

## Scientific Data that Question Vaccine Efficacy and Appropriateness

### Introduction

Vaccines are a triumph of modern medicine, responsible for saving many lives against some of the deadliest infectious diseases. However, as with any intervention, each vaccine must be judged individually according to its own merit and the risk and severity of the pathogen that it is purported to address. It is then the decision of societies, and more importantly individuals, as to whether we should utilize an intervention, after carefully weighing up the potential costs and benefits. I speak as someone who has had numerous vaccines throughout their entire life, but also as a scientist, whose job it is to question data and look for inconsistencies that would be the antidote to accepted dogma. This report is designed to provide a degree of cost-benefit analysis that may help inform decision-making at the personal and societal level.

### Clinical trial vaccine efficacy

Much of the scientific and wider reporting on vaccine trial success has championed a ~95% efficacy statistic (depending on the vaccine). However, this figure purely reflects *relative risk* of outcome, which can be useful but should not be reported without the *absolute risk*. Neglecting to report absolute risk has unfortunately become standard practice in most medical trials, but it is disingenuous and inevitably leads to inflation of the intervention's perceived success.

Absolute risk can be thought of as baseline risk. This is surely what everyone wants to know before they embark on any course of treatment i.e., what is my normal risk of this disease if I take no action? If one's baseline risk is very small, then the individual may decide that any potential downsides to an intervention do not outweigh the potential minimal benefit they could derive.

This point is illustrated in **Support Materials – Box 1**

Here we will now consider vaccine efficacy through the lens of an individual's absolute risk, versus merely relative risk differences, using the available data from the clinical trials.

#### Pfizer/BioNTech trial

<https://www.fda.gov/media/144245/download>

<https://www.nejm.org/doi/pdf/10.1056/NEJMoa2034577?articleTools=true>

During the study period, baseline risk in the placebo group of developing any type of symptoms was 0.79%, whereas in the vaccine group it was 0.04%. So, in absolute terms, the vaccine reduced your risk of developing symptomatic COVID-19 by 0.75%.

*\*Note that the more impressive 95% efficacy commonly stated is derived from a relative attack rate ratio, using these absolute values and expressed as a percentage e.g. for symptomatic COVID-19:  $1 - (0.04/0.79) = 0.95 = 95\%$ .*

Baseline risk in the placebo group of developing severe COVID-19 was 0.04%, versus 0.005% in the vaccine group. So, the vaccine reduced your risk of developing severe COVID-19 by 0.035%.

Another way to express this is with the Number Needed to Treat (NNT). With this absolute risk reduction quoted above, the NNT = 2857. This means that you would need to vaccinate 2857 people to stop 1 person from developing severe COVID-19. A STAT News [article](#) puts NNT in perspective.

### Moderna trial

<https://www.fda.gov/media/144434/download>

In the Moderna trial, baseline risk in the placebo group of developing any symptomatic COVID-19 was 1.3%, whereas in the vaccine group it was 0.08%. So, in absolute terms, the vaccine reduced your risk of developing symptomatic COVID-19 by 1.22%.

*\*Once again note that the more impressive 94% efficacy commonly stated for this trial is derived from a relative attack rate ratio, using these absolute values and expressed as a percentage. For symptomatic COVID-19:  $1 - (0.08/1.3) = 0.94 = 94\%$ .*

Baseline risk in the placebo group of developing severe COVID-19 was 0.2%, versus 0% in the vaccine group. So, the vaccine reduced your risk of developing severe COVID-19 by 0.2%.

There was also 1 death in the placebo group, but 0 deaths in the vaccine group. (Note that using the same relative risk logic, one could claim that this vaccine had 100% efficacy in protecting against death)

### Johnson & Johnson trial

<https://www.fda.gov/media/146217/download>

In the J&J trial, baseline risk in the placebo group of developing moderate/severe COVID-19 was 2.5%, whereas in the vaccine group it was 0.8%. So, in absolute terms, the vaccine reduced your risk of developing symptomatic COVID-19 by 1.7%.

*\*Once again note that the 68% efficacy commonly stated for this trial is derived from a relative attack rate ratio, using these absolute values and expressed as a percentage. For symptomatic COVID-19:  $1 - (0.8/2.5) = 0.68 = 68\%$ .*

Baseline risk in the placebo group of developing truly severe COVID-19 (hospitalization) was 0.06%, versus 0.009% in the vaccine group. So, the vaccine reduced your risk of developing truly severe COVID-19 by 0.05%.

