Young men and boosters: more harm than good?

New data suggest Pfizer boosters are unlikely to decrease Covid-19 hospitalizations in males under 30, but will hospitalize a few with myocarditis.

Ever since the Biden Administration announced plans to make booster shots available for most adults, the group that I have been most worried about has been young males. That's because, while rare, an inflammatory condition of the heart called myocarditis had been linked to both the Pfizer and Moderna Covid-19 vaccines, with far higher rates occurring after the 2nd dose. Given the small risk of myocarditis, however, it was clear that the initial 2-dose series provided important protection against severe Covid-19 for all age groups, even in younger ones in which severe disease was already unusual. In short, vaccines would prevent far more hospitalizations due to Covid-19 than they would ever cause due to side effects.

If the vaccines continued to work well in young males, even after 6

months or longer, could a 3rd dose do anything to decrease their already exceedingly low rates of Covid-19 hospitalization? And would those 3rd doses hospitalize a small number of them with vaccine-associated myocarditis? In other words, for males ages 18-29 in particular, could a 3rd dose of Pfizer possibly offer more harm than benefit with respect to hospitalizations? This unanswered question is what drove a colleague and I to question whether it was too soon to offer boosters to a majority of adults in the United States.

In the past week, important new data have emerged that help to answer this question. Based on what we've learned, it indeed appears that Pfizer boosters likely offer more harm than benefit for males under 30 with respect to hospitalization, and possibly for older males up to a certain age — where the balance tips is unclear. For other demographics, boosters appear to be safe, while offering reductions in infection across the board, and reductions in severe disease in people over 40. Whether these benefits are short-lived or longer-lasting remains to be seen. But we at least know that 3rd doses are safe for all females over 16, and older males.

However, for males ages 18-29, and possibly somewhat older males, it seems that 3rd doses of Pfizer are likely to cause more hospitalizations (due to myocarditis) than they will prevent (from Covid-19) in the coming 6 months.

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How did I reach this conclusion? By combining the safety framework used by the Centers for Disease Control and Prevention with data

appearing in a handful of newly released medical research papers. First, we have an update in the estimates of the rate of post-vaccine myocarditis. Second, we have an update on how well Pfizer's vaccine has performed during the Delta era.

First, let's understand the CDC's benefit-risk framework. Back in September, during a meeting of its vaccine safety committee, the benefits and risks of boosters were discussed and debated. Because much was unknown, experts made some important assumptions. First, for males 18-29, the rate of vaccine-associated myocarditis was estimated to be approximately 13-26 cases per million recipients. Next, experts assumed that vaccine effectiveness for this group was 90.7% (an average of various sources) and that boosters could raise that to 95%. Based on circulating coronavirus case counts at the time, it was estimated that for every 1 million booster doses given to young males, around 100 Covid-19 hospitalizations would be prevented in the coming 6 months. The implication was that decreasing Covid-19 hospitalization by 100 cases for every million people boosted would be worth the 13-26 vaccine-related myocarditis hospitalizations that would be expected to occur concurrently. So, the scales appeared to tip in favor of boosting, provided that case counts remained high, and if the myocarditis estimates weren't wildly off.

Why was I skeptical of this? Because I was convinced that the myocarditis rates were likely higher than the CDC's estimate, especially in a 3rd dose (I was more *pessimistic* than the CDC on this). Meanwhile, I believed that the vaccines were likely performing *better* than 91% in terms of effectiveness against hospitalization in the young (I was more *optimistic* than the CDC on this). This is probably why the CDC's safety panel voted *against boosters* for adults with increased risk of exposure

to Covid-19, such as healthcare workers. (The panel voted in favor of permitting boosters for adults ages 18-49 with certain Covid-19 risk factors, though there exists no evidence that two doses are inadequate for most of them, other than those with severely compromised immune systems). In my view, too much was unknown, and the young and vaccinated were *not* responsible for the Delta surge. When CDC Director Dr. Rochelle Walensky allowed boosters for most adults ages 18-49 (in part overruling the CDC's safety advisory panel), I disagreed with the decision. It wasn't that I was certain that it was the wrong decision; it was that I didn't know, and nobody could.

Now we know much more. We can update the benefit-risk analysis by applying newly released data to the CDC's safety framework. First, two studies from Israel appearing in the *New England Journal of Medicine* last week found that for young males, the rate of vaccine-associated myocarditis was substantially higher than the CDC's previous estimate. Among males 16-29, it looks like rather than 13-26 cases per million after 2nd doses of the Pfizer vaccine, the rate was actually around 107 per million. In another study, the highest risk group (males 25-29), experienced around 150 myocarditis cases per million after 2nd doses. Virtually all of these cases would require hospitalization. The Israeli numbers are likely to be more accurate than previous CDC estimates because Israeli data came from their comprehensive national database, rather than the quasi-voluntary reporting systems that we have here. While this may all sound like bad news, the upside is that myocarditis remained rare, and most of the cases were mild.

