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Breakthroughs, Boosters, and Beyond: A Practical Primer on Current Challenges with COVID-19

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Introduction

While all coronavirus disease 2019 (COVID-19) vaccines currently authorized for use in the United States are highly effective, they are not 100% effective. *Breakthrough infections*, which are defined as a new diagnosis of COVID-19 developing more than 14 days after completing the original immunization schedule, are known to occur; however, they rarely result in hospitalizations or deaths.[1] Vaccines are proven to greatly reduce the severe morbidity and mortality associated with COVID-19. Vaccines may also reduce the risk for *post-COVID conditions*, which are defined as symptoms of COVID-19 persisting more than 28 days after a new diagnosis.[2-4] Nonetheless, vaccines do not wholly prevent individuals from contracting and transmitting SARS-CoV-2, and breakthrough infections can contribute to chains of transmission.[5] Identifying the extent to which breakthrough infections are contributing to the spread of COVID-19 can help guide vaccination policies and other infection prevention and control protocols to promote public health and safety.

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Key Studies

The following tables summarize key studies on COVID-19 vaccine efficacy and effectiveness. *Efficacy* describes vaccine performance based on clinical trial data, while *effectiveness* describes vaccine performance based on real-world data. Studies are listed in chronological order from date of publication (or date of posting, for preprints and data obtained via presentations or press releases). Of note, unless otherwise stated, data presented in the tables refer to the relative risk reduction among fully vaccinated participants aged ≥16 years, and they are based primarily on wild-type strain and non-Delta variants. A discussion of the caveats to these studies follows the tables. Full descriptions of the study limitations are listed in the Appendix, on page 8.

Table 1. Vaccine Efficacy

	Pfizer	Moderna	Johnson & Johnson
Biotechnology	mRNA	mRNA	Viral vector
Overall efficacy against infection	95% Pfizer clinical trial A 91% Pfizer clinical trial B	94% Moderna clinical trial A 93% Moderna clinical trial B	66% J&J clinical trial
Efficacy against hospitalization or death	100% Pfizer clinical trial A 97% Pfizer clinical trial B	100% Moderna clinical trial A 98% Moderna clinical trial B	85% J&J clinical trial

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Table 2. Vaccine Effectiveness

	Pfizer	Moderna	Johnson & Johnson
Overall effectiveness against infection	80% Mayo Clinic A 85% NHS 97% Israel A 97% Israel B 94% CDC A 92% Scotland 86% Mayo Clinic B 89% Israel C 91% CDPH 91% CDC B 76% Mayo Clinic D* 92% NIHR* 88% ZOE** 91% CDC C 75% CDC D 97% Israel F* 92% CDC F 89% CDC H	80% Mayo Clinic A 94% CDC A 93% Mayo Clinic B 91% CDPH 91% CDC B 86% Mayo Clinic D* 91% CDC C 75% CDC D 92% CDC F 96% CDC H	77% Mayo Clinic C* 92% CDC F
Effectiveness against hospitalization or death	97% Israel A 89% Mayo Clinic B 85% Mayo Clinic D* 95% CDC D 87% CDC E 88% CDC G	86% Mayo Clinic B 92% Mayo Clinic D* 95% CDC D 87% CDC E 93% CDC G	65% Sisonke** 71% CDC G

Studies are listed in order of release date, earliest to latest.
Abbreviations: CDC, Centers for Disease Control and Prevention; CDPH, California Department of Public Health; NIHR, National Institute for Health Research; NHS, National Health Service.
*Denotes data released in preprint format that have yet to be peer-reviewed.
**Denotes data released in presentation or press release format that have yet to be peer-reviewed and published.

