/Deaths*

The argument for lockdown benefits is intuitive. If a new virus enters a population with no immunity and spreads *exponentially*, causing an overwhelming of

hospitals and subsequent large numbers of deaths, then a physical intervention that isolates people and slows down the transmission of the virus can reduce the spike of infections, allow hospitals to cope given their capacity constraints, postpone deaths, and possibly reduce deaths if a vaccine can be created in time. Lockdown is a formal, state-mandated "one size fits all" version of the social norm "keep your distance from people who are sick."

If lockdown reduces the transmission of the virus, the natural question to ask is "by how much?" In other words, "but for the lockdown" what would the level of infection/transmission/deaths be? What is the counterfactual to lockdowns?

Within the field of epidemiology it is common to model disease through what is called a SIRS model. This is a model that depends on number of people susceptible (S), infectious (I), or recovered (R). These models can vary in many ways, and can include many parameters and constraints. Early in the pandemic the Neil Ferguson *et al.* (March 2020) model (known as the Imperial College of London (ICL) model), appeared to drive many lockdown decisions, and certainly was widely covered in the media.

In these models the virus progresses through a population in a mechanical fashion. There are a number of parameters in the model, including the basic reproduction number, $R_t$. The basic reproduction number varies over time, and indicates the expected number of secondary infections in a vulnerable population that are generated by a single given infection. Lockdowns are often interpreted as a means of effectively altering the reproduction number.

Figure 1 reproduces a key figure of the Ferguson *et al.* paper, and shows the results of various types of lockdown on occupied ICU beds. The symmetry, smoothness, and orderly appearance of the functions is a result of the mechanical nature of the model. This type of figure is found, in one form or another, in most papers based on a SIRS model.

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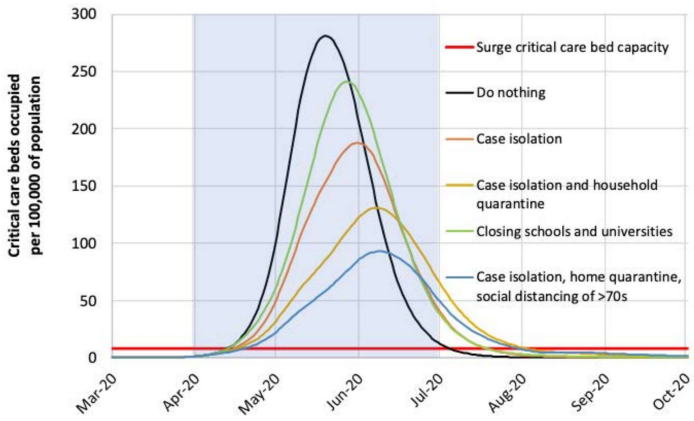



*Figure 1: ICU Predictions in ICL Model*

We can use Figure 1 to see the implications of the SIRS model for determining the counterfactual. Suppose, for the sake of argument that the blue line lockdown was enacted. Then, reading from the graph, on June 20th approximately 80 ICU beds would have been occupied. However, the counterfactual would be taken from the black "do nothing" line, and reading from the graph there would have been 200 ICU beds occupied. The blue lockdown would have reduced the number of ICU beds occupied by 120. Because SIRS models have an exponential growth characteristic until a population approaches herd immunity, the "do nothing" counterfactual can be enormous, and this automatically makes lockdown look better.

As a result, the ICL model made some dire predictions that saturated media coverage in the first wave of the pandemic. For instance: "In the (unlikely) absence of any control measures or spontaneous changes in individual behaviour ... In total, in an unmitigated epidemic, we would predict approximately 510,000 deaths in GB and 2.2 million in the US, not accounting for the potential negative effects of health systems being overwhelmed on mortality." (p. 7, 2020).

The authors also made a dramatic recommendation: "We therefore conclude that epidemic suppression is the only viable strategy at the current time. The social and economic effects of the measures which are needed to achieve this policy goal will be profound." (Ferguson *et al.* p. 16, 2020).

–

In retrospect it is remarkable that such a conclusion was drawn. The authors recognized that the "social and economic effects" would be "profound," and that the predictions were based on the "unlikely" behavioral assumption that there would be no change to individual reactions to a virus. However, given the large counterfactual numbers, presumably they felt no reasonable cost could justify not locking down.[3]

Problems with the ICL model were pointed out almost immediately. These problems included: i) the reproduction number ($R_t$) of 2.4 was too high; ii) the assumed infection fatality rate (IFR) of 0.9% was too high and not age dependent; iii) hospital capacity was assumed fixed and unchangeable; and iv) individuals in the model were assumed to not change behavior in the face of a new virus.[4] However, the point to stress is that all of these assumptions have the effect of over-estimating the counterfactual number of cases, transmissions, and deaths.[5]

*The Exogenous Behavior Assumption*

As mentioned, a critical parameter in a SIRS model is the basic reproduction number, $R_t$. A typical SIRS model shows that cases of the virus explode exponentially when the $R_t > 1$, and then collapse as herd immunity is reached and the virus recedes to an endemic state. This pattern was shown in Figure 1, and this particular evolution of the virus happens because no individual in the model ever changes behavior.

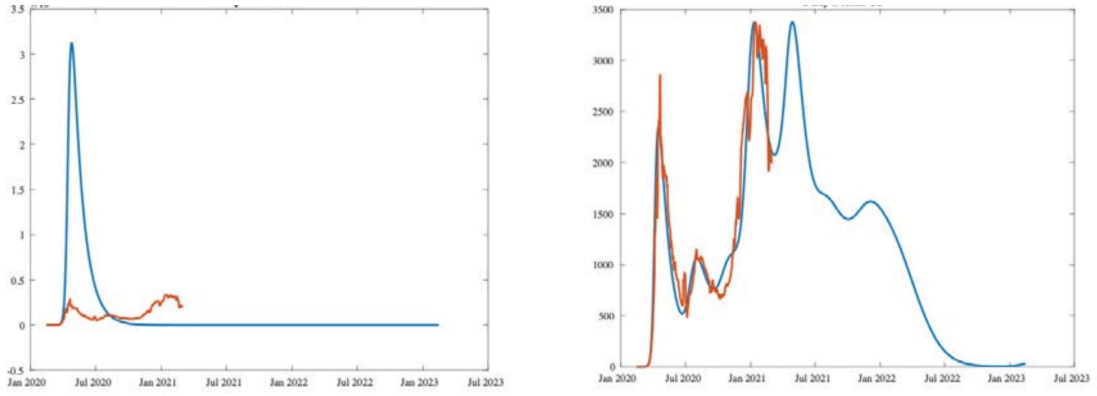
---

[3] To appreciate how far off the Ferguson *et al.* model predictions were, consider that the predicted number of deaths in the U.K. and the U.S. was to happen *by July of 2020.* Both the U.S. and U.K. have had relatively high death rates due to Covid-19, but as of March 12, 2021 the U.S. has experienced 536,914 deaths and the U.K. 125,927 deaths (OurWorldInData). The ICL model was off by a factor of four, over twice the time period.

[4] Estimates of the IFR have continued to fall over the year. The latest meta-study by Ioannidis (March 2021) estimates the average global IFR at 0.15%.

[5] There are many forms of SIRs models, and the exact channel by which the virus mechanically progresses varies across studies. For example, Ambikapathy and Krishnamurthy (April 2020) model the exponential viral growth using a system of differential equations that mimic a SIRS model. Given the assumed parameters in the model, lockdowns inhibit the transmission rates and produce a predicted benefit. See also Sjódin *et al.* April 2020, or Liu *et al.* May 2020 for other examples of mechanical virus models.

The implication of ignoring individual responses to a viral threat are dramatic. Atkeson (February 2021) uses a standard SIRS model (with exogenous behavior) that included seasonal effects and the introduction of a more contagious variant in December 2020 to forecast daily U.S. deaths out to July 2023. The results of this standard model are shown in panel (a) of Figure 2 by the blue line; the red line in panel (a) shows the actual daily deaths. The vertical axis is raised to the $10^4$ power, so daily deaths are predicted to have peaked at 30,000 in July of 2020. Compared to the red line in panel (a), the standard model over estimated the peak number of deaths by a factor of about 12.




(a) (b)

*Figure 2: Predicted and Actual Daily U.S. Deaths*

Atkeson (February 2021) then used *the same model* with a simple behavioral adjustment that allowed individuals to change behavior in light of the value of $R_t$. The new forecast of daily deaths is shown as the blue line in panel (b) of Figure 2. Adding the single behavioral response completely changed the model's predictive power. The model now tracks the actual progression of the daily deaths very closely. In correspondence with Atkeson he provided the reason for this result:

> The intuition for this result is simple. If new infections and daily deaths from the disease grow too high, people take costly efforts to avoid interaction and thus slow disease spread. Likewise, if the prevalence of the disease falls toward zero, then the demand for costly disease prevention efforts also falls towards zero, and so the

> disease will come back unless the population has already achieved herd immunity measured at pre-pandemic levels of behavior.

Whether Atkeson (February 2021) has correctly modeled the Covid-19 virus is not at issue. The point is, there is a dramatic change in predicted behavior once human reactions are included. A model lacking endogenous individual adjustment radically mis-estimates the number of daily deaths, and this is a common problem in many cost/benefit studies.

The fact that individuals privately and voluntarily respond to risks has two important implications.[6] First, it influences how any counterfactual outcome is understood with respect to the lockdown. When no voluntary response is assumed, models predict the case load and deaths explode exponentially without lockdowns. If lockdowns are imposed and cases coincidently fall, the actual number of cases is then compared to a counterfactual that never would have happened.[7] Therefore, not accounting for rational, voluntary individual responses within a SIRS model drastically overstates any benefit from lockdown.[8] When considering various cost/benefit

[6] The notion that epidemiological models need to contain endogenous human behavior was explained in a classic paper by Philipson (2000).

[7] An example of this is found in Hsiang *et al.* (August 2020), who use the pre-lockdown growth rates of the virus in their calculation of the counterfactual trajectory of new cases. This ignores the fact that transmission and infection rates vary over time, and that a major reason for this variation is voluntary changes in behavior.

[8] Looking back on statements made in March/April 2020 by medical professionals and epidemiologist shows how far off their predictions were. Michael Osterholm, director of the Center for Infectious Disease Research and Policy at the University of Minnesota, stated on The Joe Rogan Experience in March 2020 that "We conservatively estimate that this could require 48 million hospitalizations, 96 million cases actually occurring, over 480,000 deaths that can occur over the next four to seven months with this situation.." (Quoted from https://nationalinterest.org/blog/buzz/scientist-480000-people-could-die-due-coronavirus-48-million-hospitalizations-132167). The reality was that as of July 16, 2020 there were 138,000 deaths, 250,000 hospitalizations, and 3,600,000 confirmed cases. Unabashed, Osterholm stated on February 2, 2021 that the new variant would cause a 'hurricane' of new cases, and "The fact is that the surge that is likely to occur with this new variant from England is going to happen in the next six to fourteen weeks. And, if we see that happen, which my forty-five years in the trenches tell me we will, we are going to see something like we have not seen yet in this country ...". Quoted from https://nationalinterest.org/blog/coronavirus/health-expert-prepare-category-5-coronavirus-hurricane-177476. According to OurWorldInData, on February 2,

studies it is important to discount models that assume no individual response to a viral threat.

Second, any empirical work that considers *only the total* change in outcomes and does not attempt to separate the mandated effect from the voluntary effect, will necessarily attribute all of the change in outcome to the mandated lockdown. Once again, this will over-estimate the effect, and quite likely by an order of magnitude.

Individuals change behavior for two reasons. They voluntarily respond to the threat of a virus, and they react to mandated lockdowns. Both effects create a *total* change in behavior that is the result of these two channels. It is extremely important that the empirical work done on lockdown effects distinguish between the two channels of behavior to determine how much behavior changed because of mandated lockdowns and how much because of voluntary changes.[9]

### *The Assumed Value of Life*

All economic cost/benefit studies of Covid-19, either directly or indirectly, utilize some method to estimate the number of cases, infections, or deaths as the virus progresses through the population over time. Counting cases and deaths, however,

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2021 there were 428 cases per million people in the U.S. As of March 14, six weeks later, there were 163 cases per million. Cases did not rise to unprecedented hurricane levels, but rather fell by more than two times.

[9] For example, if only 10% of change in cases is caused by mandated lockdown and 90% is caused by voluntary changes in behavior, then attributing all of the effect to lockdown over-estimates the lockdown effect by nine times. The less important mandated lockdowns are, the greater the over-estimation. This issue was publicly known as early as April 2020. Abouk (April 2020) examined differences in policies across the U.S. and separated out the voluntary effect. He noted (p. 2):

> While there is strong evidence for reduced social contact in the US, not all of these reductions can be attributed to NPIs: mobility data show that people in most states had already started to reduce the time they spend outside their homes before any NPI was implemented.

He found that stay-at-home orders had a substantial effect on confirmed cases, but business and school closures, along with bans of large gatherings did not.

is only half the process. To estimate benefits and compare them to costs economists assign a dollar value to the change in outcomes. If lockdown benefits are in terms of the number of deaths delayed, then a value to these lives must be used.[10]

In economics, the concept of "value" is based on the idea of maximum sacrifice. How much one is willing to sacrifice, at most, for something determines that individual's economic value of the thing. Thus, when it comes to the value of an individual's life, this value is determined by the actual individual. In practice, what is measured is how much individuals are willing to sacrifice to extend their life a little bit by reducing some type of harm (called a 'marginal' value), and then use this to determine a total value of life.

Everyday people make decisions that directly and indirectly are based on their marginal value of life. The decisions to eat poor foods, smoke, accept dangerous employment, cross a street, drive a car, exercise, or engage with others all entail risks to life and therefore imply a value of life. Economists and policy makers in general use the notion of an individual's marginal value of life in determining what it is called "The Value of a Statistical Life" (VSL). The VSL concept was developed in the 1960s by Thomas Schelling, and is widely used in policy work.

The VSL is estimated by observing individual marginal tradeoffs. Thus, if we observed someone willing to pay \$1000 to reduce the chance of death by 1/10,000 over the next year, then this would imply a value of life of \$10,000,000 ($10,000 \times$ \$1000).

One problem with using the VSL for estimating the benefits of saving lives through lockdown is that it measures the total value of life based on a marginal value. Thus, using a VSL (which is based on observing ordinary people *not at the point of death*) as a measure of the value of a life of someone about to die, is likely to provide an *over-estimate* of the value of the life.

[10] Many object to the assignment of a number to the value of a life. To do so, however, makes it impossible to compare the costs and benefits of a policy decision. I abstract from this philosophical and moral issue.

In many Covid-19 cost/benefit studies, however, there is another more serious problem with how the VSL is used. Namely, it is often assumed that i) the VSL is independent of age, and ii) that the VSL is equal to around $10,000,000. Both of these claims are not true.[11]

Hammitt (pp. 10–12) surveys the literature on VSL estimates and shows that all studies reject the idea that the VSL is constant over the life-cycle. For example, one age based VSL estimate from Robinson, *et al.* (July 2020) is shown in Figure 2.

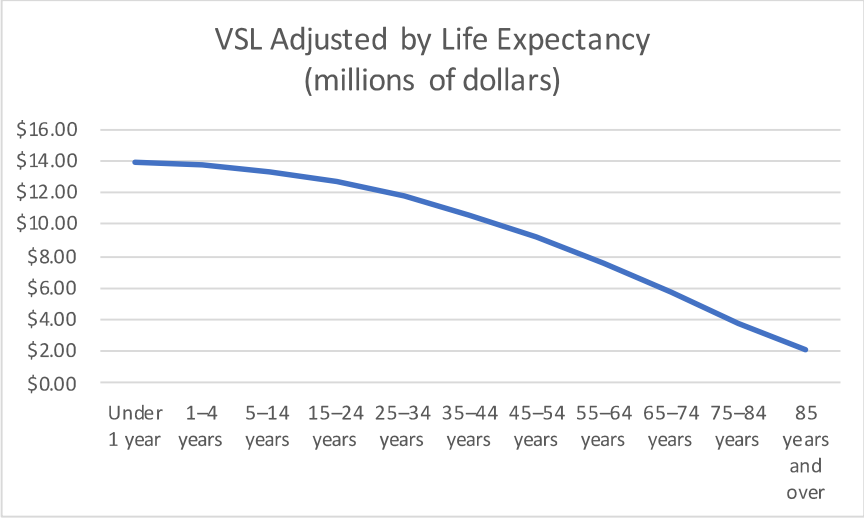


*Figure 3: Age Related Estimates of VSL*

To assume that the VSL is constant implies that individuals are indifferent between living one more day or eighty more years. Figure 3 shows more reasonable estimates, with the value of a child being seven times the value of an 85 year old. The VSL of $2,000,000 for an 85 year old is based on the assumption that life expectancy is still ten years. For someone who is 85, in poor health with multiple serious illnesses, the VSL would be much lower.[12]

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[11] See Hammitt (June, 2020) for an excellent discussion of the VLS and descriptions of how it varies with age.

[12] It has been understood for some time that those dying of Covid-19 have comorbidities. According to the March 17, 2021 CDC weekly update (https://www.cdc.gov/nchs/nvss/vsrr/covid_weekly/

Assuming a VSL of $10,000,000 creates a strong bias in the conclusion of many early cost/benefit studies. Since those over age sixty make up a minority of the population, but account for the vast majority of Covid-19 deaths, the use of a constant and large VSL leads to a vast over-estimate of the benefits of lockdown. To take the extreme case, if the ICL model estimate implies that 200,000 Canadians would die from Covid-19 without lockdown, and each life lost was worth $10,000,000, then the benefit of lockdown would be $1 trillion dollars. In 2018 Canada's GDP was just $2.1 trillion dollars. At this estimate of death and VSL, it would make sense to shut down (not just lockdown) 50% of the Canadian economy for an entire year.

## B. An Issue With Lockdown Costs

*Comparing Apples to Oranges*

One final theoretical issue needs to be dealt with before examining various cost/benefit studies. As noted, when considering the value of lockdown the VSL is used to determine the value of lives saved. The VSL is based on preferences, as it should be, and so the VSL is a dollar measure of the *utility* an individual receives from living. Most notably, the VSL is not a measure of how productive an individual is in terms of the dollar value of goods and services they produce. An infant is valuable, as is a retired senior citizen, but neither produces any marketed goods and services.

It is very common, in cost/benefit studies to simply use lost GDP as the measure for the cost of lockdown. That is, the reduction in the value of goods and services produced was attributed as the only cost of the lockdown. For example, Figure 4 shows Canada's GDP up to November 2020.[13] The estimated fall in GDP over

index.htm#ExcessDeaths) only 6% of Covid-19 deaths in the U.S. were attributed to Covid-19 alone. The average number of comorbidities of those who died was 3.8. Thus, even assigning a VSL of $2,000,000 for individuals with multiple comorbidities is too high.

[13] Taken from Stats Canada: https://www150.statcan.gc.ca/n1/daily-quotidien/210129/cg-a001-eng.htm.

the year is 5.1%, making it the worst year for economic growth since the great depression.

If 100% of the fall in GDP (approximately $107 billion) is attributed to the lockdown (that is, the virus directly had no effect on production), then compared to the trillion dollar savings in lives, the costs of lockdown are at most 10% of the value of the lives saved, and lockdown seems like a reasonable policy.

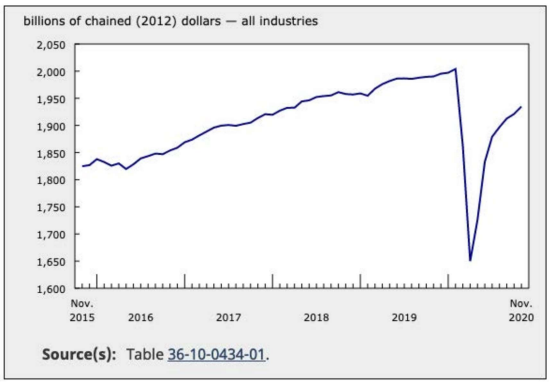


*Figure 4: Canada's GDP Up to November 2020*

This type of comparison, however, is entirely inappropriate. The VSL is based on the utility of life, and therefore, the costs of lockdown must also be based on the lost utility of lockdown. It has been understood from the very beginning of the pandemic that lockdown caused a broad range of costs through lost civil liberty, lost social contact, lost educational opportunities, lost medical preventions and procedures, increased domestic violence, increased anxiety and mental suffering, and increased deaths of despair. If the value of lockdown is measured in utility, then the costs of lockdown must be measured in the same fashion. Excluding the value of lost non-market goods (goods not measured by GDP) grossly under-estimates the cost of lockdown.

To point out the importance of the distinction, assume that instead of using the VSL to measure the value of a life, the gain (from fewer deaths) in GDP was used. If lockdown prevented the death of a 45 year old, fully employed person,

their market income could be used as a measure of their contribution to GDP. But the large majority of those who died of Covid-19 were retired, elderly, and sick.[14] The retired, elderly, and sick generally do not contribute to GDP. Hence, using a GDP only measure for a cost and benefit study would imply virtually no benefits to lockdowns and massive costs. This conclusion would be inappropriate, but it is still more appropriate than comparing utility based VSL estimates to lost GDP.

*Summary of Theoretical Issues*

Cost/Benefit studies are based on assumptions. These assumptions are often hidden in the mathematics of the theoretical or statistical model. I have pointed out four major sets of assumptions and their implications.

a. Models that use large (incorrect) values for the SIRS model parameters (e.g., $R_t$, IFR) over-estimate the counterfactual number of cases and deaths.

b. Models that assume human behavior is exogenous and independent of the virus over-estimate the counterfactual number of cases and deaths.

c. Studies that use an age independent VSL of $10,000,000 over-estimate the value of any lives saved.

d. Studies that use only lost GDP as a measure of the cost of lockdown under-estimate costs.

These four sets of assumptions bias the benefits of lockdown upwards and the costs of lockdown downwards. Below it is shown that all four of these assumptions were present in many of the earliest cost/benefit studies.