Then over the weekend, we received some good news for the vaccines. In a preprinted study (not yet peer reviewed) carried out by staff of the New York State Department of Health and appearing in *medRxiv*,

researchers found that among adults ages 18-49, the initial 2-dose Pfizer series continued to provide 95.5% effectiveness against hospitalization as recently as August, well into the Delta period. Even among January and February Pfizer recipients, vaccine effectiveness remained above 93%. Even more recent New York data suggest that the vaccines have remained steady; in fact, effectiveness appears to have improved a bit during September.

Remember: the CDC assumed that boosters could increase vaccine effectiveness to 95%. So, if the vaccine effectiveness remains *at or near 95%,* that means the number of Covid-19 hospitalizations that could be prevented by boosting 1 million young males would be zero, or close to it. Meanwhile, if rates of myocarditis after the 3rd dose replicate 2nd dose rates, up to 150 cases per million could occur in the highest risk group (males 25-29).

The conclusion is clear: boosting males 18-29 stands to cause more hospitalizations than it will prevent. Plus, as the CDC pointed out in September, if case counts fall (as they already have), the likelihood of benefit from boosting young males would only become smaller. (Note: Technically, if the vaccine continues to be 95% effective against hospitalization, more females 18-29 could be hospitalized with myocarditis than Covid-19 hospitalizations prevented by boosters. But the myocarditis numbers appear so low in females under ages 30—1 to 4 in a million—that it's difficult to imagine those rates exceed background noise in any meaningful way.

What does this mean for males 18-29 who receive boosters? Ironically, the most common outcome for boosting this demographic —and actually *all* demographics—can be summarized in one word: nothing. That may sound surprising, but it's true. It speaks to how well the

vaccines are performing and the degree to which we have slowed down this virus (not that we've done *that* well in many regions) and defanged it. For example, currently here in Massachusetts, around 1 in 8,100 people are experiencing breakthrough infections daily and of that a small fraction are hospitalized. If that continues, over the next 6 months, 2.2% of us would experience a breakthrough infection, most of which would be mild. If every one of us received boosters and that decreased infections by a factor of 20, around 97.9% of us would experience no change in outcome: no infection either way. Yes, up to 2.1% of that initial 2.2% could avoid a breakthrough over 6 months, although even that unrealistically assumes that booster effectiveness against infection will not wane (which it likely will). In case it isn't clear yet, these vaccines were not designed to, nor do they provide, long-lasting protection against infection; they *were* designed to provide long-lasting protection against severe illness and, so far, they do.

Because of this all, I sent CDC Director Dr. Rochelle Walensky a memorandum yesterday (see below). Towards the end of that document, I mentioned that even with this new information, some males 18-29 might *still* want to receive boosters. Perhaps some will be willing to take on a higher (though still small) risk of hospitalization in order to decrease the higher chance of a breakthrough infection, even if only temporarily. While Long Covid appears far less likely with vaccines, we don't know whether boosters might decrease that further. Some people may also worry about spreading the virus to people they live with who are too young to be vaccinated or who are immune-compromised and for whom even 3 doses does not suffice. In areas of low vaccine acceptance where hospital capacity is an issue, boosters could make a dent in local infection rates. For people in these situations and others, shouldering a little more myocarditis risk than expected

may not dissuade them from boosting. And that's fine, provided that they are acting on the most complete information available. But if we are to do as Dr. Walensky suggested, which is to weigh the risks and benefits of boosters for most adults 18-49, we owe it to everyone to let them know precisely what those are.

What are your questions and comments? Please join the conversation below!

Below are screenshots of the memorandum that I sent to CDC Director Dr. Rochelle Walensky on Tuesday, October 12th.

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HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

October 12, 2021

Briefing Memorandum for The Director of the Centers for Disease Control and Prevention

From: Jeremy Samuel Faust MD, MS
Brigham and Women's Hospital Department of Emergency Medicine,
Division of Health Policy and Public Health.
Harvard Medical School.

Re: Novel coronavirus (SARS-CoV-2)/COVID-19 Pfizer-BioNTech booster benefit-risk assessment for males ages 18-29.

Dear Dr. Walensky:

In light of new data, I am writing to ask you to re-evaluate or rephrase your recommendation regarding booster doses of the Pfizer-BioNTech Covid-19 vaccine for younger males ages 18-29 in particular, and possibly other male demographics.