Table 3. Vaccine Effectiveness Against Delta Variant

	Pfizer	Moderna	Johnson & Johnson
Overall effectiveness against infection from Delta variant	64% Israel D* 79% Scotland 39% Israel E* 42% Mayo Clinic D* 54% Qatar* 88% PHE 78% NIHR* 66% CDC C 53% CDC D 73% MCHD*	76% Mayo Clinic D* 85% Qatar* 66% CDC C 53% CDC D 73% MCHD*	N/A
Effectiveness against hospitalization or death from Delta variant	93% Israel D* 88% Israel E* 90% Qatar* 96% PHE 84% CDC E	100% Qatar* 84% CDC E	91-95% Sisonke*

Studies are listed in order of release date, earliest to latest.
Abbreviations: CDC, Centers for Disease Control and Prevention; MCHD, Multnomah County Health Department; N/A, not applicable; NIHR, National Institute for Health Research; PHE, Public Health England.
*Denotes data released in preprint format that have yet to be peer-reviewed.

Key Caveats

In order to understand the risk for fully vaccinated individuals to become infected with and transmit SARS-CoV-2, the true incidence of breakthrough infections must first be identified. Factors that influence the incidence of breakthrough infections include, but are not limited to: the age and underlying immunocompetency of the population at risk; the overall prevalence of disease within the community; vaccination rates and the durability of protection from vaccine-induced immunity; and emerging variants with increasing transmissibility or capacity for immune evasion.[6-11] **The incidence of breakthrough infections in the U.S. reported through the national surveillance system likely represents a substantial undercount** due to reliance on passive and voluntary channels of data collection (eg, infected individuals who are asymptomatic or who experience mild to moderate illness are less likely to seek testing).[12] In addition, as of May 1, 2021, the United States Centers for Disease Control and Prevention (CDC) no longer monitors or records breakthrough infections in asymptomatic cases or those with mild to moderate illness. While cases resulting in hospitalization or death continue to be investigated through the national surveillance system, this alteration in the reporting criteria will further obscure the true incidence of breakthrough infections in the U.S. and, consequently, our understanding of transmission risks among fully vaccinated individuals.

While the true incidence of breakthrough infections remains unknown, there is ancillary evidence to suggest a reduction in transmission risks among fully vaccinated individuals compared to those who are unvaccinated. In a study based on the HEROES-RECOVER data set of essential workers in the U.S., viral loads were 40% lower, with a shorter length of detection, in fully vaccinated participants who tested positive compared to those who were unvaccinated.[13] This suggests a lower risk for transmission among breakthrough infections. Another study based on the HOSTED data set in the United Kingdom (U.K.) showed the rate of infection among household members of positive cases was approximately 6% where the index case was fully vaccinated, compared to 10% where the index case was unvaccinated, also suggesting a lower risk for transmission among breakthrough infections.[14] It should be noted that both of these studies were based on data sets that did not include the Delta variant.

Emerging Variants

Emerging variants remain potential drivers of breakthrough infections and may impact vaccine effectiveness against transmission.[15-17] Across the U.S. where the Delta variant is now dominant, COVID-19 cases are surging, most prominently in areas of lower vaccination rates.[18] **The preponderance of hospitalizations and deaths from COVID-19 in the U.S. are among unvaccinated individuals.**[19,20] However, several regional and global outbreaks of the Delta variant involving breakthrough infections highlight rising concerns regarding the risk for transmission among fully vaccinated individuals.[21-30] Over two-thirds of cases from a recent cluster in Barnstable County, MA were fully vaccinated, and case samples

showed minimal differences in viral loads (measured via mean Ct values) between vaccinated and unvaccinated individuals.[31] Furthermore, an in vitro study examining vaccine-induced neutralizing antibodies revealed titer levels were 3- to 5-fold lower against Delta compared to Alpha.[32] This cumulative data complements a recent CDC study reassessing the HEROES-RECOVER data set, which demonstrated vaccine effectiveness against infection decreased from 91% (95% CI [confidence interval], 81-96) before Delta predominance to 66% (95% CI, 26-86) when Delta was predominant.[33] Downward trends were also reported by studies conducted in Scotland, Israel, and the U.K., which have all demonstrated **reduced vaccine effectiveness against symptomatic infection with Delta.**[34-41]

