

COVID-19 vaccines: history of the pandemic's great scientific success & flawed policy implementation

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The COVID-19 vaccine has been a miraculous, life-saving advance, offering staggering efficacy in adults, and developed with astonishing speed. The time from sequencing the virus to authorizing the first COVID-19 vaccine was so brisk even the optimists appear close-minded. Yet, simultaneously, United States' COVID-19 vaccination roll-out and related policies have contained missed opportunities, blunders, run counter to evidence-based medicine, and revealed limitations in the judgment of public policymakers. How can a single intervention simultaneously represent one of our greatest pandemic successes but also encapsulate real limitations? Misplaced utilization, contradictory messaging, and poor deployment in those who would benefit most — the elderly and high-risk — alongside unrealistic messaging, exaggeration, and coercion in those who benefit least — young, healthy Americans — is at the heart. It is important to consider the history of COVID-19 vaccines to identify where we succeeded and where we failed, and the effects that these errors may have more broadly on vaccination hesitancy and routine childhood immunization programs in the decades to come.

Breakthrough Results in Adult Volunteers

On Nov 9, 2020, Pfizer press released results¹ of their ongoing, adult COVID-19 randomized control trial. This trial randomized over 40,000 individuals to the Pfizer-BioNTech vaccine or placebo and showed, after 94 infections, a large, 90% plus reduction in symptomatic COVID-19, among volunteers who did not have COVID-19 at baseline.

A week later, Moderna reported similar results^{2,2}. Their ongoing Phase 3 COVE trial randomized over 30,000 participants to vaccine or placebo. With 95 cases of symptomatic covid, the cases split: 90 in the placebo arm and 5 in the vaccine arm, yielding a 94% reduction in symptomatic COVID-19. The Moderna trial further bolstered claims of efficacy by showing that, among 11 cases of severe disease, all occurred in the control arm. By the time the trial was ultimately published, 30 severe covid cases would occur, including 1 death – all in the control arm.³

It was clear, by the fall of 2020, COVID-19 vaccines could reduce symptomatic COVID-19 and also severe disease against prevailing strain(s) in adults. This finding will be remembered as a seminal moment in medical history, and two of these products rapidly received emergency use authorization (EUA) in the US. Pfizer received EUA on Dec 11, 2020 for ages 16 and up.⁴ Moderna received EUA on Dec 18, 2020 for 18 and up,⁵ with distribution following soon thereafter.

Sowing Doubt in the Months Prior to Emergency Use Authorization

The months preceding the positive press-releases were anything but optimistic. Top US outlets as well as medical and scientific journal articles prior to Nov 2020 continually undermined COVID-19 vaccine prospects, cast doubt on the FDA's regulatory standards, and articulated talking points that, to this day, remain co-opted by anti-vaccine groups.

On June 8 2020, two senior physicians from the University of Pennsylvania wrote an op-ed warning of Trump's potential October surprise — the idea the president would debut a vaccine that did not meet high standards for safety or efficacy prior to the election, in order to boost his

political odds.⁶ The authors drew a comparison to previously approved vaccines, RotaTeg and Rotarix vaccines (for rotavirus), which enrolled 70,000 and 63,000 children, respectively, and took 4+ years to establish safety, efficacy, and obtain approval. The COVID-19 vaccine studies, in contrast, were slated to enroll fewer participants and to be completed in far less time.

The authors lamented that President Trump might rely on antibody titers alone to declare success. The authors wrote, “even if a vaccine generates antibodies, it does not prove that the vaccine is effective at preventing infection; it only makes it more likely that the vaccine would be effective.” The article cautioned that with just 20,000 participants receiving the vaccine, “serious but rare side effects might be missed.”

On August 5, 2020, an essay appeared on the British Medical Journal opinion website entitled, “The rush to create a COVID-19 vaccine may do more harm than good.”⁷ The article lamented the fact that a vaccine may only provide short term protection or may offer only low vaccine effectiveness (less than 50%). The article quotes Phil Krause, then deputy director of vaccines at the US FDA, who said, “A weakly effective vaccine can do more harm than good.”

The BMJ piece also quotes Ken Frasier, CEO of Merck, who said those “raising hopes for a vaccine before year-end are doing ‘a grave disservice to the public.’” Finally, it noted that Trump was, “urging for a vaccine in 2020.”⁸

The idea that we were “rushing a vaccine” was common in media coverage throughout 2020. On Sept 4, 2020, a story in the Washington Post noted, at that year’s Republican National Convention, that Donald Trump promised to, “produce a vaccine before the end of the year, or maybe even sooner.”⁹ Trump added, “Nobody thought it could be done this fast. Normally it would be years, and we did it in a matter of a few months. We are producing them in advance so hundreds of millions of doses can be quickly available. We have a safe and effective vaccine this year, and together we will crush the virus.”

Yet, reporters repeatedly reminded us that we should remain skeptical. The Washington Post article described the 1976 swine flu vaccine debacle that led to hundreds of cases of Guillain-Barré, a paralytic condition, and a product that was ultimately withdrawn. The article noted the FDA’s recent embrace of EUA (for hydroxychloroquine and convalescent plasma — two therapies supported by weak or absent data) and how this could further undermine vaccine confidence.

A few days later (Sept 10, 2020), another piece echoed these concerns. Writing for CNN, an expert New York City physician lamented that, “the history of vaccines is full of alarming missteps.”¹⁰ The piece detailed examples of the erroneous administration of the wrong tuberculosis vaccine, and an unapproved polio vaccine. It revisited the 1976 swine flu vaccine debacle and detailed a 1998 blunder with an ultimately failed Lyme disease vaccine. On Oct 16, 2020, Carl Zimmer, writing for the New York Times, reiterated concern of vaccines, noting that “some vaccines may be abruptly withdrawn from the market because they turn out not to be safe.”¹¹

Some scientists argued that the FDA had asked companies to focus on incorrect outcomes. Writing with a colleague, cardiologist Dr. Eric Topol, penned a New York Times op-ed on Sept 22, 2020 suggesting COVID-19 vaccines should show evidence of lowering severe illness.¹² Symptomatic disease — the primary endpoint of ongoing trials — includes milder forms of illness, while severe COVID-19 is what we truly want to avoid.