At the meeting of the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (ACIP) on September 23, 2021, a Benefits-Risk Discussion was presented by Dr. Megan Wallace (1). As you will recall, Dr. Wallace's presentation provided a rigorous assessment of the benefits and risks that a 3rd dose of the Pfizer-BioNTech might carry, depending on a variety of input assumptions. Dr. Wallace included several scenarios in the presentation, acknowledging the uncertainty around key parameters. The clear implication was that if real-world data emerged that altered the benefit-risk assessment away from favoring boosters for males ages 18-29, it would be vital to reassess the question urgently and to alert the public of any necessary changes in guidance. Such data now exist. **Unfortunately, findings primarily from recent important studies, which I will review below, indicate that booster doses for males 18-29 (and possibly some other demographics) would likely introduce more harm than added benefit above the initial two-dose series with respect to hospitalization rates**. This determination is relatively straightforward when adjudicated by the framework that Dr. Wallace provided at the ACIP meeting.

Specifically, the benefits-risk framework began with the assumption that vaccine effectiveness against hospitalization (VE_hospitalization) for persons ages 18-29 could be increased to as high as 95% by boosters. The number of hospitalizations that boosters would ultimately prevent would depend on two factors: 1. The pre-booster VE_hospitalization and; 2. The number of circulating cases of SARS-CoV-2 during any 180-day period of assessment. If the pre-booster VE_hospitalization was >95%, only harm would be possible with respect to hospitalizations; 0 Covid-19 hospitalizations would be prevented, but approximately 12 to 24 hospitalizations due

to myocarditis per million persons boosted would occur in males 18-29, depending on whether 3rd doses replicate the rate of myocarditis after 2 doses, or if they turned out to be twice as great. Additionally, if the pre-boost VE_hospitalization was well above 90.7%, more harm was likely to result from boosting; the number of Covid-19 hospitalizations prevented would be fewer than the number of myocarditis hospitalizations that would occur.

Recently, several relevant pieces of information became available which drastically alter the benefit-risk calculation for this demographic. First, data from New York suggests that for persons ages 18-49, VE_hospitalization was 95.5% during August 2021, by when the Delta variant was the dominant form of SARS-CoV-2 in the United States (2). Even among vaccine recipients who received their first doses in January and February, VE_hospitalization remained 93.1% during this period. Both figures are higher than the input assumption used in Dr. Wallace's model (90.7%), and are likely to exceed the harm-benefit threshold (i.e. favoring harm). Second, data from Israel indicate that estimates of vaccine-associated myocarditis in young males appears higher than previously assumed. As of 42 days after the first dose of Pfizer-BioNTech, 106.9 cases of myocarditis per million males ages 18-29 vaccinated were recorded (though other data suggest that 92% of such cases occur after the 2nd dose) (3). Another study from Israel found possibly higher rates of myocarditis, with 2nd dose-associated myocarditis rates exceeding 150 per million vaccinated males ages 20-24 (4). ACIP estimates had assumed the range of myocarditis risk fell between 12 and 24 cases per million males ages 18-29 vaccinated. **Together, the new data suggest that boosting males ages 18-29 would cause more hospitalizations due to myocarditis than would be prevented due to Covid-19 breakthrough illnesses.**

As the annotated exhibit below indicates (shaded gray boxes added by me), unless the VE_hospitalization falls below 90% for persons 18-29, boosters will likely add more harm to those individuals than benefit. This has not yet occurred in this age group. Given current VE_hospitalizations, which does not appear to be waning, the only possible scenario in which boosters will not cause more proximate harm to male recipients ages 18-29 will be if myocarditis rates after the 3rd dose turn out to be far *lower* than that observed after 2nd doses. However, if case counts continue to fall, the benefit-risk balance for this age group could again increasingly favor *not* boosting males 18-29. Additionally, as Dr. Wallace's projections indicated, if case counts fell to 1/3 of the level that was being observed at the time of the September ACIP meeting (a substantial decrease in case counts has already occurred in just the 20 days since then), the VE_hospitalization for the initial two-dose series would have to drop far lower (perhaps below 80%) before boosting would again carry a net benefit over harm for recipients seeking to avoid hospitalization.