There were also 7 COVID-19-related deaths in the placebo group, but 0 deaths in the vaccine group.

### **Clinical trial vaccine efficacy summary**

	<b>Relative risk reduction</b>	<b>Absolute risk reduction</b>
<b>Pfizer/BioNTech</b>		
symptomatic COVID-19	95%	0.75%
severe/hospitalization	87.50%	0.04%
<b>Moderna</b>		
symptomatic COVID-19	94%	1.22%
severe/hospitalization	100%	0.20%
<b>J&amp;J</b>		
symptomatic COVID-19	68%	1.70%
severe/hospitalization	85%	0.05%

## **Asymmetric distribution of risk and efficacy**

What we undoubtedly want and need in these vaccines is for them to prevent very severe COVID-19 that would require medical intervention and protect against potential mortality in those individuals most at risk. It is difficult to generalize across trials because of the different conditions, but between these three, it appears as if the vaccines might reduce your risk of very severe COVID-19 by 0.035-0.2%.

The J&J vaccine may have had an effect on preventing mortality in this trial, but the sample sizes still seem too small here to make a conclusion.

### *Demographics*

It should be noted that these trials had participants from a variety of different age/race/health status groups. Although racial/ethnic demographics were quite good, these trials needed to include a greater proportion of very elderly participants, who are most at risk. At the same time, the average baseline risk of severe COVID-19 reported in these trials is spread across the range of recruited participants. Therefore, a relatively young, healthy individual for example, will have an even smaller risk (and derive a smaller potential vaccine benefit) than a 60-year-old with preexisting health conditions. These differences in risk or knowledge gaps across different subpopulations could additionally make someone from (or not from) one of these groups question personal vaccine utility.

### *Other subpopulations*

These clinical trials do not provide evidence that the vaccine is safe and effective for children under 18-years old, pregnant and lactating women or immunocompromised individuals. Given the high prevalence of autoimmune disease in society, all three of these groups constitute a considerable population. It also makes no mention of those who have strong allergic reactions, who may be at increased risk of an adverse event.

## **Adverse effects**

### *Short-term*

The short-term adverse effects of vaccine administration appear significant, and in some ways more significant than COVID-19, in terms of both rates and severity. In the Pfizer trial for example, fatigue (62.9%), headache (55.1%), muscle pain (38.3%), chills (31.9%), joint pain (23.6%) and fever (14.2%) were common in vaccinated participants. Furthermore, severe adverse reactions occurred in up to 4.6% of participants. Similar findings were made with the Moderna vaccine, with 65.3% of vaccinated individuals experiencing fatigue (9.7% severe), 59.6% experiencing muscle pain and 44.8% experiencing joint pain. Other more common and more unusual adverse events were also reported at varying rates. Given the often-marginal symptomology experienced by those who actually contract COVID-19, individuals may decide that they are willing to forgo a vaccine and accept any potential risks.

[“Breakthrough infections”](#) (COVID-19 infections in spite of vaccination) are beginning to get wider attention. These seem to be rare, but they are not to be ignored and the CDC admits that those reported are likely to be a substantial undercount of the true rates. For many people, this may not reasonably constitute enough of a cost-benefit to consider vaccination.

It is possible that these breakthrough infections were also encountered during the Pfizer trial. In the trial report, 409 “suspected but unconfirmed” COVID-19 cases were reported 7 days after participants received vaccination. It is unclear whether these were actual infections or simply adverse events, but it is an interesting finding that was omitted from their final analysis.