A Washington Post op-ed, written by a former Harvard Medical School professor William Haseltine, entitled “Beware of COVID-19 vaccine trials designed to succeed from the start” voiced similar concerns.¹³ Dr. Haseltine advanced the idea that the vaccines could have unknown side effects that occur years after approval. Haseltine wrote, “Rushed Moderna and Pfizer trials could bring about similar short-term health consequences or, potentially far worse, lead to long-term health consequences that we won’t discover until months or years after the vaccine’s approval.”

The idea that vaccines could have negative consequences was articulated very early in the pandemic. In March of 2020, in the journal *Nature*, Shibo Jiang, a vaccine researcher wrote an article entitled, “Don’t rush to deploy COVID-19 vaccines and drugs without sufficient safety guarantees.”¹⁴ In it, he noted that it was possible for a COVID-19 vaccine to accelerate acquisition of the virus. Jiang explains, “Decades ago, vaccines developed against another coronavirus, feline infectious peritonitis virus, increased cats’ risk of developing the disease caused by the virus. Similar phenomena have been seen in animal studies for other viruses, including the coronavirus that causes SARS.” A detailed timeline of these quotes appears in **Figure 1**.

An article in the *Lancet* from October 27, 2020, echoed this concern regarding adenoviral vector vaccines (AstraZeneca and Johnson & Johnson),¹⁵ “We are writing to express concern about the use of a recombinant adenovirus type-5 (Ad5) vector for a COVID-19 phase 1 vaccine study...” and described their experience with an HIV-AIDS vaccine that paradoxically enhanced infection.

On Sept 23, 2020, the National Vaccine Advisory Committee advised against the use of EUA (a lower regulatory hurdle), and instead urged the use of Biological Licensing Agreement to clear a COVID-19 vaccine, a process that would delay approval many months.¹⁶

Peter Hotez, founding dean of the National School of Tropical Medicine at Baylor College of Medicine, wrote a Twitter thread in Sept 2020 citing a “dozen reasons” why he was skeptical of using EUA -- the regulatory path used initially by all COVID-19 vaccines.¹⁷ He specifically called the pathway, “a substandard or lesser review” process than the more traditional biological licensing agreement.

Ashish Jha, at the time a professor of medicine and frequent television pundit, who would ultimately become the Biden COVID czar said that commissioner Steve Haan was “suggesting he could issue EUA for a vaccine if benefit > risk.” Jha writes, “That is totally inappropriate. Unlike therapies, which are given to sick people, vaccines are given to healthy people. Needs a higher bar. Full (expedited) review after completed phase 3.”¹⁸

Public perception of vaccine deteriorated over the summer of 2020. By mid-September 2020, [Pew research showed](#) trust in vaccines had plummeted since polling from May of that year.¹⁹ As of September, 78% of respondents felt that the greater risk was moving too fast with vaccination, rather than too slow, and 77% felt a vaccine would be approved before its safety and efficacy was fully understood. Both Republicans and Democrats were less likely to get the vaccine than in prior polls, with Republicans displaying greater reluctance than Democrats. A Gallup poll from September (eventually published in the Journal of the American Medical Association) confirmed that Republicans were less likely to seek vaccination and more likely to oppose mandates.²⁰

In short, the months preceding the successful press releases from Pfizer and Moderna witnessed juxtaposed messaging: ranging from sensational, optimistic, and promising statements by President Trump, to a concern that vaccines may be approved without sufficient safety and efficacy data from the media, politicians, and scientists. Key talking points included: stories of prior failed vaccine products, claims that long-term safety would not be known at product launch, suggestions that a COVID vaccine could theoretically enhance illness or viral acquisition, claims that 20,000 participants were insufficient to exclude rare safety signals, and arguing that the EUA process was substandard, and perhaps should not be utilized. Ironically, several of these points would prove salient to subsequent vaccine and booster authorizations, particularly in young populations, and the emerging understanding of vaccine induced myocarditis, while other points would be co-opted or misused to justify vaccine hesitancy among older adults in the months that followed.

It is difficult to separate what portion of skepticism was scientifically motivated — due to the testing of a hitherto novel vaccination platform (the mRNA technology) on an unprecedented time-scale (mere months) with implications for the fate of world and global economy — and how much was politically motivated — distrust of a divisive sitting US president, Donald J Trump, who faced a contentious re-election campaign, who was repeatedly one of the vaccines' most passionate proponents, and whose administration launched the Operation Warp Speed program, which was, in part, responsible for the rapid development.

The FDA and companies delay vaccine trial until after the US election

One major point of contention throughout 2020 was when vaccine trial results would be reported and when a vaccine would be distributed. Trump repeatedly felt that this would occur as early as October 2020, and certainly before the end of the year,²¹ while ultimately the results were released on Nov 8, 2020, and public vaccination began in December.

An *MIT Technology Review* article notes that some physicians have taken credit for delaying the trial results until November. The piece was entitled “One doctor’s campaign to stop a covid-19 vaccine being rushed through before Election Day: How heart doctor Eric Topol used his social-media account to kill off Trump’s October surprise.”²² The piece describes several tactics used to delay approval.

Topol and 60 experts sent an open letter to Albert Bourla, CEO of Pfizer, asking for a minimum of 2 months of follow up for each enrolled volunteer in vaccine trials, a change of protocol that would ensure approval could not occur until after the November election.²³ The letter did not explain why 2 months per participant would enhance safety – in contrast with a median of 2 months follow-up, meaning some participants could be followed for less time, as long as others were followed for more time. After the letter was publicized, according to Politico, Albert Bourla and Eric Topol met to discuss concerns of approval prior to the election.²⁴

The FDA did change its guidelines for EUA of COVID-19 vaccines in September of 2020,²⁵ but ultimately decided upon 2 months of median follow-up (not the Topol letter's suggestion). It also required at least 5 cases of severe disease in the control arm. This requirement had potential to extend trial duration.

