(10945) What Providers Need to Know about Covid-19 Vaccines

Supplemental Articles

What Clinicians Need to Know About COVID-19 Vaccines
Articles for Review

Answering Key Questions About COVID-19 Vaccines..... Page 2

Beyond Politics — Promoting Covid-19 Vaccination in the United States..... Page 4

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine..... Page 12

Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine..... Page 25

Experts Discuss COVID-19—Vaccine Doses, Virus Variants, and More..... Page 39

Last-Mile Logistics of Covid Vaccination — The Role of Health Care Organizations..... Page 41

VIEWPOINT

Answering Key Questions About COVID-19 Vaccines

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The US government is investing in rapid development of vaccines against coronavirus disease 2019 (COVID-19), several relying on new technologies.[1] In the US, 4 vaccine candidates are in phase 3 studies with initial results expected soon. If studies succeed, 1 or more vaccines may become available within a few months. Clinicians are likely among the first to be offered COVID-19 vaccines and have a key role in helping patients make decisions about vaccination.[2] Providing evidence-based information will be particularly important in an environment of polarization and mistrust. This Viewpoint focuses on common questions patients are likely to ask about COVID-19 vaccines.

How Much Does a Vaccine Reduce the Risk of COVID-19 and Its Complications?

The US Food and Drug Administration (FDA) guidance set as an expectation for licensure that a COVID-19 vaccine would prevent disease or decrease its severity in at least 50% of people who are vaccinated.[3]

In reviewing the results of a study it is important to know there is a margin of error in estimating the percentage of cases or complications prevented. For example, a study might report a reduction in disease from 100 cases in the placebo group to 50 in those vaccinated. This difference would meet the standard of 50%, but it will be important to explain to patients the uncertainty surrounding that value. While the study showed a 50% reduction in illness, the confidence interval for the efficacy estimate might be 30% to 80%, meaning efficacy may be as low as 30% or as high as 80%. It will also be important to understand whether a vaccine reduces not only mild but also more severe disease, as well as hospitalizations and deaths. However, studies may have insufficient numbers of patients with severe outcomes to definitively evaluate those end points.

How Safe Is a Vaccine Candidate?

Clinicians will want to know how safety was evaluated, including whether studies have been completed, as planned, with 15 000 or more people vaccinated and followed up for time periods sufficient to detect most safety issues (eg, 2 months). It is also important for vaccine developers to present all safety data, including from outside the US.

It is likely that vaccination will be associated with mild adverse events like soreness at the injection site, fever, fatigue, and myalgias. While such symptoms may be unpleasant, so long as they are not severe and resolve quickly, and patients anticipate them, these symptoms are not usually worrisome, unless they lead to additional health care encounters.

More serious reactions, such as otherwise unexplained neurologic or inflammatory processes, would raise concerns. While patients need to understand that serious adverse events may occur coincidentally following receipt of a vaccine, these adverse events could be signals of a safety problem. Comparing rates of adverse events between vaccine and placebo recipients can help determine whether a signal is vaccine-related, but for small numbers of rare events it may be inconclusive.

Patients should understand that rare adverse events may only be detected as a vaccine is widely used. Patients will want assurance that the US has mobilized enhanced safety systems to monitor, evaluate, and communicate about the safety of COVID-19 vaccines after they are released.[4]

Will the Vaccine Be Effective for All Patients?

COVID-19 is more common and severe among individuals often underrepresented in clinical trials, including older individuals, people with chronic illnesses, and persons in racial/ethnic minority populations. Different groups may not have the same responses to vaccination. When results become available, it will be important to evaluate the characteristics of people included in the trial and determine whether they are similar to patients seen in the practice setting. A given vaccine may be more appropriate for some patients than others, and knowing those differences will be important.

Trials involving children and pregnant women will start once vaccine safety is demonstrated in others, making it unlikely vaccines will initially have FDA indications for these groups. In considering use of a vaccine in patients not within FDA indications, available evidence and recommendations from the CDC's Advisory Committee on Immunization Practices (ACIP) should be consulted.

Was Important Information Made Public and Reviewed by Independent Experts?

It is important to know whether all relevant information that might support or contradict the findings of a vaccine trial has been made public. For example, preliminary reports might not include all patients studied or might include only selected results. It must be clear if any information is missing and the reasons for that missing information should be provided.

In addition, it is important that the study has been reviewed by experts without personal or financial interests in the research, as done by major medical journals. Such review helps reduce the risk of errors or bias.

Is a Vaccine Licensed or Provided Under an Emergency Use Authorization?

FDA has a long track record of licensing vaccines that have protected individuals against diseases like measles, polio, and pneumonia. FDA has stated it will apply its usual high standards to COVID-19 vaccines.[5] These standards mean clinicians can have confidence in what is known about the safety and efficacy of a licensed vaccine.

However, FDA could make an as-yet unapproved vaccine available through an Emergency Use Authorization (EUA). Rather than proven safety and effectiveness, EUAs

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only require FDA determine a product "may" be effective and that benefits are likely to outweigh risks.

In some circumstances an EUA may be appropriate. For example, substantial data demonstrating safety and efficacy may be available, but it may take additional months for the developer to submit all documentation to FDA or for FDA to review data required for licensure but unrelated to safety or efficacy. Or early results may document convincing safety and efficacy, but it may be months until final data on all enrolled patients are available.

FDA officials have stated,[6] and affirmed in recent guidance,[7] that they would only issue a COVID-19 vaccine EUA with substantial evidence of safety and efficacy. Nonetheless, there is widespread concern a vaccine might be prematurely authorized under political pressure.[8] Clinicians will want to know that any EUA is based on science, with supporting data publicly available, and that those issuing an EUA have not been pressured to do so.

If a vaccine is released under an EUA, clinicians should inform patients that the vaccine is not FDA licensed. Key questions will include why the vaccine is not licensed and what information FDA may be waiting for. If clinical trials have not been completed, there will be questions about how much confidence exists regarding estimated efficacy. Other important considerations include whether adequate safety data from all participants have been analyzed, and whether FDA has ensured the vaccine meets manufacturing and quality standards.[3,7]

FDA has indicated that prior to any decision it will bring potential EUAs or approvals to an advisory committee, allowing outside expert input and enhancing transparency of the evaluation.[3] Furthermore, after FDA makes its determination, CDC and ACIP normally provide recommendations about who should receive a vaccine. If these steps are not followed, or if, in an unprecedented action, the secretary of the Department of Health and Human Services or White House, rather than FDA, were to issue an EUA, it should be apparent. If so, the foundation of scientific expertise and integrity that clinicians rely on to make recommendations to patients would be compromised, and use of a vaccine would need to be carefully considered in that harsh light.

Will All COVID- 19 Vaccines Be the Same?

Different vaccines are likely to perform and be used differently. Clinicians will need to be aware of any differences between vaccines including dose numbers and schedules, as well as safety and efficacy. Importantly, some vaccines may be preferred for certain populations. Clinicians should understand the basics of how different vaccines perform and, if more than one is available, be able to recommend the best for a given patient.

Can Vaccinated People Stop Worrying About COVID-19?

While a vaccine will help protect individual patients and those around them, a large proportion of the population must be immunized and protected before transmission is substantially reduced. Especially for 2-dose regimens, this will take months. No vaccine will be 100% effective and a vaccine that protects against developing clinical illness may not prevent transmission to others. Also, the duration of naturally occurring immunity to infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is unknown and may wane with time.[9] Therefore, the likely duration of protection by new COVID-19 vaccines is unknown.

For these reasons, even after vaccines become available, SARS-CoV-2 will be a continuing concern. Effective public health measures, such as social distancing, limiting the size of gatherings, and wearing masks, will be needed for at least several more months, and potentially longer.

Conclusions

Many individuals are hesitant about receiving COVID-19 vaccines. Reasons include the novelty and rapid development of the vaccines, as well as the politicization of the pandemic and inconsistent messages from scientists and government leaders. It is critical that clinicians stay well informed about emerging data so that they can help patients make sound decisions about the vaccines needed to help end the pandemic.

ARTICLE INFORMATION

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MEDICINE AND SOCIETY

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Beyond Politics — Promoting Covid-19 Vaccination in the United States

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The United States has invested more than $10 billion in Operation Warp Speed to fast-track SARS-CoV-2 vaccines from conception to market in 1 year. The result is 11 candidates reaching the final stage of Food and Drug Administration testing — a phenomenal improvement over past development timelines. Indeed, two SARS-CoV-2 vaccines are already available to Americans.

Given this level of investment, skill, and good fortune in developing a vaccine, it will be tragic if we fail to curtail the virus because Americans refuse to be vaccinated. Despite widespread suffering from Covid-19, credible surveys indicate that the proportion of the U.S. population willing to be vaccinated has fluctuated from 72% in May to 51% in September and 60% in November; of the 39% of respondents who indicated that they probably or definitely would *not* get the vaccine, only 46% said they might be open to vaccination once others start getting it and more information becomes available.[1]

These findings underscore the tremendous undertaking facing vaccine communication teams, who must persuade many of these people to be vaccinated if we're to achieve the vaccination rate — as high as 80%[2] — needed to return to normalcy. Even then, 100% of people who said they would "definitely or probably" get vaccinated must follow through, and 100% of people who said they didn't plan to but could change their mind must be persuaded and motivated to act. Vaccine promoters will have to be creative in marshaling their resources and broad-minded in considering tools for addressing this enormous challenge.[3]

The slow adoption of even the most beneficial new product is unsurprising to researchers who study the diffusion of innovation.[4,5] From electrifying homes to developing personal computers, history has shown that "if you build it, they will come" makes a terrible marketing plan.

As with many disruptive trends and the innovations they spawn, Americans' attitudes toward Covid-19 and related health behaviors have been shaped by a complex combination of information, relative benefits, and social identity.[6,7] Consider that although the use of face masks was promoted on the basis of strong relative benefits (high efficacy of slowing viral spread and low cost), what predominated in many peoples' decisions about masking was its symbolic relationship to political identity.[8]

So how should we promote vaccination? The data surrounding vaccination are still evolving, and different vaccines may come to market. The likely mixed messages about these products' safety and efficacy (even if they reflect small relative differences arising from clinical trial design) may exacerbate the challenge of vaccine adoption. Add to this the interaction of attitudes toward the virus and vaccines, and it's clear that we will need myriad communication strategies to ensure widespread vaccine uptake.

Any successful marketing strategy will be multifaceted.[9,10] Consumer research and behavioral economics suggest 12 key strategies for an effective vaccine-promotion effort (Table 1). Not all strategies are equally actionable for all health agents, who range from leaders of federal agencies to leaders of local clinics; different actions are best suited for different players (Table 2). But by combining relevant strategies for various persuasive tasks, we can develop a comprehensive plan, incorporating multiple actions and tactics to promote vaccine adoption. The tactics used can be prioritized according to each population's degree of vaccine hesitancy (Fig. 1). We believe that

Table 1. Strategies for Promoting Covid-19 Vaccination.*

Strategy	Needed Action	Sample Tactics
Segment public according to identity barriers	Qualitative research or text mining of social media to determine why patients feel vaccination runs counter to their identity.	Create targeted messaging based on relevant barriers, such as a "Go out with a bang, but don't die *this* death" campaign for groups with a Covid-defiant identity.
Find a common enemy	Message testing to determine what common enemies resonate across two polarized groups. Look for an enemy that prompts more animosity than the opposite group does.	If a common enemy is poverty or recession: "This economy needs a shot in the arm. We can do that." If a common enemy is those who don't believe in America: "Think we can't vaccinate 300 million people in 3 months? Watch us."
Use analogy	Develop a list of appropriate analogies for critical facts, processes, or statistics and share them through health care channels. Encourage trusted medical providers to prepare their own analogies for common vaccine questions. Use analogies to augment more complicated discussions of fact.	Use process analogies (e.g., if asked how the vaccine works, say "mRNA is like a teacher that shows the body how to make the antibodies that fight off Covid.") Use statistical analogies (e.g., "You'd be more likely to get hit by lightning than to die from Covid after getting vaccinated.")
Increase observability	Make it easy to see, in person or online, who has been vaccinated.	Offer a wearable token — a bracelet, sticker, or pin — that can be observed by others. Offer social media frames and banners (e.g., "I'm a First Responder and I'm Vaccinated"). Partner with celebrities, respected local leaders, and members of all parties to show them, on old and new media, being vaccinated.
Leverage natural scarcity	Use a national or state referendum to decide who gains access to the vaccine first, or request community input through surveys.	Frame the chosen "first receivers" — whether the elderly, first responders, teachers, or essential workers — as nationally valued and honored.
Predict and address negative attributions	Monitor media to quickly identify negative attributions. For segment-specific attributions, partner with community leaders or influencers to identify and counter negative attributions.	If delays in vaccine accessibility are being attributed to government incompetence, use daily briefings to show a complicated "air traffic control map" tracking freezer trucks. If prioritized deployment of vaccines in historically disadvantaged neighborhoods is being attributed to a belief that these populations are expendable "lab rats," include these communities' trusted local leaders in prioritization discussions.
Prompt anticipated regret	Develop and use communications to remind people of a low-probability but high-stakes outcomes and the resulting strong emotions.	Train family practice staff to use questions and statements such as: "What would change in your family if you became a Covid long-hauler and had permanent lung or heart damage?" "I've seen the crushing guilt of families that lose someone to Covid after not being quite careful enough — don't do that to yourself."
Avoid conveying piecemeal risk information	Coordinate press releases with stakeholders to avoid letting bad news trickle out and making it seem worse than it is.	If a delay seems likely, wait until you have a clear sense of the new situation and present any bad news up front and, ideally, just once.
Promote compromise options	Find ways to promote a sense of control by offering multiple vaccination choices; introduce other actions to frame vaccination as a middle or normal choice.	Train cold-call promoters or survey takers to ask people if they will get the vaccine later, get it now, or get it now and sign up to donate plasma.
Create FOMO motivations	Frame vaccination as a desirable opportunity not to be missed. Find and provide rewards for vaccine completion.	Partner with employers to give employees a day off to be vaccinated. Create a campaign to promote the idea that families should stagger vaccinations so that each "hero" gets a day in bed with snacks and binge-watching movies. Use monetary incentives (tax deductions or insurance refunds). Encourage celebrities to hold future free events for vaccinated fans.
Combat uniqueness neglect	Work with health care providers to identify patient groups that might feel they have special conditions unlike "ordinary" people.	Train medical personal to identify uniqueness neglect (e.g., patients might say, "The vaccine is fine, but it won't work for *me*.") Offer safe (even if largely unnecessary) modifications to standard vaccine delivery (e.g., topical analgesics before injection; getting the shot late in the day).
Neutralize the case versus base-rate heuristic	Communicate with clinicians and other front-line health personnel about the base-rate fallacy. Build and use collection of positive anecdotes.	Encourage clinicians to counter patients' anecdotal "bad reaction" stories with "good reaction" stories rather than statistics. Ensure that DHHS briefings and websites include a continuous collection of real people's stories about good vaccination experiences.

* DHHS denotes Department of Health and Human Services, and FOMO fear of missing out.

Table 2. Key Actions for Players in Various Health Care Roles.*

Health Care Player	Key Actions
Local clinicians and practices; care facilities (e.g., nursing homes)	1. Prepare list of common vaccine questions. 2. Investigate specific concerns of your various segments of patients. 3. Develop list of effective responses. 4. Practice and train staff for responses. 5. Add incentives (free sports exams, prizes). 6. Develop prompts to persuade vaccine-hesitant patients and offer compromises. 7. Make vaccination status observable in your community.
Hospital management	1. Determine campaign themes and messaging for local community. 2. Train medical personnel on responses to common questions and concerns. 3. Select statistical analogies for use by staff. 4. Add incentives for employees (even if vaccination is mandated). 5. Train PR office personnel for coordinated responses to new events. 6. Develop special vaccine protocols for unique cases.
Insurance and benefits management	1. Determine campaign themes and messaging for client base. 2. Select analogies for use in messaging. 3. Add incentives for clients. 4. Train PR office personnel for coordinated responses to new events. 5. Develop mailing for client segments.
State and county health agencies	1. Prepare list of common vaccine questions. 2. Investigate specific concerns from different segments of patients locally. 3. Develop list of effective responses. 4. Determine campaign themes and messaging for regional or local community. 5. Create materials for medical personnel for responding to common questions and concerns. 6. Find local analogies for use in public announcements and messaging. 7. Create a multifaceted social media network strategy. 8. Partner with companies and organizations to create incentives. 9. Train PR office personnel for coordinated responses to new events. 10. Determine and coordinate order of vaccine access and communicate rationales. 11. Partner with local celebrities and trusted community leaders to promote vaccination.
Federal agencies (e.g., DHHS, CDC)	1. Investigate specific concerns from nationally critical segments (e.g., health care workers). 2. Develop list of effective responses. 3. Determine campaign themes and messaging for national and targeted segments. 4. Create materials for large organizations, logistics, and health care systems. 5. Select analogies for use in public announcements and messaging. 6. Create a multifaceted social media network strategy. 7. Partner with companies and organizations to create vaccine incentives. 8. Explore federal incentives (tax). 9. Train PR office personnel on coordinated responses to new events. 10. Offer advice on order of vaccine access and communicate rationales. 11. Partner with national celebrities and trusted leaders to promote vaccination.
Advocacy groups (e.g., AARP, NAACP)	1. Determine campaign themes and messaging for client base. 2. Select analogies for use in messaging. 3. Train PR office personnel for coordinated responses to new events. 4. Develop mailing for client segments.