[14] As of March 2021, 95.9% of deaths were to individuals over age 60, and 69.1% of deaths were to individuals over 80. Source: https://health-infobase.canada.ca/covid-19/epidemiological-summary-covid-19-cases.html.

## C. Reviewing Lockdown Cost/Benefit Studies

*Early Theoretical Cost/Benefit Studies*

I direct my attention mostly to economic studies directly related to cost/benefit studies or issues related to estimating costs and benefits. I have examined, to various degrees, the relevant studies located on the NBER webpage, but I have also gone through the relevant studies at the Society for Benefit-Cost Analysis, and studies from various areas that received large amounts of attention.[15]

My general opinion of the earliest theoretical studies done in spring 2020 is that they were often based on assumptions that were either known, or turned out to be, incorrect, and which biased them to conclude that the benefits of lockdown exceeded the costs.[16] There were few empirical studies done in the earliest stages of the pandemic, but those that were done often relied on mechanical SIRS models for counterfactuals, and had very limited data to work with. At the very beginning of the pandemic "studies" were mostly casual, and used "back of the envelope" methods. Consider this conclusion from a March 23, 2020 article:[17]

> ... assume we save a million lives [by lockdown] and value everyone's life equally. In this case we've preserved $9 trillion in value, more than 40 percent of a year's GDP — before we try tallying all the health-care costs of an uncontrolled pandemic and

[15] The Society webpage is located at: https://www.benefitcostanalysis.org/covid-19_benefit_cost_analysis.php

[16] I ignore the issue of "homogeneity" in SIRS models (the idea that everyone in the model is the same) because most empirical work ignored it. However, this is another significant shortcoming of many models. Acemoglu *et al.*, as early as May 2020, produced a SIRS model where there were three different age cohorts, with age-increasing risks from Covid-19. Not too surprisingly, in such a model a uniform, blanket lockdown is not optimal. By June of 2020 models started appearing where individuals could differ in many characteristics like transmissibility, locations, ages, occupations, etc. Both Ellison (June 2020), and Akbarpour *et al.* (June 2020) showed that introducing heterogeneity resulted in herd immunity being reached much faster, and which raised the costs of blanket lockdowns.

[17] Source: https://www.nationalreview.com/corner/a-covid-cost-benefit-analysis/. Another article from March 31, 2020 (https://www.sciencemag.org/news/2020/03/modelers-weigh-value-lives-and-lockdown-costs-put-price-covid-19), assuming a constant value of life of $9.5M, and a loss of GDP caused by lockdown of 22%, argued that "even a yearlong lockdown makes economic sense."

> the suffering we avert among nonfatal cases. Starting with these numbers I suspect it would be very, very difficult to make the costs add up to more than the benefits. The other is to assume we save a million lives, but on average each person only had, say, a decade to live ... In this case we're preserving only $1.25 trillion. I still think the benefits will easily prevail ...

By the late spring academic articles were being produced that contained the same sentiments. Consider Thunstrom, *et al.* (May 2020) who concluded that:

> ... social distancing likely generates net social benefits. In our benchmark case, which we view as the most plausible case among those we examined, the present value of net benefits from social distancing amount to $5.16 trillion.

The Thunstrom, *et al.* article assumed that there was no private voluntary response to the virus, $R_t = 2.4$, the VSL=$10M, there was a fixed and unchanging hospital capacity, the IFR reached 1.5% at capacity, and costs only entailed a 6.2% fall in GDP. These assumptions generated $12.4T in the value of 1.24M lives saved, and $7.21T in lost GDP. As noted above, every one of these assumptions biased the model in favor of lockdown benefits and against lockdown costs.

To see how sensitive the Thunstrom, *et al.* conclusion is, consider making just one change: using the Robinson *et al.* age-dependent VSL numbers rather than the constant VSL of $10M. Now the 1.24M lives only have a value of $5.54T, and lockdown has a negative value of $-1.66T. One realistic change in assumptions flipped the cost/benefit conclusion.[18]

[18] Almost all of the early cost/benefits studies I found from the early spring suffered from the problems of using a standard SIRS model to estimate the counterfactual, constant and high VSL, high transmission and infection fatality rates, and costs based on GDP. These include Eichenbaum *et al.* (March, 2020), Bethune and Korinek (April 2020), Jones *et al.* (April, 2020), Baker *et al.* (April, 2020), Bloom *et al.* (March, 2020), Hall *et al.* (June, 2020), and Cutler and Summers (October, 2020). An interesting example is Rowthorn and Maciejowski (August 2020). Although it came out later in the summer, it still used a basic SIRS model in its cost/benefit analysis. What makes it interesting is that the authors recognized how critical the VSL number was. When a life is worth £2m, then only a lockdown of 5.3 weeks was justifiable. When the VSL is £10m it still only justified a 10 week lockdown.

*April–June: Early Challenging Results*

Many of the early theoretical studies received wide media attention, no doubt triggered by the exceptional claims made about deaths and costs. However, even in the early months of April and May challenges to the sudden conventional wisdom on both the theoretical and empirical front were common.

On April 27, 2020, three economists at the University of Chicago (Mulligan, Murphy, and Topel) published "Some basic economics of Covid-19 policy" in the Chicago Booth Review. The title is very informative. Understanding optimal policy goes back to recognizing that total benefits and costs must be compared (and comparable), and that efforts to increase benefits involve costs. They pointed out what was mentioned above: the VSL is not constant, nor is is appropriate to consider trading off "lives for GDP.":

> The VSL for very old individuals is lower because they have fewer years of remaining life to lose, and because they are in generally poorer health than younger people. The value of a statistical life is a powerful tool because it allows us to assess some fundamental trade-offs between health and other aspects of people's lives. It is critical to remember that the trade-off here is not between "lives" and GDP — it is the trade-off between two things that people themselves value: health and other aspects of their lives.

Mulligan *et al.* go on to note that it is improper to consider models in which the individuals do not respond to the presence of a virus: "The fact that individuals put great value on their own health and longevity means that there are strong individual incentives to engage in self-protection." They also note: i) that isolation and suppression of the disease delays the development of herd immunity, which ultimately is the way a society comes out of a pandemic; ii) that since a vaccine takes time to develop, approve, and deliver, the costs of lockdown must be projected out over the entire period; and iii) that policy must evolve with new information.

Mulligan *et al.* use an average VSL of $4.2M, and given their calculations, a one year lockdown *reduced* net wealth "even ignoring other long-run costs from

reduced values of human and physical capital and any intrinsic value of reduced civil liberties." They claimed that with the given knowledge of the time, "that broad lockdowns make the most sense when the level of infection is high. In the language of economists, the marginal product of mandatory social distancing is greatest when there are many infected individuals circulating." In other words, stay-at-home orders make little sense when the fraction of the population infected is less than 1% as it is in many places in Canada.

Other studies in the early spring provided better empirical evidence about the virus. Lewis *et al.* (April 2020) found that there was a 6.19% fall in quarter GDP growth, and that this was attributed to the response to the virus (ie. lockdowns were having negative market consequences). Coibion *et al.* (May 2020) found that average individual income losses over the first wave in the U.S. were between $5000 –$33,000. Ravindrn and Manisha (July 2020) was an early paper showing that jurisdictions with lockdown saw in increase in violence against women.

Very early on in the pandemic it was clear that the theoretical predictions based on the ICL and other basic SIRS models, in terms of numbers of cases and deaths, were wrong. There were a number of reasons for this, but one factor was the assumed infection fatality rate (IFR). The IFR is the fraction of those who become infected who die of Covid-19. It is a difficult number to calculate because the total number of infected individuals is not easily known. Levin *et al.* (July 2020) was one example of an early meta-analysis that brought together a number of smaller studies from around the world to estimate the IFR. They found that the IFR for Covid-19 was extremely age-specific. Children and younger adults have a very low IFR, and this increases with age, and dramatically increases after age 70. They estimated that at age 55 the IFR is 0.4%, but by age 85 it is 14%. Thus, although younger people were bearing the costs of reduced employment and education, any benefits of lockdown were had by much older cohorts.

The months of April–June also saw the first empirical studies on the effect lockdown had on case loads at the state level. Although most of the early studies

had found that lockdown reduced case loads, these results were mixed. Friedson *et al.* (April 2020) was an early study of shelter-in-place regulations, and found that in California this policy reduced cases by between 125–219 per 100,000 population, but each death delayed cost 400 jobs. Dhaval *et al.* (May 2020a) looked at a natural experiment in Texas where there was variation across the state in the timing of lockdowns. They found that urban lockdowns reduced cases by 19–26%, but that there was no overall effect at the state level. Lin and Meissner (May 2020), was one of the first empirical studies that showed that the lockdown effect was minimal and that lower workplace interactions invoked larger residential activity. They also found that common shocks across the U.S. had a larger effect than local lockdown shocks.[19]

Perhaps the most widely cited and influential early empirical paper on lockdown was Flaxman *et al.* (June 2020) that argued lockdowns saved 3 million lives in Europe, and which according to the *Nature* webpage has almost 350,000 online accesses as of March 2021.[20] This paper looked at lockdowns across 11 European countries in the spring of 2020. It infered transmission rates based on observed deaths, assumed homogeneity across the countries, and critically assumed that the reproduction number $R(t)$ only changed because of the immediate response to the mandated lockdown. They concluded that (p. 260):

> In our analysis, we find that only the effect of lockdown is identifiable, and that it has a substantial effect (81% (75–87%) reduction in $R_t$). Taking into account

[19] Other early studies showing that lockdown reduced cases include Born *et al.* (July 2020), Courtemanche *et al.* (July 2020), Dehning *et al.* (May 2020), and Hannah *et al.* (2020) and Dhaval *et al.* (May 2020b). Most of the early studies are based on modeling exercises, which again, depend critically on the model's counterfactual prediction. An exception was Banerjee and Nayak (June 2020) who looked at county level mobility data in the U.S. and did a difference-in-difference analysis between counties with and without lockdown. They found a positive effect of lockdown, but their data only spanned February 1 – March 31 2020, and over this period most of the states without mandated lockdowns had almost no infections. Hence there is a serious endogeneity problem with the cross-section analysis. That is, the lack of response is being attributed to the absence of lockdown, when it likely reflects the absence of the virus.

[20] Public Health Ontario provided an online synopsis of the paper on June 6, 2020 (https://www.publichealthontario.ca/-/media/documents/ncov/research/2020/06/research-nature-estimating- effects-of-non-pharmaceutical.pdf?la=en), but without any critical commentary.

country-specific effects, the effect size of lockdown remains large across all countries

The Flaxman *et al.* (June 2020) paper has received criticism on a number of fronts, and these include the fact that they assumed homogeneous populations, they lump vastly different country policies into single indicator variables, and they assumed exogenous human behavior.[21] Homburg and Kuhbandner (June 2020), focus on the fact that $R_t$, by definition within a fixed population, must decline over time as recovered individuals are no longer susceptible to infection. However, Flaxman *et al.* assumed that the reproduction number was fixed at $R_t = R_0$ up until the moment of lockdown, at which point it changed to a new fixed level. This forced the model to put all of the explanatory power on the lockdown indicator variable and grossly exaggerated the effect of lockdown. Homburg and Kuhbandner conclude that "... the results of Flaxman *et al.* are artifacts of an inappropriate model."[22]

Despite the modeling issues and structural econometric tricks, one other feature of Flaxman *et al.* needs to be highlighted: the problem of attributing the "total" effect on transmission to lockdown, and not breaking down the channels by which an effect might have happened. Flaxman *et al.* state that " Our parametric form of $R_t$ assumes that changes in $R_t$ are an immediate response to interventions rather than gradual changes in behaviour, ...". This means that the only interpretation possible for the empirical results is that lockdown mattered. Thus, even if the estimated effect was true, it raised the question: was it caused by the mandated lockdown or

[21] Even Flaxman *et al.* recognize the problem of exogenous behavior: "We do not account for changes in behaviour; in reality, even in the absence of government interventions we would expect $R_t$ to decrease and therefore would overestimate deaths in the no-intervention model."

[22] Lewis (June 2020), and Lemoine (December 2020) both write devastating critiques of the Flaxman *et al.* paper. In analyzing the Flaxman *et al.* supplementary material these two critiques also point out that the study's findings related to Sweden refute the study's conclusion.

voluntary individual reactions to the virus?[23]

*Four Stylized Facts About Covid-19*

In my opinion, the Atkeson *et al.* (August 2020) paper "Four Stylized Facts About Covid-19" was a watershed paper among those written on Covid-19 within the first six months of the pandemic. It discovered an important feature of the progression of the virus across countries that cast serious doubt that any forms of lockdown had a significant large impact on transmission and death rates. The paper used data from 23 countries and all U.S. states that had experienced at least 1000 cumulative deaths up to July 2020.

They found that across all of the jurisdictions there was an initial high variance in the daily death and transmission rates, but that this ended very rapidly. After 20–30 days of the 25$^{\text{th}}$ death the growth rate in deaths falls to close to zero, and the transmission rate hovers around one.[24] This is summarized in Figure 5 which reproduces their Figure 2 in it entirety.

The black line is the median posterior estimate of the relevant rate. Both graphs show the dramatic drop and stability of the death and transmission rates. This finding means that after 20 days the virus reached a steady state where each infected person transmits the virus to one other person, and the number of daily deaths from the virus became constant over time.

[23] Ibarra-Vega (August 2020) uses a similar approach where the counterfactual number of infections is determined by a SIRS model with exogenous behavior, and then shows that in such an imaginary model lockdowns are effective.

[24] Evidence that the virus was not exponentially out of control was available very early on. Harris (April 2020) shows that after one month the case load was flattening in NY.

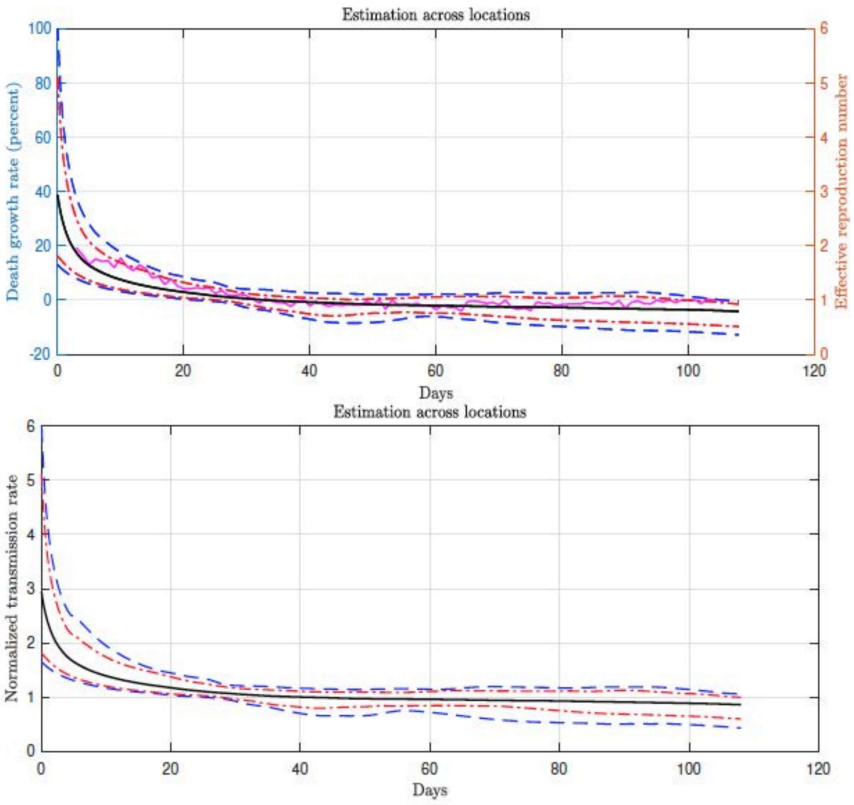


**Figure 2:** Location and sampling uncertainty. The black solid line in both charts represents the median posterior estimate. The solid magenta line in the top chart represents the median growth rate of 7-day smoothed daily deaths for all 50 locations and corresponds only to the left scale. The two dash-dotted bands in both charts contain two thirds of the posterior probability at each point in time and the two dashed bands, 0.90 of the posterior probability. The growth rates of death is estimated according to the fitted Weibull function. Effective reproduction numbers and normalized transmission rates are based on the SIR model. Day 0 is the earliest date when the cumulative death toll reached 25 in each location.

*Figure 5: Atkeson et al. Estimated Transmission and Death Rates*

The Atkeson *et al.* (August 2020) findings cast serious doubt on all of the early local, small sample, studies that found large effects of lockdown on cases and deaths.[25] Across all jurisdictions the progression of the virus was the same, despite wide ranging differences in the degree and type of lockdown. In their words:

> Our finding in Fact 1 that early declines in the transmission rate of COVID-19 were nearly universal worldwide suggest that the role of region-specific NPI's

[25] Barro (April 2020), showed early on in the pandemic that school closures, prohibitions on public gatherings, and isolation orders had no significant effect on overall mortality during the second wave of the great 1918–1919 pandemic.

> implemented in this early phase of the pandemic is likely overstated .... Our findings in Fact 2 and Fact 3 further raise doubt about the importance in NPI's (lockdown policies in particular) in accounting for the evolution of COVID-19 transmission rates over time and across locations. Many of the regions in our sample that instated lockdown policies early on in their local epidemic, removed them later on in our estimation period, or have have not relied on mandated NPI's much at all. Yet, effective reproduction numbers in all regions have continued to remain low relative to initial levels indicating that the removal of lockdown policies has had little effect on transmission rates.
>
> [pp. 15–16]

Atkeson *et al.* (August 2020) speculated on three reasons for their findings (reasons that were not unknown from previous research on pandemics). First, unlike the assumptions made in the SIRS models, individuals do not ignore risks, and when a virus enters a population people take mitigating or risky actions based on their own assessments of that risk.[26] Second, again in contrast to the classic SIRS model where individuals uniformly interact with each other, actual human networks are limited and this can limit the spread of the virus after a short period. Finally, like other pandemics, there may be natural forces associated with Covid-19 that explain the rapid move to a steady state death and transmission rate.

Any of these reasons suggest that the early findings of a correlation between lockdowns and cases may not have found a causal linkage. At best the early findings have to be considered with caution. As noted above, Atkeson (February 2021) continued pandemic modeling shows the critical importance of including seasonality, lockdown fatigue, and behavioral responses to the virus.

### *Voluntary versus Mandated Lockdown Channels*

As the summer and fall of 2020 progressed Covid-19 research continued as academics studied finer details based on new data and modeling refinements. Perhaps

[26] See Eksin *et al.* (2019) for a study of the effect of human behavior on the progression of disease. Adding behavioral responses to SIRS models in economics goes back at least to Philipson and Posner (1993). It is not a new idea. Dhaval *et al.* (July 2020) had shown early on that in the context of a large political rally local individuals recognized the increased risk of transmission and adjusted their behavior to mitigate this risk, leading to no change in transmission rates.

most significantly a number of papers found strong evidence that changes in human behavior significantly affected the progression of the virus, and that this channel was more important than mandated lockdowns for altering the number of cases, transmission rates, and deaths.

Bjørnskov (August 2020) exploited cross-country variation in European lockdown policy and found that (p. 7):

> Comparing weekly mortality in 24 European countries, the findings in this paper suggest that more severe lockdown policies have not been associated with lower mortality. In other words, the lockdowns have not worked as intended.

Eichenbaum *et al.* (October 2020) showed that elderly people in particular are more likely to reduce spending, time away from home, and the consumption of goods likely to involve high contact with other people. Hunt *et al.* (October 2020) exploited the variation in stay-at-home orders across the U.S. and found that lockdowns had only modest effects on Covid-19 transmission rates. Rather, they found that

> ...most social distancing is driven by voluntary responses. Moreover, we show that neither policy nor rates of voluntary social distancing explain a meaningful share of geographic variation. The most important predictors of which cities were hardest hit by the pandemic are exogenous characteristics such as population and density.

Large urban centers got hit harder by the virus, but consistent with the Atkeson *et al.* (August 2020) finding, the transmission rate of the virus depended on endogenous individual responses.[27]

Goolsbee, A., and C. Syverson (June 2020), using cellular phone location records, find that voluntary "self-lockdown" explains most of the enormous change in behavior in the spring, and that they "do not find evidence of large temporal or spatial shifting in response to shelter-in-place policies (p. 12).

[27] Gupta *et al.* (November 2020) survey the literature on social distancing and claim that mandates have an effect, but the volunteer response is larger.

There are, by my count, close to twenty studies that distinguish between voluntary and mandated lockdown effects. Although they vary in terms of data, locations, methods, and authors, all of them find that mandated lockdowns have only marginal effects and that voluntary changes in behavior explain large parts of the changes in cases, transmissions, and deaths. Consider the following quotes:

> This observational study, using a generalized phenomenological method based on official daily deaths records only, shows that *full lockdown policies of France, Italy, Spain and United Kingdom haven't had the expected effects in the evolution of theCOVID-19 epidemic.* Our results show a general decay trend in the growth rates and reproduction numbers two to three weeks before the full lockdown policies would be expected to have visible effects. Comparison of pre and post lockdown observations reveals a counter-intuitive slowdown in the decay of the epidemic after lockdown.
>
> [Meunier, p. 6, May 2020, emphasis added]

> Lockdowns are overall effective at curbing the spread of the disease and at reducing deaths (after about 30 days). *But the harsher is not the better: partial lockdowns are as effective as stricter ones,* but at a lower cost.
>
> [Bonardi *et al.*, June 2020, emphasis added]

> *We test and find wanting the popular notions that lockdowns with their attendant social distancing and various other NPIs confer protection.*
>
> [Nell, *et al.*, July 2020, emphasis added]

> ... our analysis shows that people voluntarily reduce their visits to workplace, retails, grocery stores, and limit their use of public transit when they receive information on a higher number of new cases and deaths. *This suggests that individuals make decisions to voluntarily limit their contact with others in response to greater transmission risks, leading to an important feedback mechanism that affects future cases and deaths.* Model simulations that ignore this voluntary behavioral response to information on transmission risks would over-predict the future number of cases and deaths.
>
> [Chernozhukov *et al.* p. 40, July 2020, emphasis added.[28]]

> Lockdowns are ineffective at reducing Covid-19 deaths. Variation amongst counties in the United States, where over one-fifth had no lockdown, shows no impact of lockdowns. Specifically,*one cannot reject the hypothesis of zero difference in deaths between lockdown and non-lockdown counties.*
>
> [Gibson, p. 8, November 2020]

[28] This paper also finds that lockdowns have a direct effect on cases and mortality.