Clinical trials may stop after a pre-defined number of events, in this case, symptomatic SARS-CoV-2 infections, and after statisticians have examined the rates by arm. If events are extremely skewed, i.e., exclusively happening in 1 arm or the other, a trial can be deemed statistically persuasive and be halted, even if the raw number of events are few. On Sept 9, 2020, Eric Topol interviewed Dr. Paul Offit for the website Medscape.²⁶ During the interview (per transcript), Dr Topol seemed shocked a trial could be persuasive with 100 events. He said:

“But this week, for example, the Pfizer CEO said they could demonstrate efficacy with very small numbers²⁷ of cases in the placebo and vaccine groups; these numbers seem totally out of line with what would be considered stopping rules. I mean, you're talking about giving a vaccine with any of these programs to tens of millions of people. And you're going to base that on 100 events?”

Dr. Offit explains that it is not the raw event numbers, but the distribution across arms that matter; one could have a significant trial even with few events, “assuming that you have just a handful or fewer people in your vaccine group who were ill.” And again, Offit replies, “I think one could only imagine stopping with 160 cases if you have virtually no cases in your vaccine group.”

Ultimately, when Pfizer announced results on Nov 8th, the company noted it had “recently elected to drop the 32-case interim analysis and conduct the first interim analysis at a minimum of 62 cases.”¹ By the time the company analyzed results, 94 cases had occurred.

An article in the journal *Science* tried to dismiss the allegation that the number of events was altered merely to delay the vaccine trial result until 5 days after the ongoing US presidential election.²⁸ The article contends that COVID19 events were accruing rapidly, and given that 62 events would occur shortly after, this was preferred for improved “statistical power”. But this explanation is problematic because 32 events was carefully chosen, and the distribution of events was deemed *a priori* to be mathematically persuasive if it were reached. Specifically, the trial would only be halted if fewer than 6 events of 32 (6 vs 26) occurred in the vaccine group. With fewer total events,²⁹ the skew would have to be more extreme to halt a trial than with far more events to preserve the statistical confidence.

Second, adherence to a pre-planned statistical plan is far better for confidence than any protocol deviations or modifications—for this precise reason: doubt can exist about the true motives. The same *Science* article discusses how because of the ongoing changes, Pfizer had stopped testing swabs to avoid a protocol deviation, which resulted in 94 events occurring before testing, and a further delay in results. And third, FDA officials postulated that between announcing trial results and FDA meeting further events would occur, likely raising the total number of events to over 100.²⁹

These changes (minimum severe disease case requirement and change in interim analysis) delayed the eventual trial results. It is unclear if these design features enhanced the scientific validity of the trial. It is also unclear on what specific day results would have been reported had it not been for changes.

The Vaccine is Rolled Out, Poorly

By December 2020 and into January 2021, vaccination began. Three decisions illustrate suboptimal vaccine deployment.

First, the US overprioritized young essential workers. While the UK prioritized nursing home residents and older individuals (>80),³⁰ the US included essential workers, including young, resident physicians. Of course, health care workers face higher risks of acquiring the virus due to occupation (though this was and is offset by available personal protective equipment), but this was less than the elevated risk of death faced by older individuals. In other words, while the increased risk of occupational exposure was on a linear scale, the increased risk of poor outcomes by age grew exponentially.

Second, actions taken by the USA repeatedly pushed to vaccinate young people prior to vaccinating older people globally.³¹ The WHO specifically stated on Nov 21, 2022:³²

“As a matter of global equity, as long as many parts of the world are facing extreme vaccine shortages, countries that have achieved high vaccine coverage in their high-risk populations should prioritize global sharing of COVID-19 vaccines through the COVAX facility before proceeding to vaccination of children and adolescents who are at low risk for severe disease.”

Third, the US insisted on a 1 dose first vaccination strategy³³ – where dose 2 would be delayed – in order to give more individuals a first dose in the setting of a constrained supply—should not be pursued. This decision would ultimately prove erroneous. A number of studies³⁴ ultimately established that delaying³⁵ the second dose would have lowered population case rates and COVID-19 mortality, and increased antibody production³⁶ and possibly durability. The United Kingdom did move forward with a 1 dose strategy, a decision that analysts believe has been totally vindicated.³⁷

Johnson and Johnson Vaccine Leads to Vaccine Induced Thrombocytopenia and Thrombosis.

The third entrant to the US market was the Johnson and Johnson adenoviral vector vaccine. The product was notable for requiring only a single dose, and was authorized on Feb 20, 2021.³⁸ The product was supported by the phase 3 ENSEMBLE study which found a 67% reduction in the primary endpoint of symptomatic SARS-CoV-2.³⁹ As the third entrant into the market, J&J never enjoyed the market share of its predecessors, but due to easier temperature requirements and a single dose administration, it offered some advantages. Yet, very quickly after product launch, an important safety signal would emerge.

In mid-April 2021,⁴⁰ a series of unprecedented vascular events were noted, mostly in women, shortly after receipt of the Johnson and Johnson vaccine, which prompted the FDA to issue a pause while it investigated. In the weeks that followed, it became clear that a real and unanticipated side effect of the adenoviral vector vaccines was vaccine induced thrombocytopenia and thrombosis (VITT) – a condition with runaway platelet activation and profound clotting. After being given the J&J vaccine, several young women died or were neurologically devastated.⁴¹

On social media, efforts were made to downplay the concern, and memes emerged contrasting the risk of clotting after J&J vaccines to clots after oral contraceptives.^{40,42,43,40} However, these were in no way analogous, as the vaccine's clots were noted to occur in the cerebral veins, and in the setting of runaway platelet activation – a far more dangerous hematologic condition than a blood clot in a lower limb. Some sought to subtract baseline rates of cerebral vein clots from population estimates of VITT. This was inappropriate because VITT is an entirely novel hematologic ailment, of which there is no baseline rate. Cerebral venous thrombosis in isolation is distinct from the same clot in the setting of runaway platelet activation that denotes VITT.