* AARP was formerly the American Association of Retired Persons. CDC denotes Centers for Disease Control and Prevention, DHHS Department of Health and Human Services, NAACP National Association for the Advancement of Colored People, and PR public relations.

the following elements should be considered in a national strategy and reinforced by local public health officials and individual clinicians.

SEGMENT PUBLIC ACCORDING TO IDENTITY BARRIERS

Medicine frequently segments patients by demographic or socioeconomic traits, but a striking aspect of the public response to the pandemic has been the association of anti-Covid efforts with personal identity, especially political identity.[11] Some groups have incorporated masks into their self-image as a symbol of community responsibility and respect, while others see wearing masks as a sign of weakness or cowardice. Some mask-protest leaders represent masks as an attack on freedom and thus democracy. Yet we must be

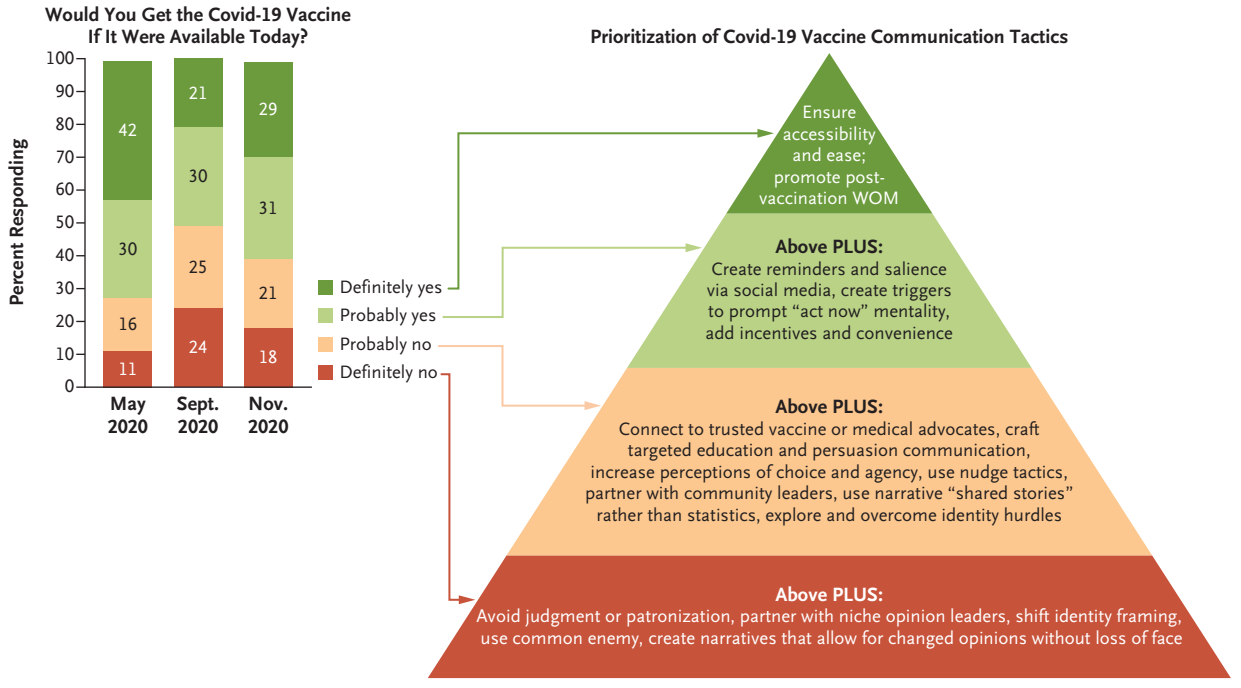

Figure 1. Prioritization of Communication Tactics Based on Vaccine-Hesitancy Level.

Survey data are from the Pew Research Center's American Trends Panel (ATP).[1] To move the public from intent to action (completing the two-dose vaccine sequence), a specific communication strategy needs to be developed for people in each of the four different response categories (Definitely yes, Probably yes, Probably no, Definitely no). WOM denotes word-of-mouth.

careful not to inadvertently reinforce the identity drivers behind mask wearing; for example, labeling vaccine-hesitant people as "conservative" or "Covid-hoaxers" tells political conservatives that vaccines are a liberal concept and open to skepticism. And it tells people who are vaccine-hesitant for other identity-related reasons (e.g., distrust of medical research by some people of color) that their concerns are not being heard or respected by the medical community.

This is not a simple case of red-state/blue-state duality. Some elderly Republicans, for example, are quietly worried by their party's failure to take the pandemic seriously, but are afraid to rock the boat; other elderly Republicans are defiant in their assertion of fearlessness. No common persuasive message will work for both groups: highlighting the virus's danger would scare the former group but might reinforce the latter's defiance. Such segmentation suggests that we need different messages targeted not according to such demographic characteristics as age, but according to barriers created by self-identity, in-groups, or social beliefs.[12] In this case, campaigns could address the first group's fear of social censure and promote the idea that the best good works are done quietly, known only to oneself, while assuring the second group that their legacy of rebellion should include dying on some fearless adventure, not alone, locked in tubes, wheezing through a plastic straw.

FIND A COMMON ENEMY

Uniting two polarized groups often depends on finding a third, more hated common enemy that can be used to build community across differences.[13] The obvious common enemy here is the virus, but demonizing it will work only if both groups see it as real and dangerous. Currently, some groups view the virus threat as inflated or a hoax,[12] though uncontrolled spread across communities may make it harder to dismiss as the winter progresses. For now, appropriate common enemies may be downstream effects: we can focus on "battling" poverty by getting people back

to work or on "racing" other countries to return to normal.

USE ANALOGY

Analogies used in communication harness understanding of some familiar concept to elucidate a complex new concept.[14] Many attitudes toward the pandemic are responses to complex medical information being communicated at a troubled time. Analogies can communicate rich information in a single image or phrase. For example, "the war against Covid" may connote coming together, making sacrifices, doing tough things, and emerging on the other side with new improvements and inventions in hand.

Or consider the difficulty of conveying statistical information. According to the National Center for Educational Statistics, more than half of Americans score 2 or lower on the 5-point numeracy scale developed by the Program for the International Assessment of Adult Competencies, and even highly educated people can make errors in understanding risk. People may ask whether the vaccine "guarantees" that they won't get Covid-19, and of course it can't, but an analogy to some extremely rare event may help: we can say, "The likelihood is about the same as being killed in a car crash," rather than simply "no."

INCREASE OBSERVABILITY

The introduction of the Apple iPod was one of the most successful product launches ever. Although there were other MP3 players, the iPod dominated the market and the mental schemas of consumers. One reason was its white earphones: even if the device itself was hidden in a pocket, observers knew that the wearer had an iPod. iPod owners became walking advertisements. An innovation known as Rogers' concept of observability suggests that consumers' ability to observe others' choices can increase an innovation's rate of adoption.[15]

Imagine how vaccination status could be made observable. Perhaps wearable tokens, such as Livestrong-style bracelets or stickers or pins similar to those given to voters, would work for in-person environments. Digital badges (such as frames or banners for one's social media profile photo) are easy to create and effective in virtual environments.

LEVERAGE NATURAL SCARCITY

In consumer markets, scarcity often signals exclusivity and prompts greater interest or desirability.[16] Because of a natural attentiveness to negative outcomes, we're attuned to goods that might run out or opportunities we might miss.[17] Although it would be wrong to create an artificial scarcity of vaccines to boost the attractiveness of securing one, we should not ignore natural scarcity's effect on attitudes toward vaccines as they're rolled out. We should frame early access to vaccines as a mark of honor or respect for people we want to protect, whether they're older Americans or people with chronic illnesses, first responders (police, firefighters, and emergency medical technicians), medical staff, schoolteachers, or essential workers. For healthy people who identify as "tough" (such as first responders), we can frame priority access as a sign of respect "awarded" to them. Leveraging scarcity may help counteract guinea pig metaphors and hesitancy to "go first." At the same time, the unexpected initial scarcity and early demand for the vaccine should not provide a false sense of security that we will not need to address resistance as we strive to achieve our population vaccination goals.

PREDICT AND ADDRESS NEGATIVE ATTRIBUTIONS

"Attribution theory," from social psychology, explores how people confronted with something unexpected or troublesome develop explanations for it.[18] For new products, consumers' attributions can help or hurt adoption. For example, if a product launch occurs later than initially announced, people might attribute the delay to a problem with the product (even if the delay was caused by bad weather slowing a shipment). If a product runs out quickly, people might assume it's highly desirable and popular (even if, really, poor supply-chain planning led to a stock-out).

The need for trust and transparency demands that vaccine promoters not fabricate positive attributions. But given attributions' power (and the ability of unconfirmed information to spread on social media), effective promotion will involve predicting negative attributions and combating them directly. For example, policymakers may choose to make vaccines available first in historically disadvantaged neighborhoods, aiming to get protec-

tion early to people who can least afford a setback. But a possible negative attribution is that these people are being treated as "lab rats" to test the vaccine's safety before it's given to wealthier people. Anticipating and combating negative attributions requires listening openly to the vaccine-hesitant, building trust, and addressing false attributions directly and consistently. There is also a clear need to work with social media platforms to limit dissemination of false information.[19]

PROMPT ANTICIPATED REGRET

Research on insurance suggests that many people overinsure themselves for highly unlikely occurrences such as flooding in areas that are not floodplains.[20] One major reason is anticipated regret: emotions, such as regret, are powerful motivators of decisions, and they can motivate us even before they're experienced.[21] Vaccination can prevent a specific anticipated regret: the fear that someone we love will die from the illness. People may be especially persuaded by a fear for their loved ones. We may also be motivated by others' anticipated regret (e.g., "Do it so your mother can stop worrying and get some sleep.")

AVOID CONVEYING PIECEMEAL RISK INFORMATION

One challenge for the pandemic response is the slow release of information about the scientific milestones in vaccine development. Although this information flow is a well-intentioned effort to improve transparency for the scientific community, it could backfire with the public. Again, consider how our evolving knowledge of the benefits of masks has sown confusion when it appears that experts are not clear on the issue.

Current research[22] suggests that piecemeal risk — risk information that trickles out over time — can be especially dangerous for uptake of pharmaceutical innovations. People are more sensitive to the risk of side effects and significantly less likely to try a new drug when risk information is presented piecemeal over time than when a single news source presents a final risk assessment. Though the efficacy and safety of Covid-19 vaccines are highly newsworthy, policymakers should recognize that negative trends that "trickle out" can disproportionately influence the public. Vaccine news cannot be covered up, but it can be presented in total, rather than with incremental updates.

PROMOTE COMPROMISE OPTIONS

Coffee shops' practice of offering three serving sizes builds on consumer research suggesting that people seek easy rules of thumb in making uncertain decisions like how much coffee we need; one robust example is our tendency to look for normal or nonextreme choices and thus choose middle, or compromise, options.[23] At the coffee shop, a tally of drink-size selections would probably follow a bell-shaped distribution, with most customers choosing the middle option.

In medicine, patients are often offered only two choices — to get or not get some recommended treatment. But the compromise effect suggests that we can nudge people to a desired choice and increase their confidence about it by making it the compromise option. To make vaccination decisions a three-option rather than two-option choice, we could allow people to get the shot now, sign up for a later date, or not get it at all. Or all three options could include the vaccine (get the shot now and donate plasma, just get the shot now, or get the shot later). The key is to avoid depicting vaccination as the most extreme action in a range of choices.

CREATE FOMO (FEAR OF MISSING OUT) MOTIVATIONS

People dislike missing out on fun things, but vaccination is not normally a fun experience — we get an injection and may incur unpleasant side effects, and some Covid vaccines require a second shot weeks after the first. Though the public health benefits are clear, there is no immediate individual reward for completing the vaccination sequence — nothing to miss out on. One possibility is to create a desirable reward so people feel an urgency to act lest they miss out on a limited opportunity.[24]

Immediate rewards could be tied to getting vaccinated and even to the potential for greater side effects of the second shot in a two-dose sequence.[19] For example, employers could offer a day off to reward an employee's contribution to a safe workplace. A public messaging campaign could create a narrative about families staggering their vaccinations so one "vaccine hero" at a

time can stay on the sofa and be coddled with snacks and movies. Universities could offer students and staff tickets to future sports or cultural events. Financial incentives such as insurance rebates and tax benefits could also be considered.

COMBAT UNIQUENESS NEGLECT

Uniqueness neglect is a phenomenon recently conceptualized as one reason patients are resistant to having artificial intelligence diagnose or treat them.[25] Some people believe they are unique or different from the average person (e.g., more sensitive, more prone to side effects). They may see vaccines as one-size-fits-all options for the average person — but not for them. Clinics may be wise to develop some variations in vaccine delivery (e.g., topical numbing of the injection site for sensitive patients) that cater to such patients. As more vaccines are approved and specific indications, such as pediatric labeling, are developed, we can address this tendency with more specific matching of patients to characteristics of different vaccines.

NEUTRALIZE THE CASE VERSUS BASE-RATE HEURISTIC

Although medical school emphasizes communication using facts and statistics, people often underweight base-rate statistics and overweight anecdotal cases — stories — in judging probability, a decision heuristic known as the base-rate fallacy or case versus base-rate effect.[26]

The first patient with a rare side effect from a vaccine, anaphylaxis from the Pfizer-BioNTech vaccine,[27] was heavily profiled in the media. Such a story is more emotionally evocative and will go more "viral" than a numerical statistic. Unfortunately, experts will probably respond by citing statistics showing that such cases are rare. But when a vaccine-hesitant patient repeats side-effect stories, clinicians can counter with their own stories, rather than elaborate statistical explanations. Furthermore, vaccine communications teams should proactively spread their own "cases" in addition to statistics. News briefings or websites could include real individual success stories — a Georgia family going out for ice cream after being vaccinated, perhaps, or Indiana retirees joyfully visiting neighbors 10 days after receiving the vaccine. Such stories, however banal, can help counteract the shock value of a few bad-effect stories.

The development of Covid-19 vaccines is an amazing scientific achievement. Adoption of vaccines by the U.S. public will require a similar level of achievement. Vaccine promotion demands a multifaceted behavioral approach if it is to succeed.

Disclosure forms provided by the authors are available at NEJM.org.

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Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

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ABSTRACT

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the resulting coronavirus disease 2019 (Covid-19) have afflicted tens of millions of people in a worldwide pandemic. Safe and effective vaccines are needed urgently.

METHODS

In an ongoing multinational, placebo-controlled, observer-blinded, pivotal efficacy trial, we randomly assigned persons 16 years of age or older in a 1:1 ratio to receive two doses, 21 days apart, of either placebo or the BNT162b2 vaccine candidate (30 μg per dose). BNT162b2 is a lipid nanoparticle–formulated, nucleoside-modified RNA vaccine that encodes a prefusion stabilized, membrane-anchored SARS-CoV-2 full-length spike protein. The primary end points were efficacy of the vaccine against laboratory-confirmed Covid-19 and safety.

RESULTS

A total of 43,548 participants underwent randomization, of whom 43,448 received injections: 21,720 with BNT162b2 and 21,728 with placebo. There were 8 cases of Covid-19 with onset at least 7 days after the second dose among participants assigned to receive BNT162b2 and 162 cases among those assigned to placebo; BNT162b2 was 95% effective in preventing Covid-19 (95% credible interval, 90.3 to 97.6). Similar vaccine efficacy (generally 90 to 100%) was observed across subgroups defined by age, sex, race, ethnicity, baseline body-mass index, and the presence of coexisting conditions. Among 10 cases of severe Covid-19 with onset after the first dose, 9 occurred in placebo recipients and 1 in a BNT162b2 recipient. The safety profile of BNT162b2 was characterized by short-term, mild-to-moderate pain at the injection site, fatigue, and headache. The incidence of serious adverse events was low and was similar in the vaccine and placebo groups.

CONCLUSIONS

A two-dose regimen of BNT162b2 conferred 95% protection against Covid-19 in persons 16 years of age or older. Safety over a median of 2 months was similar to that of other viral vaccines. (Funded by BioNTech and Pfizer; ClinicalTrials.gov number, NCT04368728.)

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*A complete list of investigators in the C4591001 Clinical Trial Group is provided in the Supplementary Appendix, available at NEJM.org.

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A Quick Take is available at NEJM.org

Coronavirus disease 2019 (Covid-19) has affected tens of millions of people globally[1] since it was declared a pandemic by the World Health Organization on March 11, 2020.[2] Older adults, persons with certain coexisting conditions, and front-line workers are at highest risk for Covid-19 and its complications. Recent data show increasing rates of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and Covid-19 in other populations, including younger adults.[3] Safe and effective prophylactic vaccines are urgently needed to contain the pandemic, which has had devastating medical, economic, and social consequences.

We previously reported phase 1 safety and immunogenicity results from clinical trials of the vaccine candidate BNT162b2,[4] a lipid nanoparticle–formulated,[5] nucleoside-modified RNA (modRNA)[6] encoding the SARS-CoV-2 full-length spike, modified by two proline mutations to lock it in the prefusion conformation.[7] Findings from studies conducted in the United States and Germany among healthy men and women showed that two 30-μg doses of BNT162b2 elicited high SARS-CoV-2 neutralizing antibody titers and robust antigen-specific CD8+ and Th1-type CD4+ T-cell responses.[8] The 50% neutralizing geometric mean titers elicited by 30 μg of BNT162b2 in older and younger adults exceeded the geometric mean titer measured in a human convalescent serum panel, despite a lower neutralizing response in older adults than in younger adults. In addition, the reactogenicity profile of BNT162b2 represented mainly short-term local (i.e., injection site) and systemic responses. These findings supported progression of the BNT162b2 vaccine candidate into phase 3.