These findings of the relative importance of voluntary responses relative to mandated lockdowns have continued to be confirmed.[29] An excellent study by Bendavid *et al.* (January 2021) that distinguished between strong and weak lockdown countries concluded:[30]

> In the framework of this analysis, *there is no evidence that more restrictive non-pharmaceutical interventions ('lockdowns') contributed substantially to bending the curve of new cases* in England, France, Germany, Iran, Italy, the Netherlands, Spain or the United States in early 2020. By comparing the effectiveness of NPIs on case growth rates in countries that implemented more restrictive measures with those that implemented less restrictive measures, the evidence points away from indicating that [more restrictive] NPIs provided additional meaningful benefit above and beyond [light restrictive] NPIs. While modest decreases in daily growth (under 30%) cannot be excluded in a few countries, the possibility of large decreases in daily growth due to [more restrictive] NPIs is incompatible with the accumulated data.
>
> emphasis added

*Unconditional Cross-Country Covid-19 Comparisons.*

One year after the pandemic started we now know the number of cumulative deaths that have been attributed to Covid-19.[31] We also know now that there

[29] Using a natural experiment methodology in Denmark, Kepp and Bjørnskov (January 2020) find that "efficient infection surveillance and voluntary compliance make full lockdowns unnecessary." A different type of study is Savaris *et al.* (March 2021) that uses mobility data to identify time spent at home, and looked at over 3700 pairwise jurisdictional comparisons, they found "... no evidence that the number of deaths/million is reduced by staying at home." Most notably, they were not studying lockdown stay-at-home orders, but actual stay-at-home behaviors.

[30] This paper received a number of critical letters and comments to the journal. The authors responded in Bendavid *et al.* (March 2021), showing that the criticisms were invalid. They conclude in their reply:

> Given their many uncontestable harms to health and society, we believe that the extant literature does not provide strong support for their [NPI] effectiveness at reducing case spread, and should be subjected to careful, critical and rigorous evaluation. If the benefits of such measures are negligible (or worse), their perpetuation may be, on balance, detrimental to the health of the public.
>
> p. 3

[31] Whether these deaths were actually caused by Covid-19 is an important matter, but one that I abstract from.

was wide ranging differences in the extent of lockdown intensity, and we know that jurisdictions with limited to no lockdowns did not systematically have death rates that exceeded hard lockdown jurisdictions. Not only did they not exceed, but often they had equal or better performance. Using the *OurWorldInData* stringency index (SI) as a measure of lockdown Pakistan (SI: 50), Finland (SI: 52), and Bulgaria (SI: 50) had similar degrees of lockdown, but the cumulative deaths per million were 61, 141, and 1023. Peru (SI: 83) and the U.K. (SI: 78) had some of the most stringent lockdowns, but also experienced some of the largest cumulative deaths per million: 1475 and 1847.[32] If lockdowns had the enormous beneficial effects many have claimed, then there should be an obvious correlation between deaths and lockdowns across country comparisons. In this section, I want to simply point out some remarkable cross country comparisons, and suggest that it is reasonable to explain them by the findings that lockdown only has (at best) a marginal impact on deaths.

Consider Figure 6 below, created using the *OurWorldInData* webpage application that compares the cumulative number of deaths between Europe and North America. North American cases are dominated by the United States, and during 2020 President Trump came under heavy fire for mishandling the pandemic. Still, despite having different policies across the two continents, after one year the number of Covid-19 deaths per million people is practically identical.

[32] Numbers as of March 28, 2021. https://ourworldindata.org/grapher/covid-stringency-index

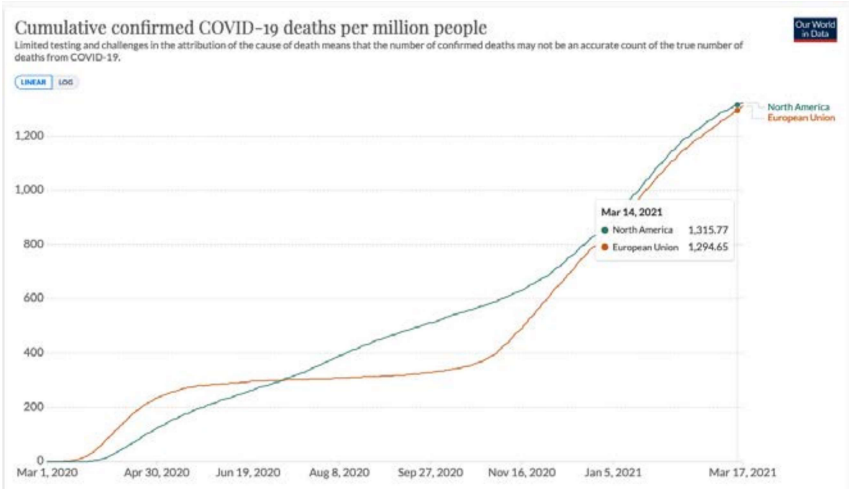


*Figure 6: Cumulative Deaths, North America v. European Union.*

Perhaps the identical result in Figure 6 is due to simple averaging; that is, on average the policies across the two continents were the same. Consider Figure 7 which contrasts Sweden, that had "light" restrictions to the European Union. As of March 16, 2021, the cumulative deaths per million in Sweden is the same as in the EU. This stands in sharp contrast to the dire predictions that were made about Sweden in the first six months of the pandemic.[33]

[33] Gardner, *et al.* (April 2020), using a standard SIRS model, claimed the following about Sweden: "This individual-based modelling project predicts that with the current mitigation approach approximately 96,000 deaths (95% CI 52,000 to 183,000) can be expected before 1 July, 2020." On March 16 2021 the total number of deaths in Sweden was just 13,228.

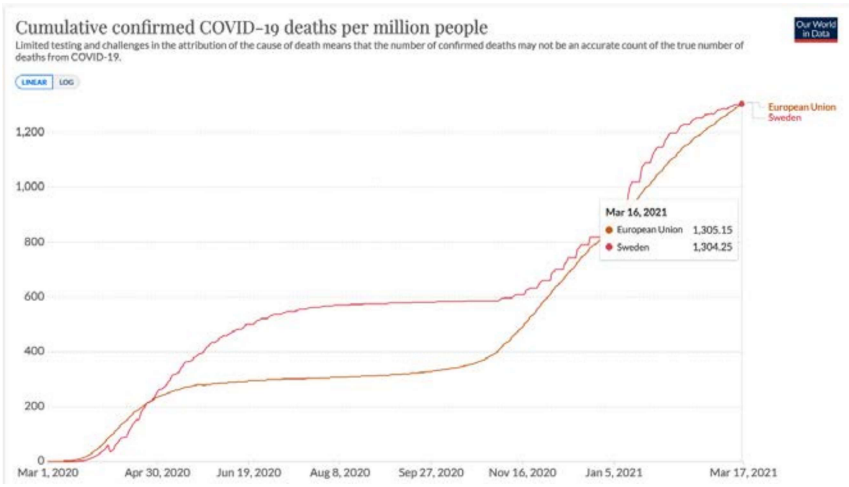


*Figure 7: Cumulative Deaths, Sweden v. European Union.*

Figure 8 looks at the daily Covid-19 deaths per million people between Sweden (light lockdown) and the UK (harsh lockdowns). The cumulative deaths per million were higher in the UK, but the figure shows that the general progression of deaths over the past year is very similar across the two countries.

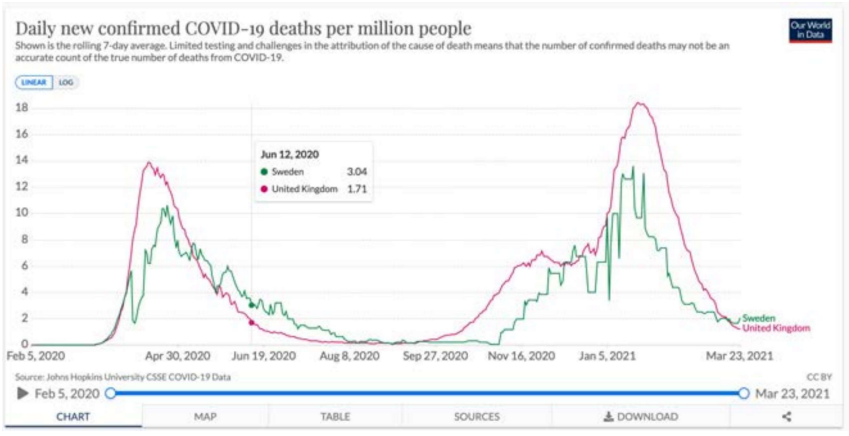


*Figure 8: Daily Deaths, Sweden v. United Kingdom.*

Different countries have obviously had different experiences with Covid-19; how-

ever, these differences are more related to country specific demographics than lockdown policy. Klein *et al.* (August 2020) pointed out 16 different factors for Sweden compared to other Nordic countries that explained their worse experience with the virus. The most important factor was the "dry tinder" situation; that is, Sweden had a light flu season in the year prior to Covid-19 which meant that it had a large number of elderly people who would have normally died in the previous year. The lower excess deaths in 2019 was then made up by the higher than average excess deaths in the spring of 2020. Overall, the excess deaths for Sweden in 2020 was just 1.5% higher than average.[34] This dry tinder effect accounted between 25–50% of the difference in death rates across the Nordic countries.

Using the CDC Data Tracker (https://covid.cdc.gov/covid-data-tracker/) similar graphs can be made comparing U.S. states. Florida and California were often compared because they are similar in terms of size and latitude, but had such different lockdown policies. Florida locked down in the spring but then started lifting restrictions, on September 25th all restrictions were lifted. California has had various mandates throughout 2020, but in early December issued stay-at-home order that remained in place until January 25th.[35] Figure 9 shows daily deaths per 100,000 in each state. The cumulative deaths per 100,000 people are practically indistinguishable: 152 for Florida and 143 for California. However, the relative experience in the second wave does not seem consistent with lockdowns having an effect. Unlocked Florida did better in the second wave than lockdown California.

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[34] Source: https://www.cebm.net/covid-19/excess-mortality-across-countries-in-2020/

[35] See John Hopkins Coronavirus Resource Center for lockdown information: https://coronavirus.jhu.edu/data/state-timeline/.

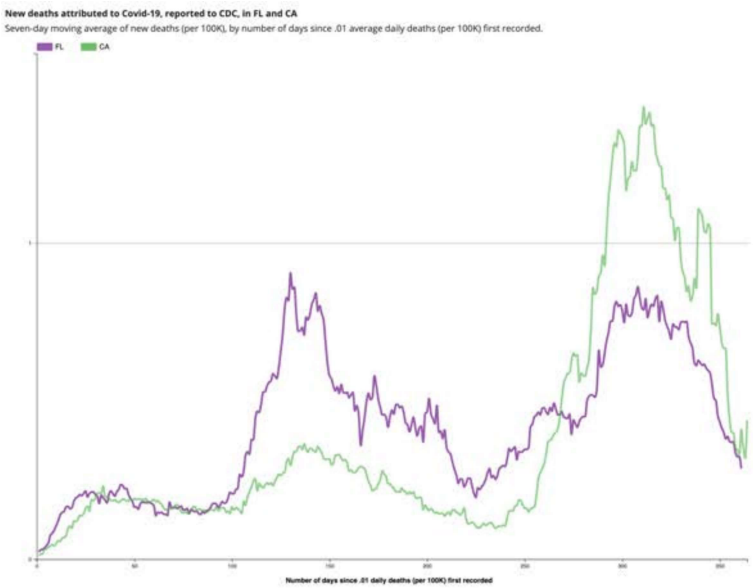


*Figure 9: Daily Deaths: California v. Florida*

Figure 10 shows one final case that has recently been covered widely in the news. Texas removed all lockdown restrictions on March 10, 2021. The reaction was overwhelmingly negative: the California Governor called it "absolutely reckless," Dr. Fauci said "It just is inexplicable why you would want to pull back now," and President Joe Biden said it was "a big mistake" and the result of "Neanderthal thinking." The red vertical line in Figure 10 shows the March 10th date. Cases and deaths have continued to fall since the removal of lockdown. This is not to say that the removal caused the fall, it only points to the fact that the simple view of lockdowns is wrong.

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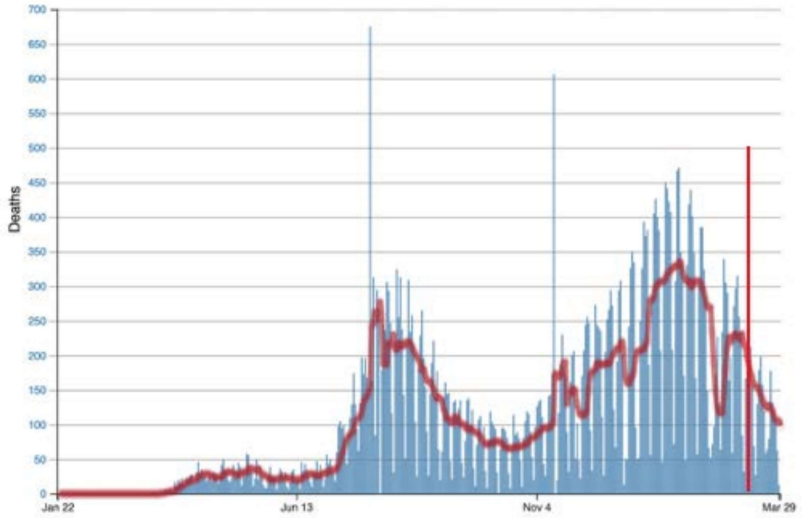


*Figure 10: Daily Deaths in Texas*

It is easy to find counter examples when using unconditional counts on deaths across different jurisdictions. That is, one can find cases where lockdown states had fewer deaths per million than some non-lockdown states (e.g., Ireland and Germany had high stringency indexes and below average deaths per million).

Table 2 provides a less *ad hoc* method of considering the relationship between cumulative deaths and lockdown. Table 2, uses information from *OurWorldInData*, and provides the coefficients and t-statistics from a simple OLS regression where the dependent variable is Cumulative Deaths per Million and the main regressor is the country's Stringency Index. The sample is all countries in North American and Europe (N=36) for which *OurWorldInData* reported data.

Column (1) is a simple one variable regression between cumulative deaths per million and the stringency index. It shows a small positive correlation that is not statistically significant. A one point increase in lockdown stringency is associated with 10.6 more deaths per million. Both the t-statistic and the F statistic show that this estimate is imprecise: there is too much noise to statistically claim a correlation.

Column (2) simply adds a dummy variable equal to 1 if the country is an island.

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Now the country index variable is slightly larger and statistically significant. There are about 45 stringency points from the least stringent country (Russia: 40.28) to the most stringent (Ireland: 84.26). Over this range, moving from the least to most stringent lockdown increases the cumulative deaths per million by 630 deaths. Contrary to the popular understanding, lockdown is not associated with fewer deaths per million, but more.

**Table 2: OLS Regression**
*Dependent Variable: Cumulative Deaths per Million*

| Variable | (1) | (2) |
|---|---|---|
| Country Index | 10.64 | 14.06 |
| | (1.59) | (2.51) |
| Island | | −932.58 |
| | | (−4.07) |
| Constant | 352.66 | 288.60 |
| | (0.80) | (0.79) |
| N | 36 | 36 |
| F | 2.53 | 10.14 |
| $R^2$ | 0.06 | 0.38 |

Table 2 only presents correlations, and it is *not* intended to substitute for the many sophisticated econometric papers that were reviewed above, and which exploited the timing and severity of lockdowns to infer or test a causal linkage. Table 2 is presented to point out that Figures 6–8 are not a matter of cherry-picking, and to drive home the point that if lockdowns had the effect that supporters claimed they had, it should show up in a simple cross country comparison.

The empirical work reviewed above provides the explanation for why lockdowns are not negatively correlated with cumulative deaths: voluntary actions, not mandated actions, account for a major portion of the evolution of the virus. Jurisdictions that locked down could never enforce the rules completely and so there was some non-compliance. Furthermore, there is some evidence that lockdown increased transmissions and deaths in inter-generational households. Jurisdictions that did

not lockdown still had many people (especially those at risk) change their behaviors to reduce risk. Liability law also likely induced many firms to enact "lockdown" like procedures at their outlets in non-lockdown jurisdictions to reduce liability risk. At the end of the day, it was close to a wash, and mandated lockdowns had little direct effect. Other differences in countries (how close they are to being an "island" in terms of border control, average income, relative humidity, age distributions, obesity, etc.) explain most differences in levels of infection and deaths.

The conclusion I draw from the research on actual outcomes over the past year is that at best lockdowns had some marginal effect on the reduction of cases, transmissions, and deaths. This means that the benefits of lockdown in terms of numbers of deaths is likely small. If these lives are valued at appropriate VSL numbers, the total benefits of lockdown are even smaller.

### D. The Costs of Lockdown

Research on the cost of lockdowns has lagged that of the benefits, and even still is very piecemeal. From the beginning it has been recognized that costs involved both the lost goods and services from shutting down economic activity and the lost utility from restricting individual freedoms. Over the course of the year the list of costly effects has increased, and the reach of lockdowns in terms of suffering has turned out to be nuanced and almost endless. Many of the costs will not be known for years as they work out in reduced graduation rates, reduced future earnings, and reduced long run health status. Here I provide a short list of some of the findings arrived at thus far.

Lockdowns that close non-essential businesses, supply chains, various service sector activities, must reduce the production of goods and services. Since these goods and services are valued, this loss is an obvious cost of lockdown. Measures of the GDP losses over the year abound. In Europe, Sweden had a $-7.4\%$ change in the second quarter of 2020, compared to $-13.9\%$ change for the EU in the

same time period (Eurostat, February 2021). As noted in Figure 4 above, Canada experienced about an 11% fall in the second quarter GDP, and overall GDP fell by 5.1% according to Stats Canada. If we used Sweden (which had GDP fall 2.8% over the year) as a lockdown counterfactual, then close to half of the fall in Canada's GDP could be attributed to lockdown.[36] This would amount to about $89 billion dollars attributed to the lockdown.[37]

The financial costs of lockdown are well known to not be evenly distributed. Figure 11 shows the twelve month percentage change in sales across three different Canadian industries.[38] The left figure shows that retail sales experienced a drop (30%) in the second quarter of 2020, but then mostly recovered. The middle graph shows that full-service dining sales dropped by 80% in the second quarter, but by the end of the year were still down 52%. The last figure on the right shows that international flights fell by an enormous 90% in the second quarter, and have not recovered over the year.

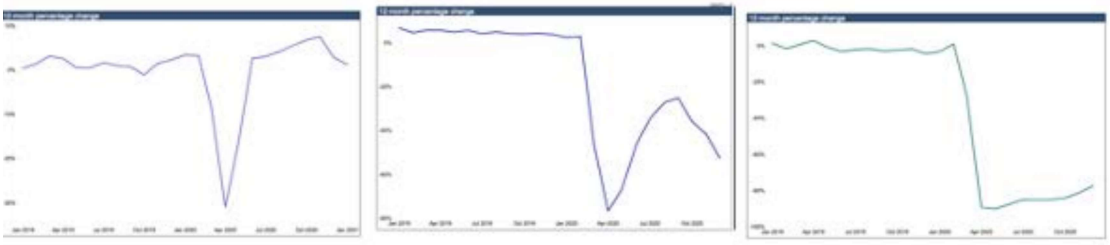

*Figure 11: 12 Month %Change in Retail, Dining, and Int. Air flight Sales.*

Other research over the past year has documented the various costs of lockdown that went beyond lost goods and services.

a. **Lost educational opportunities.** Lost, delayed, or poor education leads to reduced human capital that has life long negative consequences.[39] Not

[36] Sweden's GDP growth taken from: https://tradingeconomics.com/sweden/gdp-growth.

[37] Canada's GDP levels are from: https://tradingeconomics.com/canada/gdp.

[38] Data taken from Statistics Canada's economic dashboard: https://www150.statcan.gc.ca/n1/pub/71-607-x/71-607-x2020009-eng.htm.

[39] The role of education in the formation of human capital and its importance for individual

only has lockdown reduced educational opportunities for the young, the distribution of the effects is not equal. Bonal, X., and S. González (December 2020), find that children in low income families, with poor access to online resources, suffer more than others.

b. **Additional effects of school closures.**[40] Closing schools creates isolation for children, which is known to increase the risk of mental health conditions.[41] Agostinelli *et al.* (December 2020) showed that school closures hurt students from low income families more. Baron *et al.* (August 2020) reported that school closures inhibit the reporting of child abuse. Green *et al.* (December 2020), using Canadian data found that closing schools and having children learn from home meant that parents reduced labor force participation. Lewis, *et al.* (February 2021) provide an extensive list of literature on the harm school closures have had on children and conclude: "School closures have been implemented internationally with insufficient evidence for their role in minimising covid-19 transmission and insufficient consideration of the harms to children." [42]

c. **Increased deaths expected from unemployment.** Life expectancy is a function of wealth levels.[43] McIntyre and Lee (August 2020) predict between 418–2114 excess suicides in Canada based on increased unemployment

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wellbeing and economic growth is well established in economics. See Becker (1994) for a classic treatment.