On April 15th, 2021,⁴⁴ I argued that, given the presence of alternatives (Pfizer and Moderna), that it was “game-over” for J&J in women less than 50 years old. The US should halt its use. Yet, the FDA released the pause and took no major action until May 2022 (a full year later),⁴⁵ when it changed the label for J&J restricting it only to those who cannot take another vaccine for medical reasons. This 1-year delay led to unnecessary vaccine-induced injury.

Two lessons from the J&J fiasco carry implications going forward. First, vaccine regulation can be quick to authorize in times of crisis, but far slower to address serious safety concerns. This remains a problem. And second, in a new year, and with a new president, media and pundits would repeatedly err on the side of downplaying vaccine concerns, while before they had exaggerated them.

Myocarditis from mRNA vaccines in young, healthy men

The first reports that myocarditis⁴⁶ – an inflammation of the heart muscle – may be an important safety concern for mRNA vaccination emerged in the Jerusalem Post in February 2021.⁴⁷ By April 25, 2021, Reuters had picked up the story.⁴⁸ Yet, on April 27, 2022, the CDC commissioner specifically denied having found a link,⁴⁹ “We have not seen a signal and we've actually looked intentionally for the signal in the over 200 million doses we've given.” The European Medicines Agency launched an inquiry on May 7, 2021.⁵⁰ By May 22, 2021, the CDC

had reversed course and announced it had received reports and encouraged providers to send in more.⁵¹

As of 2022, accumulating evidence has found that mRNA vaccines are associated with myocarditis.⁵² This occurs most often in young men (aged 12-30), with peak incidence in those 16-24 years of age. It occurs more often with dose 2 (than dose 1), and some studies suggest it occurs more often with the Moderna product than Pfizer's. It also occurs after boosters (3rd doses).⁵³ As such, several European nations have restricted Moderna in young people,⁵⁴ as early as October 2021.⁵⁵

Myocarditis changed the COVID-19 vaccination calculus, yet the US never adequately responded. The goal of vaccination programs is to maximize the benefit of vaccination and minimize the harm. Now, a clear safety signal has emerged in a target demographic. This demographic faces far lower risks from SARS-CoV-2 than older ages and yet now faces non-trivial safety concerns. In June of 2021, my colleagues and I argued that the CDC's "all or nothing" approach to vaccination may be misguided.⁴⁶

Our analysis was simple. Some estimates suggest the first dose alone provides 85-95% reductions in hospitalization (Figure s6)⁵⁶. In that case, do young men truly benefit from dose 2? Or do the harms outweigh the benefits? One analysis suggests maybe not, at least for healthy adolescents.⁵⁷ Or, alternatively, what if the doses were spaced further apart? What if lower doses were tried in young men? Current schedules use 100 micrograms x 2 (Moderna), or 30 micrograms x 2 (Pfizer) in both 20-year-old men and 80-year-old women. Is this optimal? Should vaccination guidelines vary between young people with comorbidities and those who are completely healthy? And most importantly, should the guidelines be altered for young people who have had and recovered from COVID-19? In other words, do infections count as 1 or 2 doses?

The way to answer these questions with highest scientific accuracy is to demand Pfizer and Moderna conduct a randomized controlled trial for each question. There are hundreds of thousands of individuals who struggle with each of these dilemmas. Moreover, both Moderna and Pfizer have profited tremendously from the pandemic and have the resources to resolve these uncertainties. Yet, neither the CDC nor FDA have demanded companies complete these trials. The FDA did demand Pfizer collect random cardiac enzymes after vaccination to identify the extent of subclinical myocarditis,⁵⁸ but the company has yet to satisfy this requirement.

In the absence of demanding and rigorous trials, the CDC is not impotent. The agency could experiment in uncontrolled fashion. Try any of these strategies and follow young men to see if their COVID-19 outcomes were favorable. As yet, a third alternative, the CDC could make changes to mitigate harm – such as limiting Moderna or spacing doses – based on precaution.

Notably, Norway initially spaced doses in adolescents at 12 weeks, and only later permitted doses to be given 9 weeks apart.⁵⁹ Later the agency said adolescents could get 1 dose if they wished,⁶⁰ adding, "the greatest benefit has already been achieved by taking the first dose, and a second dose entails a slightly elevated risk of myocarditis." This logic was later extended to their

5 to 11 year old guidance.⁶¹ The US meanwhile waited until February 2022 to allow spacing the doses up to 8 weeks apart,⁶² but has taken no other measure to lower the risk of this unfortunate adverse event. Rhetoric has repeatedly sought to discount the concern rather than ameliorate it.

As such, the US failed the social contract of accelerated vaccine authorization, thus eroding public trust. While emergency use authorization makes sense in dire and critical situations, there must be an equal effort to act expeditiously upon safety signals. In this case, we have not explored ways to preserve efficacy while mitigating risk, and this will be remembered as a failure of COVID-19 vaccine programs.

Natural Immunity

Early in the pandemic, two physicians wrote in the *New York Times* that antibodies were not destiny.⁶ This turned out to be prescient for COVID-19, particularly among individuals who had experienced and recovered from the virus. Of course, for most adults, it is preferable to get the vaccine rather than the virus, but many individuals were unfortunately infected with sars-cov-2 prior to vaccination or boosting. For them, it is clear additional vaccine doses increase antibodies, but it is not clear whether vaccination – and how many shots – is needed to further lower risk of bad outcomes from COVID-19 reinfection.