Waning Immunity

Waning vaccine-induced immunity may also contribute to the occurrence of breakthrough infections. The ZOE COVID Symptom Study, which was based on self-reported information from approximately 1 million participants in the U.K., released data suggesting protection from symptomatic infection after 2 doses of the Pfizer vaccine decreased from 88% at 1 month to 74% at 5 to 6 months.[42] Public Health England (PHE) also reported declines in vaccine protection over time; a preprint of their test-negative study, which included 1,659,513 participants who had received 2 doses of the Pfizer vaccine, suggests vaccine effectiveness against symptomatic infection decreased from 92% (95% CI, 92.1-92.7) 1 week after receiving the second dose, to 70% (95% CI, 68.7-70.5) after more than 20 weeks.[43] Notably, no waning against severe illness was reported, and vaccine effectiveness remained >90% against hospitalization (95% CI, 90.3-94.6) and death (95% CI, 85.1-93.8). In fact, vaccines remained highly effective against hospitalization and death during the Delta surge in the U.K.; the Office for National Statistics, which reviewed all deaths in the U.K. between January 2021 through July 2021, revealed that <1% of deaths from COVID-19 were among the fully vaccinated; of the >50,000 COVID-related deaths, only 256 were recorded as "breakthrough deaths."[44]

Ongoing studies in the U.S. and Israel show similar trends in waning vaccine-induced immunity. Recent findings released by the University of California San Diego Health suggest an increased risk for infection associated with the timing of the primary series. Based on a sample of 130 fully vaccinated healthcare workers who tested positive for SARS-CoV-2, participants who were vaccinated between January and February (attack rate, 6.7 per 1000 persons) were twice as likely to become infected compared to those who completed vaccination between March through May (attack rate, 3.7 per 1000 persons).[45] Data from Israel released in preprint also suggests some degree of waning vaccine-induced immunity. From a sample of 4,785,245 fully vaccinated participants, 12,927 experienced a breakthrough infection, of which, 348 participants developed severe illness; so far, no deaths were reported in this study.[46] For participants aged ≥60 years (who represented the preponderance of positive cases), the attack rate was 3.2 per 1000 persons for participants who completed vaccination in January 2021, compared

to an attack rate of 1.6 per 1000 persons for those who completed vaccination in March 2021.[46] This coincides with additional data from Israel, also released in preprint, which demonstrated a decline in neutralizing antibody levels over time, which was most pronounced among individuals aged ≥60 years.[47] This prompted Israel to embark on a national vaccination booster campaign during the recent surge of the Delta variant and to offer a third dose of the Pfizer vaccine after completion of the original immunization schedule.[48]

Vaccination Boosters

Vaccination boosters, which are defined as vaccine doses administered after a sufficient immune response from the primary series, have been proposed both to combat variants of concern that have increasing capacity for immune evasion as well as to correct waning vaccine-induced immunity. The Advisory Committee on Immunization Practices (ACIP) has already recommended an additional dose to the original immunization schedule for certain immunocompromised individuals, given that the primary series may not be sufficient to effectively reduce mortality in this population.[49-53] However, the role of booster doses for the general population remains under consideration. Early data based on the Israeli booster campaign suggests a reduction in the risk for severe illness for individuals aged ≥60 years; among a sample of 13,009 fully vaccinated participants recently diagnosed with a breakthrough infection, 29 cases of severe illness were among those who received a booster dose of vaccine compared to 294 cases of severe illness among those who did not receive a booster dose.[54] It is important to note that the follow-up time of the study was only 12 days after receiving a booster. In addition, no deaths were reported in either the boosted or nonboosted cohorts. In fact, there is still no evidence showing boosters significantly decrease the number of deaths due to COVID-19.

Multiple recent studies published in the *Morbidity and Mortality Review Weekly Report* confirm a recent decline in COVID-19 vaccine effectiveness against symptomatic infection; however, it should be emphasized that **vaccines maintained a high level of protection against severe morbidity and mortality.**[33,39,55,56] This is corroborated by data published by Kaiser Permanente Southern California, which was cited by Pfizer in its application for authorization of booster doses. Although vaccine effectiveness against infection declined from 88% during the first month after full vaccination to 47% after ≥5 months, effectiveness against hospitalization remained high, at 93%.[57] Despite the accumulation of reassuring data on vaccine effectiveness against severe outcomes from COVID-19, the U.S. is implementing boosters for certain high-risk populations. On September 23, 2021, after reviewing the available relevant data, the ACIP voted to recommend boosters for adults aged ≥65 years, as well as for all adults at high risk for severe illness from COVID-19 (individuals must have completed the primary series ≥6 months previously to qualify).[58] In addition to these recommendations, the CDC approved boosters for groups at high risk for infection due to workplace exposures, including frontline healthcare workers.[59] This aligns with guidance issued from the Vaccines

and Related Biological Products Advisory Committee to the U.S. Food and Drug Administration on September 17, 2021.[59]