[40] Although not a research study, a Unicef bulletin contains a long list of lockdown and school closures on children. These include: lost days of education (especially for early education), food insecurity, lost access to health care, increased stress, increased risk of abuse at home, poorer infant and maternity care, failure to receive regular vaccinations, and increased mental health issues. See https://downloads.unicef.org.uk/wp-content/uploads/2020/04/Unicef-UK-Children-In-Lockdown-Coronavirus-Impacts-Snapshot.pdf

[41] Loades *et al.* (November 2020) survey 80 studies related to isolation and children and conclude "... increased the risk of depression, and possibly anxiety at the time at which loneliness was measured...".

[42] For other effects of closing schools see also Fuchs-Schundeln *et al.* (September 2020), or Buonsenso *et al.* (December 2020).

[43] See Roelfs *et al.* (January 2011) and references that show this relationship has been understood for some time. Lindo (2011) also shows that unemployment contributes to higher infant death.

over the pandemic year. Bianchi *et al.* (December 2020), using time-series data on unemployment, life expectancy, and mortality, estimate the effect of Covid-19 unemployment shocks on future deaths. They find that for the U.S. over the next 15 years unemployment shocks caused by the lockdown reaction will increase deaths by 800,000. These deaths will disproportionately effect women and African-Americans. Since the authors do not distinguish between the effect of the pandemic and lockdowns, not all of the deaths can be attributed to lockdown. However, the link between lockdowns and unemployment is well established.

d. **Increased deaths from overdoses and other deaths of despair.** Lockdowns disrupt illegal drug channels, often resulting in a more contaminated drug supply. Lockdowns also increase human isolation, leading to increased depression and suicides.[44] As early has June 2020, Jia *et al.* reported substantial increases in depression, stress, and anxiety were linked to lockdown. Mulligan (December 2020) found that over the course of 2020 across the U.S. deaths of despair increased between 10–60%. Killgore *et al.* (November 2020) found that the number of people with thoughts of suicide in the U.S. states with lockdown increased with each passing month, but remained stable in states without lockdown.

e. **Increased domestic violence.** Chalfin *et al.* (March 2021) find that much of the increased domestic violence is related to increased alcohol which increased during lockdown.[45]

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[44] This channel has been known for some time. See Steptoe *et al.* (April 2013) and references, or Holt-Lunstad *et al.* (March 2015) showing that physical isolation and social loneliness increases mortality. The CDC reported in August 2020 (Czeisler *et al.* (August 2020) that there were elevated mental health conditions brought on by the pandemic, and Newlove-Delgado *et al.* (January 2021) found that lockdown contributed to increased mental health problems among U.K. youth and that this problem was most serious among young women.

[45] Awareness about the effect of lockdown on violence against women was available as early as March 2020 when the WHO released a statement: https://www.who.int/reproductivehealth/publications/emergencies/COVID-19-VAW-full-text.pdf. Binge drinking is strongly associated with stay at home orders (Weerakoon *et al.* (December 2020). )

f. **Lost non-Covid-19 medical service.** In the spring lockdown hospitals cancelled scheduled appointments for screenings and treatments (e.g., London *et al.* (July 2020)), this created fear among individuals who required emergence treatments and, ironically, although emergency calls for treatment often fell, things like deaths from Cardiac arrest increased (e.g., Holland *et al.* (August 2020)). Woolf *et al.* (July 2020)) estimate that in the U.S. about 1/3 of the excess deaths over 2020 are not Covid-19 deaths.

## III. An Alternative Cost/Benefit Methodology

To my knowledge, as of March 2021, no one has calculated the sum of Covid-19 lockdown losses into dollar costs, nor has there been any systematic attempt to determine the total lost quality of life brought about by lockdown. Therefore, economic arguments against lockdown have run along the lines that the benefits are negligible and the costs are obviously high.

Professor Bryan Caplan at George Mason University has proposed an interesting thought experiment that provides a solution for this issue.[46] Professor Caplan proposes the following question:

> Suppose you could either live a year of life in the COVID era, or X months under normal conditions. What's the value of X that makes the AVERAGE American indifferent?

Professor Caplan's thought experiment addresses the perceived costs of lockdown for each person living under it. For some this past year has been horrific. Perhaps they suffered violence or abuse that was fueled by frustration and alcohol while locked down during a long stay-at-home order. Or perhaps they lost a business, a major career opportunity, or struggled over a long period of unemployment. How many months of 2020 would these people have been willing to sacrifice to have

[46] See https://www.econlib.org/life-years-lost-the-quantity-and-the-quality/.

avoided the negative consequences of lockdown? Many might be willing to give up years, others several months.

On the other hand, for others who are older, professional, have no children at home, live in a large house with a garden, dislike travel, and have poorer health, lockdown might have given them comfort and been no inconvenience. These folks might sacrifice nothing to avoid lockdown.

The question is: how many months would be sacrificed on average? Professor Caplan argues that $X = 10$ months is a conservative estimate. That is, on average, two months would be sacrificed to have avoided lockdown. For the sake of argument, suppose this is the true number for the average Canadian.

As of March 2021 the pandemic has lasted one year. That means that the average Canadian has lost two months of normal life. The population of Canada is about 37.7 million people, which means that 6.3 million years of life have been lost due to lockdown.

The average age of reported Covid-19 deaths in Canada is about 80.[47] In Canada an average 80 year old has a life expectancy of 9.79 years.[48] This means that the 6.3 million years of lost life is equivalent to the deaths of 643,513 80 year olds.[49] As of March 22, 2021 Canada has had a total of 22,716 deaths due to Covid-19. That amounts to 222,389 lost years of life.

The question is, however, how many lost years of life would have resulted from Covid-19 deaths if there had been no lockdown? Consider two extremes:

a. Assume that the number of Covid-19 deaths would have been 10% higher had there been no lockdown. Then Canada would have experienced an additional 2,271 deaths, which means there would have been additional 22,333

[47] https://health-infobase.canada.ca/covid-19/epidemiological-summary-covid-19-cases.html

[48] https://knoema.com/atlas/Canada/topics/Demographics/Age/Life-expectancy-at-age-80-years

[49] The life expectancy of a 25 year old Canadian is 55.2 years, so the 6.3m lost life years is the equivalent of losing 114,130 25 year olds

years of lost life due to Covid-19 deaths. The benefit of lockdown, therefore, was the avoidance of this extra 22,333 years of lost life. However, the cost of lockdown, as noted, was 6,300,000 years of lost life. The cost/benefit ratio of lockdown is $282 = 6,300,000/22,333$.

b. Assume that the initial ICL model forecasts were correct and without a lockdown Canada would have experienced 200,000 deaths. This would mean that Canada's lockdown policies prevented $177,281 (200,000 - 22,716)$ deaths. Under the same age and life expectancy assumptions lockdown prevented the loss of 1,735,580 life years. The cost/benefit ratio of lockdown is $3.6 = 6,300.000/1,735,580$.

Case (b) is highly unrealistic and nothing close to this rate of death happened anywhere in the world. However, even in this extreme case, lockdown is a failure as a policy by cost/benefit standards.

The review of the literature suggests that Case (a) is closer to reality. If lockdown only had a marginal effect on deaths, then by cost/benefit standards, lockdown has been a public policy disaster.[50]

This analysis only considers the *number* of years of lost life. A proper cost/benefit analysis would consider the *value* of these lost years. As noted above, the value of life is not constant across age. Since the life years lost to Covid-19 deaths were mostly among those older than 60, and since the years of lost life because of lockdown have mostly been among the young, adjusting the the above cost/benefit ratios for the value of life will make lockdown an even worse policy.

[50] This thought experiment can be turned around. What would be the amount of the year the average Canadian would have to give up to make the costs of lockdown equal to the benefits? Under assumption (a) where lockdowns only save 2,271 lives, the average Canadian would have to give up approximately 6 hours of the year. Under assumption (b) where lockdown saved 200,000 lives, the average Canadian would have to give up 2.5 weeks of the year.

## IV. Conclusion

A review of the Covid-19 lockdown cost/benefit literature shows that the early cases made for lockdown rested on several unrealistic assumptions. These assumptions included that the virus continues to spread exponentially until herd immunity is reached, that individuals never change behavior in light of a viral threat, and that the value of lives lost is independent of age and around $10M.

Over the course of the last year research has revealed that simple SIRS models fail to predict the progression of the virus, that individual reactions to the virus are important, and that the costs of blanket lockdowns are far reaching and large. Lockdowns have some effect on cases, transmissions, and deaths, but these effects are marginal. As a result, lockdowns fail to pass a cost/benefit test.

One could argue that the Covid-19 lockdown policy was only wrong *ex post*. Hindsight is 20/20, and looking back is unfair. In March of 2020, faced with an unknown virus and expert advice that millions of people would die without lockdown and isolation, politicians and public health officials made the correct decision at the time.

Such an argument is reasonable for March of 2020, and even possibly for April 2020. However, as noted in the literature review, by late April it was already known that i) the empirical predictions of the SIRS based models were wrong, ii) that the models made a number of questionable assumptions, iii) that the deaths were highly skewed to the elderly, and iv) that the costs were large.

The progression of understanding about the virus has improved over time, but it has not fundamentally changed. By August there was enough information available to show that any reasonable cost/benefit analysis would show that lockdown was creating more harm than good. It is unreasonable to suggest that a proper decision could not have been made in the fall when the second wave of infections hit.

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# Review of the Emerging Evidence Demonstrating the Efficacy of Ivermectin in the Prophylaxis and Treatment of COVID-19

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**Background:** After COVID-19 emerged on U.S shores, providers began reviewing the emerging basic science, translational, and clinical data to identify potentially effective treatment options. In addition, a multitude of both novel and repurposed therapeutic agents were used empirically and studied within clinical trials.

**Areas of Uncertainty:** The majority of trialed agents have failed to provide reproducible, definitive proof of efficacy in reducing the mortality of COVID-19 with the exception of corticosteroids in moderate to severe disease. Recently, evidence has emerged that the oral antiparasitic agent ivermectin exhibits numerous antiviral and anti-inflammatory mechanisms with trial results reporting significant outcome benefits. Given some have not passed peer review, several expert groups including Unitaid/World Health Organization have undertaken a systematic global effort to contact all active trial investigators to rapidly gather the data needed to grade and perform meta-analyses.

**Data Sources:** Data were sourced from published peer-reviewed studies, manuscripts posted to preprint servers, expert meta-analyses, and numerous epidemiological analyses of regions with ivermectin distribution campaigns.

**Therapeutic Advances:** A large majority of randomized and observational controlled trials of ivermectin are reporting repeated, large magnitude improvements in clinical outcomes. Numerous prophylaxis trials demonstrate that regular ivermectin use leads to large reductions in transmission. Multiple, large "natural experiments" occurred in regions that initiated "ivermectin distribution" campaigns followed by tight, reproducible, temporally associated decreases in case counts and case fatality rates compared with nearby regions without such campaigns.

**Conclusions:** Meta-analyses based on 18 randomized controlled treatment trials of ivermectin in COVID-19 have found large, statistically significant reductions in mortality, time to clinical recovery, and time to viral clearance. Furthermore, results from numerous controlled prophylaxis trials report significantly

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*Off-Label Use: This manuscript includes discussion of off-label use in COVID-19 of the FDA-approved medication ivermectin.*

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reduced risks of contracting COVID-19 with the regular use of ivermectin. Finally, the many examples of ivermectin distribution campaigns leading to rapid population-wide decreases in morbidity and mortality indicate that an oral agent effective in all phases of COVID-19 has been identified.

*Keywords:* ivermectin, COVID-19, infectious disease, pulmonary infection, respiratory failure

# INTRODUCTION

In early 2020, on the onset of the spreading pandemic, many providers and institutions began to continuously review the rapidly emerging basic science, translational, and clinical data to identify potentially effective treatment options for COVID-19. Although there is now a small and increasing number of therapeutics showing some efficacy in important clinical outcomes, chief of which are corticosteroids in moderate to severe illness, the world continues to suffer from a worsening crisis with the potential of again overwhelming hospitals and intensive care units (ICU). As of February 21, 2020, the number of deaths attributed to COVID-19 in the United States reached 510,248 with more than 9.3 million active cases, the highest number to date. In addition, multiple European countries have imposed new rounds of restrictions and lockdowns.

Further compounding these alarming developments was a wave of recently published results from therapeutic randomized controlled trials conducted on medicines believed effective for COVID-19 that found a lack of impact on mortality in hospitalized patients with the use of remdesivir, hydroxychloroquine, lopinavir/ritonavir, interferon, convalescent plasma, and monoclonal antibody therapy.[1–4] One year into the pandemic, the only therapy considered "proven" as a life-saving treatment in COVID-19 is the use of corticosteroids in patients with moderate to severe illness.[5,6] Similarly, most concerning is the fact that no agent has yet proven effective in outpatients to prevent disease progression to prevent hospitalization.

More recently, trial results of ivermectin, a widely used antiparasitic medicine with known antiviral and anti-inflammatory properties, have been showing benefits in multiple important clinical and virologic outcomes, including mortality. Although growing numbers of the studies supporting this conclusion have passed through peer review, approximately half of the remaining trials data are from manuscripts uploaded to medical preprint servers, a now standard practice for both rapid dissemination and adoption of new therapeutics throughout the pandemic. Following is a comprehensive review of the available efficacy data as of December 12, 2020, taken from in vitro, animal, clinical, and real-world studies all showing the above impacts of ivermectin in COVID-19.

### History of ivermectin

In 1975, Professor Satoshi Omura at the Kitsato institute in Japan isolated an unusual *Streptomyces* bacterium from the soil near a golf course along the southeast coast of Honshu, Japan. Omura, along with William Campbell, found that the bacterial culture could cure mice infected with the roundworm *Heligmosomoides polygyrus*. Campbell isolated the active compounds from the bacterial culture, naming them "avermectins" and the bacterium *S. avermitilis* for the compounds' ability to clear mice of worms.[7] Despite decades of searching around the world, the Japanese microorganism remains the only source of avermectin ever found. Ivermectin, a derivative of avermectin, then proved revolutionary. Originally introduced as a veterinary drug, it soon made historic impacts in human health, improving the nutrition, general health, and well-being of billions of people worldwide ever since it was first used to treat onchocerciasis (river blindness) in humans in 1988. It proved ideal in many ways, given that it was highly effective, broad-spectrum, safe, well tolerated, and could be easily administered.[7] Although it was used to treat a variety of internal nematode infections, it was most known as the essential mainstay of 2 global disease elimination campaigns that has nearly eliminated the world of two of its most disfiguring and devastating diseases. The unprecedented partnership between Merck & Co. Inc, and the Kitasato Institute combined with the aid of international health care organizations has been recognized by many experts as one of the greatest medical accomplishments of the 20th century. One example was the decision by Merck & Co to donate ivermectin doses to support the Mectizan Donation Program that then provided more than 570 million treatments in its first 20 years alone.[8] Ivermectin's impacts in controlling onchocerciasis and lymphatic filariasis, diseases which blighted the lives of billions of the poor and disadvantaged throughout the tropics, is why its discoverers were awarded the Nobel Prize in Medicine in 2015 and the reason for its inclusion on the World Health Organization's (WHO) "List of Essential Medicines." Furthermore, it has also been used to successfully overcome several other human diseases and new uses for it are continually being found.[7]

### Preclinical studies of Ivermectin's activity against SARS-CoV-2

Since 2012, a growing number of cellular studies have demonstrated that ivermectin has antiviral properties against an increasing number of RNA viruses, including influenza, *Zika*, HIV, *Dengue*, and most importantly, SARS-CoV-2.[9–17] Insights into the mechanisms of action by which ivermectin both interferes with the entrance and replication of SARS-CoV-2 within human cells are mounting. Caly et al[18] first reported that ivermectin significantly inhibits SARS-CoV-2 replication in a cell culture model, observing the near absence of all viral material 48 hours after exposure to ivermectin. However, some questioned whether this observation is generalizable clinically given the inability to achieve similar tissue concentrations used in their experimental model using standard or even massive doses of ivermectin.[19,20] It should be noted that the concentrations required for an effect in cell culture models bear little resemblance to human physiology given the absence of an active immune system working synergistically with a therapeutic agent, such as ivermectin. Furthermore, prolonged durations of exposure to a drug likely would require a fraction of the dosing in short-term cell model exposure. Furthermore, multiple coexisting or alternate mechanisms of action likely explain the clinical effects observed, such as the competitive binding of ivermectin with the host receptor-binding region of SARS-CoV-2 spike protein, as proposed in 6 molecular modeling studies.[21–26] In 4 of the studies, ivermectin was identified as having the highest or among the highest of binding affinities to spike protein S1 binding domains of SARS-CoV-2 among hundreds of molecules collectively examined, with ivermectin not being the particular focus of study in 4 of these studies.[27] This is the same mechanism by which viral antibodies, in particular, those generated by the Pfizer and Moderna vaccines contain the SARS-CoV-2 virus. The high binding activity of ivermectin to the SARS-CoV-2 spike protein could limit binding to either the ACE-2 receptor or sialic acid receptors, respectively, either preventing cellular entry of the virus or preventing hemagglutination, a recently proposed pathologic mechanism in COVID-19.[21,22,26–28] Ivermectin has also been shown to bind to or interfere with multiple essential structural and nonstructural proteins required by the virus to replicate.[26,29] Finally, ivermectin also binds to the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), thereby inhibiting viral replication.[30]

Arevalo et al investigated in a murine model infected with a type 2 family RNA coronavirus similar to SARS-CoV-2, (mouse hepatitis virus), the response to 500 μg/kg of ivermectin versus placebo.[31] The study included 40 infected mice, with 20 treated with ivermectin, 20 with phosphate-buffered saline, and then 16 uninfected control mice that were also given phosphate-buffered saline. At day 5, all the mice were killed to obtain tissues for examination and viral load assessment. The 20 nonivermectin-treated infected mice all showed severe hepatocellular necrosis surrounded by a severe lymphoplasmacytic inflammatory infiltration associated with a high hepatic viral load (52,158), whereas in the ivermectin-treated mice a much lower viral load was measured (23,192; $P < 0.05$), with only few livers in the ivermectin-treated mice showing histopathological damage such that the differences between the livers from the uninfected control mice were not statistically significant.

Dias De Melo et al[32] recently posted the results of a study they did with golden hamsters that were intranasally inoculated with SARS-CoV-2 virus, and at the time of the infection, the animals also received a single subcutaneous injection of ivermectin at a dose of 0.4 mg/kg on day 1. Control animals received only the physiologic solution. They found the following among the ivermectin-treated hamsters: a dramatic reduction in anosmia (33.3% vs. 83.3%, $P = 0.03$), which was also sex dependent in that the male hamsters exhibited a reduction in clinical score while the treated female hamsters failed to show any sign of anosmia. They also found significant reductions in cytokine concentrations in the nasal turbinates and lungs of the treated animals, despite the lack of apparent differences in viral titers.

Despite these mounting insights into the existing and potential mechanisms of action of ivermectin both as a prophylactic and treatment agent, it must be emphasized that significant research gaps remain and that many further in vitro and animal studies should be undertaken to better define not only these mechanisms but also to further support ivermectin's role as a prophylactic agent, especially in the optimal dose and frequency required.

### Preclinical studies of ivermectin's anti-inflammatory properties

Given that little viral replication occurs in the later phases of COVID-19, nor can virus be cultured, and only in a minority of autopsies can viral cytopathic changes be found,[33–35] the most likely pathophysiologic mechanism is that identified by Li et al[36] where they showed that the nonviable RNA fragments of SARS-CoV-2 lead to a high mortality and morbidity in COVID-19 through the provocation of an overwhelming and injurious inflammatory response. Based on these insights and the clinical benefits of ivermectin in the late phase of disease to be reviewed below, it seems that the increasingly well-described in vitro properties of ivermectin as an inhibitor of inflammation are far more clinically potent than previously recognized. The growing list of studies demonstrating the anti-inflammatory properties of ivermectin include its

ability to inhibit cytokine production after lipopolysaccharide exposure, downregulate transcription of NF-kB, and limit the production of both nitric oxide and prostaglandin $E_2$.[37–39]

### Exposure prophylaxis studies of ivermectin's ability to prevent transmission of COVID-19

Data are also now available showing large and statistically significant decreases in the transmission of COVID-19 among human subjects based on data from 3 randomized controlled trials (RCTs) and 5 observational controlled trials (OCTs) with 4 of the 8 (2 of them RCTs) published in peer-reviewed journals.[40–46]

Elgazzar and colleagues[45] at Benha University in Egypt randomized 200 health care and household contacts of patients with COVID-19 where the intervention group consisted of 100 patients given a high dose of 0.4 mg/kg on day 1 and a second dose on day 7 in addition to wearing personal protective equipment, whereas the control group of 100 contacts wore personal protective equipment alone. They reported a large and statistically significant reduction in contacts testing positive by Reverse Transcriptase Polymerase Chain Reaction (PCR) when treated with ivermectin versus controls, 2% versus 10%, $P < 0.05$.

Shouman conducted an RCT at Zagazig University in Egypt, including 340 (228 treated and 112 control) family members of patients positive for SARS-CoV-2 through PCR.[44] Ivermectin (approximately 0.25 mg/kg) was administered twice, on the day of the positive test and 72 hours later. After a two-week follow-up, a large and statistically significant decrease in COVID-19 symptoms among household members treated with ivermectin was found, 7.4% versus 58.4%, $P < 0.001$.