Here, we report safety and efficacy findings from the phase 2/3 part of a global phase 1/2/3 trial evaluating the safety, immunogenicity, and efficacy of 30 μg of BNT162b2 in preventing Covid-19 in persons 16 years of age or older. This data set and these trial results are the basis for an application for emergency use authorization.[9] Collection of phase 2/3 data on vaccine immunogenicity and the durability of the immune response to immunization is ongoing, and those data are not reported here.

Methods

Trial Objectives, Participants and Oversight

We assessed the safety and efficacy of two 30-μg doses of BNT162b2, administered intramuscularly 21 days apart, as compared with placebo. Adults 16 years of age or older who were healthy or had stable chronic medical conditions, including but not limited to human immunodeficiency virus (HIV), hepatitis B virus, or hepatitis C virus infection, were eligible for participation in the trial. Key exclusion criteria included a medical history of Covid-19, treatment with immunosuppressive therapy, or diagnosis with an immunocompromising condition.

Pfizer was responsible for the design and conduct of the trial, data collection, data analysis, data interpretation, and the writing of the manuscript. BioNTech was the sponsor of the trial, manufactured the BNT162b2 clinical trial material, and contributed to the interpretation of the data and the writing of the manuscript. All the trial data were available to all the authors, who vouch for its accuracy and completeness and for adherence of the trial to the protocol, which is available with the full text of this article at NEJM.org. An independent data and safety monitoring board reviewed efficacy and unblinded safety data.

Trial Procedures

With the use of an interactive Web-based system, participants in the trial were randomly assigned in a 1:1 ratio to receive 30 μg of BNT162b2 (0.3 ml volume per dose) or saline placebo. Participants received two injections, 21 days apart, of either BNT162b2 or placebo, delivered in the deltoid muscle. Site staff who were responsible for safety evaluation and were unaware of group assignments observed participants for 30 minutes after vaccination for any acute reactions.

Safety

The primary end points of this trial were solicited, specific local or systemic adverse events and use of antipyretic or pain medication within 7 days after the receipt of each dose of vaccine or placebo, as prompted by and recorded in an electronic diary in a subset of participants (the reactogenicity subset), and unsolicited adverse events (those reported by the participants without prompts from the electronic diary) through 1 month after the second dose and unsolicited serious adverse events through 6 months after the second dose. Adverse event data through approximately 14 weeks after the second dose are included in this report. In this report, safety

data are reported for all participants who provided informed consent and received at least one dose of vaccine or placebo. Per protocol, safety results for participants infected with HIV (196 patients) will be analyzed separately and are not included here.

During the phase 2/3 portion of the study, a stopping rule for the theoretical concern of vaccine-enhanced disease was to be triggered if the one-sided probability of observing the same or a more unfavorable adverse severe case split (a split with a greater proportion of severe cases in vaccine recipients) was 5% or less, given the same true incidence for vaccine and placebo recipients. Alert criteria were to be triggered if this probability was less than 11%.

EFFICACY

The first primary end point was the efficacy of BNT162b2 against confirmed Covid-19 with onset at least 7 days after the second dose in participants who had been without serologic or virologic evidence of SARS-CoV-2 infection up to 7 days after the second dose; the second primary end point was efficacy in participants with and participants without evidence of prior infection. Confirmed Covid-19 was defined according to the Food and Drug Administration (FDA) criteria as the presence of at least one of the following symptoms: fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhea, or vomiting, combined with a respiratory specimen obtained during the symptomatic period or within 4 days before or after it that was positive for SARS-CoV-2 by nucleic acid amplification–based testing, either at the central laboratory or at a local testing facility (using a protocol-defined acceptable test).

Major secondary end points included the efficacy of BNT162b2 against severe Covid-19. Severe Covid-19 is defined by the FDA as confirmed Covid-19 with one of the following additional features: clinical signs at rest that are indicative of severe systemic illness; respiratory failure; evidence of shock; significant acute renal, hepatic, or neurologic dysfunction; admission to an intensive care unit; or death. Details are provided in the protocol.

An explanation of the various denominator values for use in assessing the results of the trial is provided in Table S1 in the Supplementary Appendix, available at NEJM.org. In brief, the safety population includes persons 16 years of age or older; a total of 43,448 participants constituted the population of enrolled persons injected with the vaccine or placebo. The main safety subset as defined by the FDA, with a median of 2 months of follow-up as of October 9, 2020, consisted of 37,706 persons, and the reactogenicity subset consisted of 8183 persons. The modified intention-to-treat (mITT) efficacy population includes all age groups 12 years of age or older (43,355 persons; 100 participants who were 12 to 15 years of age contributed to person-time years but included no cases). The number of persons who could be evaluated for efficacy 7 days after the second dose and who had no evidence of prior infection was 36,523, and the number of persons who could be evaluated 7 days after the second dose with or without evidence of prior infection was 40,137.

STATISTICAL ANALYSIS

The safety analyses included all participants who received at least one dose of BNT162b2 or placebo. The findings are descriptive in nature and not based on formal statistical hypothesis testing. Safety analyses are presented as counts, percentages, and associated Clopper–Pearson 95% confidence intervals for local reactions, systemic events, and any adverse events after vaccination, according to terms in the *Medical Dictionary for Regulatory Activities* (MedDRA), version 23.1, for each vaccine group.

Analysis of the first primary efficacy end point included participants who received the vaccine or placebo as randomly assigned, had no evidence of infection within 7 days after the second dose, and had no major protocol deviations (the population that could be evaluated). Vaccine efficacy was estimated by $100 \times (1 - \mathrm{IRR})$, where IRR is the calculated ratio of confirmed cases of Covid-19 illness per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group. The 95.0% credible interval for vaccine efficacy and the probability of vaccine efficacy greater than 30% were calculated with the use of a Bayesian beta-binomial model. The final analysis uses a success boundary of 98.6% for probability of vaccine efficacy greater than 30% to compensate for the interim analysis and to control the overall type 1 error rate at 2.5%. Moreover, primary and secondary efficacy end points are evaluated sequentially to control the

familywise type 1 error rate at 2.5%. Descriptive analyses (estimates of vaccine efficacy and 95% confidence intervals) are provided for key subgroups.

RESULTS

PARTICIPANTS

Between July 27, 2020, and November 14, 2020, a total of 44,820 persons were screened, and 43,548 persons 16 years of age or older underwent randomization at 152 sites worldwide (United States, 130 sites; Argentina, 1; Brazil, 2; South Africa, 4; Germany, 6; and Turkey, 9) in the phase 2/3 portion of the trial. A total of 43,448 participants received injections: 21,720 received BNT162b2 and 21,728 received placebo (Fig. 1). At the data cut-off date of October 9, a total of 37,706 participants had a median of at least 2 months of safety data available after the second dose and contributed to the main safety data set. Among these 37,706 participants, 49% were female, 83% were White, 9% were Black or African American, 28% were Hispanic or Latinx, 35% were obese (body mass index [the weight in kilograms divided by the square of the height in meters] of at least 30.0), and 21% had at least one coexisting condition. The median age was 52 years, and 42% of participants were older than 55 years of age (Table 1 and Table S2).

Figure 1 (facing page). Enrollment and Randomization.
The diagram represents all enrolled participants through November 14, 2020. The safety subset (those with a median of 2 months of follow-up, in accordance with application requirements for Emergency Use Authorization) is based on an October 9, 2020, data cut-off date. The further procedures that one participant in the placebo group declined after dose 2 (lower right corner of the diagram) were those involving collection of blood and nasal swab samples.

SAFETY

Local Reactogenicity

The reactogenicity subset included 8183 participants. Overall, BNT162b2 recipients reported more local reactions than placebo recipients. Among BNT162b2 recipients, mild-to-moderate pain at the injection site within 7 days after an injection was the most commonly reported local reaction, with less than 1% of participants across all age groups reporting severe pain (Fig. 2). Pain was reported less frequently among participants older than 55 years of age (71% reported pain after the first dose; 66% after the second dose) than among younger participants (83% after the first dose; 78% after the second dose). A noticeably lower percentage of participants reported injection-site redness or swelling. The proportion of participants reporting local reactions did not increase after the second dose (Fig. 2A), and no participant reported a grade 4 local reaction. In general, local reactions were mostly mild-to-moderate in severity and resolved within 1 to 2 days.

Systemic Reactogenicity

Systemic events were reported more often by younger vaccine recipients (16 to 55 years of age) than by older vaccine recipients (more than 55 years of age) in the reactogenicity subset and more often after dose 2 than dose 1 (Fig. 2B). The most commonly reported systemic events were fatigue and headache (59% and 52%, respectively, after the second dose, among younger vaccine recipients; 51% and 39% among older recipients), although fatigue and headache were also reported by many placebo recipients (23% and 24%, respectively, after the second dose, among younger vaccine recipients; 17% and 14% among older recipients). The frequency of any severe systemic event after the first dose was 0.9% or less. Severe systemic events were reported in less than 2% of vaccine recipients after either dose, except for fatigue (in 3.8%) and headache (in 2.0%) after the second dose.

Fever (temperature, ≥38°C) was reported after the second dose by 16% of younger vaccine recipients and by 11% of older recipients. Only 0.2% of vaccine recipients and 0.1% of placebo recipients reported fever (temperature, 38.9 to 40°C) after the first dose, as compared with 0.8% and 0.1%, respectively, after the second dose. Two participants each in the vaccine and placebo groups reported temperatures above 40.0°C. Younger vaccine recipients were more likely to use antipyretic or pain medication (28% after dose 1; 45% after dose 2) than older vaccine recipients (20% after dose 1; 38% after dose 2), and placebo recipients were less likely (10 to 14%) than vaccine recipients to use the medications,

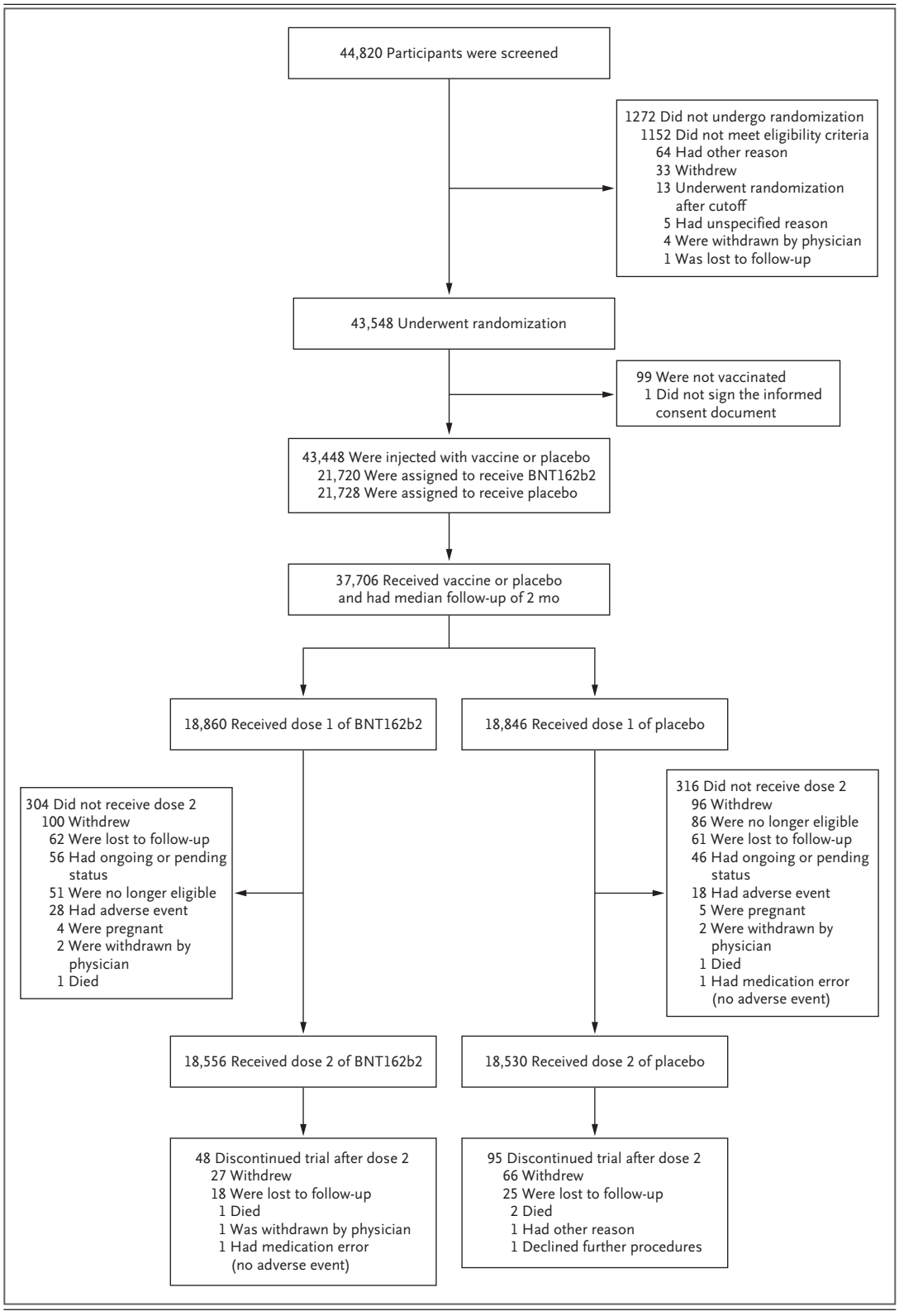


Table 1. Demographic Characteristics of the Participants in the Main Safety Population.*

Characteristic	BNT162b2 (N=18,860)	Placebo (N=18,846)	Total (N=37,706)
Sex — no. (%)			
Male	9,639 (51.1)	9,436 (50.1)	19,075 (50.6)
Female	9,221 (48.9)	9,410 (49.9)	18,631 (49.4)
Race or ethnic group — no. (%)†			
White	15,636 (82.9)	15,630 (82.9)	31,266 (82.9)
Black or African American	1,729 (9.2)	1,763 (9.4)	3,492 (9.3)
Asian	801 (4.2)	807 (4.3)	1,608 (4.3)
Native American or Alaska Native	102 (0.5)	99 (0.5)	201 (0.5)
Native Hawaiian or other Pacific Islander	50 (0.3)	26 (0.1)	76 (0.2)
Multiracial	449 (2.4)	406 (2.2)	855 (2.3)
Not reported	93 (0.5)	115 (0.6)	208 (0.6)
Hispanic or Latinx	5,266 (27.9)	5,277 (28.0)	10,543 (28.0)
Country — no. (%)			
Argentina	2,883 (15.3)	2,881 (15.3)	5,764 (15.3)
Brazil	1,145 (6.1)	1,139 (6.0)	2,284 (6.1)
South Africa	372 (2.0)	372 (2.0)	744 (2.0)
United States	14,460 (76.7)	14,454 (76.7)	28,914 (76.7)
Age group — no. (%)			
16–55 yr	10,889 (57.7)	10,896 (57.8)	21,785 (57.8)
>55 yr	7,971 (42.3)	7,950 (42.2)	15,921 (42.2)
Age at vaccination — yr			
Median	52.0	52.0	52.0
Range	16–89	16–91	16–91
Body-mass index‡			
≥30.0: obese	6,556 (34.8)	6,662 (35.3)	13,218 (35.1)

* Percentages may not total 100 because of rounding.
† Race or ethnic group was reported by the participants.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

regardless of age or dose. Systemic events including fever and chills were observed within the first 1 to 2 days after vaccination and resolved shortly thereafter.

Daily use of the electronic diary ranged from 90 to 93% for each day after the first dose and from 75 to 83% for each day after the second dose. No difference was noted between the BNT162b2 group and the placebo group.

ADVERSE EVENTS

Adverse event analyses are provided for all enrolled 43,252 participants, with variable follow-up time after dose 1 (Table S3). More BNT162b2 recipients than placebo recipients reported any adverse event (27% and 12%, respectively) or a related adverse event (21% and 5%). This distribution largely reflects the inclusion of transient reactogenicity events, which were reported as adverse events more commonly by vaccine recipients than by placebo recipients. Sixty-four vaccine recipients (0.3%) and 6 placebo recipients (<0.1%) reported lymphadenopathy. Few participants in either group had severe adverse events, serious adverse events, or adverse events leading to withdrawal from the trial. Four related serious adverse events were reported among BNT162b2 recipients (shoulder injury related to vaccine administration, right axillary lymphadenopathy, paroxysmal ventricular arrhythmia, and right leg

paresthesia). Two BNT162b2 recipients died (one from arteriosclerosis, one from cardiac arrest), as did four placebo recipients (two from unknown causes, one from hemorrhagic stroke, and one from myocardial infarction). No deaths were considered by the investigators to be related to the vaccine or placebo. No Covid-19–associated deaths were observed. No stopping rules were met during the reporting period. Safety monitoring will continue for 2 years after administration of the second dose of vaccine.