Effectiveness of Nonpharmaceutical Interventions

While the future role of boosters is being reassessed continuously, nonpharmaceutical interventions (NPIs) remain an invaluable tool to mitigate the spread of COVID-19. **The recognition of aerosols as a principal source of transmission underscores the importance of masking within indoor environments.**[60,61] This is especially important in spaces with poor ventilation or where crowding is uncontrolled. Multiple studies have shown that masking can reduce the chances of both contracting and transmitting SARS-CoV-2, and there is some evidence to suggest that masking may be more impactful compared to physical distancing, though concurrent use of multiple NPIs provides the highest level of protection.[62-68] Physical distancing may be unfeasible without a mechanism for enforcement, capacity limits, or other crowd-control measures, and the absence of these controls may inadvertently promote bottlenecks in throughput and, consequently, crowding. Given these barriers to operationalizing physical distancing requirements, masking presents a practical and reliable tool for infection prevention and control. Local, regional, and international jurisdictional guidance regarding masking will vary despite research demonstrating that mask mandates are associated with reduced spread of COVID-19.[69,70] Given that breakthrough infections may be partially contributing to the transmission of SARS-CoV-2, implementation of universal masking protocols within indoor environments should be considered where vaccinated and unvaccinated individuals are commingling, in order to reduce the risk of airborne transmission for both groups.

Summary

Vaccines currently authorized for use in the U.S. are highly effective against hospitalizations and deaths from COVID-19. Nonetheless, breakthrough infections are known to occur and are likely underreported. Emerging variants with increasing transmissibility or immune evasion, as well as the potential waning of vaccine-induced immunity may impact transmission dynamics, resulting in an increase in breakthrough infections. While boosters may provide additional protection against severe disease for certain high-risk populations, more research is needed to assess the broader utility and necessity of boosters for the general population. Furthermore, unvaccinated individuals remain more susceptible to developing severe disease and dying from COVID-19. Immunization campaigns targeting unvaccinated populations will likely provide a greater reduction in the severe morbidity and mortality associated with COVID-19. Finally, NPIs continue to provide demonstrable protection in addition to vaccination. Within indoor environments where poor ventilation and crowding cannot be controlled, the spread of COVID-19 may be mitigated through implementation of universal masking policies.

Appendix: Study Limitations

- **The Mayo Clinic A study** (published 10 March 2021) used an observational design to analyze data from vaccinated and unvaccinated patients who underwent one-time testing before surgery and were asymptomatic at the time of testing.[71] Effect size was calculated based on data from asymptomatic patients who tested positive for SARS-CoV-2 on RT-PCR. Given that this study focused on asymptomatic infections alone, results may not be comparable to studies examining rates of overall infection after vaccination. Furthermore, there was no longitudinal follow-up to monitor the development of subsequent symptoms, and presymptomatic cases may be inadvertently included in the data set, overstating the effect size for asymptomatic cases.

- **The National Health Service (NHS) study** (published 23 April 2021) was based on the SARS-CoV-2 Immunity and Reinfection Evaluation (SIREN) data set, which utilized a prospective cohort of healthcare workers in the U.K. who were followed for 2 months and tested every 2 weeks. This testing cadence may increase the risk for missed cases and bias the short-term effect size toward vaccination.[36]

- **The Mayo Clinic C study** (posted 30 April 2021) is a preprint that has yet to undergo peer review.[72] The study was based on data collected from a single healthcare system, using a limited cohort size (2195 vaccinated patients), and a participant sample (>90% White) that was not demographically representative of the population at risk. This limits the generalizability of the findings from the study.