Recently, Alam et al from Bangladesh performed a prospective observational study of 118 patients who were evenly split into those who volunteered for either the treatment or control arms, described as a persuasive approach. Although this method, along with the study being unblinded, likely led to confounders, the difference between the 2 groups was so large (6.7% vs. 73.3%, $P < 0.001$) and similar to the other prophylaxis trial results that confounders alone are unlikely to explain such a result.[47] Carvallo et al also performed a prospective observational trial where they gave healthy volunteers ivermectin and carrageenan daily for 28 days and matched them to similarly healthy controls who did not take the medicines.[40] Of the 229 study subjects, 131 were treated with 0.2 mg of ivermectin drops taken by mouth 5 times per day. After 28 days, none of those receiving ivermectin in the prophylaxis group had tested positive for SARS-COV-2 versus 11.2% of patients in the control arm ($P < 0.001$). In a much larger follow-up prospective, observational controlled trial by the same group that included 1195 health care workers, they found that over a 3-month period there were no infections recorded among the 788 workers who took weekly ivermectin prophylaxis, whereas 58% of the 407 controls had become ill with COVID-19. This study demonstrates that remarkable protection against transmission can be achieved among high-risk health care workers by taking 12 mg once weekly.[40] The Carvallo IVERCAR protocol was also separately tested in a prospective RCT by the Health Ministry of Tucuman, Argentina, where they found that among 234 health care workers, the intervention group that took 12 mg once weekly, only 3.4% contracted COVID-19 versus 21.4% of controls, $P < .0001$.[46]

The need for weekly dosing in the Carvallo study over a 4-month period may not have been necessary given that, in a recent RCT from Dhaka, Bangladesh, the intervention group (n = 58) took 12 mg once monthly for a similar 4-month period and also reported a large and statistically significant decrease in infections compared with controls, 6.9% versus 73.3%, $P < 0.05$.[47] Then, in a large retrospective observational case–control study from India, Behera et al[41] reported that among 186 case–control pairs (n = 372) of health care workers, they identified 169 participants who had taken some form of prophylaxis, with 115 participants that had taken ivermectin. After matched pair analysis, they reported that in the workers who had taken 2 dose ivermectin prophylaxis, the odds ratio for contracting COVID-19 was markedly decreased (0.27, 95% confidence interval (CI) 0.15–0.51). Notably, one dose prophylaxis was not found to be protective in this study. Based on both their study finding and the Egyptian prophylaxis study, the All India Institute of Medical Sciences instituted a prophylaxis protocol for their health care workers where they now take two 0.3 mg/kg doses of ivermectin 72 hours apart and repeat the dose monthly.

Data that further illuminates the potential protective role of ivermectin against COVID-19 come from a study of nursing home residents in France which reported that in a facility that suffered a scabies outbreak where all 69 residents and 52 staff were treated with ivermectin,[41] they found that during the period surrounding this event, 7 of the 69 residents fell ill with COVID-19 (10.1%). In this group with an average age of 90 years, only one resident required oxygen support and no resident died. In a matched control group of residents from surrounding facilities, they found 22.6% of residents fell ill and 4.9% died.

Further evidence supporting the efficacy of ivermectin as a prophylaxis agent was published recently in the *International Journal of Antimicrobial agents* where a group of researchers analyzed data using the prophylactic chemotherapy databank administered by the WHO along with case counts obtained by Worldometers, a public data

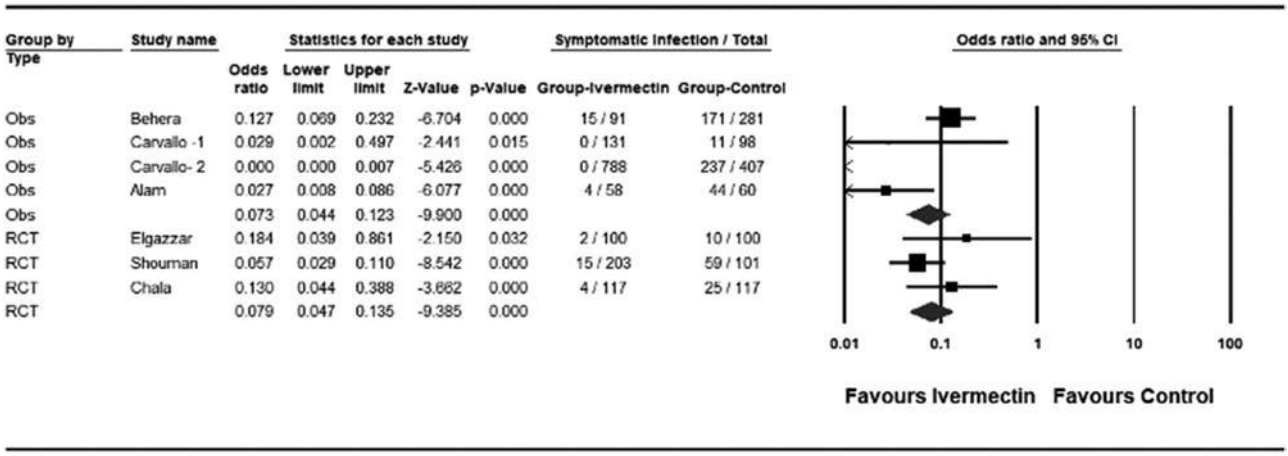


**FIGURE 1.** Meta-analysis of ivermectin prophylaxis trials in COVID-19. OBS, observational study; RCT, randomized controlled trial. Symbols: Squares: Indicate treatment effect of an individual study. Large diamond: Reflect summary of study design immediately above. Size of each symbol correlates with the size of the confidence interval around the point estimate of treatment effect with larger sizes indicating a more precise confidence interval.

aggregation site used by among others, the Johns Hopkins University.[42] When they compared the data from countries with active ivermectin mass drug administration programs for the prevention of parasite infections, they discovered that the COVID-19 case counts were significantly lower in the countries with recently active programs, to a high degree of statistical significance, $P < 0.001$.

Figure 1 presents a meta-analysis performed by the study authors of the controlled ivermectin prophylaxis trials in COVID-19.

Further data supporting a role of ivermectin in decreasing transmission rates can be found from South American countries where, in retrospect, large "natural experiments" seem to have occurred. For instance, beginning as early as May, various regional health ministries and governmental authorities within Peru, Brazil, and Paraguay initiated "ivermectin distribution" campaigns to their citizen populations.[48] In one such example from Brazil, the cities of Itajai, Macapa, and Natal distributed massive amounts of ivermectin doses to their city's population, where in the case of Natal, 1 million doses were distributed. The distribution campaign of Itajai began in mid-July, in Natal they began on June 30th, and in Macapa, the capital city of Amapa and others nearby, they incorporated ivermectin into their treatment protocols in late May after they were particularly hard hit in April. The data in Table 1 were obtained from the official Brazilian government site and the national press consortium and show large decreases in case counts in the 3 cities soon after distribution began compared with their neighboring cities without such campaigns.

The decreases in case counts among the 3 Brazilian cities given in Table 1 were also associated with reduced mortality rates as summarized in Table 2.

## Clinical studies on the efficacy of ivermectin in treating mildly ill outpatients

Currently, 7 trials that include a total of more than 3000 patients with mild outpatient illness have been completed, a set composed of 7 RCTs and 4 case series.[49–60]

**Table 1.** Comparison of case count decreases among Brazilian cities with and without ivermectin distribution campaigns.

| Region | New cases | June | July | August | Population 2020 (1000) | % Decline in new cases between June and August 2020 |
|---|---|---|---|---|---|---|
| South | **Itajaí** | **2123** | **2854** | **998** | **223** | **−53%** |
| | Chapecó | 1760 | 1754 | 1405 | 224 | −20% |
| North | **Macapá** | **7966** | **2481** | **2370** | **503** | **−70%** |
| | Ananindeua | 1520 | 1521 | 1014 | 535 | −30% |
| North East | **Natal** | **9009** | **7554** | **1590** | **890** | **−82%** |
| | João Pessoa | 9437 | 7963 | 5384 | 817 | −43% |

Bolded cities distributed ivermectin, neighboring regional city below did not.

**Table 2.** Change in death rates among neighboring regions in Brazil.

| Region | State | % Change in average deaths/week compared with 2 weeks before |
|---|---|---|
| South | **Santa Catarina** | **–36%** |
| | PARANÁ | –3% |
| | Rio Grande do Sul | –5% |
| North | **Amapá** | **–75%** |
| | AMAZONAS | –42% |
| | Pará | +13% |
| North East | **Rio Grande do Norte** | **–65%** |
| | CEARÁ | +62% |
| | Paraíba | –30% |

Bolded regions contained a major city that distributed ivermectin to its citizens, the other regions did not.

The largest, a double-blinded RCT by Mahmud[49] was conducted in Dhaka, Bangladesh, and targeted 400 patients with 363 patients completing the study. In this study, as in many other of the clinical studies to be reviewed, either a tetracycline (doxycycline) or macrolide antibiotic (azithromycin) was included as part of the treatment. The importance of including antibiotics such as doxycycline or azithromycin is unclear; however, both tetracycline and macrolide antibiotics have recognized anti-inflammatory, immunomodulatory, and even antiviral effects (58–61). Although the posted data from this study does not specify the amount of mildly ill outpatients versus hospitalized patients treated, important clinical outcomes were profoundly affected, with increased rates of early improvement (60.7% vs. 44.4% $P < 0.03$) and decreased rates of clinical deterioration (8.7% vs. 17.8%, $P < 0.02$). Given that mildly ill outpatients mainly comprised the study cohort, only 2 deaths were observed (both in the control group).

Ravikirti performed a double-blinded RCT of 115 patients, and although the primary outcome of PCR positivity on day 6 was no different, the secondary outcome of mortality was 0% versus 6.9%, $P = .019$.[60] Babalola in Nigeria also performed a double-blinded RCT of 62 patients, and in contrast to Ravikirti, they found a significant difference in viral clearance between both the low-dose and high-dose treatment groups and controls in a dose dependent fashion, $P = .006$.[59]

Another RCT by Hashim et al[53] in Baghdad, Iraq, included 140 patients equally divided; the control group received standard care, and the treated group included a combination of both outpatient and hospitalized patients. In the 96 patients with mild-to-moderate outpatient illness, they treated 48 patients with a combination of ivermectin/doxycycline and standard of care and compared outcomes with the 48 patients treated with standard of care alone. The standard of care in this trial included medicines such as dexamethasone 6 mg/d or methylprednisolone 40 mg twice per day if needed, vitamin C 1000 mg twice/day, zinc 75–125 mg/d, vitamin D3 5000 IU/day, azithromycin 250 mg/d for 5 days, and acetaminophen 500 mg as needed. Although no patients in either group progressed or died, the time to recovery was significantly shorter in the ivermectin-treated group (6.3 days vs. 13.7 days, $P < 0.0001$).

Chaccour et al conducted a small, double-blinded RCT in Spain where they randomized 24 patients to ivermectin versus placebo, and although they found no difference in PCR positivity at day 7, they did find statistically significant decreases in viral loads, patient days of anosmia (76 vs. 158, $P < 0.05$), and patient days with cough (68 vs. 98, $P < 0.05$).[57]

Another RCT of ivermectin treatment in 116 outpatients was performed by Chowdhury et al in Bangladesh where they compared a group of 60 patients treated with the combination of ivermectin/doxycycline to a group of 60 patients treated with hydroxychloroquine/doxycycline with a primary outcome of time to negative PCR.[54] Although they found no difference in this outcome, in the treatment group, the time to symptomatic recovery approached statistical significance (5.9 days vs. 7.0 days, $P = 0.07$). In another smaller RCT of 62 patients by Podder et al, they also found a shorter time to symptomatic recovery that approached statistical significance (10.1 days vs. 11.5 days, $P > 0.05$, 95% CI, 0.86–3.67).[55]

A medical group in the Dominican Republic reported a case series of 2688 consecutive symptomatic outpatients seeking treatment in the emergency department, most whom were diagnosed using a clinical algorithm. The patients were treated with a high-dose ivermectin of 0.4 mg/kg for one dose along with 5 days of azithromycin. Remarkably, only 16 of the 2688 patients (0.59%) required subsequent hospitalization with only a single death recorded.[61]

In another case series of 100 patients in Bangladesh, all treated with a combination of 0.2 mg/kg ivermectin and doxycycline, they found that no patient required hospitalization nor died, and all patients' symptoms improved within 72 hours.[62]

A case series from Argentina reported on a combination protocol that used ivermectin, aspirin, dexamethasone, and enoxaparin. In the 135 mild illness patients, all survived.[50] Similarly, a case series from Mexico of 28 consecutively treated patients with ivermectin, all were reported to have recovered with an average time to full recovery of only 3.6 days.[58]

### Clinical studies of the efficacy of ivermectin in hospitalized patients

Studies of ivermectin among more severely ill hospitalized patients include 6 RCTs, 5 OCTs, and a database analysis study.[45,51–53,63–70]

The largest RCT in hospitalized patients was performed concurrent with the prophylaxis study reviewed above by Elgazzar et al.[45] Four hundred patients were randomized among 4 treatment groups of 100 patients each. Groups 1 and 2 included mild/moderate illness patients alone, with group 1 treated with one dose 0.4 mg/kg ivermectin plus standard of care (SOC) and group 2 received hydroxychloroquine 400 mg twice on day 1 then 200 mg twice daily for 5 days plus standard of care. There was a statistically significant lower rate of progression in the ivermectin-treated group (1% vs. 22%, $P < 0.001$), with no deaths and 4 deaths, respectively. Groups 3 and 4 included only severely ill patients, with group 3 again treated with a single dose of 0.4 mg/kg plus SOC, whereas group 4 received hydroxychloroquine plus SOC. In this severely ill subgroup, the differences in outcomes were even larger, with lower rates of progression 4% versus 30% and mortality 2% versus 20% ($P < 0.001$).

The one largely outpatient RCT conducted by Hashim reviewed above also included 22 hospitalized patients in each group. In the ivermectin/doxycycline-treated group, there were 11 severely ill patients and 11 critically ill patients, whereas in the standard of care group, only severely ill patients (n = 22) were included because of their ethical concerns of including critically ill patients in the control group (*45*). This decision led to a marked imbalance in the severity of illness between these hospitalized patient groups. However, despite the mismatched severity of illness between groups and the small number of patients included, beneficial differences in outcomes were seen, but not all reached statistical significance. For instance, there was a large reduction in the rate of progression of illness (9% vs. 31.8%, $P = 0.15$) and, most importantly, there was a large difference in mortality among the severely ill groups that reached a borderline statistical significance (0% vs. 27.3%, $P = 0.052$). Another important finding was the relatively low mortality rate of 18% found among the subset of critically ill patients, all of whom were treated with ivermectin.

A recent RCT from Iran found a dramatic reduction in mortality with ivermectin use.[65] Among multiple ivermectin treatment arms (different ivermectin dosing strategies were used in the intervention arms), the average mortality was reported as 3.3%, whereas the average mortality within the standard care and placebo arms was 18.8%, with an odds ratio (OR) of 0.18 (95% CI 0.06–0.55, $P < 0.05$).

Spoorthi[64] and Sasanak performed a prospective trial of 100 hospitalized patients whereby they treated 50 with ivermectin and doxycycline, whereas the 50 controls were given a placebo consisting of vitamin B6. Although no deaths were reported in either group, the ivermectin treatment group had a statistically significant shorter hospital length of stay (LOS) 3.7 days versus 4.7 days, $P = 0.03$, and shorter time to complete resolution of symptoms, 6.7 days versus 7.9 days, $P = 0.01$.

The largest OCT (n = 280) in hospitalized patients was conducted by Rajter et al at Broward Health Hospitals in Florida and was recently published in the major medical journal *Chest* (*43*). They performed a retrospective OCT using a propensity-matched design on 280 consecutive treated patients and compared those treated with ivermectin to those without. One hundred seventy-three patients were treated with ivermectin (160 received a single dose and 13 received a second dose at day 7) while 107 were not.[63] In both unmatched and propensity-matched cohort comparisons, similar, large, and statistically significant lower mortality was found among ivermectin-treated patients (15.0% vs. 25.2%, $P = 0.03$). Furthermore, in the subgroup of patients with severe pulmonary involvement, mortality was profoundly reduced when treated with ivermectin (38.8% vs. 80.7%, $P = 0.001$).

Another large OCT in Bangladesh compared 115 patients treated with ivermectin to a standard care cohort consisting of 133 patients.[51] Despite a significantly higher proportion of patients in the ivermectin group being men (ie, with well-described, lower survival rates in COVID), the groups were otherwise well matched, yet the mortality decrease was statistically significant (0.9% vs. 6.8%, $P < 0.05$). The largest OCT is a study from Brazil, published as a letter to the editor and included almost 1500 patients.[66] Although the primary data were not provided, they reported that in 704 hospitalized patients treated with a single dose of 0.15 mg/kg ivermectin, compared with 704 controls, overall mortality was reduced (1.4% vs. 8.5%, HR 0.2, 95% CI 0.12–0.37, $P < 0.0001$). Similarly, in the patients on mechanical ventilation, mortality was also reduced (1.3% vs. 7.3%). A small study from Baghdad, Iraq, compared 16 ivermectin-treated patients with 71

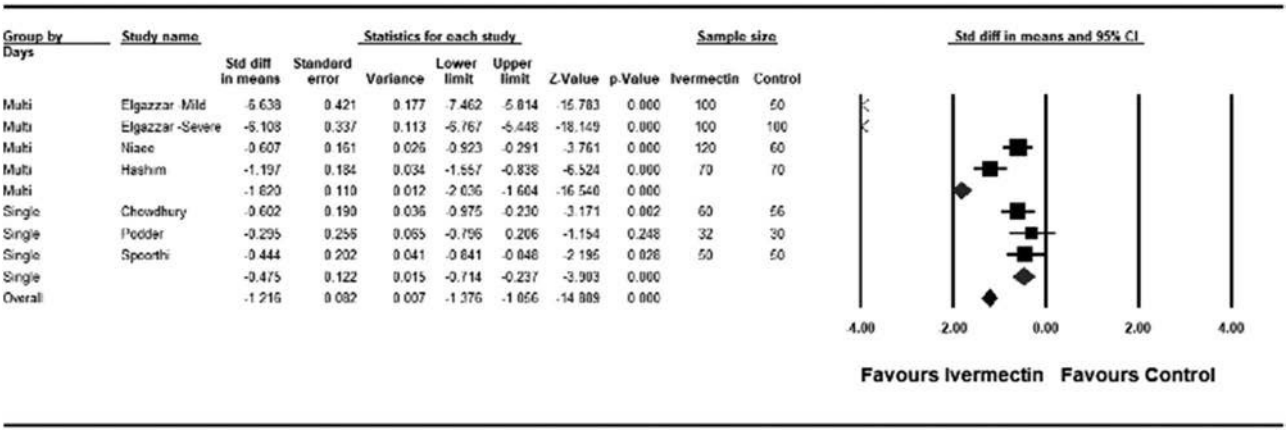


**FIGURE 2.** Meta-analysis of the outcome of time to clinical recovery from controlled trials of ivermectin treatment in COVID-19. OBS, observational study; RCT, randomized controlled trial. Symbols: Squares: Indicate treatment effect of an individual study. Large diamond: Reflect summary of study design immediately above. Small diamond: Sum effect of all trial designs. Size of each symbol correlates with the size of the confidence interval around the point estimate of treatment effect with larger sizes indicating a more precise confidence interval.

controls.[52] This study also reported a significant reduction in length of hospital stay (7.6 days vs. 13.2 days, $P < 0.001$) in the ivermectin group. In a study reporting on the first 1000 patients treated in a hospital in India, they found that in the 34 patients treated with ivermectin alone, all recovered and were discharged, whereas in more than 900 patients treated with other agents, there was an overall mortality of 11.1%.[70]

Meta-analyses of the above controlled treatment trials were performed by the study authors focused on the 2 important clinical outcomes: time to clinical recovery and mortality (Figures 2 and 3). The consistent and reproducible signals leading to large overall statistically significant benefits from within both study designs are remarkable, especially given that in several of the studies treatment was initiated late in the disease course.

Details of the prophylaxis, early, and late treatment trials of ivermectin in COVID-19 can be found in Table 3.

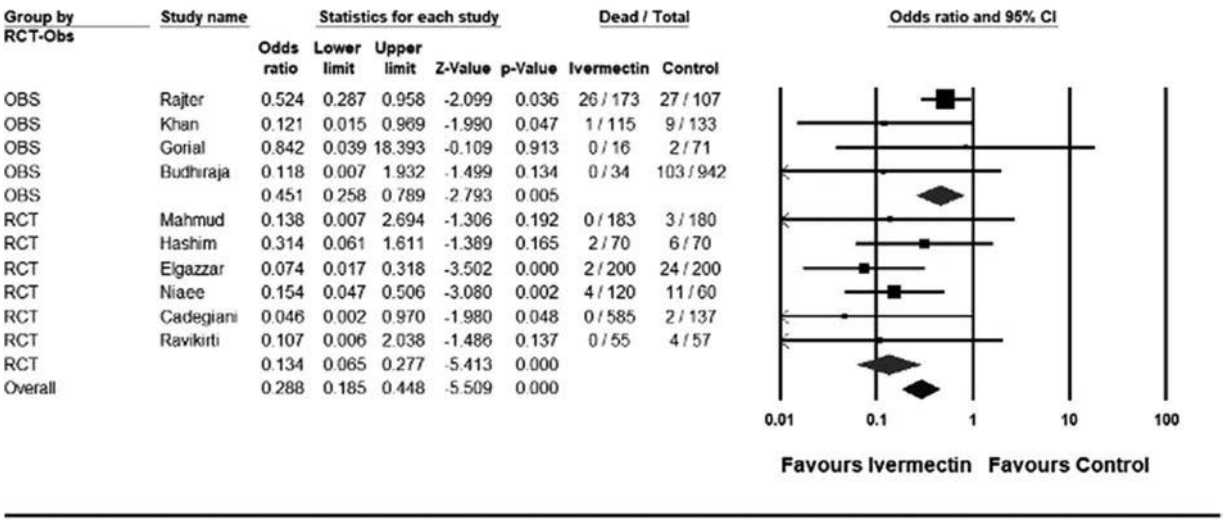


**FIGURE 3.** Meta-analysis of the outcome of mortality from controlled trials of ivermectin treatment in COVID-19. OBS, observational study; RCT, randomized controlled trial. Symbols: Squares: Indicate treatment effect of an individual study. Large diamond: Reflect summary of study design immediately above. Small diamond: Sum effect of all trial designs. Size of each symbol correlates with the size of the confidence interval around the point estimate of treatment effect with larger sizes indicating a more precise confidence interval.