Data suggest that having had and survived COVID-19 means the risk of bad outcomes following reinfection are staggeringly low. A paper that analyzes New York and California shows this clearly.⁶³ Risks of hospitalization among those who had not had a previous COVID-19 diagnosis and were not vaccinated was 11.5 per 1,000, while the risk of hospitalization for those who had a prior infection, regardless of vaccination, was 0.3 per 1,000. The risk for those who were vaccinated without a prior diagnosis was 0.7 per 1,000. These results indicate that it is those who are unvaccinated without a prior infection, and not those who are unvaccinated with a prior infection who have a much higher relative risk of being hospitalized – somewhere between 2- and 17-times higher.

People who have been vaccinated or those who survived prior infection do not need proactive targeting by public health agencies. Instead, unvaccinated and uninfected adults deserve our focus. Yet, COVID-19 vaccine policies never acknowledged this. We could easily have accepted natural immunity as a vaccination equivalent, but the US CDC chose not to do this.

On an episode of a popular medical YouTube channel, the ZDoggMD show, vaccine researcher Paul Offit admitted that the White House conducted an informal poll to decide if natural immunity would count as a vaccine equivalent,⁶⁴ but this vote narrowly fell short. This error had severe negative repercussions for US faith in experts and public health and should not have been the subject of an informal, private vote.

Mandates

An ethical prerequisite for mandating medical interventions is that there is sufficient benefit to others such that loss of individual autonomy is permissible. On Sept 9, 2021⁶⁵⁶⁶, the Biden

administration moved forward with vaccine mandates both for federal employees and private employees through OSHA regulation.⁶⁷ Of course, as noted, polls showed that Republicans would be far more reluctant to embrace mandates than Democrats,²⁰ and this action would further inject politics into vaccination campaigns.

More importantly, it is unclear whether the ethical prerequisite of benefit to others was met for vaccination. Available data in 2021 and early 2022 suggested that being vaccinated conferred tremendous personal benefit to the recipient, such that it was unclear if there could be added gain for demanding others be vaccinated too for added protection. By mid-2022, vaccines did offer modest reduction in transmission, but personal health benefits against severe disease were largely retained. Yet, by the fall of 2022, and rise of the Omicron variant, a new verdict had emerged. Vaccines were unable to halt transmission in the presence of escape variants; thus, here too, mandates failed to meet the ethical pre-requisite of benefit to others, as a vaccinated person could still spread the virus. A study in the *New England Journal of Medicine* showed comparable rates of viral shedding comparing vaccinated to unvaccinated people with COVID19.⁶⁸

Even if one believed that mandates were ever ethically permissible, it is not clear they were wise public policy in a divided nation with strong political preferences around mandates.⁶⁹ First, gains in vaccination must be discounted by the secular trend, i.e., mandates should only be given credit for vaccination beyond what was expected in their absence. Second, gains from mandates would be offset by a fraction of employees being displaced from work – their negative socioeconomic and health outcomes must be added to the ledger. Third, mandates were an exercise of the sheer power of the federal government, and may still yield unanticipated effects, such as shifts in political power or voting preferences or erosion of trust in public health. These choices may erode health outcomes for decades to come.

One place where COVID-19 vaccine mandates have caused great consternation is as a prerequisite to attend public school. Famously, Los Angeles announced one such mandate. At the time, in *US News and World Report*, I argued that this would be unnecessarily draconian, disproportionately exclude minority and poor children from public education, and have unclear public health gain.⁷⁰ Ultimately, Los Angeles backed away from this proposal,⁷¹ likely when it became evident the policy would disproportionately target black and Hispanic communities. A similarly misguided bill was offered at the California State level, but ultimately did not become law.⁷² Yet, the fall of 2022, saw some districts—such as the District of Columbia—pursuing these policies, despite concern of disproportionate impact on black children.⁷³

Colleges took harsher actions. Many colleges rapidly embraced both vaccine and booster mandates.⁷⁴ Boosting requirements often did not contain exemptions for a prior or recent COVID-19 infection. It remains unclear and reasonably unlikely, that boosting a 20 year old healthy man who already had 2 doses and then gets breakthrough Omicron would benefit him or others, and yet that was precisely the requirement to attend in-person college.⁷⁵ Emboldened by federal mandates, schools and colleges pushed mandates of their own which seemed to defy logic. Thousands of students petitioned for these to be dropped.⁷⁶

Vaccine Effectiveness against symptomatic disease (not severe disease) plummets

While vaccine effectiveness gradually fell during 2021 – i.e., the ability of the vaccine to prevent any symptomatic disease was reduced – the rise of Omicron led to plummeting vaccine effectiveness, being reduced from about 50-90% to about 10% or lower.⁷⁷ (Protection against severe disease remained strong.)

Of course, plummeting vaccine effectiveness has implications for the ethics of vaccine mandates⁷⁸ – loss of autonomy is not justified if a vaccine cannot benefit a third party – as well as the use of vaccine passports (used by restaurants and bars or airline travel (in Canada)⁷⁹) – excluding individuals by vaccination status is not ethically permissible when vaccination cannot separate individuals who can spread from those who cannot.

Beyond this, the rise of immune evasive viral variants meant that no amount of vaccination would halt viral spread. The goals of vaccine campaigns, particularly additional doses, had to shift to focus solely on further reductions in severe disease – beyond what was achieved by the first 2 doses – and not merely to reduce symptomatic infection. Ironically, this was the original point by Topol and colleagues in 2020. This is true for a simple reason, that, if one lives long enough, with repeated exposure, infection and re-infection are inevitable, likely many times over a long life. Instead, avoiding bad outcomes is the only justification for repeated dosing of mRNA vaccination.

Boosters and FDA Resignations

In April 2021, the Pfizer CEO Albert Bourla announced that we would likely need boosters in the next 12 months.⁸⁰ In the months that followed, there was initially push back from the administration, including from Dr. Anthony Fauci. In July 2021 however, a private meeting would occur between senior administration officials and Pfizer, and from that moment forward, the White House began to push the message that a booster would be necessary.