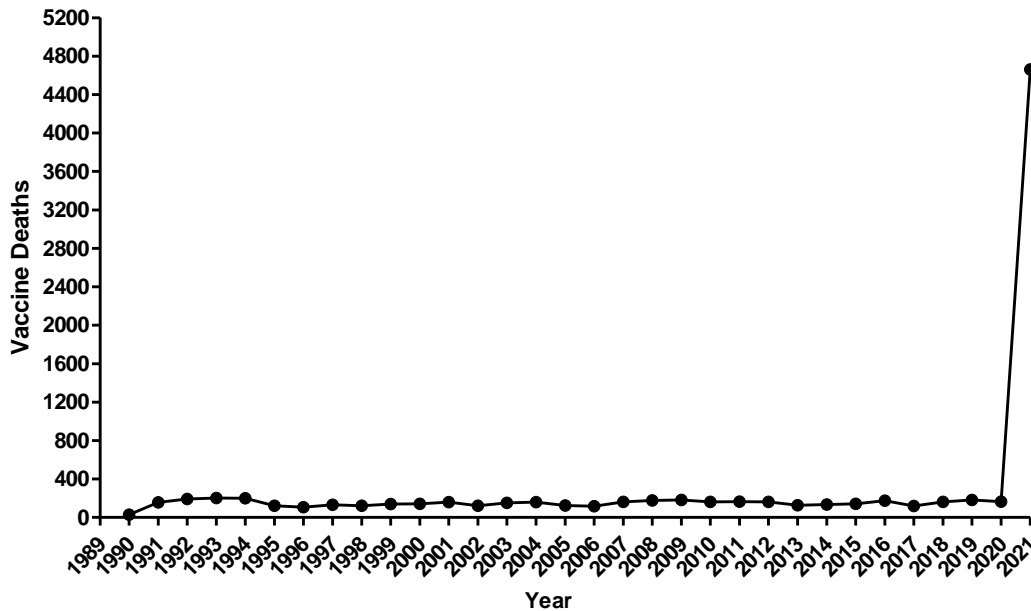
### Long-term

Given the accelerated development of these vaccines, the rapid trial completion and fast-tracked EUA, combined with the fact that this is completely novel vaccine technology, it is undeniably still far too early to know the long-term effects of these vaccines. Most other vaccines commonly administered have been developed and monitored for many years/decades.

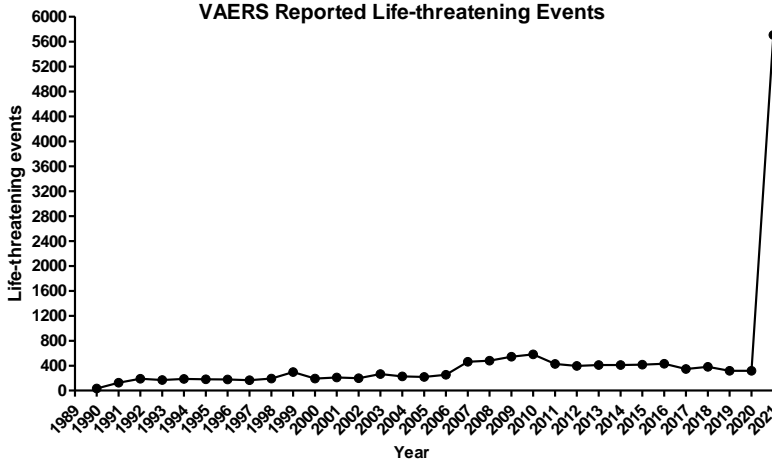
In the months since mass vaccinations have progressed, cases of aberrant blood clotting have been linked to the J&J vaccine, while cases of heart inflammation have been linked to the Pfizer vaccine. While these cases seem rare, they are still very much cause for concern and may be an important deciding factor for those with certain genetic predispositions or family histories of cardiovascular disease.

More alarming still are the very serious effects documented in the CDC's [Vaccine Adverse Event Reporting System](#) (VAERS). This system allows you to search for the rates of any vaccine's adverse events over the past three decades. Since 1990, annual deaths in the US from all vaccines fluctuate at only ~100-200. For COVID-19 vaccine deaths so far in 2021, this figure is at over 4,600 (data displayed below). This increase of ~2,200% is also apparent in the rates of "life-threatening events" and "permanent disability."

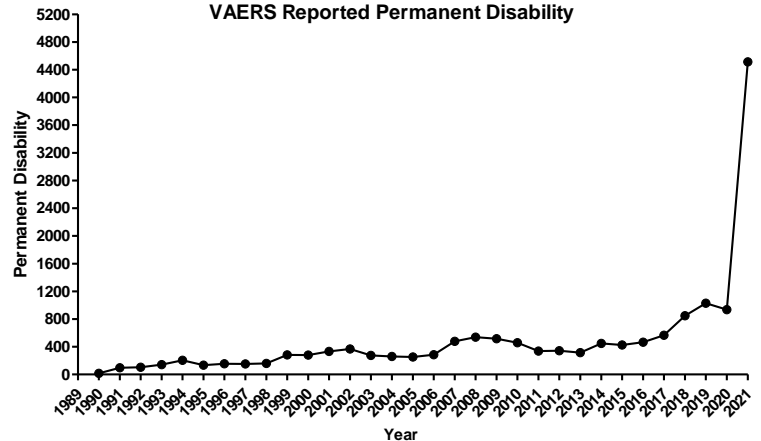
#### VAERS Reported Deaths



#### VAERS Reported Life-threatening Events



#### VAERS Reported Permanent Disability



## Transmission

These rigorously-controlled trials do not provide evidence that vaccination prevents the spread of SARS-CoV-2. Some of the observational studies since then suggest reduced rates of asymptomatic infections, which could prevent transmission, but this has not been confirmed with contact tracing. Even still, a recent [study](#) from a CDC journal reported that asymptomatic cases are unlikely to contribute substantially to the spread of SARS-CoV-2.