EFFICACY

Among 36,523 participants who had no evidence of existing or prior SARS-CoV-2 infection, 8 cases of Covid-19 with onset at least 7 days after the second dose were observed among vaccine recipients and 162 among placebo recipients. This case split corresponds to 95.0% vaccine efficacy (95% confidence interval [CI], 90.3 to 97.6; Table 2). Among participants with and those without evidence of prior SARS CoV-2 infection, 9 cases of Covid-19 at least 7 days after the second dose were observed among vaccine recipients and 169 among placebo recipients, corresponding to 94.6% vaccine efficacy (95% CI, 89.9 to 97.3). Supplemental analyses indicated that vaccine efficacy among subgroups defined by age, sex, race, ethnicity, obesity, and presence of a coexisting condition was generally consistent with that observed in the overall population (Table 3 and Table S4). Vaccine efficacy among participants with hypertension was analyzed separately but was consistent with the other subgroup analyses (vaccine efficacy, 94.6%; 95% CI, 68.7 to 99.9; case split: BNT162b2, 2 cases; placebo, 44 cases). Figure 3 shows cases of Covid-19 or severe Covid-19 with onset at any time after the first dose (mITT population) (additional data on severe Covid-19 are available in Table S5). Between the first dose and the second dose, 39 cases in the BNT162b2 group and 82 cases in the placebo group were observed, resulting in a vaccine efficacy of 52% (95% CI, 29.5 to 68.4) during this interval and indicating early protection by the vaccine, starting as soon as 12 days after the first dose.

DISCUSSION

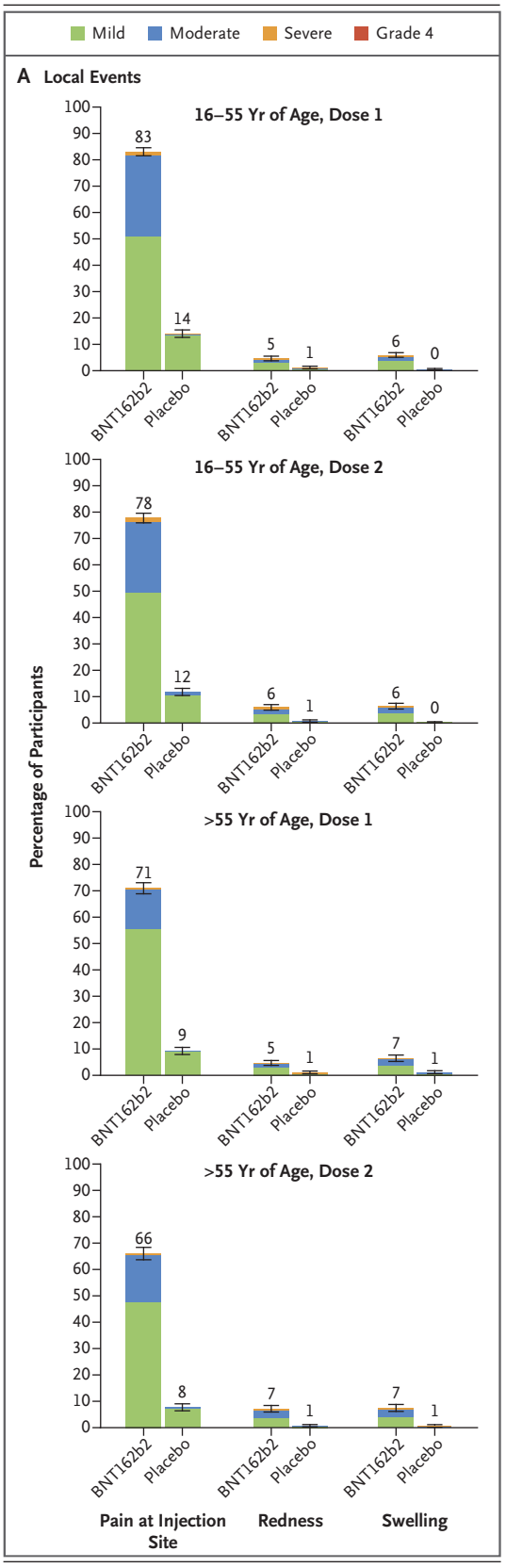
A two-dose regimen of BNT162b2 (30 μg per dose, given 21 days apart) was found to be safe and 95% effective against Covid-19. The vaccine met both primary efficacy end points, with more than a 99.99% probability of a true vaccine efficacy greater than 30%. These results met our prespecified success criteria, which were to establish a probability above 98.6% of true vaccine efficacy being greater than 30%, and greatly exceeded the minimum FDA criteria for authorization.[9] Although the study was not powered to definitively assess efficacy by subgroup, the point estimates of efficacy for subgroups based on age, sex, race, ethnicity, body-mass index, or the presence of an underlying condition associated with a high risk of Covid-19 complications are also high. For all analyzed subgroups in which more than 10 cases of Covid-19 occurred, the lower limit of the 95% confidence interval for efficacy was more than 30%.

The cumulative incidence of Covid-19 cases over time among placebo and vaccine recipients begins to diverge by 12 days after the first dose, 7 days after the estimated median viral incubation period of 5 days,[10] indicating the early onset of a partially protective effect of immunization. The study was not designed to assess the efficacy of a single-dose regimen. Nevertheless, in the interval between the first and second doses, the observed vaccine efficacy against Covid-19 was 52%, and in the first 7 days after dose 2, it was 91%, reaching full efficacy against disease with onset at least 7 days after dose 2. Of the 10 cases of severe Covid-19 that were observed after the first dose, only 1 occurred in the vaccine group. This finding is consistent with overall high efficacy against all Covid-19 cases. The severe case split provides preliminary evidence of vaccine-mediated protection against severe disease, alleviating many of the theoretical concerns over vaccine-mediated disease enhancement.[11]

The favorable safety profile observed during phase 1 testing of BNT162b2[4,8] was confirmed in the phase 2/3 portion of the trial. As in phase 1, reactogenicity was generally mild or moderate, and reactions were less common and milder in older adults than in younger adults. Systemic reactogenicity was more common and severe after the second dose than after the first dose, although local reactogenicity was similar after the two doses. Severe fatigue was observed in approximately 4% of BNT162b2 recipients, which is higher than that observed in recipients of some vaccines recommended for older adults.[12] This rate of severe fatigue is also lower than that

Figure 2. Local and Systemic Reactions Reported within 7 Days after Injection of BNT162b2 or Placebo, According to Age Group.

Data on local and systemic reactions and use of medication were collected with electronic diaries from participants in the reactogenicity subset (8,183 participants) for 7 days after each vaccination. Solicited injection-site (local) reactions are shown in Panel A. Pain at the injection site was assessed according to the following scale: mild, does not interfere with activity; moderate, interferes with activity; severe, prevents daily activity; and grade 4, emergency department visit or hospitalization. Redness and swelling were measured according to the following scale: mild, 2.0 to 5.0 cm in diameter; moderate, >5.0 to 10.0 cm in diameter; severe, >10.0 cm in diameter; and grade 4, necrosis or exfoliative dermatitis (for redness) and necrosis (for swelling). Systemic events and medication use are shown in Panel B. Fever categories are designated in the key; medication use was not graded. Additional scales were as follows: fatigue, headache, chills, new or worsened muscle pain, new or worsened joint pain (mild: does not interfere with activity; moderate: some interference with activity; or severe: prevents daily activity), vomiting (mild: 1 to 2 times in 24 hours; moderate: >2 times in 24 hours; or severe: requires intravenous hydration), and diarrhea (mild: 2 to 3 loose stools in 24 hours; moderate: 4 to 5 loose stools in 24 hours; or severe: 6 or more loose stools in 24 hours); grade 4 for all events indicated an emergency department visit or hospitalization. I bars represent 95% confidence intervals, and numbers above the I bars are the percentage of participants who reported the specified reaction.



observed in recipients of another approved viral vaccine for older adults.[13] Overall, reactogenicity events were transient and resolved within a couple of days after onset. Lymphadenopathy, which generally resolved within 10 days, is likely to have resulted from a robust vaccine-elicited immune response. The incidence of serious adverse events was similar in the vaccine and placebo groups (0.6% and 0.5%, respectively).

This trial and its preliminary report have several limitations. With approximately 19,000 participants per group in the subset of participants with a median follow-up time of 2 months after the second dose, the study has more than 83% probability of detecting at least one adverse event, if the true incidence is 0.01%, but it is not large enough to detect less common adverse events reliably. This report includes 2 months of follow-up after the second dose of vaccine for half the trial participants and up to 14 weeks' maximum follow-up for a smaller subset. Therefore, both

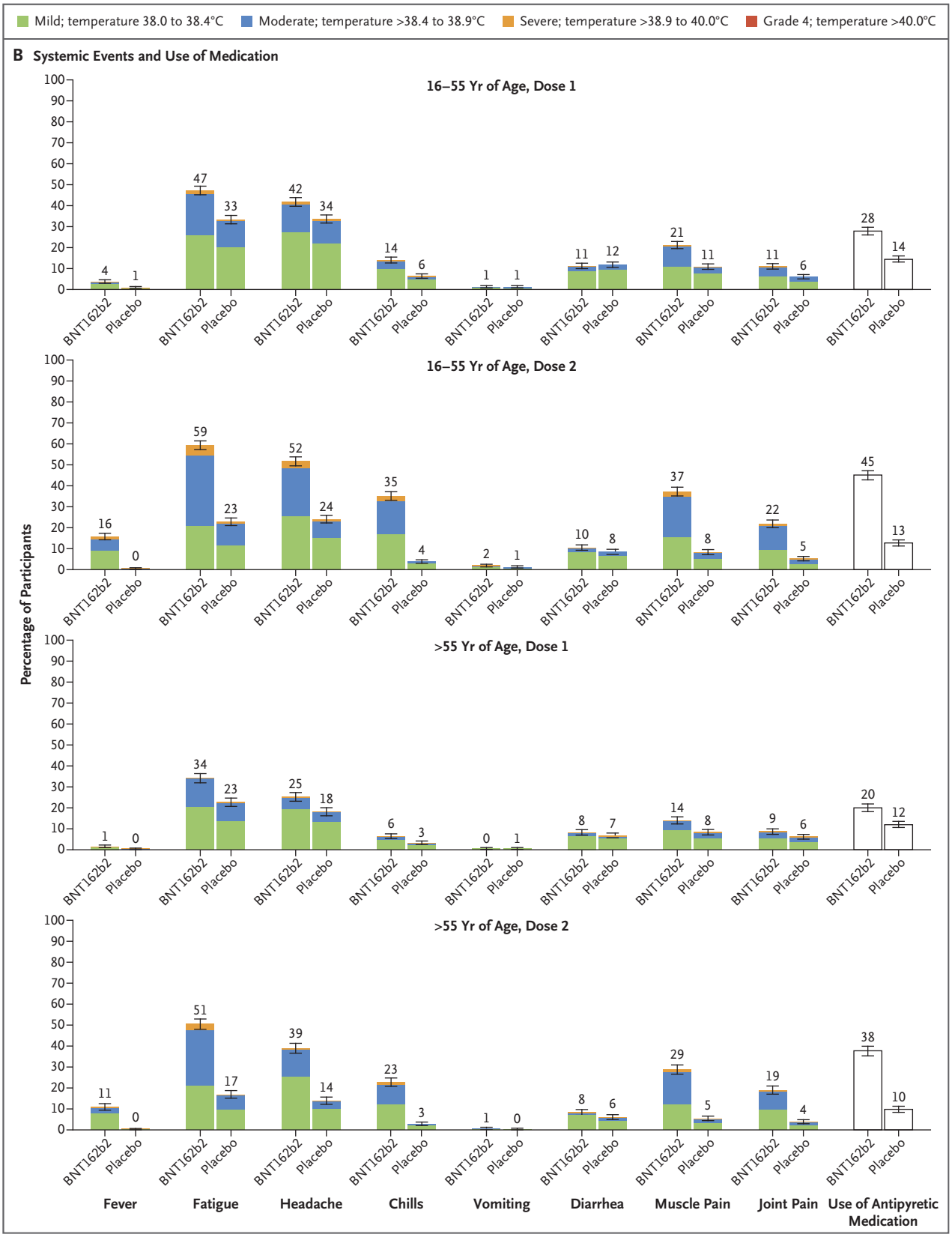


Table 2. Vaccine Efficacy against Covid-19 at Least 7 days after the Second Dose.*

Efficacy End Point	BNT162b2		Placebo		Vaccine Efficacy, % (95% Credible Interval)‡	Posterior Probability (Vaccine Efficacy >30%)§
	No. of Cases	Surveillance Time (n)†	No. of Cases	Surveillance Time (n)†		
		(N=18,198)		(N=18,325)		
Covid-19 occurrence at least 7 days after the second dose in participants without evidence of infection	8	2.214 (17,411)	162	2.222 (17,511)	95.0 (90.3–97.6)	>0.9999
		(N=19,965)		(N=20,172)		
Covid-19 occurrence at least 7 days after the second dose in participants with and those without evidence of infection	9	2.332 (18,559)	169	2.345 (18,708)	94.6 (89.9–97.3)	>0.9999

* The total population without baseline infection was 36,523; total population including those with and those without prior evidence of infection was 40,137.
† The surveillance time is the total time in 1000 person-years for the given end point across all participants within each group at risk for the end point. The time period for Covid-19 case accrual is from 7 days after the second dose to the end of the surveillance period.
‡ The credible interval for vaccine efficacy was calculated with the use of a beta-binomial model with prior beta (0.700102, 1) adjusted for the surveillance time.
§ Posterior probability was calculated with the use of a beta-binomial model with prior beta (0.700102, 1) adjusted for the surveillance time.

the occurrence of adverse events more than 2 to 3.5 months after the second dose and more comprehensive information on the duration of protection remain to be determined. Although the study was designed to follow participants for safety and efficacy for 2 years after the second dose, given the high vaccine efficacy, ethical and practical barriers prevent following placebo recipients for 2 years without offering active immunization, once the vaccine is approved by regulators and recommended by public health authorities. Assessment of long-term safety and efficacy for this vaccine will occur, but it cannot be in the context of maintaining a placebo group for the planned follow-up period of 2 years after the second dose. These data do not address whether vaccination prevents asymptomatic infection; a serologic end point that can detect a history of infection regardless of whether symptoms were present (SARS-CoV-2 N-binding antibody) will be reported later. Furthermore, given the high vaccine efficacy and the low number of vaccine breakthrough cases, potential establishment of a correlate of protection has not been feasible at the time of this report.

This report does not address the prevention of Covid-19 in other populations, such as younger adolescents, children, and pregnant women. Safety and immune response data from this trial after immunization of adolescents 12 to 15 years of age will be reported subsequently, and additional studies are planned to evaluate BNT162b2 in pregnant women, children younger than 12 years, and those in special risk groups, such as immunocompromised persons. Although the vaccine can be stored for up to 5 days at standard refrigerator temperatures once ready for use, very cold temperatures are required for shipping and longer storage. The current cold storage requirement may be alleviated by ongoing stability studies and formulation optimization, which may also be described in subsequent reports.

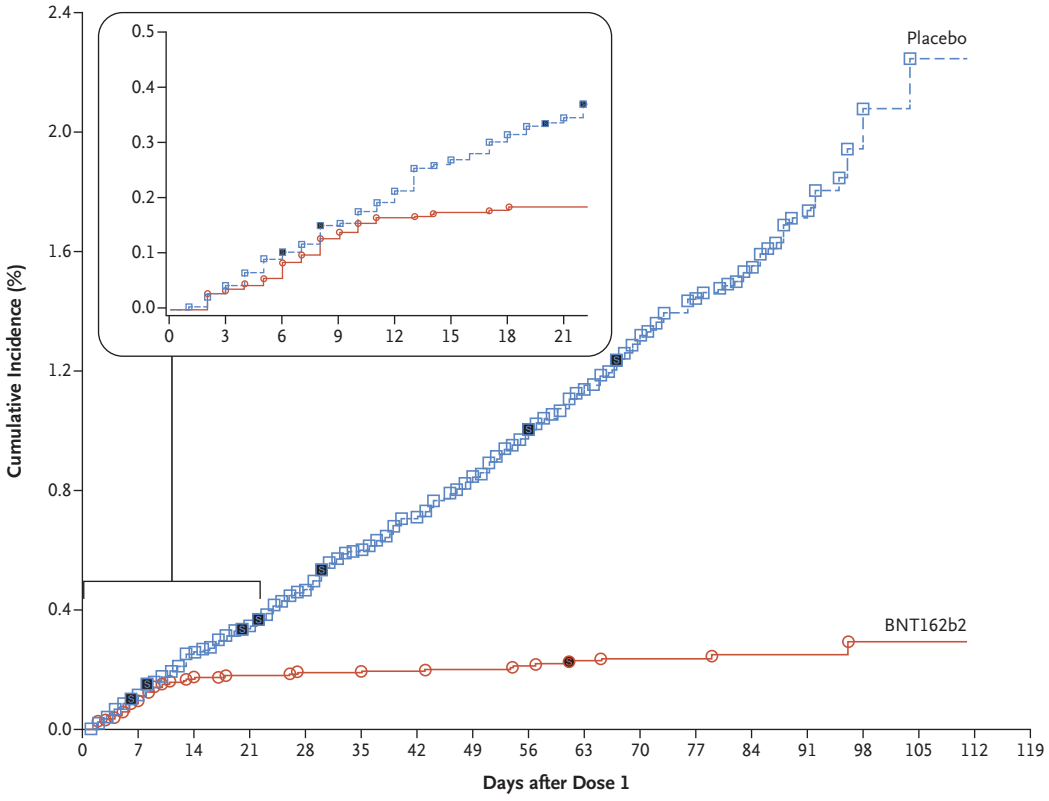
The data presented in this report have significance beyond the performance of this vaccine candidate. The results demonstrate that Covid-19 can be prevented by immunization,

Table 3. Vaccine Efficacy Overall and by Subgroup in Participants without Evidence of Infection before 7 Days after Dose 2.