**Table 3.** Clinical studies assessing the efficacy of ivermectin in the prophylaxis and treatment of COVID-19.

| Prophylaxis Trials Author, Country, source | Study design, size | Study subjects | Ivermectin dose | Dose frequency | Clinical outcomes reported |
|---|---|---|---|---|---|
| Prophylaxis trials | | | | | |
| Shouman W, Egypt<br>*www.clinicaltrials.gov*<br>NCT04422561 | RCT<br>N = 340 | Household members of pts with +COVID-19 PCR test | 40–60 kg: 15 mg, 60–80 kg: 18 mg, and > 80 kg: 24 mg | Two doses, 72 hours apart | 7.4% versus 58.4% developed COVID-19 symptoms, $P < 0.001$ |
| Elgazzar A, Egypt<br>ResearchSquare<br>doi.org/10.21203/rs.3.rs-100956/v1 | RCT<br>N = 200 | Health care and household contacts of pts with +COVID-19 PCR test | 0.4 mg/kg | Two doses, day 1 and day 7 | 2% versus 10% tested positive for COVID-19 $P < 0.05$ |
| Chala R, Argentina<br>NCT04701710<br>*Clinicaltrials.gov* | RCT<br>N = 234 | Health care workers | 12 mg | Every 7 d | 3.4% versus 21.4%, $P = 0.0001$. |
| Carvallo H, Argentina<br>*Journal of Biochemical Research and Investigation*<br>doi.org/10.31546/2633–8653.1007 | OCT<br>N = 229 | Healthy patients negative for COVID-19 PCR test | 0.2 mg drops | 1 drop 5 times a d x 28 d | 0.0% versus 11.2% contracted COVID-19 $P < 0.001$ |
| Alam MT, Bangladesh<br>*European J Med Hlth Sciences*<br>10.24018/ejmed.2020.2.6.599 | OCT<br>N = 118 | Health care workers | 12 mg | Monthly | 6.9% versus 73.3%, $P < 0.05$ |
| Carvallo H, Argentina<br>*Journal of Biochemical Research and Investigation*<br>doi.org/10.31546/2633–8653.1007 | OCT<br>N = 1195 | Health care workers | 12 mg | Once weekly for up to 10 wk | 0.0% of the 788 workers taking ivermectin versus 58% of the 407 controls contracted COVID-19. |
| Behera P, India<br>*medRxiv*<br>doi.org/10.1101/2020.10.29.20222661 | OCT<br>N = 186 case control pairs | Health care workers | 0.3 mg/kg | Day 1 and day 4 | 2 doses reduced odds of contracting COVID-19 (OR 0.27 95% CI 0.16–0.53) |
| Bernigaud C, France<br>*Annales de Dermatologie et de Venereologi*<br>doi.org/10.1016/j.annder.2020.09.231 | OCT<br>N = 69 case control pairs | Nursing home residents | 0.2 mg/kg | Once | 10.1% versus 22.6% residents contracted COVID-19 0.0% versus 4.9% mortality |
| Hellwig M, USA<br>*J Antimicrobial Agents*<br>doi.org/10.1016/j.ijantimicag.2020.106,248 | OCT<br>N = 52 countries | Countries with and without IVM prophylaxis programs | Unknown | Variable | Significantly lower-case incidence of COVID-19 in African countries with IVM prophylaxis programs $P < 0.001$ |

**Clinical trials–Outpatients**

| Prophylaxis Trials Author, Country, source | Study design, size | Study subjects | Ivermectin dose | Dose frequency | % Ivermectin versus % Controls Clinical outcomes reported |
|---|---|---|---|---|---|
| Mahmud R, Bangladesh *www.clinicaltrials.gov* NCT0452383 | DB-RCT N = 363 | Outpatients and hospitalized | 12 mg + doxycycline | Once, within 3 days of PCR+ test | Early improvement 60.7% versus 44.4%, $P < 0.03$, deterioration 8.7% versus 17.8%, $P < 0.02$ |
| Chowdhury A, Bangladesh *Research Square* doi.org/10.21203/rs.3.rs-38896/v1 | RCT N = 116 | Outpatients | 0.2 mg//kg + doxycycline | Once | Recovery time 5.9 versus 9.3 days ($P = 0.07$) |
| Ravikirti, India *medRxiv* doi.org/10.1101/2021.01.05.21249310 | DB-RCT N = 115 | Mild–moderate illness | 12 mg | Daily for 2 d | No diff in day 6 PCR + 0% versus 6.9% mortality, $P = 0.019$ |
| Babalola OE, Nigeria medRxiv doi.org/10.1101/2021.01.05.21249131 | DB-RCT N = 62 | Mild–moderate illness | 6 mg and 12 mg | Every 48 hours × 2 wk | Time to viral clearance: 4.6 days high dose versus 6.0 days low dose versus 9.1 days control ($P = 0.006$) |
| Podder CS, Bangladesh *IMC J Med Sci 2020;14(2)* | RCT N = 62 | Outpatients | 0.2 mg/kg | Once | Recovery time 10.1 versus 11.5 days (NS), average time 5.3 versus 6.3 (NS) |
| Chaccour C. Spain *Research Square* doi.org/10.21203/rs.3.rs-116547/v1 | DB-RCT N = 24 | Outpatients | 0.4 mg/kg | Once | No diff in PCR+ day 7, lower viral load d 4 and 7, ($P < 0.05$), 76 versus 158 pts. d of anosmia ($P < 0.05$), 68 versus 98 pts. d of cough ($P < 0.05$) |
| Morgenstern J, Dominican Republic *medRxiv* doi.org/10.1101/2020.10.29.20222505 | Case series N = 3099 | Outpatients and hospitalized | Outpatients: 0.4 mg/kg hospital patients: 0.3 mg/kg | Outpatients: 0.3 mg/kg × 1 dose Inpatients: 0.3 mg/kg, days 1,2,6, and 7 | Mortality = 0.03% in 2688 outpatients, 1% in 300 non-ICU hospital patients, and 30.6% in 111 ICU patients |
| Carvallo H, Argentina *medRxiv* doi.org/10.1101/2020.09.10.20191619 | Case series N = 167 | Outpatients and hospitalized | 24 mg = mild, 36 mg = moderate, and 48 mg = severe | Days 0 and 7 | All 135 with mild illness survived, 1/32 (3.1% of hospitalized) patients died |
| Alam A, Banglades *J of Bangladesh College Phys and Surg*, 2020; 38:10-15 doi.org/10.3329/jbcps.v38i0.47512 | Case series N = 100 | Outpatients | 0.2 mg/kg/kg + doxycycline | Once | All improved within 72 h |

(*Continued on next page*)

**Table 3.** (*Continued*) Clinical studies assessing the efficacy of ivermectin in the prophylaxis and treatment of COVID-19.

| **Clinical trials–Outpatients** | | | | | % Ivermectin versus % Controls |
|---|---|---|---|---|---|
| Prophylaxis Trials Author, Country, source | Study design, size | Study subjects | Ivermectin dose | Dose frequency | Clinical outcomes reported |
| Espatia-Hernandez G, Mexico *Biomedical Research* www.biomedres.info/biomedi..-proof-of-concept-study-14435.html | Case series N = 28 | Outpatients | 6 mg | Days 1,2, 7, and 8 | All pts recovered average recovery time 3.6 d |

| **Clinical trials–Hospitalized patients** | | | | | % Ivermectin versus % Controls |
|---|---|---|---|---|---|
| Prophylaxis Trials Author, Country, source | Study design, size | Study subjects | Ivermectin dose | Dose frequency | Clinical outcomes reported |
| Elgazzar A, Egypt ResearchSquare doi.org/10.21203/rs.3.rs-100956/v1 | OL-RCT N = 400 | Hospitalized patients | 0.4 mg/kg | Daily for 4 days | Moderately ill: worsened 1% versus 22%, $P<0.001$. Severely ill: worsened 4% versus 30% mortality 2% versus 20% both with $P < 0.001$ |
| Niaee S. M, Research Square doi.org/10.21203/rs.3.rs-109670/v1 | DB-RCT N = 180 | Hospitalized patients | 0.2, 0.3, and 0.4 mg/kg (3 dosing strategies) | Once versus Days 1,3,5 | Mortality 3.3% versus 18.3%. OR 0.18, (0.06–0.55, $P < 0.05$) |
| Hashim H, Iraq medRxiv doi.org/10.1101/2020.10.26.20219345 | SB-RCT N=140 | 2/3 outpatients and 1/3 hospital pts | 0.2 mg/kg + doxycycline | Daily for 2–3 d | Recovery time 6.3 versus 13.6 days ($P<0.001$), 0% versus 27.3% mortality in severely ill ($P = 0.052$) |
| Spoorthi S, India AIAM, 2020; 7(10):177-182 | PCT N = 100 | Hospitalized patients | 0.2 mg/kg+ doxycycline | Once | Shorter hospital LOS, 3.7 versus 4.7 days, $P = 0.03$, faster resolution of symptoms, 6.7 versus 7.9 days, $P = 0.01$ |
| Ahmed S. Dhaka, Bangladesh International journal of Infectious disease doi.org/10.1016/j.ijid.2020.11.191 | DB-RCT N = 72 | Hospitalized patients | 12 mg | Daily for 5 d | Faster viral clearance 9.7 versus 12.7 days, $P = 0.02$ |
| Chachar AZK, Pakistan Int J Sciences doi.org/10.18483/ijSci.2378 | DB-RCT N = 50 | Hospitalized patients-mild | 12 mg | Two doses day 1 and one dose day 2 | 64% versus 60% asymptomatic by day 7 |
| Portman-Baracco A, Brazil | OCT | | 0.15 mg/kg | Once | |

(*Continued on next page*)

**Table 3.** (*Continued*) Clinical studies assessing the efficacy of ivermectin in the prophylaxis and treatment of COVID-19.

| **Clinical trials–Hospitalized patients** | | | | | % Ivermectin versus % Controls |
|---|---|---|---|---|---|
| Prophylaxis Trials Author, Country, source | Study design, size | Study subjects | Ivermectin dose | Dose frequency | Clinical outcomes reported |
| Arch Bronconeumol. 2020 doi.org/10.1016/j.arbres.2020.06.011 | N = 1408 | Hospitalized patients | | | Overall mortality 1.4% versus 8.5%, HR 0.2, 95% CI 0.12–0.37, $P < 0.0001$ |
| Rajter JC, Florida Chest 2020 doi.org/10.1016/j.chest.2020.10.009 | OCT N=280 | Hospitalized patients | 0.2 mg/kg + azithromycin | Day 1 and day 7 if needed | Overall mortality 15.0% versus 25.2%, $P = 0.03$, severe illness mortality 38.8% versus 80.7%, $P = 0.001$ |
| Khan X, Bangladesh Arch Bronconeumol. 2020 doi.org/10.1016/j.arbres.2020.08.007 | OCT N = 248 | Hospitalized patients | 12 mg | Once on admission | Mortality 0.9% versus 6.8%, $P <$ 0.05, LOS 9 versus 15 days, $P < 0.001$ |
| Gorial FI, Iraq medRxiv doi.org/10.1101/2020.07.07.20145979 | OCT N = 87 | Hospitalized patients | 0.2 mg/kg + HCQ and azithromycin | Once on admission | LOS 7.6 versus 13.2 days, $P <$ 0.001, 0/15 versus 2/71 died |
| Budiraja S. India medRxiv doi.org/10.1101/2020.11.16.20232223 | OCT N = 1000 IVM=34 | Hospitalized patients | n/a | n/a | 100% IVM pts recovered 11.1% mortality in non-IVM-treated pts |

DB-RCT, double-blinded randomized controlled trial; HCQ, hydroxychloroquine; IVM, ivermectin; LOS, length of stay; NS, nonstatistically significant, $P > .05$; OCT, observational controlled trial; OL, open label; PCR, polymerase chain reaction; RCT, randomized controlled trial; SB-RCT, single blinded randomized controlled trial.

### Ivermectin in post-COVID-19 syndrome

Increasing reports of persistent, vexing, and even disabling symptoms after recovery from acute COVID-19 have been reported and that many have termed the condition as "Long COVID" and patients as "long haulers," estimated to occur in approximately 10%–30% of cases.[71–73] Generally considered as a postviral syndrome consisting of a chronic and sometimes disabling constellation of symptoms which include, in order, fatigue, shortness of breath, joint pains, and chest pain. Many patients describe their most disabling symptom as impaired memory and concentration, often with extreme fatigue, described as "brain fog," and is highly suggestive of the condition myalgic encephalomyelitis/chronic fatigue syndrome, a condition well reported to begin after viral infections, in particular with Epstein–Barr virus. Although no specific treatments have been identified for Long COVID, a recent manuscript by Aguirre-Chang et al from the National University of San Marcos in Peru reported on their experience with ivermectin in such patients.[74] They treated 33 patients who were between 4 and 12 weeks from the onset of symptoms with escalating doses of ivermectin; 0.2 mg/kg for 2 days if mild and 0.4 mg/kg for 2 days if moderate, with doses extended if symptoms persisted. They found that in 87.9% of the patients, resolution of all symptoms was observed after 2 doses with an additional 7% reporting complete resolution after additional doses. Their experience suggests the need for controlled studies to better test efficacy in this vexing syndrome.

### Epidemiological data showing impacts of widespread ivermectin use on population case counts and case fatality rates

Similar to the individual cities in Brazil that measured large decreases in case counts soon after distributing ivermectin in comparison to neighboring cities without such campaigns, in Peru, the government approved the use of ivermectin by decree on May 8, 2020, solely based on the in vitro study by Caly et al from Australia.[48] Soon after, multiple state health ministries initiated ivermectin distribution campaigns in an effort to decrease what was at that time some of the highest COVID-19 morbidity and mortality rates in the world. Juan Chamie,[48] a data analyst and member of the FLCCC Alliance, recently posted an article based on 2 critical sets of data that he compiled and compared; first, he identified the timing and magnitude of each region's ivermectin interventions through a review of official communications, press releases, and the Peruvian Situation Room database to confirm the dates of effective delivery, and second, he extracted data on the total all-cause deaths from the region along with COVID-19 case counts in selected age groups over time from the registry of the National Computer System of Deaths (SINADEF) and from the National Institute of Statistics and Informatics.[48] It should be noted that he restricted his analyses to only those citizens older than 60 years to avoid the confounding of rises in the numbers of infected younger patients. With these data, he was then able to compare the timing of major decreases in this age group of both total COVID-19 cases and total excess deaths per 1000,000 people among 8 states in Peru with the initiation dates of their respective ivermectin distribution campaigns as shown in Figure 4.

Figure 5 from the same study presents data on the case fatality rates in patients older than 60 years, again among the 8 states in Peru. Note the dramatically decreased case fatality rates among older patients diagnosed with COVID-19 after ivermectin became widely distributed in those areas, a result which cannot be explained by changes in mask-wearing or lock-downs.

In an even more telling example, Chamie compared the case counts and fatality rates of the 8 states above with the city of Lima, where ivermectin was not distributed nor widely used in treatment during the same period. Figure 6 compares the lack of significant or sustained reductions in case counts or fatalities in Lima with the dramatic reductions in both outcomes among the 8 states with widespread ivermectin distribution.

Another example can be seen from the data compiled from Paraguay, again by Chamie who noted that the government of the state of Alto Parana had launched an ivermectin distribution campaign in early September. Although the campaign was officially described as a "deworming" program, this was interpreted as a guise by the regions' governor to avoid reprimand or conflict with the National Ministry of Health that recommended against the use of ivermectin to treat COVID-19 in Paraguay. The program began with a distribution of 30,000 boxes of ivermectin, and by October 15, the governor declared that there were very few cases left in the state as can be seen in Figure 7.

### The evidence base for ivermectin against COVID-19

To date, the efficacy of ivermectin in COVID-19 has been supported by the following:

1. Since 2012, multiple in vitro studies have demonstrated that Ivermectin inhibits the replication of many viruses, including influenza, *Zika, Dengue*, and others.[9–17]
2. Ivermectin inhibits SARS-CoV-2 replication and binding to host tissue through several observed and proposed mechanisms.[18]
3. Ivermectin has potent anti-inflammatory properties with in vitro data demonstrating profound

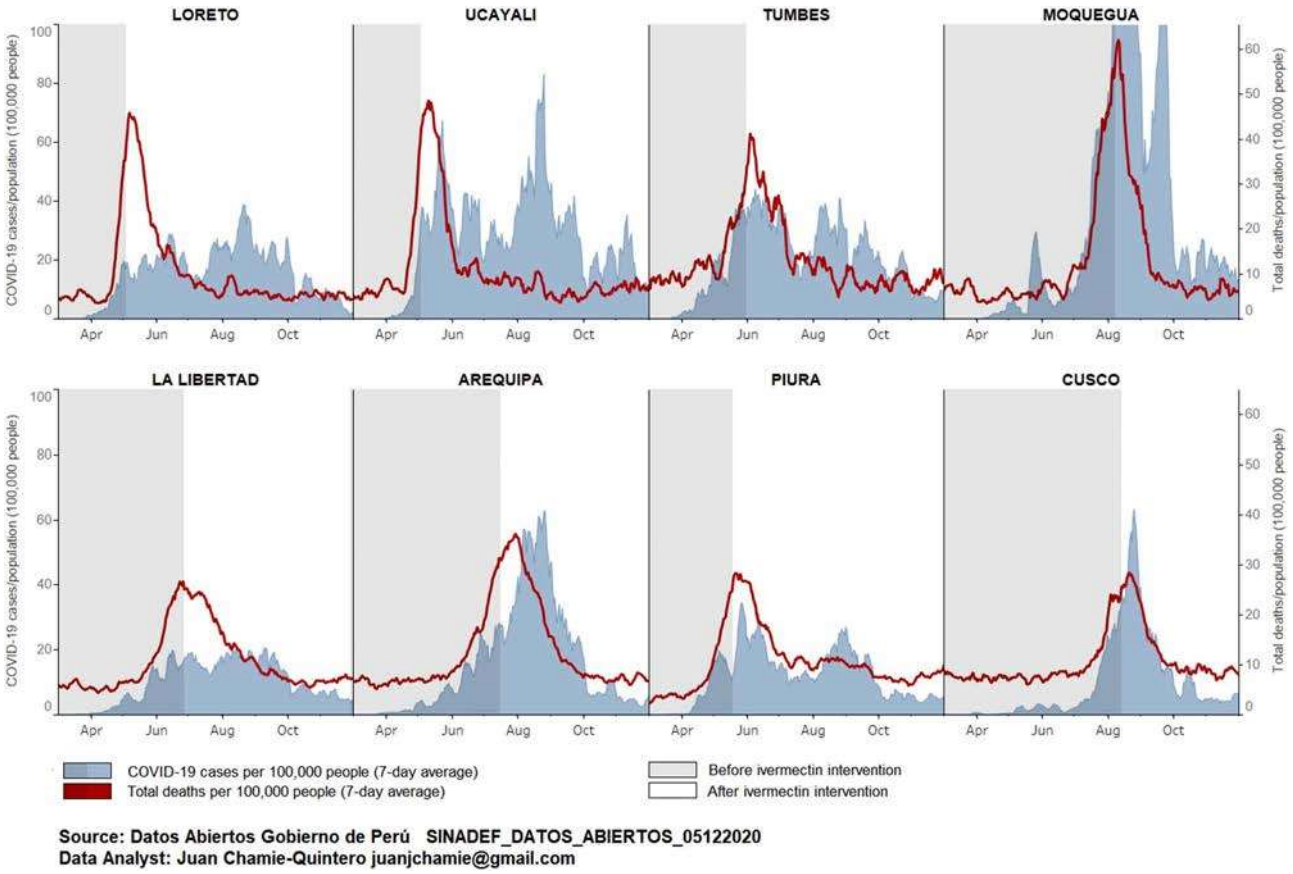


**FIGURE 4.** Decrease in total case incidences and total deaths/population of COVID-19 in the over 60 population among 8 Peruvian states after deploying mass ivermectin distribution campaigns.

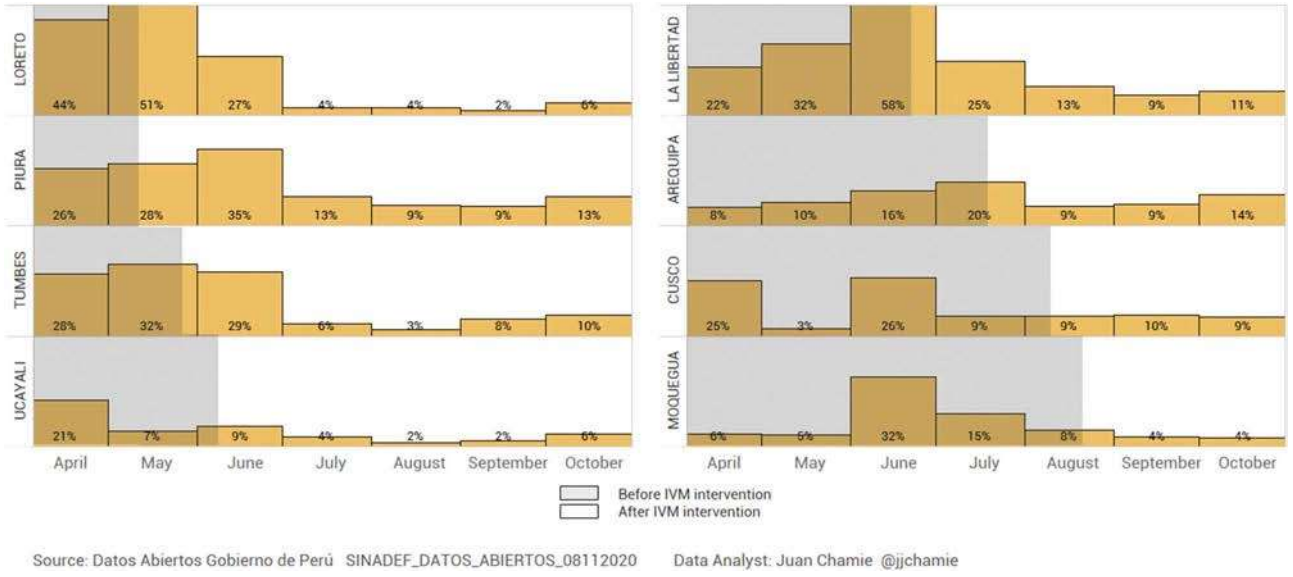


**FIGURE 5.** Daily total deaths, case fatalities, and case incidence for COVID-19 in populations of patients aged 60 and older for 8 states in Peru deploying early mass ivermectin treatments versus the state of Lima, including the capital city, where ivermectin treatment was applied months later.