## Vaccine efficacy/effectiveness in the real world

### *Current morbidity and mortality trends*

Looking at the available data for hospitalization and death rates for the currently [most vaccinated](#) countries (excluding small territories/island nations), it is not automatically apparent how significantly the vaccination campaigns have reduced these rates beyond what would naturally be expected from the seasonal triggering of viral infections (see **Support Materials – Figure 1**) and the natural increase in immunity with time.

\*When describing efficacy and COVID-19 impact, we should be focusing on hospitalizations and deaths. These are clearly what we care most about in the real world in terms of human suffering and burden on the healthcare system. To focus on “cases” is shortsighted. The way cases have been defined during this pandemic has been simply the presence of a positive SARS-CoV-2 test. This is not a case of disease nor has it ever been. At any given time, a significant proportion of the population are likely walking around unaware with a whole host of “common cold” viruses circulating inside of them. If they went and got tested for these, they might be positive for the virus, but this does not make them a case of the disease. A rise in COVID-19 case numbers, without concurrent increases in morbidity and mortality is often simply the result of increased testing capacity.

\*\*Anthony Fauci [commented](#) on this true case definition at the beginning of the pandemic, comparing true case fatality rate of COVID-19 to the pandemic influenzas of 1957 and 1968.

### *Observational studies*

Admittedly, it is difficult to make conclusions about vaccine effectiveness in the real world based on gross trends from publicly available population-level data. Perhaps the most highly powered (~600,000 participants per group) [analysis](#) of vaccine efficacy in a real-world setting was performed in Israel following rapid, successful mass vaccinations with the Pfizer candidate.

In this study, baseline risk of developing symptomatic COVID-19 in the unvaccinated group was 0.6%, compared with 0.4% in the vaccinated group. So, the vaccine reduced your risk of developing COVID-19 by 0.2%.

Baseline risk of being hospitalized for COVID-19 in the unvaccinated group was 0.04%, compared with 0.02% in the vaccinated group. So, the vaccine reduced your risk of being hospitalized by 0.02%.

Baseline risk of very severe COVID-19 in the unvaccinated group was 0.029%, compared with 0.009% in the vaccinated group. So, the vaccine reduced your risk of very severe COVID-19 by 0.02%.

Baseline risk of death from COVID-19 was 0.005% in the unvaccinated group, compared with 0.0015% in the vaccinated group. So, vaccination reduced your risk of death from COVID-19 by 0.0035%.

These outcome measures again come from the whole sample population studied. Along with age, bear in mind that each study group had significant numbers of people with preexisting conditions that would already make them more vulnerable to COVID-19. This included obesity (16% of participants), diabetes

(11%), high blood pressure (17%), smoking (19%), kidney disease (6%), heart disease (6%). Only 56% of people in each group had no known risk factors. COVID-19 risk is therefore likely to be much lower in younger, healthier individuals.

Other real-world cohort studies in healthcare workers across multiple sites do appear to show protection from symptomatic COVID-19 by the current vaccines to [greater](#) or [lesser](#) degrees. Healthcare personnel and first responders are also likely to have a greater level of exposure to COVID-19, suggesting that vaccination would be appropriate for this population. While vaccine efficacy for elderly individuals was largely lacking in the randomized, clinical trial setting, an observational [study](#) in >80-year-olds has at least shown very promising effects of the Pfizer and AstraZeneca vaccine on rates of hospitalization and mortality. Since these individuals are most at risk, vaccination again seems appropriate for this demographic and should be prioritized.

### **SARS-CoV-2 immunity**

Professor John Ioannidis is a celebrated Stanford University physician-scientist and one of the most highly cited researchers in the world. Initially working with the WHO, Ioannidis published a [meta-analysis](#) of multiple studies to investigate seroprevalence i.e. the degree of immunity within the population from levels of antibodies. This systematic global analysis of seroprevalence estimated 1.5-2 billion infections worldwide, compared with the 112 million documented cases (as of late February 2021). This would mean that documented cases (only PCR-positive infections and not true symptomatic cases) only make up about 7% of total infections and that a significant majority of the population are not at risk and may already have preexisting immunity.