I would be incomplete if I did not acknowledge that vaccine effectiveness against infection (VE_infection) may actually be *lower* than the assumptions Dr. Wallace used in the ACIP presentation (a VE_infection for males 18-49 of 69% was reported at the end of August in New York, which is lower than the pre-boost 78% figure used in the ACIP slides). The implication is

that boosting males 18-29 could prevent even more than the 9,500 infections per million recipients over 180 days, as estimated in the ACIP presentation. In some communities, decreasing infections (and therefore forward transmission) may be an important goal. However, as an ethical matter, all booster recipients should be informed as to the known benefits and known risks of any intervention. Accordingly, the public should be updated. Indeed, many people would be willing to accept the approximately 1 in 6,600 to 9,300 risk of myocarditis implied by the data from Israel, if that risk came with a decrease in the odds of infection over the next 6 months (assuming static rates for both the pre-boost and boosted populations)—for example, the odds of breakthrough infection could decrease from 1 in 60-70 (pre-boost odds of breakthrough infection) to 1 in 150 (post-boost odds of breakthrough infection) over several months. The magnitude of the absolute changes would of course depend on circulating case counts, though both risks are likely to decrease as more people receive initial doses and other populations receive booster doses.

I do not have adequate data available to perform a similar risk assessment for males up to age 49, but data from Israel suggests that for persons under 40, the benefit of boosting with regard to reducing severe disease cannot currently be calculated because the two-dose series remains so effective. I would ask that your expert teams conduct a review of these data for all males, including up to age 49, as the rate of severe disease appears to be the same in this age group regardless of booster status.

You have asked the American people to make decisions on boosting based on their "individual benefits and risks." Those being asked to weigh these factors of course deserve to know and understand the implications of these new figures and incorporate them into their decision-making. I believe it would be prudent to explicitly advise the public of this information now so that they can make the most informed choices. Therefore, I believe you and your counterparts at the Food and Drug Administration and elsewhere in the administration should urgently amend the previous guidance to acknowledge the safety concerns regarding booster doses for males 18-29 to indicate that the risks of receiving a booster likely exceed the benefits, with respect to rare vaccine-associated hospitalizations. However, because both breakthrough hospitalization and booster-associated myocarditis are likely to remain very rare, many people may still choose to receive boosters in an effort to protect others in their community or in their workplaces, or to reduce their own incidence of milder but still bothersome and potentially debilitating SARS-CoV-2 infections. It is not my goal to dissuade anyone from receiving a booster on the scientific merits, provided that the benefits and risks are explicitly shared and understood. However, if any person were to proceed with boosting without access to the knowledge that we now have regarding this question, we would be in breach of our ethical responsibilities, including our duty to warn.

Thank you for receiving and considering this memorandum which is:

Most Respectfully Submitted.

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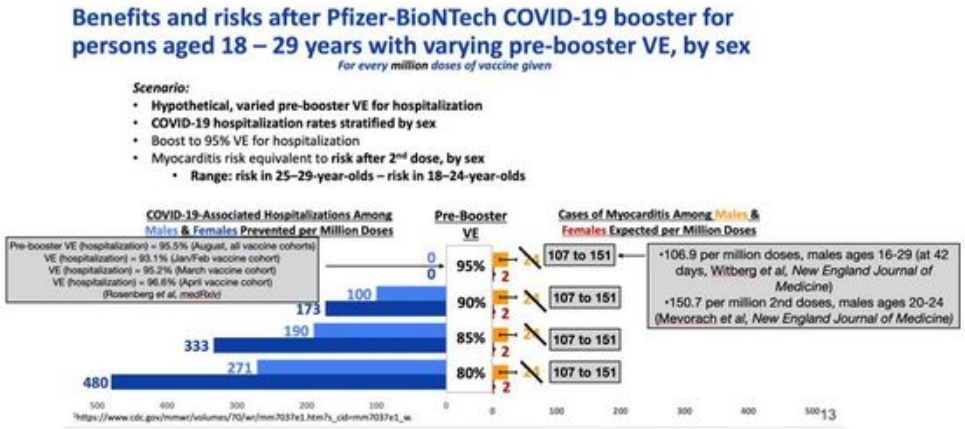
Exhibit 1.



Original slide source: Dr. Megan Wallace, DrPH, MPH, ACIP meeting, September 23, 2021. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-9-23/02-COVID-Wallace-508.pdf. They gray boxes haves been added for this memorandum to reflect updated information since the slide was presented on 9/23/21.

Data sources:
(1) Wallace, M. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-9-23/02-COVID-Wallace-508.pdf
(2) Rosenberg *et al*: https://www.medrxiv.org/content/10.1101/2021.10.08.21264595v1
(3) Witberg *et al*:
https://www.nejm.org/doi/full/10.1056/NEJMoa2110737?query=featured_home
(4) Mevorach *et al:*
https://www.nejm.org/doi/full/10.1056/NEJMoa2109730?query=featured_home

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