Yet, two senior FDA officials were not persuaded – Marion Gruber and Philip Krause (aforementioned). These two served as director and deputy director of vaccine products for years and survived all 4 years under Trump. They authored a piece in the Lancet on Sept 13, 2021 critical of the evidence for universal boosters.⁸¹ They wrote, “Current evidence does not, therefore, appear to show a need for boosting in the general population, in which efficacy against severe disease remains high.”

Unfortunately, facing immense White House pressure to authorize a booster for all ages, the two resigned in protest.⁸² Despite Trump’s many forward-looking statements on vaccine authorization, these two remained, but resigned in protest under his successor Joseph Biden. Of course, given plummeting vaccine effectiveness against symptomatic disease, it was possible that a 3rd dose would transiently lower the risk of breakthrough infection, but this would be beside the point. In a world where breakthrough is inevitable only severe disease, hospitalization and death are suitable endpoints to judge the success of repeated vaccine injections. To date, there are no high-quality data supporting vaccines in young ages (which was

the root of Gruber and Krause's objection). This was further described in multiple op-eds by Dr. Krause.^{83,84} Paul Offit famously advised his own son—in his twenties—not to receive the booster.⁸⁵

EUA in Kids

COVID-19 was initially an emergency in adults, but for kids it was unclear. The UK's Financial Times reported the infection fatality rate by age in two periods of time (2020 and 2022).⁸⁶ The analysis makes clear that in 2020, influenza had a comparable rate of death per infection than COVID-19, but by 2022, COVID-19 was far lower for children. An analysis from Germany found that the risk of death to a healthy child, during the height of the pandemic and pre-vaccine June 2020 - May 2021, with COVID-19 was 3 in 1,000,000.⁸⁷

Whether or not kids faced an emergency has regulatory consequences. The use of the EUA pathway – which Dr. Hotez called “a substandard or lesser review” in 2020 – hinges on whether an emergency is taking place. On May 7, 2021, with my colleagues Drs. Stefan Baral from Johns Hopkins and Wes Pegden from Carnegie Mellon, I wrote an essay in *BMJ Opinion* arguing that use of EUA pathways was not warranted for kids vaccine, and that the traditional biological licensing agreement pathway ought to be used.⁸⁸

As mentioned, the argument for traditional approval had been advanced by the National Vaccine Advisory Committee for adult COVID-19 vaccination in Sept 2020,¹⁶ but that argument made little sense at that moment, as COVID-19 posed tremendous risk to adults and was an emergency. Instead, for children the argument did hold. At the time we wrote, “Controversy surrounding mass child vaccination under emergency use authorizations could feed vaccine hesitancy in the United States at a time when public attitudes towards vaccination are critical.” This argument has proven prophetic as both the COVID-19 kids vaccine uptake is low (~33%), and we have seen a decline in routine childhood vaccination. The *New York Times* reports this is, in part, attributable to “a groundswell of resistance to COVID-19 shots spilling into unease about other vaccines.”⁸⁹

Before the resignation of Gruber and Krause, in July 2021, the FDA had asked Pfizer and Moderna to expand the sample size of their kids vaccine studies.⁹⁰ Kids vaccine trials used the primary endpoint of geometric mean antibody titers – i.e., antibody levels – and sought to show the antibody levels generated in kids were not inferior to those generated at older ages. The vaccine tested in kids was at a lower dose than in adults, but fundamentally directed against the original viral sequence isolated in Wuhan. The motivation for trial expansion was unlikely to further solidification of knowledge of antibody levels, but more likely for exploration of safety and other, more relevant, measures of efficacy, such as rates of COVID-19 disease.

Arguably, the endpoint (antibody levels) of the kids' vaccine trial was inadequate.⁹¹ Parents and doctors did not merely want to know that the vaccine generated antibodies, but instead that vaccination lowered the risk of severe disease, death, or the multi-inflammatory syndrome (MIS-c) in kids. As mentioned in the op-ed from June of 2020, antibodies alone were generally not sufficient to draw this conclusion. They especially were not sufficient against the backdrop of an

evolving and changing virus. Prior commenters noted the much larger size of the Rotavirus (60k and 70k +) and Polio trials (400k+), but the Pfizer 5 to 11 year old trial would begin with a plan to recruit just 2000 kids and, after expansion, eventually enrolled under 5000 kids.⁹² This sample size would be too low to draw any conclusions regarding whether, or to what degree, the vaccine protected against the endpoints that parents care about. Moreover, data from 2022 would show that, in the face of Omicron, the effectiveness of a kids vaccine would wane rapidly.⁹³ Again, the US FDA could have compelled Pfizer to conduct large randomized trials to definitively settle the question, but did not.

In the absence of randomized studies, experts relied on a case-control design to infer that kids vaccines (5 to 11) lower severe disease.⁹⁴ Yet these studies contain a fatal flaw worth understanding. In a case control study, you select cases – kids hospitalized for COVID-19 – and controls – kids hospitalized for something else – and ask how often each group received antecedent vaccination. If the controls have much higher rates than cases, the inference is that vaccination confers protection against disease.

Yet, this analysis hinges on the assumption that cases and controls are otherwise comparable. Are they? Controls – kids hospitalized for other reasons – also includes a subset of kids with severe underlying medical problems or those at risk for hospitalization. Some of these kids may be expected to be hospitalized beyond what we might expect for cases. Pediatricians and parents of these kids would be intensely interested in promoting vaccination in this group– because they know these kids are vulnerable– and thus a case control study that shows “vaccines lower severe disease” may in reality be showing little more than “parents of kids likely to be hospitalized were eager to vaccinate their kid.” It is difficult, if not impossible, to overcome this limitation in case-control studies, and other designs suffer from deep methodologic challenges beyond the scope of this essay. It is still uncertain whether, and to what degree, vaccinating kids 5 to 11 will reduce severe disease, hospitalization, MIS-c, and death.