- **The Israel A study** (published 5 May 2021) analyzed aggregated data from Israel's national surveillance system, comparing infection rates in vaccinated versus unvaccinated groups between January 17, 2021 and February 6, 2021.[73] However, as the study authors noted, the testing criteria from the Ministry of Health exempted vaccinated people from requirements such as testing after travel or after close contact with a confirmed or suspected case of COVID-19, which may bias toward vaccination.

- **The Israel B study** (published 6 May 2021) monitored 6710 healthcare workers over a median period of 63 days.[74] Participants were tested either monthly or bimonthly, and vaccinated healthcare workers underwent fewer tests than unvaccinated healthcare workers. Because detection of infections (especially asymptomatic infection) increases with increasing frequency of testing, the transmission-blocking effect size may be overstated.

- **The CDC study A** (published 21 May 2021) was limited by a sample size of approximately 623 case-patients and 1220 case-controls selected from a population of healthcare workers. Testing for infection was based on routine

screening protocols at each healthcare facility, leading to reporting variability and a potential bias toward vaccination, given that many vaccinated healthcare workers are not routinely tested unless symptomatic.[75]

- **The Scotland study** (published 14 June 2021) used an observational design to compare vaccine effectiveness.[34] As a consequence, the analysis did not account for differences in the number of recipients vaccinated with AstraZeneca versus Pfizer, among other potential confounding factors. In addition, insufficient numbers of hospital admissions may have contributed to seemingly diminished protection of the vaccines against hospitalizations from Delta compared to those for Alpha, biasing against vaccination.

- **The Mayo Clinic B study** (published 28 June 2021) is a retrospective analysis of participants who were either unvaccinated or vaccinated with the Pfizer or Moderna vaccines. Despite a large cohort, >90% of individuals were White; 60% of individuals who received the Pfizer vaccine were female; and >50% of individuals who received the Moderna vaccine were aged ≥65 years; therefore, the study cohort is not demographically representative of the population at risk. Furthermore, the study did not account for several potential confounding factors, including geographic and socioeconomic differences, specific comorbidities, and testing behavior.[76]

- **The Israel D study** (posted 5 July 2021) is a preprint that has yet to undergo peer review.[35] The effect size was calculated using a looser set of criteria that likely included near-asymptomatic cases captured via more frequent, systematic testing. As a result, the reported figures may not be comparable to peer-reviewed studies.

- **Israel C study** (published 7 July 2021) was conducted using data from a single health system where the majority of the population are younger females and not demographically representative of the population at risk. Furthermore, the study used an observational design, and the analysis did not account for differences in testing behavior between those who were unvaccinated, partially vaccinated, and fully vaccinated, as well as other potentially confounding measures.[77]

- **The Israel E study** (posted 20 July 2021) is comprised of data provided by the Israel Ministry of Health that has yet to undergo peer review. The methodology was consistent with that outlined previously for Israel A study and is therefore subject to the same limitations.[78]

- **The California Department of Public Health (CDPH) study** (published 20 July 2021) did not include data beyond April 29, 2021. As a result, the positive cases do not reflect the bulk of the spread of the Delta variant and its impact on positive cases, hospitalizations, and deaths. The study also used an observational design, meaning that the analysis did not account for differences in

testing behavior between those who were unvaccinated, partially vaccinated, and fully vaccinated, as well as other potentially confounding measures.[79]

- **The CDC B study** (published 22 July 2021) references data collected until March 31, 2021, which was prior to escalation of Delta within the sampling regions.[13] In addition, the study relied on a weekly testing cadence, which may not be sufficient in capturing the true burden of disease within the population at risk, leading to a bias toward vaccination.