Interestingly, this same analysis puts the infection fatality rate at 0.15%, considerably lower than fearful estimates earlier in the pandemic. It should also be noted that the years of life lost are overwhelmingly one's final years, as the median age of death from COVID-19 is often older than life expectancy (versus other infectious diseases that can impact children more significantly and lead to greater years of life lost).

This analysis is reinforced by a seroprevalence [study](#) carried out in multiple locations in Tokyo in the midst of their pandemic second wave. This is also perhaps the only real-world repeat sampling of antibodies taken serially (every 2 weeks) across 4 months, in conjunction with SARS-CoV-2 PCR testing. Albeit a small cohort size, this study illustrates that antibody levels rose sharply and significantly, even prior to confirmed new cases, and remained elevated during the pandemic, nearing 50% seroprevalence. This also suggests that Japan did not stop the spread of the coronavirus, they were simply healthy enough to combat the pandemic and had a high level of population immunity.

However, it is myopic to focus solely on antibodies as an important source of acquired or preexisting immunity. Other critical sources include mucosal immunity (at the sites of tissue infection) and our immune B and T cell responses. A large body of data suggests that a significant fraction of the population (in some cases ~50%) have long-lasting, preexisting immunity to COVID-19 despite having never been exposed. This cross-protection has been documented with past epidemics and is indeed more than just mediated by antibody levels. These data have been nicely [summarized](#) by the editor of the British Medical Journal.

For those who have already recovered from COVID-19, some recent studies suggest that sustained B cell, T cell and antibody responses can still be identified at least [8](#) to [11](#) months after infection. More importantly, researchers [here](#) also demonstrate that prior infection also induces special bone marrow immune cells (BMPCs), suggesting that for those who have already had COVID-19, lifelong immunity

could be provided by quiescent cells in the bone marrow. This is [echoed](#) by expert virologists at the La Jolla Institute of Immunology, who indicate that complex immune memory may provide protection for many years. The data are additionally supported by the very low rates of reinfection, even among [studies](#) of frontline healthcare workers who may be maximally exposed. [Evidence](#) in this population suggests that prior infection provides a relative risk reduction against symptomatic COVID-19 that would certainly be comparable to the efficacy of current vaccines. Natural infection in general is also considered to give superior immunity to vaccinations, and for many people the price paid for immunity via COVID-19 exposure is very low. Recent [observations](#) from the Cleveland Clinic openly state that those who have already had a natural infection are unlikely to benefit from vaccination.

Given the likely high rates of preexisting immunity in those never exposed, as well as the promising duration of immunity in those previously infected, vaccine administration may simply not be appropriate or necessary in this population. Furthermore, vaccination may in fact be directly inappropriate in those who have been previously infected, given an environment of excessive immune activation and the documented potential for [greater adverse events](#).

### **Summary**

The data and arguments put forward above are intended to question the current assumptions and perceptions around the following:

- The real-world risk and severity of COVID-19.
- The true effectiveness of current vaccines in clinical trials and at the population level.
- The possible short-term and long-term unwanted/unknown side effects of these specific vaccines.
- The population-specificity of any potential vaccine benefits (i.e. not a one-size-fits-all-approach).
- The likelihood of significant population-level preexisting immunity.
- The multiple sources of long-lived immunity from natural infection.
- The appropriateness/risks of vaccines for those previously infected.

## Support Materials

### *Box 1*

#### **Pandemic thought experiment:**

##### **Scenario 1:**

Risk of disease X is an alarming 50% in the placebo trial group. In the vaccine group, the risk of disease X is 20%.

This means that in the trial, risk of disease X was reduced by an absolute 30%.

However,  $1 - (20/50) = 0.6$  relative risk or attack rate ratio = only 60% efficacy.

##### **Scenario 2:**

Risk of disease Y is only 1% in the placebo trial group. In the vaccine group, the risk of disease Y is 0.2%.

This means that in the trial, risk of disease Y was only reduced by an absolute 0.8%.

However,  $1 - (0.2/1) = 0.8$  relative risk or attack rate ratio = 80% efficacy

##### **Conclusion**

Something is very wrong here in only reporting relative risk. Our hyper focus on efficacy, and the way it is being calculated/reported, makes scenario 1 look like an inferior intervention, even though it was cutting a very high disease risk by 30% in absolute terms. My baseline risk in scenario 2 would not give me much cause for concern. To have that absolute nominal risk cut slightly more may result in a better efficacy value simply because of how the ratio plays out, but it does not seem like a more effective societal strategy.