6 Months to 4-Year-Olds

The growing list of COVID-19 vaccine errors – pushing it in populations at low risk, mandating it when ethical pre-requisites were not met, and failing to generate reliable, informative evidence – came to include vaccine approval for kids 6 months to 4 years old. The series of events around EUA in the United States raised countless concerns. I will highlight the most important ones, and refer readers to other essays that lay out the full case.⁹⁵ These are also shown in the timeline in **Figure 2**.

First, the US FDA again tasked vaccine makers with showing non-inferior antibody levels, and not improvements in symptomatic disease, severe disease, hospitalization, MIS-c, or death. Next, Pfizer famously failed to meet even this modest bar. The company was permitted by FDA to add a third dose to the trial.⁹⁶ This protocol modification showed immense flexibility from regulators. If additional doses could be added until non-inferiority was reached, then the likelihood the findings could occur by chance alone, swells, alternatively, the trial should have been halted and restarted with a higher dose.

In January 2022, a series of leaks suggested the FDA may have invited Pfizer to submit for EUA based on an interim analysis of symptomatic cases that favored the vaccine arm.⁹⁵ This would have been an astonishing and unprecedented lowering of regulatory standards (an unplanned look at an endpoint that was not the study's primary endpoint), and the idea faced strong pushback. Ultimately on the cusp of an advisory meeting, Pfizer abruptly withdrew their EUA. This back and forth spanned a two-week period, when some American parents got their hopes up, only to have them dashed. Vaccine regulators seemed unconcerned their erratic actions might spawn doubt in the American public.

Then, several months later in June of 2022, both Pfizer and Moderna ultimately received EUA for kids aged 6 months to 4 years old. Both companies reported meager vaccine efficacy against symptomatic disease in the face of Omicron. For Pfizer, the US FDA declined to endorse a specific numerical estimate of vaccine efficacy. The FDA writes, "An additional analysis pertaining to the occurrence of COVID-19 cases was determined not to be reliable due to the low number of COVID-19 cases that occurred in study participants."⁹⁷ For Moderna, the agency endorsed a vaccine efficacy of 50.6% in kids 6 months to 2 years and 36.8% in kids aged 2 to 5.⁹⁷

However, one crucial development was, by the time these studies were conducted, that home based testing had gained popularity. The primary study analysis relied on laboratory testing and excluded home tests. If home tests were included (page 116),⁹⁸ the vaccine effectiveness for Moderna plummeted to 28.5%. Recall the argument from 2020, "A weakly effective vaccine can do more harm than good." -- that quote was from Phil Krause, one of the two resigned FDA reviewers, and that line of thinking and those standards had been entirely forgotten.

There is one more major issue with the kids less than 5 years old vaccine trials. These studies included very few children who had previously recovered from COVID-19. That is in stark contrast to the reality in America according to the CDC's own statistics,⁹⁹ where at least 75% of kids already had COVID-19. As mentioned, natural immunity means that it is harder for someone to become reinfected with the virus and suffer a severe consequence. Frankly, the FDA has no reliable data that vaccinating a healthy child who already had COVID-19 with an old, ancestral Wuhan strain-based mRNA vaccine (the only vaccines used to date) lowers that child's risk of severe disease, MIS-c, hospitalization, or death. Worse, this is most kids. As vaccines appear powerless, with time, to halt transmission, there is no evidence that vaccination benefits parents, grandparents, teachers, or the community. At the same time, myocarditis appears to be largely a post-pubescent phenomenon, and rates in children are lower than adolescents; thus, the vaccine is safer.

Ultimately, the FDA's and CDC's actions with kids' vaccines are a complete medical, public health, and regulatory gamble with complex spill-over effects for other vaccines.⁸⁹

A Yearly Covid Shot?

We are rapidly moving toward a yearly vaccine taken in perpetuity—based on preclinical data, including animal studies, but without randomized trials measuring clinical outcomes. FDA

leaders have sketched out this possibility in the Journal of the American Medical Association.¹⁰⁰ And recently Reuters announced, “FDA will not require clinical trial data to authorize redesigned COVID boosters -official”.¹⁰¹ The general idea is the agency will assign vaccine-makers a series of variant sequences they believe will be problematic in the fall and winter. Then, without trials proving that these vaccines lower the risk of bad outcomes, they will be debuted. Possibly, merely showing evidence of antibodies will be sufficient.

In the fall of 2022, this occurred with the development of the Bivalent Wuhan-Omicron BA.4/5 booster shot. This shot received emergency use authorization in the US, while the Bivalent Wuhan-Omicron BA.1 vaccine, which did have modest human data, received authorization in Canada. The US is notable for casting a wide net in booster authorizations—the vaccine product can be given to children as young as 12. The US campaign is not focused on those at highest risk—people over the age of 70 or those living in nursing care facilities.

The decision to authorize a novel covid booster without human trials has 3 negative consequences. First, the precise mechanism of myocarditis has never been fully understood, and as such modifications may make the vaccine safer, or possibly more dangerous. There will be no mechanism to detect this before launch. Myocarditis seen with Novavax suggests that spike itself is implicated, and not the mRNA delivery mechanism. Second, there is no evidence we are better off from taking these vaccines. We don't have trials measuring severe disease. Third, universities, employers, or the government may compel these yearly shots based on faulty reasoning, as a number of universities, including Tufts college,¹⁰² have already done.

Additionally, in an unusual action, FDA officials have advertised the shot with factually incorrect statements. The commissioner of the US FDA, Robert Califf tweeted, “The updated booster also increases your chances of being in attendance at upcoming gatherings with family and friends.”¹⁰³ Of course, that statement is unsupported. Without human trials, he has no basis to make such a claim. Had the company said this, the FDA could fine them for false statement.