- **The Mayo Clinic D study** (posted 8 August 2021) is a preprint that has yet to undergo peer review. This study is a retrospective analysis of participants who were either unvaccinated or were vaccinated with the Pfizer or Moderna vaccines in a single health system that is not demographically representative of the general population. Although matched cohorts were used in the study design, impacts of potentially confounding factors may not be accounted for, including unknown underlying health conditions and unknown exposure risks. The vaccine effectiveness against infection for both Pfizer and Moderna declined to 42% and 76%, respectively, in the month of July when Delta was predominant. However, timing of vaccination and dose intervals were not examined, and results may also be attributed to waning protection over the 7-month study period from January to July 2021.[38]

- **The Sisonke study** (posted 6 August 2021) reports on data released in a presentation that have yet to be published and undergo peer review. The overall vaccine effectiveness figure reported primarily reflects effectiveness against the Beta variant, which originated and was dominant in South Africa, where the data were collected.[80]

- **The Qatar study** (posted 11 August 2021) is a preprint that has yet to undergo peer review. The study used an observational test-negative case-control design, which did not account for differences in exposure rate due to social contacts or adherence to safety measures. In addition, the Moderna vaccine was incorporated into the national immunization campaign approximately 3 months later than the Pfizer vaccine, biasing against the Pfizer vaccine. Finally, a large proportion of the study population is also elderly, which limits the generalizability of the findings from the study.[37]

- **The Public Health England study** (published 12 August 2021) did not include data beyond May 17, 2021.[81] As a result, positive cases were comprised mainly of Alpha variants; 12,675 sequenced cases were included in the analysis, of which only 1054 were identified as Delta. As a result, the effect size with respect to Delta may be overstated.[36]

- **The National Institutes of Health Research (NIHR) study** (posted 16 August 2021) is a preprint that has yet to undergo peer review. The lower vaccine

effectiveness against infection reported for Delta may also be attributed to waning protection over the 90-day period since receipt of the second dose of the vaccine. Participants were initially tested weekly, but were later tested monthly, which may lead to late detection of older infections that, in turn, impacts estimation of vaccine effectiveness over time.[40]

- **The ZOE Covid Symptom App study** (posted 25 August 2021) reports on data released in a presentation that has yet to be published and undergo peer review. This study uses self-reported data, which is vulnerable to information bias, and does not control for other potential confounding factors such as behavior. Vaccine effectiveness against infection declined from 88% to 74% over 5 to 6 months after receiving the second vaccine dose.[42]

- **The CDC C study** (published 27 August 2021) is limited by its observational study design, which can give rise to unmeasured and confounding factors. Testing for infection was based on routine screening protocols at each healthcare facility, leading to reporting variability and a potential bias toward vaccination, given many vaccinated healthcare workers are not routinely tested unless symptomatic. The lower vaccine effectiveness against infection reported for Delta may also be attributed to waning protection over the 35-week study period (December 14, 2020-August 14, 2021).[33]

- **The CDC D study** (published 27 August 2021) is limited by its observational study design, which does not account for potential confounders such as age, presence of underlying health conditions, or history of prior SARS-CoV-2 infection. Of these, the older age of nursing home residents involved in the study limits the generalizability of the study's findings. Furthermore, nursing home staff vaccination data, which were incomplete and may vary across the study sites, can be a potentially confounding factor impacting vaccine effectiveness. The lower vaccine effectiveness against infection reported for Delta may also be attributed to waning protection over the 22-week study period (March 1-August 1, 2021).[39]

- **The CDC E study** (published 27 August 2021) is limited by its observational study design and short follow-up period of up to 24 weeks after full vaccination with an mRNA vaccine. The lower vaccine effectiveness against hospitalization reported for Delta may also be attributed to waning protection over the 24-week study period (March-July 2021).[55]

- **The Israel F study** (posted 2 September 2021) is a preprint that has yet to undergo peer review. While the study involved weekly testing and use of electronic medical records to characterize participants' demographic information, clinical history, and vaccination history, participation was voluntary. As a result, findings are potentially confounded by selection bias, thereby limiting generalizability.[82]

- **The Multnomah County Health Department (MCHD)** study (posted 3 September 2021) is a preprint that has yet to undergo peer review.[41] This study is limited by its observational study design that is potentially confounded by testing behavior and disease severity, among other variables. Furthermore, while the study reports on reduced vaccine effectiveness during a period when the Delta variant achieved predominance, samples used in this analysis to estimate vaccine effectiveness were not sequenced for the Delta variant. As a result, the lower vaccine effectiveness may also be attributed to waning vaccine-induced protection.