Efficacy End-Point Subgroup	BNT162b2 (N=18,198)		Placebo (N=18,325)		Vaccine Efficacy, % (95% CI)†
	No. of Cases	Surveillance Time (No. at Risk)*	No. of Cases	Surveillance Time (No. at Risk)*	
Overall	8	2.214 (17,411)	162	2.222 (17,511)	95.0 (90.0–97.9)
Age group					
16 to 55 yr	5	1.234 (9,897)	114	1.239 (9,955)	95.6 (89.4–98.6)
>55 yr	3	0.980 (7,500)	48	0.983 (7,543)	93.7 (80.6–98.8)
≥65 yr	1	0.508 (3,848)	19	0.511 (3,880)	94.7 (66.7–99.9)
≥75 yr	0	0.102 (774)	5	0.106 (785)	100.0 (–13.1–100.0)
Sex					
Male	3	1.124 (8,875)	81	1.108 (8,762)	96.4 (88.9–99.3)
Female	5	1.090 (8,536)	81	1.114 (8,749)	93.7 (84.7–98.0)
Race or ethnic group‡					
White	7	1.889 (14,504)	146	1.903 (14,670)	95.2 (89.8–98.1)
Black or African American	0	0.165 (1,502)	7	0.164 (1,486)	100.0 (31.2–100.0)
All others	1	0.160 (1,405)	9	0.155 (1,355)	89.3 (22.6–99.8)
Hispanic or Latinx	3	0.605 (4,764)	53	0.600 (4,746)	94.4 (82.7–98.9)
Non-Hispanic, non-Latinx	5	1.596 (12,548)	109	1.608 (12,661)	95.4 (88.9–98.5)
Country					
Argentina	1	0.351 (2,545)	35	0.346 (2,521)	97.2 (83.3–99.9)
Brazil	1	0.119 (1,129)	8	0.117 (1,121)	87.7 (8.1–99.7)
United States	6	1.732 (13,359)	119	1.747 (13,506)	94.9 (88.6–98.2)

* Surveillance time is the total time in 1000 person-years for the given end point across all participants within each group at risk for the end point. The time period for Covid-19 case accrual is from 7 days after the second dose to the end of the surveillance period.
† The confidence interval (CI) for vaccine efficacy is derived according to the Clopper–Pearson method, adjusted for surveillance time.
‡ Race or ethnic group was reported by the participants. "All others" included the following categories: American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, multiracial, and not reported.

provide proof of concept that RNA-based vaccines are a promising new approach for protecting humans against infectious diseases, and demonstrate the speed with which an RNA-based vaccine can be developed with a sufficient investment of resources. The development of BNT162b2 was initiated on January 10, 2020, when the SARS-CoV-2 genetic sequence was released by the Chinese Center for Disease Control and Prevention and disseminated globally by the GISAID (Global Initiative on Sharing All Influenza Data) initiative. This rigorous demonstration of safety and efficacy less than 11 months later provides a practical demonstration that RNA-based vaccines, which require only viral genetic sequence information to initiate development, are a major new tool to combat pandemics and other infectious disease outbreaks. The continuous phase 1/2/3 trial design may provide a model to reduce the protracted development timelines that have delayed the availability of vaccines against other infectious diseases of medical importance. In the context of the current, still expanding pandemic, the BNT162b2 vaccine, if approved, can contribute, together with other public health measures, to reducing the devastating loss of health,



Efficacy End-Point Subgroup	BNT162b2, 30 μg (N=21,669)		Placebo (N=21,686)		VE (95% CI)
	No. of participants	Surveillance time person-yr (no. at risk)	No. of participants	Surveillance time person-yr (no. at risk)	percent
Covid-19 occurrence					
After dose 1	50	4.015 (21,314)	275	3.982 (21,258)	82.0 (75.6–86.9)
After dose 1 to before dose 2	39		82		52.4 (29.5–68.4)
Dose 2 to 7 days after dose 2	2		21		90.5 (61.0–98.9)
≥7 Days after dose 2	9		172		94.8 (89.8–97.6)

Figure 3. Efficacy of BNT162b2 against Covid-19 after the First Dose.

Shown is the cumulative incidence of Covid-19 after the first dose (modified intention-to-treat population). Each symbol represents Covid-19 cases starting on a given day; filled symbols represent severe Covid-19 cases. Some symbols represent more than one case, owing to overlapping dates. The inset shows the same data on an enlarged y axis, through 21 days. Surveillance time is the total time in 1000 person-years for the given end point across all participants within each group at risk for the end point. The time period for Covid-19 case accrual is from the first dose to the end of the surveillance period. The confidence interval (CI) for vaccine efficacy (VE) is derived according to the Clopper–Pearson method.

life, and economic and social well-being that has resulted from the global spread of Covid-19.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine

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ABSTRACT

BACKGROUND

Vaccines are needed to prevent coronavirus disease 2019 (Covid-19) and to protect persons who are at high risk for complications. The mRNA-1273 vaccine is a lipid nanoparticle–encapsulated mRNA-based vaccine that encodes the prefusion stabilized full-length spike protein of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes Covid-19.

METHODS

This phase 3 randomized, observer-blinded, placebo-controlled trial was conducted at 99 centers across the United States. Persons at high risk for SARS-CoV-2 infection or its complications were randomly assigned in a 1:1 ratio to receive two intramuscular injections of mRNA-1273 (100 μg) or placebo 28 days apart. The primary end point was prevention of Covid-19 illness with onset at least 14 days after the second injection in participants who had not previously been infected with SARS-CoV-2.

RESULTS

The trial enrolled 30,420 volunteers who were randomly assigned in a 1:1 ratio to receive either vaccine or placebo (15,210 participants in each group). More than 96% of participants received both injections, and 2.2% had evidence (serologic, virologic, or both) of SARS-CoV-2 infection at baseline. Symptomatic Covid-19 illness was confirmed in 185 participants in the placebo group (56.5 per 1000 person-years; 95% confidence interval [CI], 48.7 to 65.3) and in 11 participants in the mRNA-1273 group (3.3 per 1000 person-years; 95% CI, 1.7 to 6.0); vaccine efficacy was 94.1% (95% CI, 89.3 to 96.8%; P<0.001). Efficacy was similar across key secondary analyses, including assessment 14 days after the first dose, analyses that included participants who had evidence of SARS-CoV-2 infection at baseline, and analyses in participants 65 years of age or older. Severe Covid-19 occurred in 30 participants, with one fatality; all 30 were in the placebo group. Moderate, transient reactogenicity after vaccination occurred more frequently in the mRNA-1273 group. Serious adverse events were rare, and the incidence was similar in the two groups.

CONCLUSIONS

The mRNA-1273 vaccine showed 94.1% efficacy at preventing Covid-19 illness, including severe disease. Aside from transient local and systemic reactions, no safety concerns were identified. (Funded by the Biomedical Advanced Research and Development Authority and the National Institute of Allergy and Infectious Diseases; COVE ClinicalTrials.gov number, NCT04470427.)

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*A complete list of members of the COVE Study Group is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Baden and El Sahly contributed equally to this article.

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A Quick Take is available at NEJM.org

The emergence in December 2019 of a novel coronavirus, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has had devastating consequences globally. Control measures such as the use of masks, physical distancing, testing of exposed or symptomatic persons, contact tracing, and isolation have helped limit the transmission where they have been rigorously applied; however, these actions have been variably implemented and have proved insufficient in impeding the spread of coronavirus disease 2019 (Covid-19), the disease caused by SARS-CoV-2. Vaccines are needed to reduce the morbidity and mortality associated with Covid-19, and multiple platforms have been involved in the rapid development of vaccine candidates.[1-9]

The mRNA vaccine platform has advantages as a pandemic-response strategy, given its flexibility and efficiency in immunogen design and manufacturing. Earlier work had suggested that the spike protein of the coronavirus responsible for the 2002 SARS outbreak was a suitable target for protective immunity.[10] Numerous vaccine candidates in various stages of development are now being evaluated.[11-13] Shortly after the SARS-CoV-2 genetic sequence was determined in January 2020, mRNA-1273, a lipid-nanoparticle (LNP)–encapsulated mRNA vaccine expressing the prefusion-stabilized spike glycoprotein, was developed by Moderna and the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases (NIAID), within the National Institutes of Health (NIH).[14] The mRNA-1273 vaccine demonstrated protection in animal-challenge experiments[15] and encouraging safety and immunogenicity in early-stage human testing.[1,4] The efficacy and safety of another mRNA vaccine, BNT162b2, was recently demonstrated.[16]

The Coronavirus Efficacy (COVE) phase 3 trial was launched in late July 2020 to assess the safety and efficacy of the mRNA-1273 vaccine in preventing SARS-CoV-2 infection. An independent data and safety monitoring board determined that the vaccine met the prespecified efficacy criteria at the first interim analysis. We report the primary analysis results of this ongoing pivotal phase 3 trial.

Methods

Trial Oversight

This phase 3 randomized, stratified, observer-blinded, placebo-controlled trial enrolled adults in medically stable condition at 99 U.S. sites. Participants received the first trial injection between July 27 and October 23, 2020. The trial is being conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Good Clinical Practice guidelines, and applicable government regulations. The central institutional review board approved the protocol and the consent forms. All participants provided written informed consent before enrollment. Safety is reviewed by a protocol safety review team weekly and by an independent data and safety monitoring board on a continual basis. The trial Investigational New Drug sponsor, Moderna, was responsible for the overall trial design (with input from the Biomedical Advanced Research and Development Authority, the NIAID, the Covid-19 Prevention Network, and the trial cochairs), site selection and monitoring, and data analysis. Investigators are responsible for data collection. A medical writer funded by Moderna assisted in drafting the manuscript for submission. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The trial is ongoing, and the investigators remain unaware of participant-level data. Designated team members within Moderna have unblinded access to the data, to facilitate interface with the regulatory agencies and the data and safety monitoring board; all other trial staff and participants remain unaware of the treatment assignments.

Participants, Randomization, and Data Blinding

Eligible participants were persons 18 years of age or older with no known history of SARS-CoV-2 infection and with locations or circumstances that put them at an appreciable risk of SARS-CoV-2 infection, a high risk of severe Covid-19, or both. Inclusion and exclusion criteria are provided in the protocol (available with the full text of this article at NEJM.org). To enhance the diversity of the trial population in accordance with Food and Drug Administration Draft Guidance, site-selection and enrollment processes were adjusted to increase the number of persons from racial and ethnic minorities in the trial, in addition to the persons at risk for SARS-CoV-2 infection in the local population. The upper limit for stratification of enrolled participants considered

to be "at risk for severe illness" at screening was increased from 40% to 50%.[17]

Participants were randomly assigned in a 1:1 ratio, through the use of a centralized interactive response technology system, to receive vaccine or placebo. Assignment was stratified, on the basis of age and Covid-19 complications risk criteria, into the following risk groups: persons 65 years of age or older, persons younger than 65 years of age who were at heightened risk (at risk) for severe Covid-19, and persons younger than 65 years of age without heightened risk (not at risk). Participants younger than 65 years of age were categorized as having risk for severe Covid-19 if they had at least one of the following risk factors, based on the Centers for Disease Control and Prevention (CDC) criteria available at the time of trial design: chronic lung disease (e.g., emphysema, chronic bronchitis, idiopathic pulmonary fibrosis, cystic fibrosis, or moderate-to-severe asthma); cardiac disease (e.g., heart failure, congenital coronary artery disease, cardiomyopathies, or pulmonary hypertension); severe obesity (body mass index [the weight in kilograms divided by the square of the height in meters] ≥40); diabetes (type 1, type 2, or gestational); liver disease; or infection with the human immunodeficiency virus.[18]

Vaccine dose preparation and administration were performed by pharmacists and vaccine administrators who were aware of treatment assignments but had no other role in the conduct of the trial. Once the injection was completed, only trial staff who were unaware of treatment assignments performed assessments and interacted with the participants. Access to the randomization code was strictly controlled at the pharmacy. The data and safety monitoring board reviewed efficacy data at the group level and unblinded safety data at the participant level.

TRIAL VACCINE

The mRNA-1273 vaccine, provided as a sterile liquid at a concentration of 0.2 mg per milliliter, was administered by injection into the deltoid muscle according to a two-dose regimen. Injections were given 28 days apart, in the same arm, in a volume of 0.5 ml containing 100 μg of mRNA-1273 or saline placebo.[1] Vaccine mRNA-1273 was stored at 2° to 8°C (35.6° to 46.4°F) at clinical sites before preparation and vaccination. No dilution was required. Doses could be held in syringes for up to 8 hours at room temperature before administration.

SAFETY ASSESSMENTS

Safety assessments included monitoring of solicited local and systemic adverse events for 7 days after each injection; unsolicited adverse reactions for 28 days after each injection; adverse events leading to discontinuation from a dose, from participation in the trial, or both; and medically attended adverse events and serious adverse events from day 1 through day 759. Adverse event grading criteria and toxicity tables are described in the protocol. Cases of Covid-19 and severe Covid-19 were continuously monitored by the data and safety monitoring board from randomization onward.

EFFICACY ASSESSMENTS

The primary end point was the efficacy of the mRNA-1273 vaccine in preventing a first occurrence of symptomatic Covid-19 with onset at least 14 days after the second injection in the per-protocol population, among participants who were seronegative at baseline. End points were judged by an independent adjudication committee that was unaware of group assignment. Covid-19 cases were defined as occurring in participants who had at least two of the following symptoms: fever (temperature ≥38°C), chills, myalgia, headache, sore throat, or new olfactory or taste disorder, or as occurring in those who had at least one respiratory sign or symptom (including cough, shortness of breath, or clinical or radiographic evidence of pneumonia) and at least one nasopharyngeal swab, nasal swab, or saliva sample (or respiratory sample, if the participant was hospitalized) that was positive for SARS-CoV-2 by reverse-transcriptase–polymerase-chain-reaction (RT-PCR) test. Participants were assessed for the presence of SARS-CoV-2–binding antibodies specific to the SARS-CoV-2 nucleocapsid protein (Roche Elecsys, Roche Diagnostics International) and had a nasopharyngeal swab for SARS-CoV-2 RT-PCR testing (Viracor, Eurofins Clinical Diagnostics) before each injection. SARS-CoV-2–infected volunteers were followed daily, to assess symptom severity, for 14 days or until symptoms resolved, whichever was longer. A nasopharyngeal swab for RT-PCR testing and a blood sample for identifying serologic evidence of SARS-CoV-2 infection were collected from participants with symptoms of Covid-19.

The consistency of vaccine efficacy at the primary end point was evaluated across various subgroups, including age groups (18 to <65 years

of age and ≥65 years), age and health risk for severe disease (18 to <65 years and not at risk; 18 to <65 years and at risk; and ≥65 years), sex (female or male), race and ethnic group, and risk for severe Covid-19 illness. If the number of participants in a subgroup was too small, it was combined with other subgroups for the subgroup analyses.

A secondary end point was the efficacy of mRNA-1273 in the prevention of severe Covid-19 as defined by one of the following criteria: respiratory rate of 30 or more breaths per minute; heart rate at or exceeding 125 beats per minute; oxygen saturation at 93% or less while the participant was breathing ambient air at sea level or a ratio of the partial pressure of oxygen to the fraction of inspired oxygen below 300 mm Hg; respiratory failure; acute respiratory distress syndrome; evidence of shock (systolic blood pressure <90 mm Hg, diastolic blood pressure <60 mm Hg, or a need for vasopressors); clinically significant acute renal, hepatic, or neurologic dysfunction; admission to an intensive care unit; or death. Additional secondary end points included the efficacy of the vaccine at preventing Covid-19 after a single dose or at preventing Covid-19 according to a secondary (CDC), less restrictive case definition: having any symptom of Covid-19 and a positive SARS-CoV-2 test by RT-PCR (see Table S1 in the Supplementary Appendix, available at NEJM.org).

STATISTICAL ANALYSIS

For analysis of the primary end point, the trial was designed for the null hypothesis that the efficacy of the mRNA-1273 vaccine is 30% or less. A total of 151 cases of Covid-19 would provide 90% power to detect a 60% reduction in the hazard rate (i.e., 60% vaccine efficacy), with two planned interim analyses at approximately 35% and 70% of the target total number of cases (151) and with a one-sided O'Brien–Fleming boundary for efficacy and an overall one-sided error rate of 0.025. The efficacy of the mRNA-1273 vaccine could be demonstrated at either the interim or the primary analysis, performed when the target total number of cases had been observed. The Lan–DeMets alpha-spending function was used for calculating efficacy boundaries at each analysis. At the first interim analysis on November 15, 2020, vaccine efficacy had been demonstrated in accordance with the prespecified statistical criteria. The vaccine efficacy estimate, based on a total of 95 adjudicated cases (63% of the target total), was 94.5%, with a one-sided P value of less than 0.001 to reject the null hypothesis that vaccine efficacy would be 30% or less. The data and safety monitoring board recommendation to the oversight group and the trial sponsor was that the efficacy findings should be shared with the participants and the community (full details are available in the protocol and statistical analysis plan).