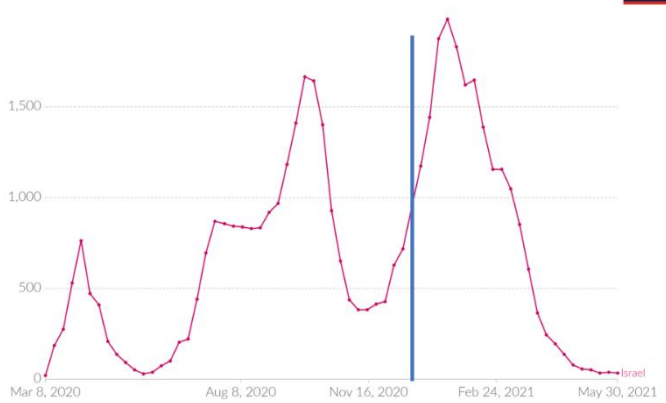


## SUPPORT MATERIALS

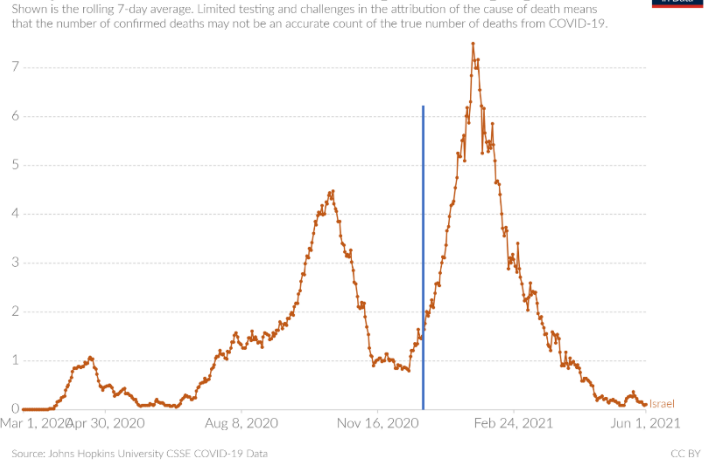
Figure 1. Population level hospitalization (where available) and mortality rates

### Israel. Mass vaccination begins December 19, 2020

Weekly new hospital admissions for COVID-19

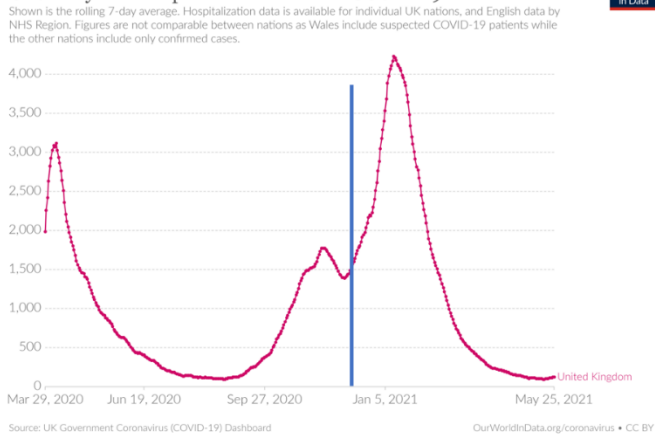


Daily new confirmed COVID-19 deaths per million people

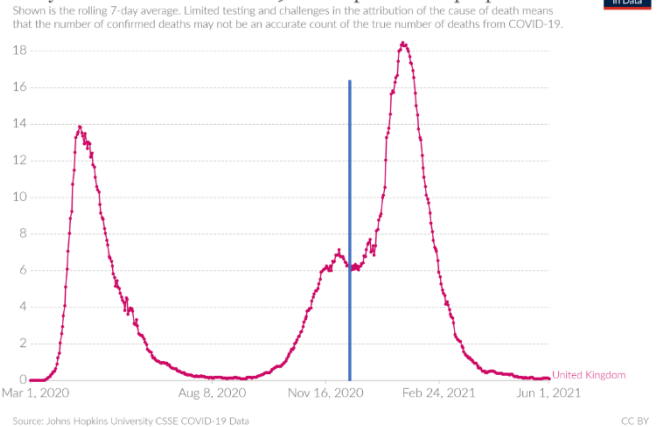


### United Kingdom. Mass vaccination begins December 8, 2020

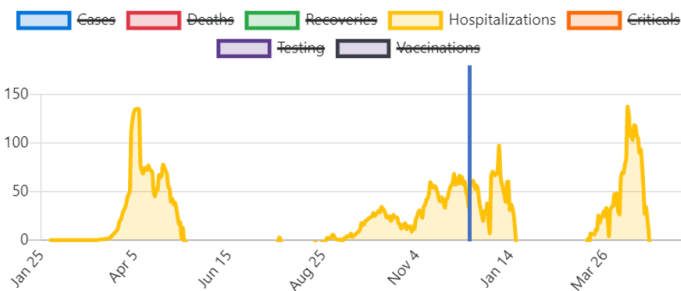
UK: Daily new hospital admissions for COVID-19



