VIEWPOINT

COVID-19: BEYOND TOMORROW

Potential COVID-19 Endgame Scenarios
Eradication, Elimination, Cohabitation, or Conflagration?

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High vaccination rates of the adult US population have given rise to the hope that a return to prepandemic life may be in the offing. However, differential vaccine access, persistent vaccine hesitancy, emerging viral variants, and deadly global disease waves may well stand in the way. In that volatility has heretofore been the invariant attribute of SARS-CoV-2, envisioning a future steady state can be inherently problematic. This Viewpoint describes 4 potential scenarios—eradication, elimination, cohabitation, and conflagration—comprising a spectrum of "endgames" that may constitute the resolution of the COVID-19 pandemic; however, other scenarios also may be possible.

What would it take to eradicate SARS-CoV-2? By definition, eradication would require the permanent global reduction of the prevalence of SARS-CoV-2–mediated disease to zero. To realize such an outcome, sufficient herd immunity would have to be achieved through vaccination and prior infection. Both vaccine- and infection-derived immunity would have to be highly effective, long-lasting, adept at preventing secondary transmission and reinfection, and protective against all manner of present and future viral variants.

> [W]here on the endgame spectrum individual countries end up will depend on both the collective choices and realities of the global community and the oft-inscrutable and perhaps unpredictable dynamics of SARS-CoV-2.

Given these relatively astringent requirements, eradication may prove to be too aspirational a goal even as a thought experiment, let alone as a public health strategy. However, smallpox, yet another highly contagious respiratory infection, was irreversibly eradicated, an outcome once considered unimaginable. Other vaccine-preventable airborne diseases such as measles and rubella have been the subject of elimination, that is, the regional, rather than global reduction of disease prevalence to zero. Elimination may well constitute a more realistic near-term goal for SARS-CoV-2 especially if slow-to-distribute booster vaccines become necessary to target emerging viral variants. Evidence of the successful elimination of SARS-CoV-2 is rapidly accumulating. Elimination may be close-at-hand in Israel, a model of vaccination efficiency wherein incident SARS-CoV-2 cases are presently at 0.7% of their all-time high.[1] Similar successes could be realized in other nations wherein sufficiently high vaccination rates have been achieved. Temporary elimination of SARS-CoV-2 absent the advent of vaccines may well prove feasible as well as demonstrated by New Zealand in early August of 2020.

Were eradication or elimination to be achieved in the US or elsewhere, ongoing vaccination against SARS-CoV-2 and its variants would be required to counter the ongoing risk of suspected zoonotic transfer from bats, farmed minks, or yet-to-be uncovered animal reservoirs.[2] In this regard, SARS-CoV-2 stands out relative to smallpox for which no known animal reservoir has been identified. It follows that absent indefinite future vaccination efforts against SARS-CoV-2, durable elimination, let alone eradication, may prove infeasible.

Alternatively, might a more civil cohabitation be achieved with SARS-CoV-2, an outcome short of all-out eradication or substantial elimination? In this scenario, vaccine-mediated protection would go so far as to prevent the most severe manifestations of COVID-19, interrupt the chain of viral transmission, and counter the majority of emergent viral variants. Evidence in support of the realization of such scenario is likely to include, but not be limited to, the documentation of sparse reinfections, rare vaccine breakthroughs, and negligible secondary transmission even in the face of most viral variants.[3-5]

In a world with a state of immunologic cohabitation, distinct viral-free pockets of infection may well exist wherein vaccine uptake is high. Whereas most incident infections would slow down significantly, some may well persist at either low levels or in the form of sporadic outbreaks outside of the viral-free pockets in question. Such new infections would be expected to occur predominantly among the undervaccinated. Rare breakthrough infections among vaccinated people may come to pass due to limited vaccine efficacy, immunocompromised states, sporadic vaccine supply or quality control issues, or future viral variants. Overall, however, despite occasional new infections, a more tolerable endemicity may well replace the volatility of the pandemic phase.

As vaccine accessibility expands globally, as vaccine hesitancy and access challenges subside, and as viral replication and variant generation are reduced, the number of viral-free pockets may well grow. Although vaccination may well continue to provide high levels of immunity against viral variants, boosters may be required to maintain the status quo. Where and when vaccination rates sputter and infections reoccur,

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new localized outbreaks may be seeded. In these instances, the implementation of and adherence to preventive public health measures may still be required. However, for those who are either vaccinated or who reside in geographic areas with low case prevalence, with limited selection of viral variants, or both, the risk of infection is likely to be manageably low. Over the long-term, however, as global immunity due to exposure or vaccination becomes commonplace, the disease symptoms experienced may come to resemble those of the common cold, which is brought about by seasonal coronaviruses.