Vaccine efficacy was assessed in the full analysis population (randomized participants who received at least one dose of mRNA-1273 or placebo), the modified intention-to-treat population (participants in the full analysis population who had no immunologic or virologic evidence of Covid-19 on day 1, before the first dose), and the per-protocol population (participants in the modified intention-to-treat population who received two doses, with no major protocol deviations). The primary efficacy end point in the interim and primary analyses was assessed in the per-protocol population. Participants were evaluated in the treatment groups to which they were assigned. Vaccine efficacy was defined as the percentage reduction in the hazard ratio for the primary end point (mRNA-1273 vs. placebo). A stratified Cox proportional hazards model was used to assess the vaccine efficacy of mRNA-1273 as compared with placebo in terms of the percentage hazard reduction. (Details regarding the analysis of vaccine efficacy are provided in the Methods section of the Supplementary Appendix.)

Safety was assessed in all participants in the solicited safety population (i.e., those who received at least one injection and reported a solicited adverse event). Descriptive summary data (numbers and percentages) for participants with any solicited adverse events, unsolicited adverse events, unsolicited severe adverse events, serious adverse events, medically attended adverse events, and adverse events leading to discontinuation of the injections or withdrawal from the trial are provided by group. Two-sided 95% exact confidence intervals (Clopper–Pearson method) are provided for the percentages of participants with solicited adverse events. Unsolicited adverse events are presented according to the *Medical Dictionary for Regulatory Activities* (MedDRA), version 23.0, preferred terms and system organ class categories.

To meet the regulatory agencies' requirement of a median follow-up duration of at least 2 months

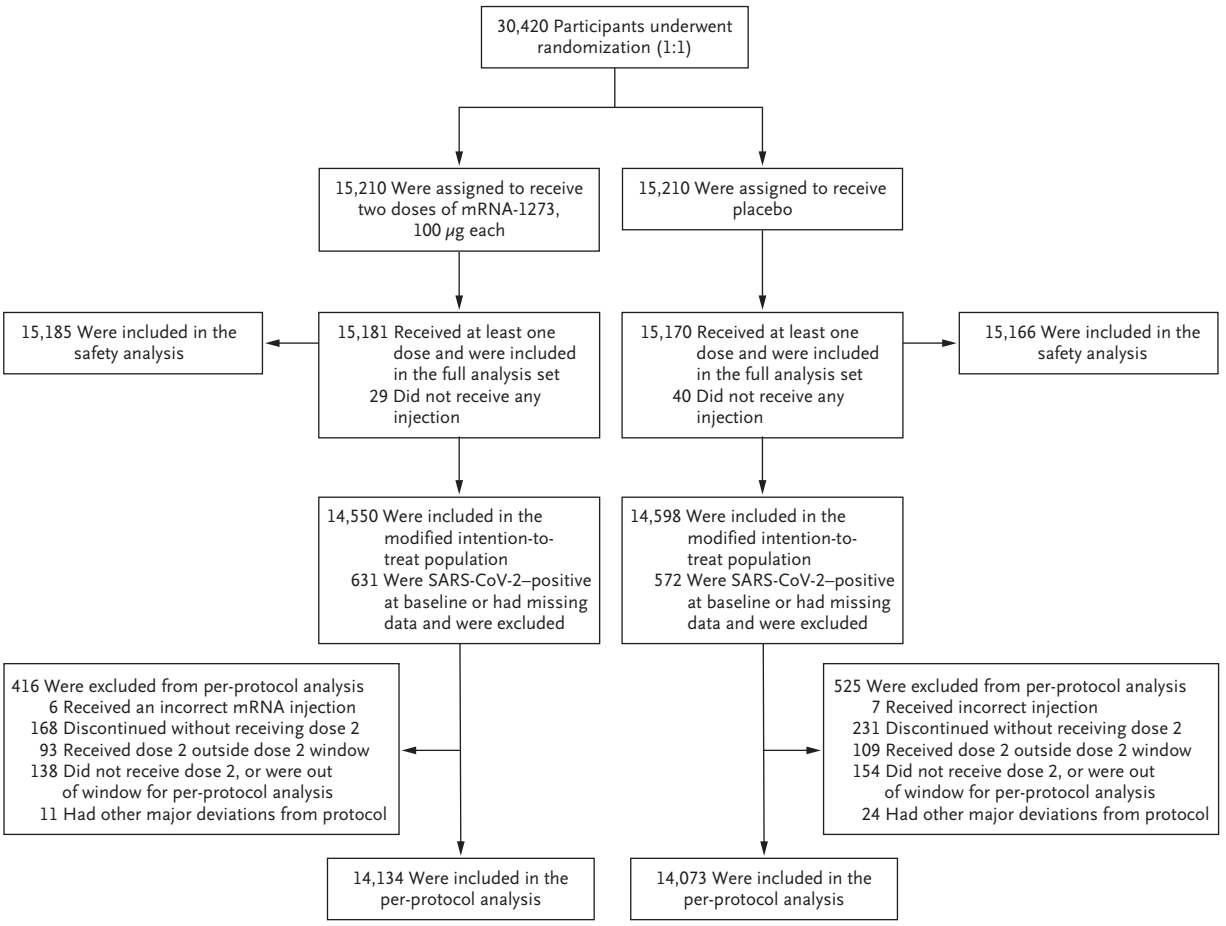


Figure 1. Randomization and Analysis Populations.

The data cutoff for the primary analysis occurred on November 25, 2020. The full analysis population consisted of participants who underwent randomization and received at least one dose of mRNA-1273 or placebo; the modified intention-to-treat population comprised participants in the full analysis population who had no immunologic or virologic evidence of Covid-19 on day 1, before the first dose; and the per-protocol analysis population included participants in the modified intention-to-treat population who received two doses, with no major protocol deviations. The safety population included all participants who received at least one injection. Among participants who received an incorrect injection, three participants in the mRNA-1273 group received at least one dose of placebo and no dose of mRNA-1273 and were included in the placebo safety population, and three received one dose of placebo and one dose of mRNA-1273 and were included in the mRNA-1273 safety population; in the placebo group all seven received mRNA-1273 and were included in the mRNA-1273 safety population. Participants who received dose 2 outside the window for the per-protocol analysis are those who did not receive the second dose between 7 days before and 14 days after day 29.

after completion of the two-dose regimen, a second analysis was performed, with an efficacy data cutoff date of November 21, 2020. This second analysis is considered the primary analysis of efficacy, with a total of 196 adjudicated Covid-19 cases in the per-protocol population, which exceeds the target total number of cases (151) specified in the protocol. This was an increase from the 95 cases observed at the first interim analysis data cutoff on November 11, 2020. Results from the primary analysis are presented in this report. Subsequent analyses are considered supplementary.

RESULTS

TRIAL POPULATION

Between July 27, 2020, and October 23, 2020, a total of 30,420 participants underwent randomization, and the 15,210 participants in each group were assigned to receive two doses of either placebo or mRNA-1273 (100 μg) (Fig. 1).

Table 1. Demographic and Clinical Characteristics at Baseline.*

Characteristics	Placebo (N=15,170)	mRNA-1273 (N=15,181)	Total (N=30,351)
Sex — no. of participants (%)			
Male	8,062 (53.1)	7,923 (52.2)	15,985 (52.7)
Female	7,108 (46.9)	7,258 (47.8)	14,366 (47.3)
Mean age (range) — yr	51.3 (18–95)	51.4 (18–95)	51.4 (18–95)
Age category and risk for severe Covid-19 — no. of participants (%)†			
18 to <65 yr, not at risk	8,886 (58.6)	8,888 (58.5)	17,774 (58.6)
18 to <65 yr, at risk	2,535 (16.7)	2,530 (16.7)	5,065 (16.7)
≥65 yr	3,749 (24.7)	3,763 (24.8)	7,512 (24.8)
Hispanic or Latino ethnicity — no. of participants (%)‡			
Hispanic or Latino	3,114 (20.5)	3,121 (20.6)	6,235 (20.5)
Not Hispanic or Latino	11,917 (78.6)	11,918 (78.5)	23,835 (78.5)
Not reported and unknown	139 (0.9)	142 (0.9)	281 (0.9)
Race or ethnic group — no. of participants (%)‡			
White	11,995 (79.1)	12,029 (79.2)	24,024 (79.2)
Black or African American	1,527 (10.1)	1,563 (10.3)	3,090 (10.2)
Asian	731 (4.8)	651 (4.3)	1,382 (4.6)
American Indian or Alaska Native	121 (0.8)	112 (0.7)	233 (0.8)
Native Hawaiian or Other Pacific Islander	32 (0.2)	35 (0.2)	67 (0.2)
Multiracial	321 (2.1)	315 (2.1)	636 (2.1)
Other	316 (2.1)	321 (2.1)	637 (2.1)
Not reported and unknown	127 (0.8)	155 (1.0)	282 (0.9)
Baseline SARS-CoV-2 status — no. of participants (%)§			
Negative	14,598 (96.2)	14,550 (95.8)	29,148 (96.0)
Positive	337 (2.2)	343 (2.3)	680 (2.2)
Missing data	235 (1.5)	288 (1.9)	523 (1.7)
Baseline RT-PCR test — no. of participants (%)			
Negative	14,923 (98.4)	14,917 (98.3)	29,840 (98.3)
Positive	95 (0.6)	87 (0.6)	182 (0.6)
Missing data	152 (1.0)	177 (1.2)	329 (1.1)
Baseline bAb anti–SARS-CoV-2 assay — no. of participants (%)			
Negative	14,726 (97.1)	14,690 (96.8)	29,416 (96.9)
Positive	303 (2.0)	305 (2.0)	608 (2.0)
Missing data	141 (0.9)	186 (1.2)	327 (1.1)
Risk factor for severe Covid-19 — no. of participants (%)			
Chronic lung disease	744 (4.9)	710 (4.7)	1,454 (4.8)
Significant cardiac disease	744 (4.9)	752 (5.0)	1,496 (4.9)
Severe obesity	1,021 (6.7)	1,025 (6.8)	2,046 (6.7)
Diabetes	1,440 (9.5)	1,435 (9.5)	2,875 (9.5)
Liver disease	96 (0.6)	100 (0.7)	196 (0.6)
Human immunodeficiency virus infection	87 (0.6)	92 (0.6)	179 (0.6)

Table 1. (Continued.)

Characteristics	Placebo (N=15,170)	mRNA-1273 (N=15,181)	Total (N=30,351)
Body-mass index¶			
No. of participants	15,007	14,985	29,992
Mean ±SD	29.3±6.7	29.3±6.9	29.3±6.8

* Internet-based randomization was used to assign participants to treatment groups on the basis of information entered by the investigator regarding the participant's age and coexisting conditions. Percentages are based on the full analysis population; baseline demographics and characteristics for the per-protocol population are provided in the Supplementary Appendix. Percentages may not total 100 because of rounding. The abbreviation bAb denotes binding antibody concentration, and RT-PCR reverse-transcriptase polymerase chain reaction.
† Risk was based on a stratification factor from the Internet-based interactive response system used for randomization; participants who were younger than 65 years of age were categorized as at risk for severe Covid-19 illness if they had at least one of the risk factors specified in the trial protocol at screening.
‡ Race or ethnic group was reported by the participant. Participants could be included in more than one category.
§ Baseline SARS-CoV-2 status was positive if there was immunologic or virologic evidence of previous illness with Covid-19, as defined by a positive RT-PCR test or a positive bAb against SARS-CoV-2 nucleocapsid assay result that was above the limit of detection or by a lower limit of quantification at day 1. Baseline SARS-CoV-2 status was negative if there was a negative RT-PCR test and negative bAb against SARS-CoV-2 assay result at day 1.
¶ The body-mass index is the weight in kilograms divided by the square of the height in meters.

More than 96% of participants received the second dose (Fig. S1). Common reasons for not receiving the second dose were withdrawal of consent (153 participants) and the detection of SARS-CoV-2 by PCR before the administration of the second dose on day 29 (114 participants: 69 in the placebo group and 45 in the mRNA-1273 group). The primary efficacy and safety analyses were performed in the per-protocol and safety populations, respectively. Of the participants who received a first injection, 14,073 of those in the placebo group and 14,134 in the mRNA-1273 group were included in the primary efficacy analysis; 525 participants in the placebo group and 416 in the mRNA-1273 group were excluded from the per-protocol population, including those who had not received a second dose by the day 29 data cutoff (Fig. 1). As of November 25, 2020, the participants had a median follow-up duration of 63 days (range, 0 to 97) after the second dose, with 62% of participants having more than 56 days of follow-up.

Baseline demographic characteristics were balanced between the placebo group and the mRNA-1273 vaccine group (Table 1 and Table S2). The mean age of the participants was 51.4 years, 47.3% of the participants were female, 24.8% were 65 years of age or older, and 16.7% were younger than 65 years of age and had predisposing medical conditions that put them at risk for severe Covid-19. The majority of participants were White (79.2%), and the racial and ethnic proportions were generally representative of U.S. demographics, including 10.2% Black or African American and 20.5% Hispanic or Latino. Evidence of SARS-CoV-2 infection at baseline was present in 2.3% of participants in the mRNA-1273 group and in 2.2% in the placebo group, as detected by serologic assay or RT-PCR testing.

SAFETY

Solicited adverse events at the injection site occurred more frequently in the mRNA-1273 group than in the placebo group after both the first dose (84.2%, vs. 19.8%) and the second dose (88.6%, vs. 18.8%) (Fig. 2 and Tables S3 and S4). In the mRNA-1273 group, injection-site events were mainly grade 1 or 2 in severity and lasted a mean of 2.6 and 3.2 days after the first and second doses, respectively (Table S5). The most common injection-site event was pain after injection. Delayed injection-site reactions (those with onset on or after day 8) were noted in 244 participants (0.8%) after the first dose and in 68 participants (0.2%) after the second dose. Reactions were characterized by erythema, induration, and tenderness, and they resolved over the following 4 to 5 days. Solicited systemic adverse events occurred more often in the mRNA-1273 group than in the placebo group after both the first dose (54.9%, vs. 42.2%) and the second dose (79.4%, vs. 36.5%). The severity of the solicited systemic events increased after the second dose in the mRNA-1273 group, with an increase

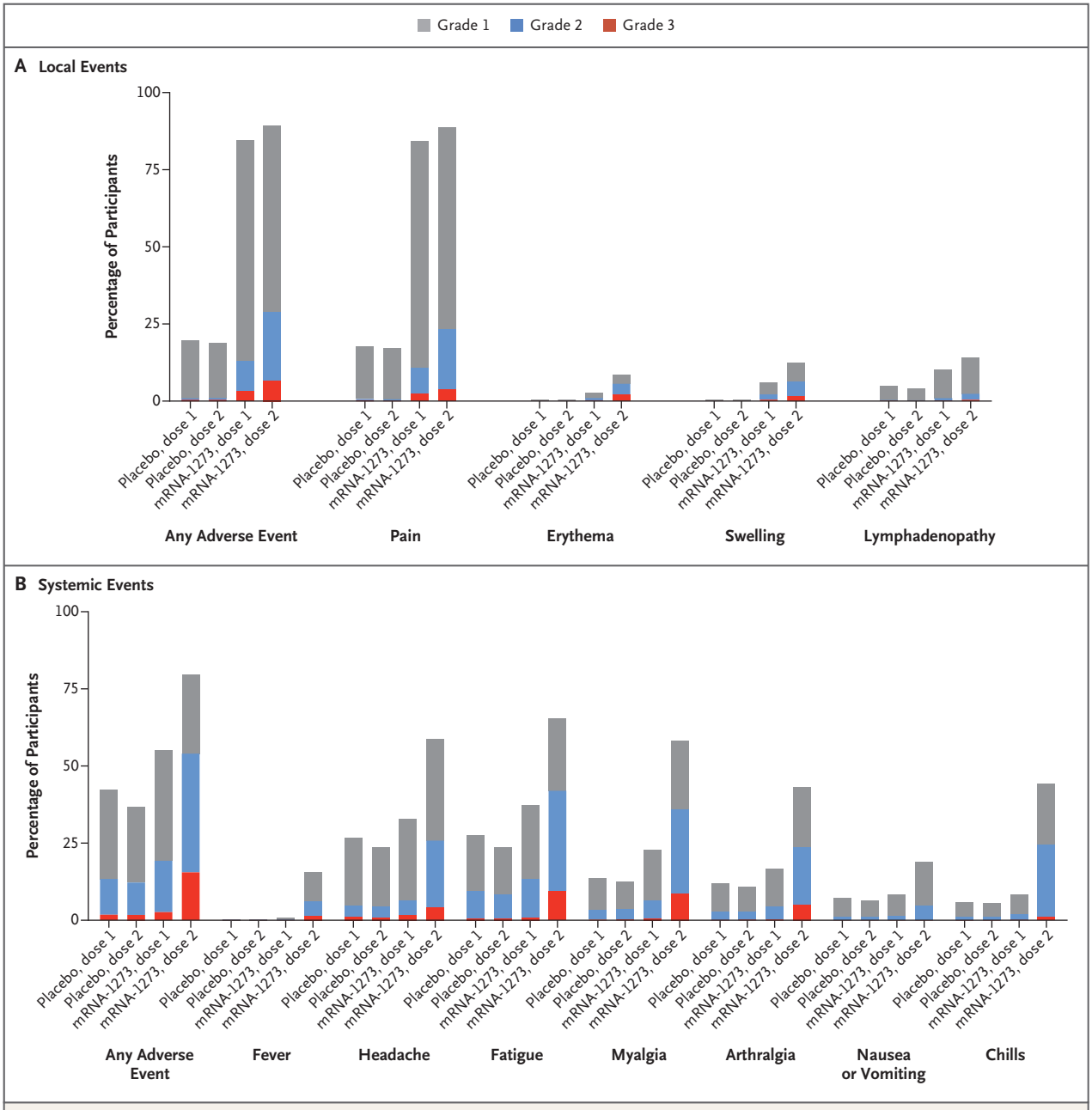


Figure 2. Solicited Local and Systemic Adverse Events.