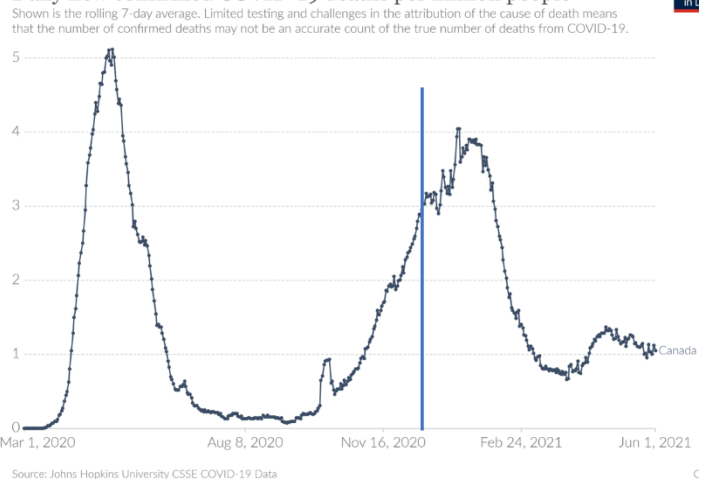
Daily new confirmed COVID-19 deaths per million people



### Canada. Mass vaccination begins December 14, 2020



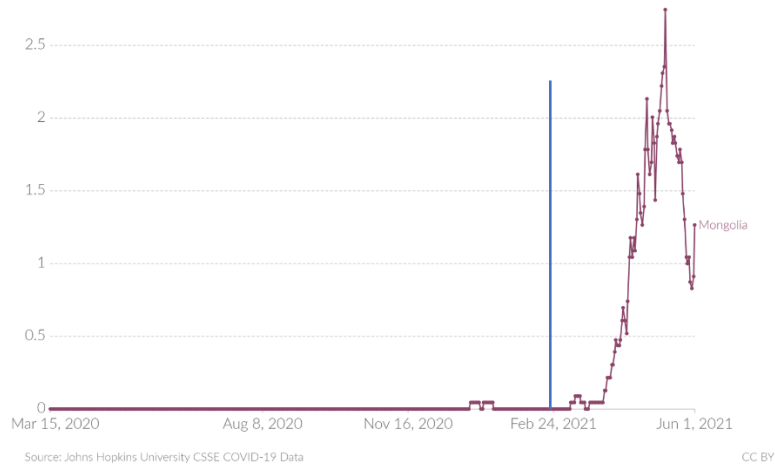
Daily new confirmed COVID-19 deaths per million people



## Mongolia. Mass vaccination begins February 23, 2021

### Daily new confirmed COVID-19 deaths per million people

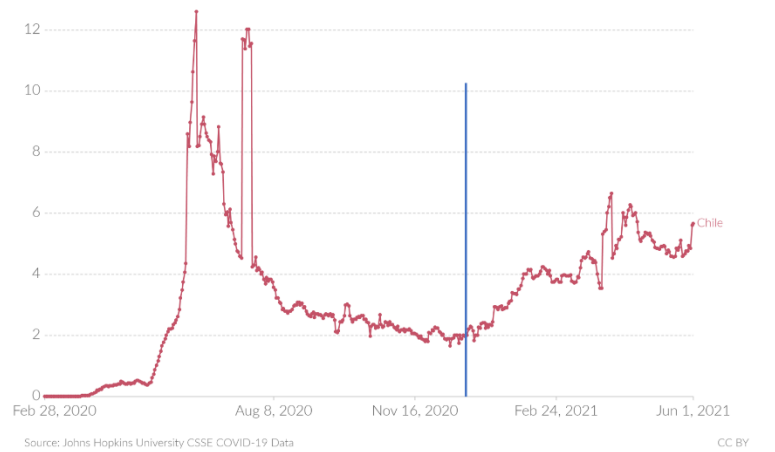
Shown is the rolling 7-day average. Limited testing and challenges in the attribution of the cause of death means that the number of confirmed deaths may not be an accurate count of the true number of deaths from COVID-19.