- **The CDC F study** (published 17 September 2021) is limited by potentially confounding factors such as testing behavior and social exposures, which may affect estimates of vaccine effectiveness. This study also did not estimate vaccine effectiveness by vaccine product, which may fail to account for differing time points at which the vaccines reached peak effectiveness. The vaccine effectiveness against infection also declined from 92% to 80% over 3 months (May 3 to July 25, 2021).[56]

- **The CDC G study** (published 17 September 2021) was a case-control analysis among 3689 immunocompetent adults aged ≥18 years who were hospitalized at 21 U.S. hospitals across 18 states from March 11 to August 15, 2021. The small sample of patients who received the J&J vaccine (113 patients) may bias the effect size for this vaccine. Follow-up times were also limited to approximately 29 weeks after full vaccination, and long-term vaccine durability remains unknown. Finally, though vaccine effectiveness estimates were adjusted for relevant potential confounders, residual confounding is possible. Of note, vaccine effectiveness against Delta, which was predominant in the U.S. during the latter half of the study period, was not evaluated.[83]

- **The CDC H study** (published 22 September 2021) is based on a test-negative case-control design, which did not account for differences in exposure rate due to social contacts or adherence to safety measures. In addition, the small sample size of the observed subgroups limits the generalizability of the findings. Longer follow-up times are also needed to understand the long-term durability of vaccines.[84]

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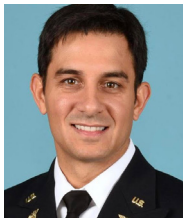
Opinion: Public Health Inequities Exist at Home and Abroad, But We Can Fix Both Without Sacrificing One for the Other



By Nicholas D. Caputo, MD
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Note: *The opinions expressed are solely those of Dr. Caputo and do not express the views or opinions of Dr. Caputo's employers.*

The COVID-19 pandemic has taught us many lessons learned through loss and despair. Hard truths. One of those hard truths for me is the understanding that there are no real experts out there. That our leaders can and often do make mistakes, including our leaders in public health. That although I am well-trained and highly accomplished in my field, I am no expert—and I can and sometimes do make mistakes.

I'm an emergency medicine physician who has had the privilege of serving the underserved in the South Bronx for the past 10 years. Daily, I wake up at 5 am, hit the gym, and then hop on my motorcycle to go to work, crossing the Harlem River into one of the poorest congressional districts in the country. Working in this environment has exposed me to some of the starkest of contrasts one can experience in this life, where the extremes of extravagance and poverty are separated by only a few hundred feet. I should not have been surprised that when the pandemic hit, these disparities would be amplified exponentially.

It's hard for me to describe the level of chaos and carnage brought on by those early days of the pandemic in New York City. Like many of my colleagues working on the front lines, I contracted COVID-19 during the first wave. Luckily, I had a robust antibody response with measurable natural immunity that lasted for many months. When the vaccines first became available, I initially deferred my turn to be vaccinated. I thought I was doing my part because, with limited vaccine supply, those without any defense and at high risk for exposure—specifically, my front-line colleagues—should get vaccinated first. When my postinfectious immunity waned, and with the vaccine supply thankfully a nonissue in the U.S., I finally elected to receive the vaccine.

After becoming vaccinated, like many of my colleagues, I thought the worst was behind us. The second wave in the U.S. came and went, brought on by the Alpha

variant. Then a third wave ensued, this time dominated by the Delta variant. At first, I thought we would be okay. It would be nothing like it was back in the first wave in New York. The ICUs would not be overrun, we would not be shutting down elective surgeries and clinics and converting labor and delivery wards to flex ICUs. We would not be hunting desperately for ventilators and PPE. I felt that maybe life would get back to normal. I was wrong. With newer, stronger variants, and with the potential for waning vaccine-induced immunity, there's a risk that those bad times can return. And I am once again scared for my colleagues.