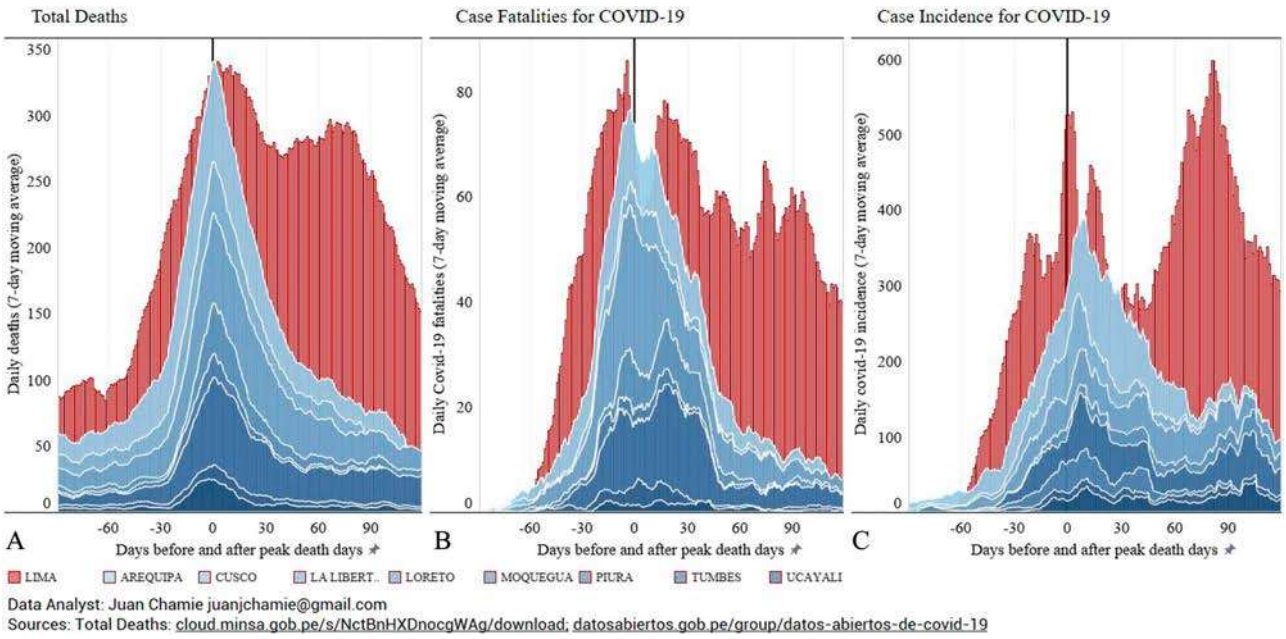


**FIGURE 6.** Covid-19 case fatalities and total deaths with and without mass ivermectin in different states of Peru.

inhibition of both cytokine production and transcription of nuclear factor-κB (NF-κB), the most potent mediator of inflammation.[37–39]

4. Ivermectin significantly diminishes viral load and protects against organ damage in multiple animal models when infected with SARS-CoV-2 or similar coronaviruses.[31,32]
5. Ivermectin prevents transmission and development of COVID-19 disease in those exposed to infected patients.[40–45]

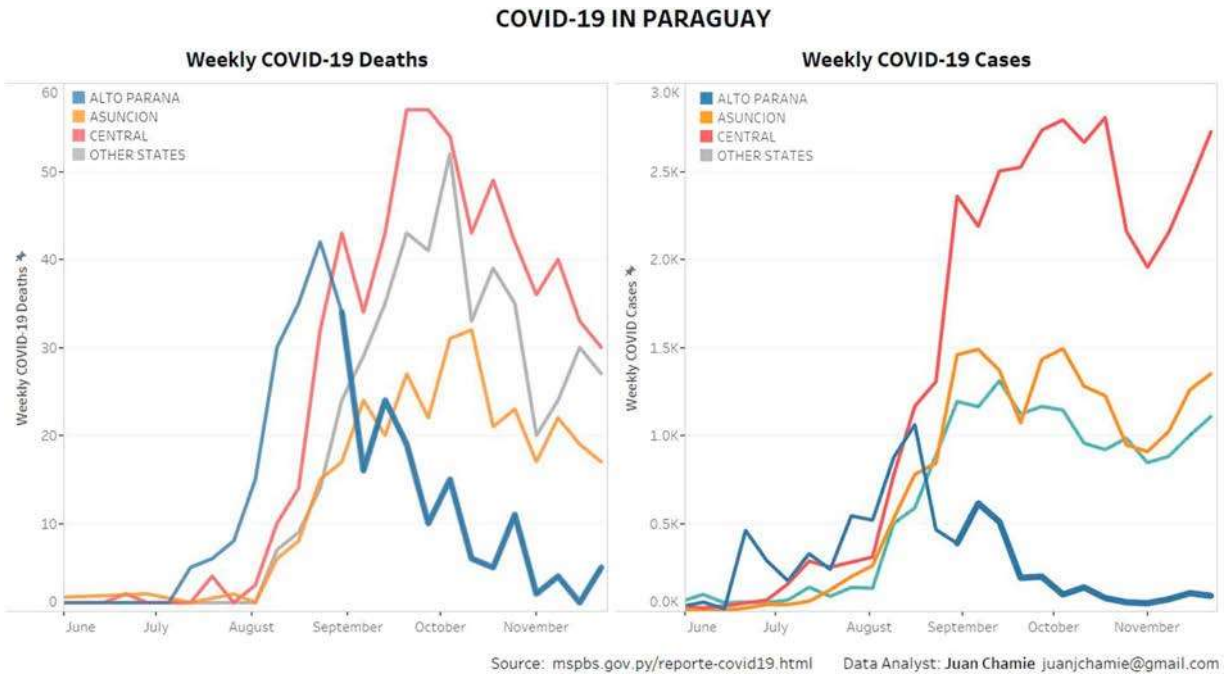


**FIGURE 7.** Paraguay – COVID-19 case counts and deaths in Alto Parana (bolded blue line) after ivermectin distribution began compared to other regions.

6. Ivermectin hastens recovery and prevents deterioration in patients with mild to moderate disease treated early after symptoms.[45,49–52,61,62]
7. Ivermectin hastens recovery and avoidance of ICU admission and death in hospitalized patients.[45,51,53,63–66]
8. Ivermectin reduces mortality in critically ill patients with COVID-19.[45,53,63]
9. Ivermectin leads to temporally associated reductions in case fatality rates in regions after ivermectin distribution campaigns.[48]
10. The safety, availability, and cost of ivermectin are nearly unparalleled given its low incidence of important drug interactions along with only mild and rare side effects observed in almost 40 years of use and billions of doses administered.[75]
11. The World Health Organization has long included ivermectin on its "List of Essential Medicines."

A summary of the statistically significant results from the above controlled trials are as follows:

Controlled trials in the prophylaxis of COVID-19 (8 studies)

1. All 8 available controlled trial results show statistically significant reductions in transmission.
2. Three RCTs with large statistically significant reductions in transmission rates, N = 774 patients.[44–46]
3. Five OCTs with large statistically significant reductions in transmission rates, N = 2052 patients.[40–43,47]

Controlled trials in the treatment of COVID-19 (19 studies)

1. Five RCTs with statistically significant impacts in time to recovery or hospital length of stay.[45,49,53,64,65]
2. One RCT with a near statistically significant decrease in time to recovery, $P = 0.07$, N = 130.[54]
3. One RCT with a large, statistically significant reduction in the rate of deterioration or hospitalization, N = 363.[49]
4. Two RCTs with a statistically significant decrease in viral load, days of anosmia, and cough, N = 85.[57,60]
5. Three RCTs with large, statistically significant reductions in mortality (N = 695).[45,60,65]
6. One RCT with a near statistically significant reduction in mortality, $P = 0.052$ (N = 140).[53]
7. Three OCTs with large, statistically significant reductions in mortality (N = 1688).[51,63,66]

### Safety of ivermectin

Numerous studies report low rates of adverse events, with the majority mild, transient, and largely attributed to the body's inflammatory response to the death of the parasites and include itching, rash, swollen lymph nodes, joint paints, fever, and headache.[75] In a study that combined results from trials including more than 50,000 patients, serious events occurred in less than 1% and largely associated with administration in Loa loa.[76] Furthermore, according to the pharmaceutical reference standard *Lexicomp*, the only medications contraindicated for use with ivermectin are the concurrent administration of antituberculosis and cholera vaccines while the anticoagulant warfarin would require dose monitoring. Another special caution is that immunosuppressed or organ transplant patients who are on calcineurin inhibitors, such as tacrolimus or cyclosporine, or the immunosuppressant sirolimus should have close monitoring of drug levels when on ivermectin given that interactions exist that can affect these levels. A longer list of drug interactions can be found on the *drugs.com* database, with nearly all interactions leading to a possibility of either increased or decreased blood levels of ivermectin. Given studies showing tolerance and lack of adverse effects in human subjects given escalating high doses of ivermectin, toxicity is unlikely, although a reduced efficacy because of decreased levels may be a concern.[77]

Concerns of safety in the setting of liver disease are unfounded given that, to the best of our knowledge, only 2 cases of liver injury have ever been reported in association with ivermectin, with both cases rapidly resolved without need for treatment.[78,79] Furthermore, no dose adjustments are required in patients with liver disease. Some have described ivermectin as potentially neurotoxic, yet one study performed a search of a global pharmaceutical database and found only 28 cases among almost 4 billion doses with serious neurological adverse events, such as ataxia, altered consciousness, seizure, or tremor.[80] Potential explanations included the effects of concomitantly administered drugs that increase absorption past the blood–brain barrier or polymorphisms in the mdr-1 gene. However, the total number of reported cases suggests that such events are exceedingly rare. Finally, ivermectin has been used safely in pregnant women, children, and infants.

## DISCUSSION

Currently, as of December 14, 2020, there is accumulating evidence that demonstrates both the safety and efficacy of ivermectin in the prevention and treatment of COVID-19. Large-scale epidemiologic analyses validate the findings of in vitro, animal, prophylaxis, and clinical studies. Epidemiologic data from regions of the world with widespread ivermectin use have demonstrated a temporally associated reduction in case counts, hospitalizations, and fatality rates.

In the context of ivermectin's long-standing safety record, low cost, and wide availability along with the

consistent, reproducible, large magnitude of findings on transmission rates, need for hospitalization, and mortality, widespread deployment in both prevention and treatment has been proposed. Although a subset of trials are of an observational design, it must be recognized that in the case of ivermectin (1) half of the trials used a randomized controlled trial design (12 of the 24 reviewed above) and (2) observational and randomized trial designs reach equivalent conclusions on average as reported in a large Cochrane review of the topic from 2014.[81] In particular, OCTs that use propensity-matching techniques (as in the Rajter study from Florida) find near identical conclusions to later-conducted RCTs in many different disease states, including coronary syndromes, critical illness, and surgery.[82–84] Similarly, as evidenced in the prophylaxis (Figure 1) and treatment trial (Figures 2 and 3) meta-analyses as well as the summary trials table (Table 3), the entirety of the benefits found in both OCT and RCT trial designs aligns in both direction and magnitude of benefit. Such a consistency of benefit among numerous trials of varying sizes designs from multiple different countries and centers around the world is unique and provides strong, additional support.

The continued challenges faced by health care providers in deciding on appropriate therapeutic interventions in patients with COVID-19 would be greatly eased if more updated and commensurate evidence-based guidance came from the leading governmental health care agencies. Currently, in the United States, the treatment guidelines for COVID-19 are issued by the National Institutes of Health. Their most recent recommendation on the use of ivermectin in patients with COVID-19 was last updated on February 11, 2021, where they found that "there was insufficient evidence to recommend for or against ivermectin in COVID-19." For a more definitive recommendation to be issued by major leading public health agencies (PHA), it is apparent that even more data on both the quality and quantity of trials are needed, even during a global health care emergency, and in consideration of a safe, oral, low-cost, widely available and deployable intervention such as ivermectin.

Fortunately, large teams sponsored by 2 different organizations have embarked on this effort. One team, sponsored by the Unitaid/WHO's ACT Accelerator Program and led by the University of Liverpool Senior Research Fellow Dr. Andrew Hill, is performing a systematic review and meta-analysis focused solely on ivermectin treatment RCTs in COVID-19. Although a preliminary meta-analysis of 17 RCTs was posted to a preprint server in February, it is expected that by March 19, 2021, results from approximately 27–29 RCTs including almost 4500 patients will be presented to the WHO Guidelines Committee and that the epidemiologic studies reviewed above by Chamie et al were already presented to the committee in early March (personal communication with Dr. Andrew Hill). It is important to note that on February 5, the WHO Guidelines Committee announced that they had begun a review of the accumulating ivermectin data and expected to arrive at their own formal treatment recommendation within 4–6 weeks. If the above benefits in clinical outcomes continue to be reported in the remaining trials, it is hoped that this almost doubling of the current supportive evidence base would merit a recommendation for use by the WHO, NIH, and other PHA's would be forthcoming.

Because of the urgency of the pandemic, and in response to the surprising persistent inaction by the leading PHA's, the British Ivermectin Recommendation Development Panel was recently coordinated by the Evidence-Based Medicine Consultancy Ltd to more rapidly formulate an ivermectin treatment guideline using the standard guideline development process followed by the WHO. Made up of long-time research consultants to numerous national and international public health organizations including the WHO, they convened both a steering committee and a technical working group that then performed a systematic review and meta-analysis. On February 12, 2021, a meeting was held that included an international consortium of 75 practitioners, researchers, specialists, and patient representatives representing 16 countries and most regions of the world. This Recommendation Development Panel was presented the results of the meta-analysis of 18 treatment RCTs and 3 prophylaxis RCTs including more than 2500 patients along with a summary of the observational trials and the epidemiologic analyses related to regional ivermectin use. After a discussion period, a vote was held on multiple aspects of the data on ivermectin, according to standard WHO guideline development processes. The Panel *found the certainty of evidence for ivermectin's effects on survival to be strong and they recommended unconditional adoption for use in the prophylaxis and treatment of COVID-19.*

In summary, based on the totality of the trials and epidemiologic evidence presented in this review along with the preliminary findings of the Unitaid/WHO meta-analysis of treatment RCTs and the guideline recommendation from the international BIRD conference, ivermectin should be globally and systematically deployed in the prevention and treatment of COVID-19.

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CITY JOURNAL

EYE ON THE NEWS

# Do Masks Work?

**A review of the evidence**

Jeffrey H. Anderson
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"Seriously people—STOP BUYING MASKS!" So tweeted then–surgeon general Jerome Adams on February 29, 2020, adding, "They are NOT effective in preventing general public from catching #Coronavirus." Two days later, Adams said, "Folks who don't know how to wear them properly tend to touch their faces a lot and actually can increase the spread of coronavirus." Less than a week earlier, on February 25, public-health authorities in the United Kingdom had published guidance that masks were unnecessary even for those providing community or residential care: "During normal day-to-day activities facemasks do not provide protection from respiratory viruses, such as COVID-19 and do not need to be worn by staff." About a month later, on March 30, World Health Organization (WHO) Health Emergencies Program executive director Mike Ryan said that "there is no specific evidence to suggest that the wearing of masks by the mass population has any particular benefit." He added, "In fact there's some evidence to suggest the opposite" because of the possibility of not "wearing a mask properly or fitting it properly" and of "taking it off and all the other risks that are otherwise associated with that."

Surgical masks were designed to keep medical personnel from inadvertently infecting patients' wounds, not to prevent the spread of viruses. Public-health officials' advice in the early days of Covid-19 was consistent with that understanding. Then, on April 3, 2020, Adams announced that the CDC was changing its guidance and that the general public should hereafter wear masks whenever sufficient social distancing could not be maintained.

Fast-forward 15 months. Rand Paul has been suspended from YouTube for a week for saying, "Most of the masks you get over the counter don't work." Many cities across the country, following new CDC guidance handed down amid a spike in cases nationally caused by the Delta variant, are once again mandating indoor mask-wearing for everyone, regardless of inoculation status. The CDC further recommends that all schoolchildren and teachers, even those who have had Covid-19 or have been vaccinated, should wear masks.

The CDC asserts this even though its own statistics show that Covid-19 is not much of a threat to schoolchildren. Its numbers show that more people under the age of 18 died of influenza during the 2018–19 flu season—a season of "moderate severity" that lasted eight months—than have died of Covid-19 across more than 18 months. What's more, the CDC says that out of every 1,738 Covid-19-related deaths in the U.S. in 2020 and 2021, just one has involved someone under 18 years of age; and out of every 150 deaths of someone under 18 years of age, just one has been Covid-related. Yet the CDC declares that schoolchildren, who learn in part from communication conveyed through facial expressions, should nevertheless hide their faces—and so should their teachers.

How did mask guidance change so profoundly? Did the medical research on the effectiveness of masks change—and in a remarkably short period of time—or just the guidance on wearing them?

Since we are constantly told that the CDC and other public-health entities are basing their recommendations on science, it's crucial to know what, specifically, has been found in various medical studies. Significant choices about how our republic should function cannot be made on the basis of science alone—they require judgment and the weighing of countless considerations—but they must be informed by knowledge of it.

In truth, the CDC's, U.K.'s, and WHO's earlier guidance was much more consistent with the best medical research on masks' effectiveness in preventing the spread of viruses. That research suggests that Americans' many months of mask-wearing has likely provided little to no health benefit and might even have been counterproductive in preventing the spread of the novel coronavirus.

It's striking how much the CDC, in marshalling evidence to justify its revised mask guidance, studiously avoids mentioning randomized controlled trials. RCTs are uniformly regarded as the gold standard in medical research, yet the CDC basically ignores them apart from disparaging certain ones that particularly contradict the agency's position. In a "Science Brief" highlighting studies that "demonstrate that mask wearing reduces new infections" and serving as the main public justification for its mask guidance, the CDC provides a helpful matrix of 15 studies—none RCTs. The CDC instead focuses strictly on observational studies completed after Covid-19 began. In general, observational studies are not only of lower quality than RCTs but also are more likely to be politicized, as they can inject the researcher's judgment more prominently into the inquiry and lend themselves, far more than RCTs, to finding what one wants to find.

A particular favorite of the CDC's, so much so that the agency put out a glowing press release on it and continues to give it pride of placement in its brief, is an observational (specifically, cohort) study focused on two Covid-positive hairstylists at a beauty salon in Missouri. The two stylists, who were masked, provided services for 139 people, who were mostly masked, for several days after developing Covid-19 symptoms. The 67 customers who subsequently chose to get tested for the coronavirus tested negative, and none of the 72 others reported symptoms.

This study has major limitations. For starters, any number of the 72 untested customers could have had Covid-19 but been asymptomatic, or else had symptoms that they chose not to report to the Greene County Health Department, the entity doing the asking. The apparent lack of spread of Covid-19 could have been a result of good ventilation, good hand hygiene, minimal coughing by the stylists, or the fact that stylists generally, as the researchers note, "cut hair while clients are facing away from them." The researchers also observe that "viral shedding" of the coronavirus "is at its highest during the 2 to 3 days before symptom onset." Yet no customers who saw the stylists when they were at their most contagious were tested for Covid-19 or asked about symptoms. Most importantly, this study does not have a control group. Nobody has any idea how many people, if any, would have been infected had no masks been worn in the salon. Late last year, at a gym in Virginia in which people apparently did not wear masks most of the time, a trainer tested positive for the coronavirus. As CNN reported, the gym contacted everyone whom the trainer had coached before getting sick—50 members in all—"but not one member developed symptoms." Clearly, this doesn't prove that *not* wearing masks prevents transmission.

Another CDC-highlighted study, by Rader et al., invited people across the country to answer a survey. The low (11 percent) response rate—including about twice as many women as men—indicated that the mix of respondents was hardly random. The study found that "a high percentage of self-reported face mask-wearing is associated with a higher probability of transmission control," and "the highest percentage of reported mask wearers" are found, unsurprisingly, "along the coasts and southern border, and in large urban areas." However, as the researchers note, "It is difficult to disentangle individuals' engagement in mask-wearing from their adoption of other preventive hygiene practices, and mask-wearing might serve as a proxy for other risk avoidance behaviors not queried." Moreover, achieving greater "transmission control" is not remotely the same thing as ensuring fewer deaths. For example, per capita, Utah is in the top ten in the nation in Covid-19 cases and the bottom ten in Covid-19 deaths, while Massachusetts is in the bottom half in cases and the top five in deaths.

An additional observational study, but one that the CDC does not reference in its brief, is a large, international Bayesian study by Leech, et al. It finds that mask-wearing by 100 percent of the population "corresponds to" a 24.6 percent reduction in transmission of the novel coronavirus. Mask mandates correspond to no decrease in transmission: "For mandates we see no reduction: 0.0 percent." Like all observational studies, however, this study is ill-equipped to show causation, to separate out the effects of just one variable from among other, frequently related, ones.

Mask supporters often claim that we have no choice but to rely on observational studies instead of RCTs, because RCTs cannot tell us whether masks work or not. But what they really mean is that they don't like what the RCTs show.

The randomized controlled trial dates, in a sense, to 1747, when Royal Navy surgeon James Lind divided seamen suffering from similar cases of scurvy into six pairs and tried different methods of treatment on each. Lind writes, "The consequence was, that the most sudden and visible good effects were perceived from the use of oranges and lemons."