## Chile. Mass vaccination begins December 24, 2020

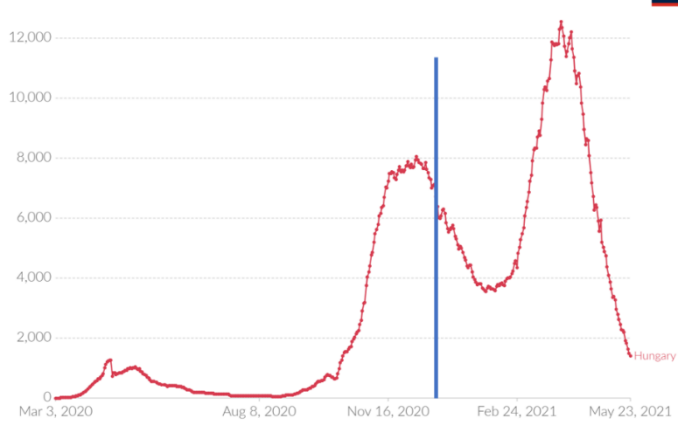
### Daily new confirmed COVID-19 deaths per million people

Shown is the rolling 7-day average. Limited testing and challenges in the attribution of the cause of death means that the number of confirmed deaths may not be an accurate count of the true number of deaths from COVID-19.



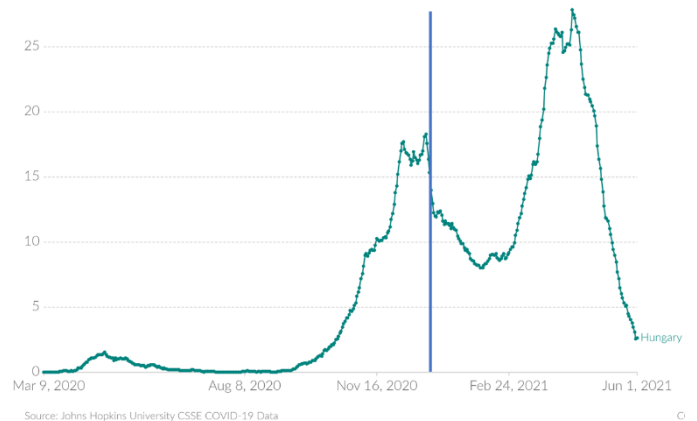
## Hungary. Mass vaccination begins December 26, 2020

### Number of COVID-19 patients in hospital



### Daily new confirmed COVID-19 deaths per million people

Shown is the rolling 7-day average. Limited testing and challenges in the attribution of the cause of death means that the number of confirmed deaths may not be an accurate count of the true number of deaths from COVID-19.

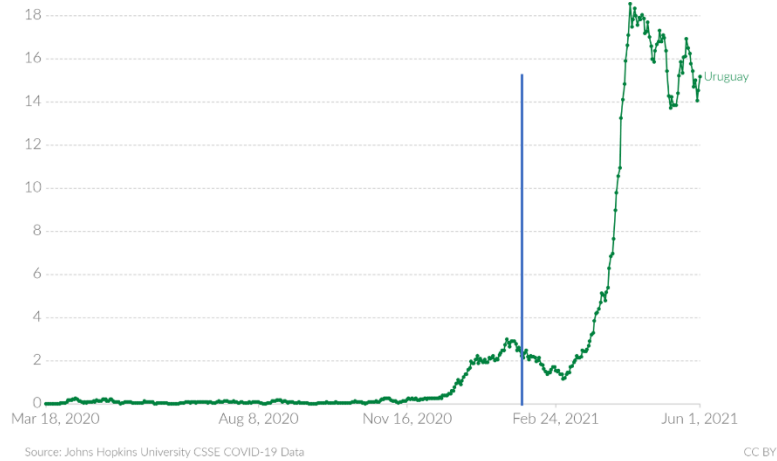


## Uruguay. Mass vaccination begins February 1, 2021

### Daily new confirmed COVID-19 deaths per million people

Shown is the rolling 7-day average. Limited testing and challenges in the attribution of the cause of death means that the number of confirmed deaths may not be an accurate count of the true number of deaths from COVID-19.

Our World  
in Data



## Qatar. Mass vaccination begins December 23, 2021

### Daily new confirmed COVID-19 deaths per million people

Shown is the rolling 7-day average. Limited testing and challenges in the attribution of the cause of death means that the number of confirmed deaths may not be an accurate count of the true number of deaths from COVID-19.

Our World  
in Data