Shown is the percentage of participants who had a solicited local or systemic adverse event within 7 days after injection 1 or injection 2 of either the placebo or the mRNA-1273 vaccine.

in proportions of grade 2 events (from 16.5% after the first dose to 38.1% after the second dose) and grade 3 events (from 2.9% to 15.8%). Solicited systemic adverse events in the mRNA-1273 group lasted a mean of 2.9 days and 3.1 days after the first and second doses, respectively (Table S5). Both solicited injection-site and systemic adverse events were more common among younger participants (18 to <65 years of age) than among older participants (≥65 years of age). Solicited adverse events were less common in participants who were positive for SARS-

CoV-2 infection at baseline than in those who were negative at baseline (Tables S6 and S7).

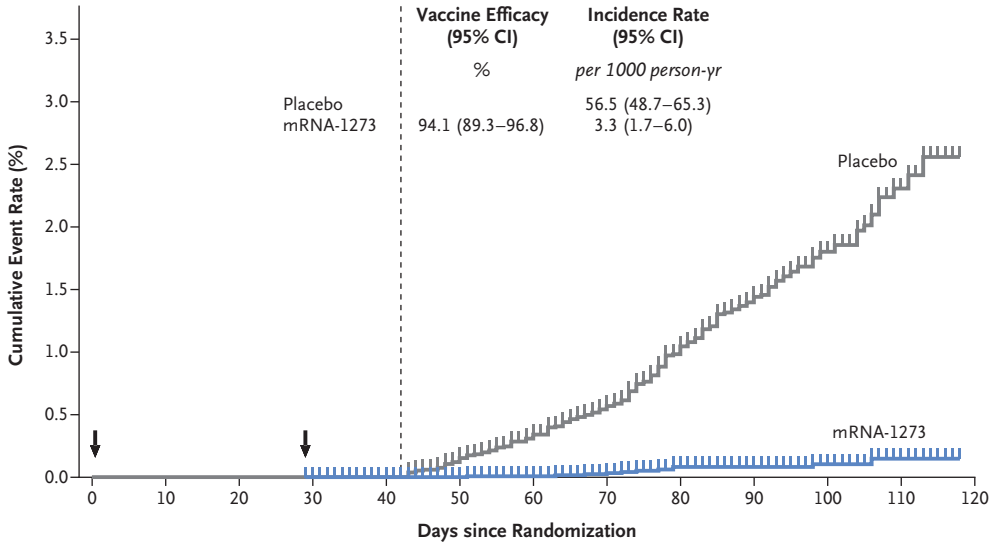
The frequency of unsolicited adverse events, unsolicited severe adverse events, and serious adverse events reported during the 28 days after injection was generally similar among participants in the two groups (Tables S8 through S11). Three deaths occurred in the placebo group (one from intraabdominal perforation, one from cardiopulmonary arrest, and one from severe systemic inflammatory syndrome in a participant with chronic lymphocytic leukemia and diffuse bullous rash) and two in the vaccine group (one from cardiopulmonary arrest and one by suicide). The frequency of grade 3 adverse events in the placebo group (1.3%) was similar to that in the vaccine group (1.5%), as were the frequencies of medically attended adverse events (9.7% vs. 9.0%) and serious adverse events (0.6% in both groups). Hypersensitivity reactions were reported in 1.5% and 1.1% of participants in the vaccine and placebo groups, respectively (Table S12). Bell's palsy occurred in the vaccine group (3 participants [<0.1%]) and the placebo group (1 participant [<0.1%]) during the observation period of the trial (more than 28 days after injection). Overall, 0.5% of participants in the placebo group and 0.3% in the mRNA-1273 group had adverse events that resulted in their not receiving the second dose, and less than 0.1% of participants in both groups discontinued participation in the trial because of adverse events after any dose (Table S8). No evidence of vaccine-associated enhanced respiratory disease was noted, and fewer cases of severe Covid-19 or any Covid-19 were observed among participants who received mRNA-1273 than among those who received placebo (Tables S13 and S14). Adverse events that were deemed by the trial team to be related to the vaccine or placebo were reported among 4.5% of participants in the placebo group and 8.2% in the mRNA-1273 group. The most common treatment-related adverse events (those reported in at least 1% of participants) in the placebo group and the mRNA-1273 group were fatigue (1.2% and 1.5%) and headache (0.9% and 1.4%). In the overall population, the incidence of treatment-related severe adverse events was higher in the mRNA-1273 group (71 participants [0.5%]) than in the placebo group (28 participants [0.2%]) (Tables S8 and S15). The relative incidence of these adverse events according to vaccine group was not affected by age.

EFFICACY

After day 1 and through November 25, 2020, a total of 269 Covid-19 cases were identified, with an incidence of 79.7 cases per 1000 person-years (95% confidence interval [CI], 70.5 to 89.9) among participants in the placebo group with no evidence of previous SARS-CoV-2 infection. For the primary analysis, 196 cases of Covid-19 were diagnosed: 11 cases in the vaccine group (3.3 per 1000 person-years; 95% CI, 1.7 to 6.0) and 185 cases in the placebo group (56.5 per 1000 person-years; 95% CI, 48.7 to 65.3), indicating 94.1% efficacy of the mRNA-1273 vaccine (95% CI, 89.3 to 96.8%; P<0.001) for the prevention of symptomatic SARS-CoV-2 infection as compared with placebo (Fig. 3A). Findings were similar across key secondary analyses (Table S16), including assessment starting 14 days after dose 1 (225 cases with placebo, vs. 11 with mRNA-1273, indicating a vaccine efficacy of 95.2% [95% CI, 91.2 to 97.4]), and assessment including participants who were SARS-CoV-2 seropositive at baseline in the per-protocol analysis (187 cases with placebo, vs. 12 with mRNA-1273; one volunteer assigned to receive mRNA-1273 was inadvertently given placebo], indicating a vaccine efficacy of 93.6% [95% CI, 88.6 to 96.5]). Between days 1 and 42, seven cases of Covid-19 were identified in the mRNA-1273 group, as compared with 65 cases in the placebo group (Fig. 3B).

A key secondary end point evaluated the efficacy of mRNA-1273 at preventing severe Covid-19. Thirty participants in the trial had severe Covid-19; all 30 were in the placebo group (indicating vaccine efficacy of 100% [95% CI, could not be estimated to 1.0]), and one death among these participants was attributed to Covid-19 (Table S16). The vaccine efficacy to prevent Covid-19 was consistent across subgroups stratified by demographic and baseline characteristics (Fig. 4): age groups (18 to <65 years of age and ≥65 years), presence of risk for severe Covid-19, sex, and race and ethnic group (non-Hispanic White and communities of color). Among participants who were positive for SARS-CoV-2, by serologic or virologic testing, at baseline (337 in the placebo group and 343 in the mRNA-1273

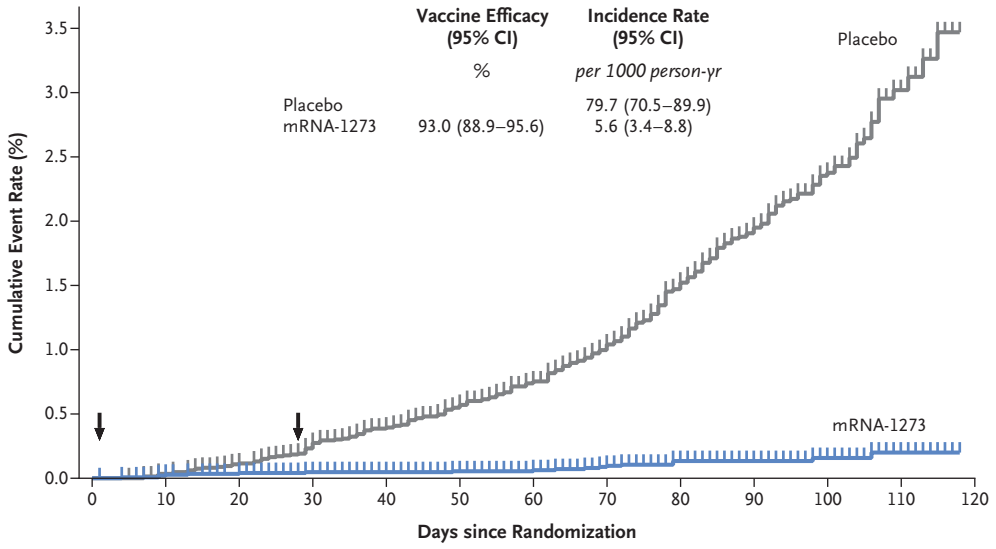
A Per-Protocol Analysis



No. at Risk

Placebo	14,073	14,073	14,073	14,072	13,416	12,992	12,361	11,147	9474	6563	3971	1172	0
mRNA-1273	14,134	14,134	14,134	14,133	13,483	13,073	12,508	11,315	9684	6721	4094	1209	0

B Modified Intention-to-Treat Analysis



No. at Risk

Placebo	14,598	14,590	14,567	14,515	13,806	13,352	12,694	11,450	9736	6729	4067	1200	0
mRNA-1273	14,550	14,543	14,532	14,504	13,825	13,398	12,791	11,573	9911	6871	4179	1238	0

Covid-19 Onset	Placebo (N=14,598)	mRNA-1273 (N=14,550)
Randomization to 14 days after dose 1	11	5
14 Days after dose 1 to dose 2	35	2
Dose 2 to 14 days after dose 2	19	0
Starting 14 days after dose 2	204	12
Total (any time after randomization)	269	19

Figure 3 (facing page). Vaccine Efficacy of mRNA-1273 to Prevent Covid-19.

Shown is the cumulative incidence of Covid-19 events in the primary analysis based on adjudicated assessment starting 14 days after the second vaccination in the per-protocol population (Panel A) and after randomization in the modified intention-to-treat population (Panel B) (see the Supplementary Appendix). The dotted line in Panel A indicates day 42 (14 days after vaccination 2), when the per-protocol follow-up began, and arrows in both panels indicate days 1 and 29, when injections were administered. Tick marks indicate censored data. Vaccine efficacy was defined as 1 minus the hazard ratio (mRNA vs. placebo), and the 95% confidence interval was estimated with the use of a stratified Cox proportional hazards model, with Efron's method of tie handling and with treatment group as a covariate, with adjustment for stratification factor. Incidence was defined as the number of events divided by number of participants at risk and was adjusted by person-years. Symptomatic Covid-19 case accrual for placebo and vaccine in the modified intention-to-treat population is displayed (does not include asymptomatic cases of SARS-CoV-2 detected at the day 29 by nasopharyngeal swab).

group), one case of Covid-19 was diagnosed by RT-PCR testing in a placebo recipient and no cases were diagnosed in mRNA-1273 recipients (Table S17). Among participants who were negative for SARS-CoV-2 at baseline (by RT-PCR or antibody testing), in addition to symptomatic Covid-19 cases 39 (0.3%) in the placebo group and 15 (0.1%) in the mRNA-1273 group had nasopharyngeal swabs that were positive for SARS-CoV-2 by RT-PCR at the second dose visit (surveillance swab) but had no evidence of Covid-19 symptoms (Table S18).

DISCUSSION

The COVE trial provides evidence of short-term efficacy of the mRNA-1273 vaccine in preventing symptomatic SARS-CoV-2 infection in a diverse adult trial population. Of note, the trial was designed for an infection attack rate of 0.75%, which would have necessitated a follow-up period of 6 months after the two vaccine doses to accrue 151 cases in 30,000 participants. The pandemic trajectory accelerated in many U.S. regions in the late summer and fall of 2020, resulting in rapid accrual of 196 cases after a median follow-up of 2 months. It is important to note that all the severe Covid-19 cases were in the placebo group, which suggests that mRNA-1273 is likely to have an effect on preventing severe illness, which is the major cause of health care utilization, complications, and death. The finding of fewer occurrences of symptomatic SARS-CoV-2 infection after a single dose of mRNA-1273 is encouraging; however, the trial was not designed to evaluate the efficacy of a single dose, and additional evaluation is warranted.

The magnitude of mRNA-1273 vaccine efficacy at preventing symptomatic SARS-CoV-2 infection is higher than the efficacy observed for vaccines for respiratory viruses, such as the inactivated influenza vaccine against symptomatic, virologically confirmed disease in adults, for which studies have shown a pooled efficacy of 59%.[19] This high apparent efficacy of mRNA-1273 is based on short-term data, and waning of efficacy over time has been demonstrated with other vaccines.[20] Also, the efficacy of the vaccine was tested in a setting of national recommendations for masking and social distancing, which may have translated into lower levels of infectious inoculum. The efficacy of mRNA-1273 is in line with that of the recently reported BNT162b2 mRNA vaccine.[16] The COVE trial is ongoing, and longitudinal follow-up will allow an assessment of efficacy changes over time and under evolving epidemiologic conditions.

Overall, the safety of the mRNA-1273 vaccine regimen and platform is reassuring; no unexpected patterns of concern were identified. The reactogenicity associated with immunization with mRNA-1273 in this trial is similar to that in the phase 1 data reported previously.[1,4] Overall, the local reactions to vaccination were mild; however, moderate-to-severe systemic side effects, such as fatigue, myalgia, arthralgia, and headache, were noted in about 50% of participants in the mRNA-1273 group after the second dose. These side effects were transient, starting about 15 hours after vaccination and resolving in most participants by day 2, without sequelae. The degree of reactogenicity after one dose of mRNA-1273 was less than that observed for the recently approved recombinant adjuvanted zoster vaccine and after the second mRNA-1273 dose was similar to that of the zoster vaccine.[21,22] Delayed injection-site reactions, with an onset

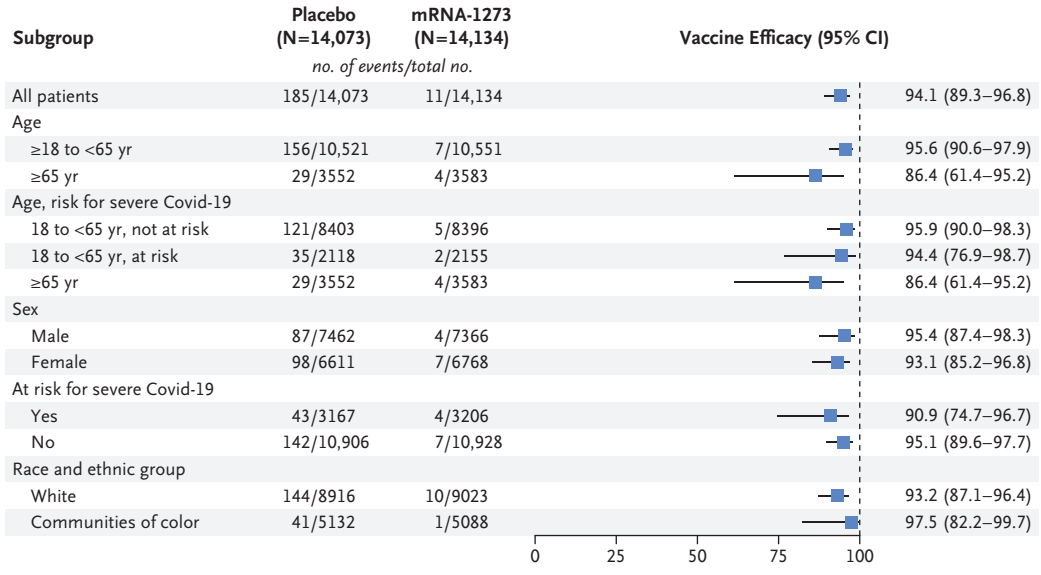


Figure 4. Vaccine Efficacy of mRNA-1273 to Prevent Covid-19 in Subgroups.

The efficacy of the RNA-1273 vaccine in preventing Covid-19 in various subgroups in the per-protocol population was based on adjudicated assessments starting 14 days after the second injection. Vaccine efficacy, defined as 1 minus the hazard ratio (mRNA-1273 vs. placebo), and 95% confidence intervals were estimated with the use of a stratified Cox proportional hazards model, with Efron's method of tie handling and with the treatment group as a covariate, adjusting for stratification factor if applicable. Race and ethnic group categories shown are White (non-Hispanic) and communities of color (all others, excluding those whose race and ethnicity were both reported as unknown, were not reported, or were both missing at screening). Data for communities of color were pooled owing to limited numbers of participants in each racial or ethnic group, to ensure that the subpopulations would be large enough for meaningful analyses.

8 days or more after injection, were uncommon. The overall incidence of unsolicited adverse events reported up to 28 days after vaccination and of serious adverse events reported throughout the entire trial was similar for mRNA-1273 and placebo. A risk of acute hypersensitivity is sometimes observed with vaccines; however, no such risk was evident in the COVE trial, although the ability to detect rare events is limited, given the trial sample size. The anecdotal finding of a slight excess of Bell's palsy in this trial and in the BNT162b2 vaccine trial arouses concern that it may be more than a chance event, and the possibility bears close monitoring.[16]

The mRNA-1273 vaccine did not show evidence in the short term of enhanced respiratory disease after infection, a concern that emerged from animal models used in evaluating some SARS and Middle East respiratory syndrome (MERS) vaccine constructs.[23-25] A hallmark of enhanced respiratory disease is a Th2-skewed immune response and eosinophilic pulmonary infiltration on histopathological examination. Of note, preclinical testing of mRNA-1273 and other SARS-CoV-2 vaccines in advanced clinical evaluation has shown a Th1-skewed vaccine response and no pathologic lung infiltrates.[15,26-28] Whether mRNA-1273 vaccination results in enhanced disease on exposure to the virus in the long term is unknown.