So now the debate has come up about whether or not boosters are necessary. Last week, the director of the CDC overruled recommendations from the CDC's own advisory panel of outside experts. Now those at high risk for exposure to COVID-19 can receive a booster, including frontline healthcare workers. Many of my colleagues in emergency medicine are relieved by this ruling. Some have disagreed with the decision because they believe it will mean less vaccine supply for the rest of the world that still has yet to receive even a first dose. I understand both sides, and I think the hard truth is that none of us are experts. We can and do make mistakes, and no one is absolutely right or wrong. A piece of advice I learned as a resident is that if you think you're 100% right, you're probably at least 50% wrong.

In fact, it's not about right and wrong, but about responsibility. Just as I did before, I feel a responsibility not only to my patients but to my fellow providers. I want to keep them all safe. Allowing them to take a booster when they are putting themselves at high risk every day on the job is the responsible thing to do. And if we are going to talk about global inequities, we need to acknowledge we have huge problems with inequities right here in our own backyard. There are essential workers in the South Bronx who have no choice but to put themselves at risk every day going to work, just like those of us in emergency medicine. There are public health inequities both at home and around the world that need solutions, and I believe that as a country with vast resources, we can solve both without sacrificing one for the other.

Opinion: We Need Global Solutions for Global Challenges

By Tsion Firew, MD
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Note: *The opinions expressed are solely those of Dr. Firew and do not express the views or opinion of Dr. Firew's employers.*

Two weeks ago, the advisory committee to the United States Food and Drug Administration voted to recommend a Pfizer booster vaccine dose for certain groups at higher risk from COVID-19. Almost immediately after the announcement, my social media feeds became a battlefield for two opposing views: those who wanted boosters right away for all Americans versus those who wanted to vaccinate the rest of the world first. As an emergency physician based in America but with a background in Ethiopia where I was born and raised, I can't fathom the urgency for boosters. Breakthrough infections are happening, but those who are fully vaccinated are protected from being hospitalized or dying from COVID-19. Meanwhile, the majority of people from my homeland, like most African nations, have yet to receive even a single dose of vaccine. The mortality rates without any protection have been shocking.

Earlier this year, the World Health Organization called on all countries for a massive push to vaccinate at least 10% of the population of every country by September 2021, and at least 30 percent by the end of 2021. As of today, there are still more than 50 countries that have vaccinated less than 2% of their population. At the same time, more than 380 million doses of vaccine have been administered in the United States, and millions more have been wasted or gone unused. It is morally incomprehensible to discuss boosters for rich countries that are literally throwing away vaccine doses while those living in the poorest places in the world are struggling just to survive.

I worked on the front lines in New York City during the peak of the pandemic. I contracted COVID-19 and survived, and then I went back to work. A few months later, I received the vaccine while I was pregnant and still working. I was relieved, like the rest of my colleagues who became vaccinated. I finally felt safe, and I believed it was the beginning of the end to the pandemic. When the Delta surge overtook the United States, I was beyond disappointed, so I understand and share the frustrations held by many Americans who want to see a return to normal as soon as possible. But boosting small fractions of the global population is not the way to end the pandemic faster.

Many people will agree that all of us are at risk so long as a few of us are at risk, a notion evidenced in wave after wave of COVID-19. We have seen new variants of concern emerge and envelop the world in a matter of months. Some of the new variants are also affecting children, unlike anything seen in previous surges. If we fail to vaccinate the majority of the global population, we face the risk of newer variants, from which we will not be protected by our current vaccines.

When I think back to those early days during the first wave of COVID-19 in New York City, I remember the havoc in our hospitals as we faced shortages in staffing, spacing, and supplies, all the while as more and more patients flooded our emergency department. I remember the fear of coming to work and not having enough PPE, the fear of getting sick—or worse—the fear of coming home and getting my husband sick. That is what it is still like for many of our global health colleagues working in limited-resource settings today.

Last week at the United Nations General Assembly, President Joe Biden pledged to donate 500 million more doses of the Pfizer vaccine to countries in need. The European Union, Canada, and other high-income countries also committed to resolving ongoing disparities in vaccine distribution. This is welcome news, but following through on these commitments will take time, coordination, and oversight. I am not suggesting we withhold boosters forever. I am only asking we first fulfill our promise to protect those most in need. By doing so, we will also be protecting ourselves from a future of more variants, more chaos, and more tragedy.

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