The RCT eventually became firmly established as the most reliable way to test medical interventions. The following passage, from Abdelhamid Attia, an M.D. and professor of obstetrics and gynecology at Cairo University in Egypt, conveys its dominance:

> The importance of RCTs for clinical practice can be illustrated by its impact on the shift of practice in hormone replacement therapy (HRT). For decades HRT was considered the standard care for all postmenopausal, symptomatic and asymptomatic women. Evidence for the effectiveness of HRT relied always on observational studies[,] mostly cohort studies. But a single RCT that was published in 2002 . . . has changed clinical practice all over the world from the liberal use of HRT to the conservative use in selected symptomatic cases and for the shortest period of time. In other words, one well conducted RCT has changed the practice that relied on tens, and probably hundreds, of observational studies for decades.

A randomized controlled trial divides participants into different groups on a randomized basis. At least one group receives an "intervention," or treatment, that is generally tested against a control group not receiving the intervention. The twofold strength of an RCT is that it allows researchers to isolate one variable—to test whether a given intervention causes an intended effect—while at the same time making it very hard for researchers to produce their own preferred outcomes.

This is true at least so long as an RCT's findings are based on "intention-to-treat" analysis, whereby all participants are kept in the treatment group to which they were originally assigned and none are excluded from the analysis, regardless of whether they actually received the intended treatment. Eric McCoy, an M.D. at the University of California, Irvine, explains that intention-to-treat analysis avoids bias and "preserves the benefits of randomization, which cannot be assumed when using other methods of analysis."

Such other methods of analysis include subgroup, multivariable, and per-protocol analysis. Subgroup analysis is susceptible to "cherry-picking"—as researchers hunt for anything showing statistical significance—or to being swayed by random chance. In one famous example, aspirin was found to help prevent fatal heart attacks, but not in the subgroups where patients' astrological signs were Gemini or Libra.

"Multivariable analysis," writes Marlies Wakkee, an M.D. and Ph.D. at Erasmus University Medical Center in the Netherlands, "only adjusts for measured confounding"—that which a researcher decides is worth examining. (Confounders are extra variables that affect the analysis; for example, eating ice cream may be found to correlate with sunburns, but heat is a confounding variable influencing both.) She adds, "This is a significant difference compared to randomized controlled trials, where the randomization process results in an equal distribution of all potential confounders, known and unknown."

Per-protocol analysis departs from randomization by basically allowing participants to self-select into, or out of, an intervention group. McCoy writes, "Empirical evidence suggests that participants who adhere [to research protocols] tend to do better than those who do not adhere,

regardless of assignment to active treatment or placebo." In other words, per-protocol analysis is more likely to suggest that an intervention, even a fake one, worked. Of these three departures from intention-to-treat analysis, per-protocol analysis is perhaps the most extreme.

With these different methods of analysis in mind, it becomes easier to evaluate the 14 RCTs, conducted around the world, that have tested the effectiveness of masks in reducing the transmission of respiratory viruses. Of these 14, the two that have directly tested "source control"—the oft-repeated claim that wearing a mask benefits others—are a good place to start.

A 2016 study in Beijing by MacIntyre, et al. that claimed to find a possible benefit of masks did not prove very informative, as only one person in the control group—and one in the mask group—developed a laboratory-confirmed infection. Much more illuminating was a 2010 study in France by Canini, et al., which randomly placed sick people, or "index patients," and their household contacts together into either a mask group or a no-mask control group. The authors "observed a good adherence to the intervention," meaning that the index patients generally wore the furnished three-ply masks as intended. (No one else was asked to wear them.) Within a week, 15.8 percent of household contacts in the no-mask control group and 16.2 percent in the mask group developed an "influenza-like illness" (ILI). So, the two groups were essentially dead even, with the sliver of an advantage observed in the control group not being statistically significant. The authors write that the study "should be interpreted with caution since the lack of statistical power prevents us to draw formal conclusion regarding effectiveness of facemasks in the context of a seasonal epidemic." However, they state unequivocally, "In various sensitivity analyses, we did not identify any trend in the results suggesting effectiveness of facemasks."

With the two RCTs that directly tested source control providing essentially no support for the claim that wearing a mask benefits others, what about RCTs that test the combination of source control and wearer protection? By dividing participants into a hand-hygiene group, a hand-hygiene group that also wore masks, and a control group, three RCTs allow us to see whether the addition of masks (worn both by the sick person and others) provided any benefit over hand hygiene alone.

A 2010 study by Larson, et al. in New York found that those in the hand-hygiene group were less likely to develop any symptoms of an upper respiratory infection (42 percent experienced symptoms) than those in the mask-plus-hand-hygiene group (61 percent). This statistically significant finding suggests that wearing a mask actually undermines the benefits of hand hygiene.

A multivariable analysis of this same study found a significant difference in secondary attack rates (the rate of transmission to others) between the mask-plus-hands group and the control group. On this basis, the authors maintain that mask-wearing "should be encouraged during outbreak situations." However, this multivariable analysis also found significantly lower rates in crowded homes—"i.e., more crowded households had less transmission"—which tested at a higher confidence level. Thus, to the extent that this multivariable analysis provided any support for masks, it provided at least as much support for crowding.

Two other studies found no statistically significant differences between their mask-plus-hands and hands-only groups. A 2011 study in Bangkok by Simmerman, et al. observed very similar results for both groups. A CDC-funded 2009 study in Hong Kong by Cowling, et al. observed that the hands-only group generally did better than the mask-plus-hands group, but not to a statistically significant degree. Subgroup analysis by Cowling, et al., limited to interventions started within 36 hours of the onset of symptoms, found that the mask-plus-hands group beat the control group to a statistically significant degree in one measure, while the hands-only group beat the control group to a statistically significant degree in two measures. Summarizing this study, Canini writes that "no additional benefit was observed when facemask [use] was added to hand hygiene by comparison with hand hygiene alone."

So, if masks don't improve on hand hygiene alone, what about masks versus nothing?

Various RCTs have studied this question, with evidence of masks' effectiveness proving sparse at best. Aside from a 2009 study in Japan by Jacobs, et al.—which found that those in the mask group were significantly more likely to experience headaches and that "face mask use in health care workers has not been demonstrated to provide benefit"—only two RCTs have produced statistically significant findings in intention-to-treat analysis, and one of those studies contradicted itself.

The previously mentioned 2011 study in Bangkok by Simmerman, et al. found that the secondary attack rate of ILI was twice as high in the mask-plus-hand-hygiene group (18 percent) as in the control group (9 percent), a statistically significant difference. (The ILI rate was 17 percent in the hand-hygiene-only group.) Finding essentially the same thing in multivariable analysis, the researchers wrote that, relative to the control group, the odds ratios for both the mask-plus-hands group and the hands-only group "were twofold in the opposite direction from the hypothesized protective effect."

Subsequently, a small 2014 study—with 164 participants—by Barasheed, et al. of Australian pilgrims in Saudi Arabia, staying in close quarters in tents, found that significantly fewer people in the mask group developed an ILI than in the control group (31 percent to 53 percent). Unlike the exact fever specifications utilized in other RCTs, however, this study accepted self-reporting of "subjective" fever in determining whether someone had an ILI. Lab tests revealed opposite results, with twice as many participants having developed respiratory viruses in the mask group as in the control group. These lab-test findings were not statistically significant; still, the lab tests' greater reliability makes it far from clear that the masks in this study provided any genuine benefit.

Other RCTs found no statistically significant benefit from masks in intention-to-treat analysis. A 2008 pilot study by Cowling et al. in Hong Kong observed that secondary attack rates, using the CDC's definition of ILI, were twice as high in the mask group (8 percent) as in the hand hygiene (4 percent) or control (4 percent) groups, but these observed differences were not statistically significant.

Other methods of analysis, deviating from intention-to-treat analysis, found the following.

A per-protocol analysis of a 2009 study in Sydney by MacIntyre, et al. found a significant effect when combining the surgical-mask group with a group wearing N95 hospital respirators. However, the authors write, a "causal link cannot be demonstrated because adherence was not randomized."

In subgroup analysis of 2010 and 2012 studies in Michigan by Aiello, et al., limited to the final several weeks of the respective studies, each study's mask-plus-hands group had significantly lower rates of ILI than its control group, while its mask-only group did not. In 2010, the results for the mask-only group also hinted at a slight benefit, reducing ILI by an observed (but not statistically significant) 8 percent to 10 percent. In 2012, the authors concluded, "Masks alone did not provide a benefit." They nevertheless recommended the combination of mask use and hand hygiene, despite not having tested whether that combination works better than hand hygiene alone.

A multivariable analysis of a smallish (218 participants) 2012 study in Germany by Suess, et al. found that combining the mask group and mask-plus-hands group, while limiting analysis to interventions begun within 48 hours, produced a finding of significantly lower levels of lab-confirmed influenza (but not of ILI) in that combined group (but not in either group separately). The authors, from Berlin, recommended masking and hand hygiene, while opining, "Concerns about acceptability and tolerability of the interventions should not be a reason against their recommendation."

The only RCT to test mask-wearing's specific effectiveness against Covid-19 was a 2020 study by Bundgaard, et al. in Denmark. This large (4,862 participants) RCT divided people between a mask-wearing group (providing "high-quality" three-layer surgical masks) and a control group. It took place at a time (spring 2020) when Denmark was encouraging social distancing but not mask use, and 93 percent of those in the mask group wore the masks at least "predominately as recommended." The study found that 1.8 percent of those in the mask group and 2.1 percent of those in the control group became infected with Covid-19 within a month, with this 0.3-point difference not being statistically significant.

This study—the first RCT on Covid-19 transmission—apparently had difficulty getting published. After the study's eventual publication, Vinay Prasad, an M.D. at the University of California, San Francisco, described it as "thoughtful," "useful," and "well done," but noted (with criticism), "Some have turned to social media to ask why a trial that may diminish enthusiasm for masks and may be misinterpreted was published in a top medical journal."

Meanwhile, the CDC website portrays the Danish RCT (with its 4,800 participants) as being far less relevant or important than the observational study of Missouri hairdressers with no control group, dismissing the former as "inconclusive" and "too small" while praising the latter, amazingly, as "showing that wearing a mask prevented the spread of infection"—when it showed nothing of the sort.

Each of the RCTs discussed so far, 13 in all, examined the effectiveness of *surgical* masks, finding little to no evidence of their effectiveness and some evidence that they might actually increase viral transmission. None of these 13 RCTs examined the effectiveness of *cloth* masks. "Cloth face coverings," according to former CDC director Robert Redfield, "are one of the most powerful weapons we have."

One RCT tested these masks that so many high-profile public-health officials have touted. This "first RCT of cloth masks," in the trial's own words (it is apparently still the only one), was a 2015 study by MacIntyre, et al. in Hanoi, Vietnam. A relatively large study, with over 1,100 participants, it tested cloth masks against surgical masks and did not feature a no-mask control group. The trial tested the protection of health-care workers, instructing them to wear a two-layer cloth mask at all times on every shift ("except in the toilet or during tea or lunch breaks") across four weeks.

The study found that those in the cloth-mask group were 13 times more likely (2.28 percent to 0.17 percent) to develop an influenza-like illness than those in the surgical-mask group—a statistically significant difference. The trial also lab-tested penetration rates and found that while surgical masks were "poor" at preventing the penetration of particles—letting 44 percent through—cloth masks were "extremely poor," letting 97 percent through. (N95 hospital respirators let 0.1 percent through.)

The authors write that wearing a cloth mask "may potentially increase the infection risk" for health-care workers. "The virus may survive on the surface of the facemasks," they explain, while "a contaminated cloth mask may transfer pathogen from the mask to the bare hands of the wearer," which could lead to hand hygiene being "compromised." As for double-masking, the authors write, "Observations during SARS suggested double-masking . . . increased the risk of infection because of moisture, liquid diffusion and pathogen retention." Absent further research, they conclude, "cloth masks should not be recommended."

MacIntyre and several other authors of this study, perhaps under pressure from the CDC or other entities with similar agendas, released what the CDC calls a "follow up study," in September 2020. This follow-up isn't really a study at all, certainly not a new RCT, yet the CDC cites it favorably while disparaging the original study, which, the CDC asserts, "had a number of limitations." This 2020 follow-up pretty much amounts to publishing the finding that when hospitals washed the cloth masks, health-care workers were only about half as likely to get infected as when they washed the cloth masks themselves. Still, the 2020 publication says, "We do not recommend cloth masks for health workers," much as the 2015 one said.

Other reviews of the evidence have been mixed but generally have come to similar conclusions. Certain masking advocates admit that the RCT evidence is "inconclusive" but cite other forms of evidence that have held up poorly. A study for Cochrane Reviews by Jefferson, et al. that examines 13 of the 14 RCTs discussed herein (all but the Denmark Covid-19 study) notes "uncertainty about the effects of face masks" and writes that "the pooled results of randomised trials did not show a clear reduction in respiratory viral infection with the use of medical/surgical masks

during seasonal influenza." Meantime, a study by Perski, et al., which performed a Bayesian analysis on 11 of the 14 RCTs discussed herein, concluded that when it comes to "the benefits or harms of wearing face masks . . . the scientific evidence should be considered equivocal." They write, "Available evidence from RCTs is equivocal as to whether or not wearing face masks in community settings results in a reduction in clinically- or laboratory-confirmed viral respiratory infections."

In sum, of the 14 RCTs that have tested the effectiveness of masks in preventing the transmission of respiratory viruses, three suggest, but do not provide any statistically significant evidence in intention-to-treat analysis, that masks might be useful. The other eleven suggest that masks are either useless—whether compared with no masks or because they appear not to add to good hand hygiene alone—or actually counterproductive. Of the three studies that provided statistically significant evidence in intention-to-treat analysis that was not contradicted within the same study, one found that the combination of surgical masks and hand hygiene was less effective than hand hygiene alone, one found that the combination of surgical masks and hand hygiene was less effective than nothing, and one found that cloth masks were less effective than surgical masks.

Hiram Powers, the nineteenth-century neoclassical sculptor, keenly observed, "The eye is the window to the soul, the mouth the door. The intellect, the will, are seen in the eye; the emotions, sensibilities, and affections, in the mouth." The best available scientific evidence suggests that the American people, credulously trusting their public-health officials, have been blocking the door to the soul without blocking the transmission of the novel coronavirus.

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**Photo by Michael M. Santiago/Getty Images**

# Universal Declaration of Human Rights

## Preamble

Whereas recognition of the inherent dignity and of the equal and inalienable rights of all members of the human family is the foundation of freedom, justice and peace in the world,
Whereas disregard and contempt for human rights have resulted in barbarous acts which have outraged the conscience of mankind, and the advent of a world in which human beings shall enjoy freedom of speech and belief and freedom from fear and want has been proclaimed as the highest aspiration of the common people,
Whereas it is essential, if man is not to be compelled to have recourse, as a last resort, to rebellion against tyranny and oppression, that human rights should be protected by the rule of law,
Whereas it is essential to promote the development of friendly relations between nations,
Whereas the peoples of the United Nations have in the Charter reaffirmed their faith in fundamental human rights, in the dignity and worth of the human person and in the equal rights of men and women and have determined to promote social progress and better standards of life in larger freedom,
Whereas Member States have pledged themselves to achieve, in cooperation with the United Nations, the promotion of universal respect for and observance of human rights and fundamental freedoms,
Whereas a common understanding of these rights and freedoms is of the greatest importance for the full realization of this pledge,
Now, therefore,
The General Assembly,
Proclaims this Universal Declaration of Human Rights as a common standard of achievement for all peoples and all nations, to the end that every individual and every organ of society, keeping this Declaration constantly in mind, shall strive by

teaching and education to promote respect for these rights and freedoms and by progressive measures, national and international, to secure their universal and effective recognition and observance, both among the peoples of Member States themselves and among the peoples of territories under their jurisdiction.

### Article I

All human beings are born free and equal in dignity and rights. They are endowed with reason and conscience and should act towards one another in a spirit of brotherhood.

### Article 2

Everyone is entitled to all the rights and freedoms set forth in this Declaration, without distinction of any kind, such as race, colour, sex, language, religion, political or other opinion, national or social origin, property, birth or other status. Furthermore, no distinction shall be made on the basis of the political, jurisdictional or international status of the country or territory to which a person belongs, whether it be independent, trust, non-self-governing or under any other limitation of sovereignty.

### Article 3

Everyone has the right to life, liberty and the security of person.

### Article 4

No one shall be held in slavery or servitude; slavery and the slave trade shall be prohibited in all their forms.

### Article 5

No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment.

## Article 6

Everyone has the right to recognition everywhere as a person before the law.

## Article 7

All are equal before the law and are entitled without any discrimination to equal protection of the law. All are entitled to equal protection against any discrimination in violation of this Declaration and against any incitement to such discrimination.

## Article 8

Everyone has the right to an effective remedy by the competent national tribunals for acts violating the fundamental rights granted him by the constitution or by law.

## Article 9

No one shall be subjected to arbitrary arrest, detention or exile.

## Article 10

Everyone is entitled in full equality to a fair and public hearing by an independent and impartial tribunal, in the determination of his rights and obligations and of any criminal charge against him.

## Article 11

1. Everyone charged with a penal offence has the right to be presumed innocent until proved guilty according to law in a public trial at which he has had all the guarantees necessary for his defence.
2. No one shall be held guilty of any penal offence on account of any act or omission which did not constitute a penal offence, under national or international law, at the time when it was committed. Nor shall a heavier

penalty be imposed than the one that was applicable at the time the penal offence was committed.

### Article 12

No one shall be subjected to arbitrary interference with his privacy, family, home or correspondence, nor to attacks upon his honour and reputation. Everyone has the right to the protection of the law against such interference or attacks.

### Article 13

1. Everyone has the right to freedom of movement and residence within the borders of each State.
2. Everyone has the right to leave any country, including his own, and to return to his country.

### Article 14

1. Everyone has the right to seek and to enjoy in other countries asylum from persecution.
2. This right may not be invoked in the case of prosecutions genuinely arising from non-political crimes or from acts contrary to the purposes and principles of the United Nations.

### Article 15

1. Everyone has the right to a nationality.
2. No one shall be arbitrarily deprived of his nationality nor denied the right to change his nationality.

### Article 16

1. Men and women of full age, without any limitation due to race, nationality or religion, have the right to marry and to found a family. They are entitled to equal rights as to marriage, during marriage and at its dissolution.
2. Marriage shall be entered into only with the free and full consent of the intending spouses.
3. The family is the natural and fundamental group unit of society and is entitled to protection by society and the State.

### Article 17

1. Everyone has the right to own property alone as well as in association with others.
2. No one shall be arbitrarily deprived of his property.

### Article 18

Everyone has the right to freedom of thought, conscience and religion; this right includes freedom to change his religion or belief, and freedom, either alone or in community with others and in public or private, to manifest his religion or belief in teaching, practice, worship and observance.

### Article 19

Everyone has the right to freedom of opinion and expression; this right includes freedom to hold opinions without interference and to seek, receive and impart information and ideas through any media and regardless of frontiers.

### Article 20

1. Everyone has the right to freedom of peaceful assembly and association.
2. No one may be compelled to belong to an association.

### Article 21

1. Everyone has the right to take part in the government of his country, directly or through freely chosen representatives.
2. Everyone has the right to equal access to public service in his country.
3. The will of the people shall be the basis of the authority of government; this will shall be expressed in periodic and genuine elections which shall be by universal and equal suffrage and shall be held by secret vote or by equivalent free voting procedures.

### Article 22

Everyone, as a member of society, has the right to social security and is entitled to realization, through national effort and international co-operation and in accordance with the organization and resources of each State, of the economic, social and cultural rights indispensable for his dignity and the free development of his personality.

### Article 23

1. Everyone has the right to work, to free choice of employment, to just and favourable conditions of work and to protection against unemployment.
2. Everyone, without any discrimination, has the right to equal pay for equal work.
3. Everyone who works has the right to just and favourable remuneration ensuring for himself and his family an existence worthy of human dignity, and supplemented, if necessary, by other means of social protection.
4. Everyone has the right to form and to join trade unions for the protection of his interests.

### Article 24

Everyone has the right to rest and leisure, including reasonable limitation of working hours and periodic holidays with pay.

## Article 25

1. Everyone has the right to a standard of living adequate for the health and well-being of himself and of his family, including food, clothing, housing and medical care and necessary social services, and the right to security in the event of unemployment, sickness, disability, widowhood, old age or other lack of livelihood in circumstances beyond his control.
2. Motherhood and childhood are entitled to special care and assistance. All children, whether born in or out of wedlock, shall enjoy the same social protection.

## Article 26

1. Everyone has the right to education. Education shall be free, at least in the elementary and fundamental stages. Elementary education shall be compulsory. Technical and professional education shall be made generally available and higher education shall be equally accessible to all on the basis of merit.
2. Education shall be directed to the full development of the human personality and to the strengthening of respect for human rights and fundamental freedoms. It shall promote understanding, tolerance and friendship among all nations, racial or religious groups, and shall further the activities of the United Nations for the maintenance of peace.
3. Parents have a prior right to choose the kind of education that shall be given to their children.

## Article 27

1. Everyone has the right freely to participate in the cultural life of the community, to enjoy the arts and to share in scientific advancement and its benefits.

2. Everyone has the right to the protection of the moral and material interests resulting from any scientific, literary or artistic production of which he is the author.

### Article 28

Everyone is entitled to a social and international order in which the rights and freedoms set forth in this Declaration can be fully realized.

### Article 29

1. Everyone has duties to the community in which alone the free and full development of his personality is possible.
2. In the exercise of his rights and freedoms, everyone shall be subject only to such limitations as are determined by law solely for the purpose of securing due recognition and respect for the rights and freedoms of others and of meeting the just requirements of morality, public order and the general welfare in a democratic society.
3. These rights and freedoms may in no case be exercised contrary to the purposes and principles of the United Nations.

### Article 30

Nothing in this Declaration may be interpreted as implying for any State, group or person any right to engage in any activity or to perform any act aimed at the destruction of any of the rights and freedoms set forth herein.