Paul Offit, a member of the FDA's vaccine advisory committee, and a frequent commenter during the pandemic—disagreed with the FDA's push for a yearly vaccine without clinical trials in all ages, and steadily found fault with the scientific basis in a series of op-eds and interviews.^{104,105}

The ultimate legacy of an untested, unproven, mandatory yearly shot will be to enrich the shareholders of pharmaceutical companies. Whether Americans will be better off, or which ones, remains unknown.

Lessons Learned

The COVID-19 vaccine history carries many deep lessons. First it shows great ingenuity. Indeed it is a scientific and technological accomplishment to develop COVID-19 vaccines in an unprecedented timespan, potentially saving tens of millions of lives globally.¹⁰⁶ At the same time, vaccine development occurred during a contentious and divisive election year, and concern that the vaccine would be rushed to market prior to election day resulted in negative

messaging in the media. Vaccine confidence in the American people declined during the election season. Petitions for enhanced safety follow up and greater events offered unclear scientific advantage, and worked to delay authorization, raising question regarding their motives. Perhaps some scientists and vaccine proponents were willing to play politics, even unknowingly, and their messaging shifted dramatically depending on who controlled the White House.¹⁰⁷

A vaccine can be lifesaving and miraculous in high-risk populations, but that does not necessarily mean that giving more of it, giving it to younger populations, and giving it indefinitely is better. Carefully done randomized trials are needed to show whether we continue to benefit, or if we face diminishing returns—the flat of the curve.¹⁰⁸ We need better evidence from large trials in populations that face the least risk from COVID-19, yet, ironically, we had the largest trials in adult populations were the original studies. We tolerated less data for younger populations, who have less to gain. Unanticipated safety signals are always possible, and 20,000 participants is not enough to exclude signals you do not anticipate (e.g., myocarditis). Regulators who are eager to deploy therapeutics should be equally quick to deal with unanticipated safety signals. To this day, we lack reliable information about the amount, number of doses, and timing of vaccination in young men that would minimize myocarditis. Finally, the role of mandates and their spillover effects remains controversial, as does a year COVID19 vaccine program for young healthy people.

COVID-19 vaccines: how can a single intervention represent one of our greatest pandemic successes capture many weaknesses of public policy? The answer is vaccine development was a laboratory science exercise, under controlled and stable conditions, while policy occurs in the messy reality of the world — with complex human interactions, political forces, and diverse motivation. The COVID19 vaccine has been both a story of the success of science and the failure of policy.

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Figure 1. Timeline of quotes regarding vaccine roll-out.

ARTICLE	DATE	QUOTE
<p>DON'T RUSH TO DEPLOY COVID-19 VACCINES AND DRUGS WITHOUT SUFFICIENT SAFETY GUARANTEES</p> <p>- Shibo Jiang, Nature</p>	<p>March 2020</p>	<p><i>"Decades ago, vaccines developed against another coronavirus, feline infectious peritonitis virus, increased cats' risk of developing the disease caused by the virus. Similar phenomena have been seen in animal studies for other viruses, including the coronavirus that causes SARS"</i></p>
<p>COULD TRUMP TURN A VACCINE INTO A CAMPAIGN STUNT?</p> <p>- Ezekiel Emanuel & Paul Offit, New York Times</p>	<p>June 2020</p>	<p><i>"Even if a vaccine generates antibodies, it does not prove that the vaccine is effective at preventing infection; it only makes it more likely that the vaccine would be effective...serious but rare side effects might be missed"</i></p>
<p>THE RUSH TO CREATE A COVID-19 VACCINE MAY DO MORE HARM THAN GOOD</p> <p>- Els Torrelee, British Medical Journal</p>	<p>August 2020</p>	<p><i>"A weakly effective vaccine can do more harm than good" - Phil Krause</i></p> <p><i>"Raising hopes for a vaccine before year-end are doing 'a grave disservice to the public" - Ken Frasier</i></p> <p><i>"Cautions, however, have been little heeded, drowned out by media hype and political demands such as Trump's urging for a vaccine in 2020"</i></p>
<p>TRUMP'S RUSH FOR A COVID VACCINE COULD MAKE IT LESS LIKELY TO WORK</p> <p>- Jennifer Reich & Seth Masket, Washington Post</p>	<p>September 2020</p>	<p><i>"Past attempts to distribute unlicensed vaccines and therapeutics through emergency means have often been unsuccessful, undermining trust"</i></p>
<p>WHY TRUMP SHOULD WORRY ABOUT A RUSHED VACCINE</p> <p>- Kent Sepkowitz, CNN</p>	<p>September 2020</p>	<p><i>"The history of vaccines is full of alarming missteps"</i></p>
<p>BEWARE OF COVID-19 VACCINE TRIALS DESIGNED TO SUCCEED FROM THE START</p> <p>- William Haseltine, Washington Post</p>	<p>September 2020</p>	<p><i>"Rushed Moderna and Pfizer trials could bring about similar short-term health consequences or, potentially far worse, lead to long-term health consequences that we won't discover until months or years after the vaccine's approval"</i></p>
<p>FIRST, A VACCINE APPROVAL. THEN 'CHAOS AND CONFUSION.'</p> <p>- Carl Zimmer, New York Times</p>	<p>October 2020</p>	<p><i>"Some vaccines may be abruptly withdrawn from the market because they turn out not to be safe"</i></p>
<p>USE OF ADENOVIRUS TYPE-5 VECTORED VACCINES: A CAUTIONARY TALE</p> <p>- Susan Buchbinder, Juliana McElrath, Carl Dieffenbach & Lawrence Corey, Lancet</p>	<p>October 2020</p>	<p><i>"We are writing to express concern about the use of a recombinant adenovirus type-5 (Ad5) vector for a COVID-19 phase 1 vaccine study..."</i></p>

Figure 2. Timeline of approval for COVID vaccine for children, ages 6 months to 4 years (2020)