Absent a cohabitation option, the endgame may well come to resemble a conflagration, that is, a steady state characterized by moderate-level endemicity of SARS-CoV-2. With large segments of the population undervaccinated due to access constraints, hesitancy, or immunocompromised states, the circulation of SARS-CoV-2 is bound to remain robust. This would afford the virus with continuous opportunities to replicate and adapt so as to evade host-mediated and vaccine-derived immune responses. Among vaccinated populations, infections could still arise periodically due to incomplete vaccine-derived immunity, the waning of vaccine efficacy, evasion by new viral variants, or transmission from the unvaccinated. Two recent breakthrough cases of variant SARS-CoV-2 serve as an important reminder of such a possibility.[6]

The degree of conflagration may come to depend substantially on the efficacy and acceptance of vaccines by geography. Potential coverage gaps against specific variants have been noted for several vaccines. The utility of the AstraZeneca vaccine against the B.1.351 variant is one such example.[7] Similar gaps in the coverage of worrisome variants may exist for other vaccines for which publicly available data have heretofore been either absent, sparse, or limited to in vitro studies. Assuming a state of conflagration, with much of the world subject to limited availability of vaccines or to less-effective ones, ongoing outbreaks on a wider scale are to be expected.

Only a year ago, much of the world was united in lockdown in the midst of the first outbreak of COVID-19. Today, the global experience is widely divergent. Israel, New Zealand, Vietnam, and Brunei may well be approaching elimination. The United Kingdom, the United States, and China, for their part, appear to exist in a state of cohabitation. In contrast, India, other parts of Southeast Asia, and much of South America appear to be weighed down by a conflagration-like state. Reversing the fortunes of nations in the grip of a conflagration-like state will require the buildup of population-level immunity via vaccines capable of neutralizing new viral variants. Breakthroughs in the development of highly effective therapeutics, should they occur, stand to further disrupt the global status quo with an eye toward accelerating recovery, especially in the conflagration context. Ultimately, where on the endgame spectrum individual countries end up will depend on both the collective choices and realities of the global community and the oft-inscrutable and perhaps unpredictable dynamics of SARS-CoV-2.

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VIEWPOINT

Lay Epidemiology and Vaccine Acceptance

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As vaccination rates against SARS-CoV-2 slowed across the US, increasing vaccine uptake became a national priority. Concerns about lack of confidence in the vaccine dominated lay and professional headlines and hundreds of programs were created to increase vaccine confidence, particularly among vulnerable populations who were most affected by the COVID-19 pandemic. In general, these programs focused on providing more information about the vaccine to communities thought to be at increased risk for vaccine refusal. This approach assumed that the decision to avoid or delay vaccination was based on inadequate understanding or information, perhaps overlaid by distrust of those involved in creating or delivering the vaccine. In that model, more information delivered by "trusted messengers," including community leaders and local physicians, is the solution.

Reality, however, is more complicated. Behavioral science has long demonstrated that knowledge of the risks and benefits of a given intervention has a surprisingly limited relationship with health behaviors. For instance, across dozens of studies, perception of the risk or severity of the disease has only a small to moderate correlation with the decision to undergo cancer screening, attempt to stop smoking, or get a vaccination.[1-3] A similar pattern is seen with perceptions of the benefit of an intervention and with studies of interventions to increase understanding of risk and benefits. These factors matter, but they generally explain much less than half of the variance in why someone does or does not follow a recommendation.

Lay epidemiology is how inferences are drawn from patterns of disease in small groups like friends and family, larger groups from social media or other sources, and even entire populations from public information or news stories.

Why does this gap exist? Sometimes other factors determine whether an individual can or will want to follow the recommendation. For example, if a patient cannot afford out-of-pocket costs, information about risks and benefits is irrelevant. If the social norms in a person's group are not aligned with the recommendation, they may struggle to override that pressure even when they understand the risks and benefits. If people do not believe the source of the information, they are unlikely to follow it. But sometimes it occurs because there is a difference between the average, population-based information that is provided and the assessment of the likelihood that an individual would experience a positive or negative outcome from the intervention.

How could that likelihood be judged? Across cultures, people try to make sense of the world around them, including how likely it is that a negative outcome will occur for them and what will increase or reduce that risk. This concept has been referred to as *lay epidemiology*.[4] Lay epidemiology is how inferences are drawn from patterns of disease in small groups like friends and family, larger groups from social media or other sources, and even entire populations from public information or news stories.