Key limitations of the data are the short duration of safety and efficacy follow-up. The trial is ongoing, and a follow-up duration of 2 years is planned, with possible changes to the trial design to allow participant retention and ongoing data collection. Another limitation is the lack of an identified correlate of protection, a critical tool for future bridging studies. As of the data cutoff, 11 cases of Covid-19 had occurred in the mRNA-1273 group, a finding that limits our ability to detect a correlate of protection. As cases accrue and immunity wanes, it may be-

come possible to determine such a correlate. In addition, although our trial showed that mRNA-1273 reduces the incidence of symptomatic SARS-CoV-2 infection, the data were not sufficient to assess asymptomatic infection, although our results from a preliminary exploratory analysis suggest that some degree of prevention may be afforded after the first dose. Evaluation of the incidence of asymptomatic or subclinical infection and viral shedding after infection are under way, to assess whether vaccination affects infectiousness. The relatively smaller numbers of cases that occurred in older adults and in participants from ethnic or racial minorities and the small number of previously infected persons who received the vaccine limit efficacy evaluations in these groups. Longer-term data from the ongoing trial may allow a more careful evaluation of the vaccine efficacy in these groups. Pregnant women and children were excluded from this trial, and additional evaluation of the vaccine in these groups is planned.

Within 1 year after the emergence of this novel infection that caused a pandemic, a pathogen was determined, vaccine targets were identified, vaccine constructs were created, manufacturing to scale was developed, phase 1 through phase 3 testing was conducted, and data have been reported. This process demonstrates what is possible in the context of motivated collaboration among key sectors of society, including academia, government, industry, regulators, and the larger community. Lessons learned from this endeavor should allow us to better prepare for the next pandemic pathogen.

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APPENDIX

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Medical News & Perspectives | JAMA LIVE HIGHLIGHTS

Experts Discuss COVID-19—Vaccine Doses, Virus Variants, and More

JAMA Live Highlights features comments from livestream interviews by JAMA Network Editor in Chief Howard Bauchner, MD. His discussions with experts in clinical care, public health, and health policy focus on critical issues related to the coronavirus disease 2019 (COVID-19) pandemic. Comments have been edited for clarity.

Rochelle P. Walensky, MD, MPH

Director of the Centers for Disease Control and Prevention (CDC) and former chief of the Infectious Diseases Division at Massachusetts General Hospital

On leading the CDC: How is it that I make sure that these incredible scientists, these incredible civil servants for their entire career, understand and feel the value that we should be giving them? They have been diminished. I think they've been muzzled. This top-tier agency hasn't really been appreciated over the last 4 years, and really markedly over the last year, so I have to fix that. The good news in my mind is there hasn't been a mass exodus of the talent. And so what I need to do is make sure that those voices get heard again, that I'm leading with trust, that this science is actually conveyed.

On CDC communications: I have to make sure that we're communicating to the American people. I've done numerous media appearances where I've heard people say, "This is the first time we've heard from the CDC director in a year on this show." So I want to be able to convey, in layman's terms, what the science shows, when guidelines change, when *Morbidity and Mortality Weekly Reports* are released.

I can do television appearances, I can do interviews, we can do media briefings, but science is now conveyed through Twitter. Science is conveyed on social media, on podcasts, and in many different ways, and I think that's critical. As we talk about vaccine hesitancy, or as we talk about anti-vaxxers, what's the CDC saying on Twitter about that? We have to have a social media plan for the agency.

On emerging virus variants: We worry about increased transmissibility, and we've seen that with some of the variants. We worry about increased morbidity and mortality. We haven't yet seen that, although I think we should worry about it because with more disease and more cases, we're going to have more morbidity and mortality. And then we worry about how well and how robust our vaccines and our therapies are in tackling the variants when they arise. I think the good news is that the efficacy of the vaccine is so high that we have a little bit of a cushion. I just want to remind people that almost no vaccine we have is 95% accurate. Will it be 95%? Maybe. Will it be 70%? Maybe. But our flu vaccines aren't 75% effective every year, and we still get them. I'm still currently pretty optimistic.

On monoclonal antibody therapy: It's been so hard and clumsy to implement. And then we have this sort of concern in the back of our heads—are they going to work on the variants? If you have a cocktail, maybe that's a little bit better. Monoclonal antibodies may be a step in the path to get us to a better place, but I don't think that anybody envisions that this is going to be the panacea for outpatient treatment. It's just too hard.

Full video and audio of this interview are available online.

Paul A. Offit, MD

Director of the Vaccine Education Center and professor of Pediatrics in the Division of Infectious Diseases at the Children's Hospital of Philadelphia

On why getting the second vaccine dose is important: When Pfizer did its trial it gave a first dose and then 3 weeks later it gave a second dose. In that 3-week period of time the vaccine was roughly 52% effective. With Moderna, probably because it was a longer period of time between dose 1 and dose 2, it was somewhere in the vicinity of 80% to 90% effective in that 4-week period.

After 1 dose you have a neutralizing antibody response in your circulation that is considerably less than after the second dose. You clearly get a booster dose with a second dose, and you get a T-cell response. You will have longer-term immunity with that second dose. You can't wait very long. If you're waiting 2 months, 3 months, 4 months later, I think that's a problem.

On how many people must be vaccinated: I would think that if you can vaccinate say 60, 65 million people with 2 doses, that we can stop the spread of this. And to do that we need to be vaccinating at

least a couple million people a day and probably closer to 3 million if we're going to try and stop spread of this virus by summer.

About virus variants and vaccine effectiveness: What we need to do initially is to see whether or not the sera that are obtained from people who are immunized with these mRNA vaccines neutralize that virus variant. If people who are vaccinated with these mRNA vaccines who are then exposed to these variant viruses get sick, then we're going to have to have essentially a multivalent vaccine strategy where it's not just, for example, 1 mRNA in there, but also the variant strains.

Full video and audio of this interview are available online.

Christopher W. Seymour, MD, MSc

Associate professor of Critical Care Medicine and Emergency Medicine at the University of Pittsburgh and a *JAMA* associate editor

On anticoagulants in COVID-19: We see coagulation abnormalities in these patients. When you round on these patients in your unit, you're seeing maybe more deep vein thrombi or arterial thrombi that you hadn't before. And so there's good scientific rationale to move forward with trials of systemic anticoagulation and then, as we move out of the [intensive care unit], different approaches to prophylaxis. There will be side effects when you give a blood thinner. But the question is whether those side effects are balanced by the potential benefit to the patient from the drug. Three groups are working together to understand the best way to treat patients with heparin.

On what's unique about COVID-19: I've been surprised to see the significance and severity of the lung injury. We're really giving a lot of support to these patients. And it is just unusual and a bit of a reset to think that you're going to walk into your place of work and care for 6 people that are proned. It's just very different. And that may speak to characteristics of the virus, maybe the host tolerance, but then also the aggressiveness of the host response. Very difficult to handle as an intensivist.

On COVID-19 long haulers: I don't know yet if the sort of symptomatology that we describe in the long haulers or the "long COVID" is actually that different than a bad case of bacterial pneumonia. In part because that research is still forthcoming. I think we're hearing a heck of a lot more about this because there's way more people that are getting COVID. And so the frequency of these issues in our population is much, much more common than perhaps the elder with bacterial pneumonia, who then is not themself 6 months later.

Full video and audio of this interview are available online.

Arnold S. Monto, MD

Thomas Francis Jr Collegiate Professor of Public Health at the University of Michigan School of Public Health and acting chair of the US Food and Drug Administration's Vaccines and Related Biological Products Advisory Committee

On the initial vaccine rollout: I don't think anybody is ready for this. And I think this is the ultimate demonstration of problems with the American health care system, which is fragmented, which probably has some of the wrong priorities. We're all into billing and everything else. Flu vaccination is probably the closest thing we have to what we're trying to do now because people get vaccinated every year. Everybody knows where to go and how to get it. The supplies are there. This is totally new, and I think we totally underestimated the challenges that this would provide because we're really not as organized as countries that have health care as a more systematic component of the government.

About vaccinating pregnant women: I think a pregnant woman should look at her risk group and get vaccinated as she would if she were not pregnant. I think that when vaccine is available for the general public, a pregnant woman should be vaccinated. By that time, I hope we have more information about some of the theoretical risks, and there are always theoretical risks, especially about the first trimester. Looking at the flu story, we've come from most pregnant women not being vaccinated to pregnant women being the highest priority.

About vaccination for previously infected people: Going to the back of the line if you're infected—that gets to be very cumbersome. We've not done it with anything else simply because it requires an even more cumbersome system of testing people and categorizing them. Let's hope we have enough vaccine to just go ahead and vaccinate whoever comes up in line. We know it is safe for a previously infected individual to get vaccinated.

About the lack of serious disease among most children: This is very unusual for a respiratory virus. Usually, children are the major sources of not only infection but transmission in the community. If there's anything standard about flu pandemics, it's the fact that young children are at particular risk of severe morbidity and mortality. And we saw the opposite here. Maybe it has to do with some kind of receptor issue. I hope we can work this out to try to figure out why this is.

Full video and audio of this interview are available online.

Nicholas Christakis, MD, PhD, MPH

Sterling Professor of Social and Natural Science, Internal Medicine, and Biomedical Engineering at Yale University and author of *Apollo's Arrow: The Profound and Enduring Impact of Coronavirus on the Way We Live*

On how hospitals have fared during COVID-19: Many hospitals, even though they are providing a crucial service in the history of our nation in taking care of people who are sick from a deadly contagion, lost money. Many hospitals were at the risk of going out of business. Hospitals make money from elective procedures and high-value procedures and, apparently, taking care of people who are infected with a deadly virus is not very remunerative. This is no way to organize a health care system.

On plagues throughout history: We have to appreciate that we are not the first ones to be enduring a serious plague. Bad as it is, the best estimates of the infection-fatality rate of this pathogen are between 0.5 and 0.8 percent. It's going to be a leading killer in our society, but it's not as bad a plague as it could have been. Bubonic plague would kill 50% of the people in a city within a couple of months. There's no sort of God-given reason why this particular pathogen that we are facing isn't worse. It could have been so much worse. We need to cope with it in the wisest way possible, taking advantage of all of the prior knowledge that our species has accumulated about how to deal with this.

Full video and audio of this interview are available online. ■

Note: Source references are available through embedded hyperlinks in the article text online.

Editor's Note: For more coronavirus livestream interviews visit *JAMA*'s COVID-19 Q&A page.

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

Last-Mile Logistics of Covid Vaccination — The Role of Health Care Organizations

Thomas H. Lee, M.D., and Alice H. Chen, M.D., M.P.H.

The development, evaluation, and production of vaccines for Covid-19 was the remarkable success story of 2020; the challenge for 2021 is getting those vaccines into the bodies of a critical mass of the world's population. This work is being compared with managing the last mile in other business sectors: once companies get products or information to regional hubs, they must deliver them to individual customers whose settings and habits are infinitely varied. Effectiveness in those last steps determines success.

For Covid vaccination in the United States, that last mile is a difficult one. About one third of U.S. "customers" are unsure that they want the product and are worried that vaccination might be made mandatory. Most of the others are worried that they cannot be vaccinated soon enough because of limited supplies and uncertainty about how immunizations are being scheduled and managed.

Vaccination has gotten off to a faster start where there is tight integration among public and private health care stakeholders. Israel, for example, has universal insurance coverage and a nationwide digital network integrated with its public health system. Clinical data are available for every person, enabling segmentation of the population by age and medical condition and reliable communication with immunization candidates. Although Israel has failed to include most Palestinians in its vaccination program, by January 17, about 27% of Israeli citizens had been vaccinated, as compared with about 4% of the U.S. population.[1]

In the United States, however, public–private health care integration is a state-by-state, county-by-county improvisation, and patients have turned to their health care providers for information about vaccination. To respond to these needs, health care systems are having to master four types of new and unfamiliar work.

The first task is earning the trust of people — both in the public and in the health care workforce — who are reluctant to be vaccinated. Though shrinking, this group is still sizable, particularly in the Black and Latinx communities, which have been disproportionately affected by Covid. The proportion of patients saying they were likely to get vaccinated increased from 39% during the week of October 15, 2020, to 64% during the week of January 3, 2021, according to a survey of

66,818 patients conducted by Press Ganey (where one of us is chief medical officer). Over that period, the proportion saying they were likely to be vaccinated was 60% among White patients but 36% among Black patients.

Vaccine skepticism is not based only on mistrust of systems by communities of color. There is also a core group of people who do not trust any vaccine, joined by skeptics who normally believe in vaccinations but have lost trust in the Food and Drug Administration because of the political pressure it faced to approve vaccines before the presidential election. Strategies and messages may need to be different for each of these groups.

In this context, clinicians have a critical role in addressing vaccine reluctance, in part because of lack of trust in alternative messengers. Between mid-November and early January, only 37% of Press Ganey survey respondents indicated that they had confidence in government advice on vaccination, but 67% said they had confidence in their clinician's advice.

So it was helpful that the first person in the United States to get vaccinated outside a research trial was Sandra Lindsay, a Black critical care nurse at Long Island Jewish Medical Center. Similarly, the first person in Florida to be vaccinated was Leon Haley, chief executive officer of the University of Florida at Jacksonville and a Black emergency medicine physician. Both volunteered to go early and be interviewed by the media because of vaccine resistance among Black Americans, and they highlighted that they were doing so because, as Lindsay put it, "I trust science."

Beyond symbolic public events, many organizations are also urging their clinicians to do the "door-to-door fighting" of assessing patients' attitudes toward vaccination and working to persuade those who are resistant. Some organizations are intensively surveying their workforces to understand and address where resistance is most intense. A few organizations are offering employees financial incentives to get vaccinated, but most are relying on behaviorally informed strategies for both employees and patients.[2,3]

The second task is managing demand and immunizing people who are ready to be vaccinated. Health care organizations got a taste of the complexity of this task when they began vaccinating employees. In this relatively small population with whom interactions should be reasonably straightforward, organizations had to address the same issues they will face on a much larger scale in vaccinating the public, including communication, prioritization, and management of the vaccinations themselves.

For example, Geisinger Health System began planning its program for immunizing its workforce in March 2020.[4] In addition to doing the basics, such as acquiring storage for the vaccines and setting up high-throughput vaccination sites with Covid precautions, Geisinger spent months developing and communicating plans for who would be immunized first. They developed a scheduling system for both doses of vaccine and staggered the scheduling of frontline workers within each department to reduce the impact of absences due to side effects. They developed a digital application to manage registration, eligibility, and scheduling and integrated that into a multipronged communication program. And they made clear that unexpected issues would be communicated to their Incident Command Center, a small multidisciplinary group that could make decisions quickly for Covid-related problems.

Other large organizations took similar steps — though they didn't all work right away. At Mass General Brigham, 50,000 people tried to log onto the vaccination-scheduling app as soon as it went live; the app immediately crashed. Despite similar problems throughout the country, by early January, vaccination of caregivers was well under way and many organizations were planning for vaccinating first responders and the rest of society. Performing the same functions for patients as they have for their workforces will be a consuming body of work for many months, and organizations can succeed only if they are effective in the third and fourth tasks.

The third task is engaged communication with the public, aiming to go beyond answering "Frequently Asked Questions" to building trust. For example, the community-facing Covid-19 site of Hartford Health has both nationally sourced and locally relevant news items, videos, and podcasts about Covid-related issues, including testing, recovery, and vaccination.[5] Patients can sign up for vaccine updates by text. The goal is to provide one-stop shopping for information in various formats and to allow patients to have information pushed to them.

Hartford Health's investment in this site reflects Covid-induced insights into the nature of trust.

Traditional health care is a high-stakes, low-frequency event, and patients are somewhat trusting because they are accustomed to the trappings of office visits and the social standing of clinicians. But in times of turmoil, trust can also be built through high-frequency, low-stakes interactions — such as going to an organization's website to get questions answered and needs met, reliably and with transparency about what is known and what is not.

Many of the unknowns can be addressed only by plunging into the fourth task: regional coordination with government and other institutions. Health care providers have had to innovate and improvise to fill the gaps resulting from a long-standing underinvestment in our public health system and the enormity of vaccinating every American rapidly. Working with local government to set up sites for vaccinations at locations such as sports arenas and shopping malls and publicizing prioritization frameworks are two key steps. Another is facilitating information flow. For example, Intermountain Health developed an interoperable interface with the Utah immunization registry that gives clinicians from different health organizations real-time access to its patients' vaccine information — helping to ensure that people receive their second dose of the right vaccine at the right time.

These are just a few examples of the work needed to bridge the divide in the United States between private and public sectors and between health care and public health. The government may be purchasing, allocating, and distributing the vaccine, but last-mile logistics depend heavily on the private sector. Neither government nor private organizations can be successful on their own.

All four tasks represent new types of work for U.S. health care organizations, but the skills they learn as they adapt will make them better organizations in general. To be speedy and equitable in crossing that last mile, they have to build trust, manage operations well, communicate more effectively, and collaborate with other public and private entities. Covid vaccination is providing a stress test that will help organizations prepare for other challenges that lie ahead.

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