An example is the concern about the possible link between vaccines and autism. Many parents heard news stories linking autism with vaccination, believed there could be an increased risk from vaccination, and were hesitant to give their children vaccines even when given vaccine information by a trusted pediatrician. The same phenomenon occurs when parents draw inferences about what exposure led to a newborn having a birth defect, women attribute their breast cancer to a breast injury, or people believe that they will not get cancer from smoking because of all the smokers they know who do not have cancer.[5]

What happens when people must make a new decision like whether to get the COVID-19 vaccine? In the same way, they extrapolate from what they know and have heard, past and present. For disadvantaged groups in the US especially, the message is clear. Outcomes for these groups are worse than others. The average life expectancy in the US is 78 years, but life expectancy for men in the lowest strata of socioeconomic status is less than 73 years and is 71 years or less for men in many areas of the rural South.[6] Individuals who are poor or from a racial or ethnic minority group are more likely to develop a disease, less likely to access needed treatment, and more likely to experience morbidity and mortality. For some groups, the government has conducted medical experiments without their consent in the past. The evidence is consistent across media, public data, and lived experience. Furthermore, these facts have been known for a long time without much done to address them. The greater burden of COVID-19 among disadvantaged communities has further reinforced this lay epidemiology over the last year, a critical period for influencing current decisions about vaccination.

From the lay epidemiologic perspective, it makes sense that groups with clear evidence of experiencing worse outcomes from most aspects of the US health care system should be skeptical of the information about the average risks and benefits of vaccination. In fact, lack of confidence is a rational response to these experiences. What can be done?

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First, tailored messaging and data are needed. People adjust their perceptions of their expected health outcomes based on data that they find relevant to themselves and often ignore information that does not seem relevant. Information that is tailored to individual patient characteristics has been demonstrated to improve the use of a wide range of preventive services.[7] For COVID-19 vaccination, information about risk of infection, effectiveness of vaccination, and the chance of vaccine-related adverse effects could be shown by age, sex, race and ethnicity, geography, job type, and even socioeconomic background. Such information would be most effective when shared through images and stories, rather than numbers alone. By providing information about lay groups, health professions can use lay epidemiology in their favor.

Second, it is essential to engage local leadership who understand local beliefs, know the local data, and can address the lay epidemiology in their communities. The marked geographic variation in vaccine use in the US highlights the reality that information provided by government sources is unlikely to be effective in driving lay perceptions of risk and benefit in many communities across the South and West in particular. While the politicization of vaccination may contribute to low uptake in some areas, there are also positive stories of collaborative efforts to address local concerns leading to high levels of vaccination. Perhaps the most striking example is the high levels of vaccination in many tribal communities (estimated at 88% vaccine uptake in Navajo Nation as of May 2021) where local leaders and epidemiologists collaborated to address lay concerns and provide salient information to community members.[8]

In addition, medical professionals need to move from a focus on distrust to a focus on being trustworthy. Thus far, much of the discussion has centered on why certain groups are not taking the vaccine. This places the blame, directly or indirectly, on the people affected, often disadvantaged groups. From one perspective, vaccine hesitancy is a symptom of a system that has created (and largely ignored) wide differences in health in the US. Addressing such inequities is an important step toward ensuring that all patients believe that the health care system will bring them just as much benefit at just as little risk as it does to the most advantaged in US society.

While lay epidemiology is far from the only factor driving vaccine hesitancy, it is too often overlooked. In many communities, vaccination rates are increasing as people see their friends, colleagues, and neighbors get vaccinated without adverse events. But in some areas, vaccine uptake is lagging and efforts to address lay epidemiology may be an important factor to ensure that the country is able to reach vaccination goals over the months ahead.

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JAMA | Original Investigation

Association Between BNT162b2 Vaccination and Incidence of SARS-CoV-2 Infection in Pregnant Women

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Supplemental content

IMPORTANCE Data on BNT162b2 messenger RNA (mRNA) vaccine (Pfizer-BioNTech) effectiveness and safety in pregnancy are currently lacking because pregnant women were excluded from the phase 3 trial.

OBJECTIVE To assess the association between receipt of BNT162b2 mRNA vaccine and risk of SARS-CoV-2 infection among pregnant women.

DESIGN, SETTING, AND PARTICIPANTS This was a retrospective cohort study within the pregnancy registry of a large state-mandated health care organization in Israel. Pregnant women vaccinated with a first dose from December 19, 2020, through February 28, 2021, were 1:1 matched to unvaccinated women by age, gestational age, residential area, population subgroup, parity, and influenza immunization status. Follow-up ended on April 11, 2021.

EXPOSURES Exposure was defined by receipt of the BNT162b2 mRNA vaccine. To maintain comparability, nonexposed women who were subsequently vaccinated were censored 10 days after their exposure, along with their matched pair.

MAIN OUTCOMES AND MEASURES The primary outcome was polymerase chain reaction–validated SARS-CoV-2 infection at 28 days or more after the first vaccine dose.

RESULTS The cohort included 7530 vaccinated and 7530 matched unvaccinated women, 46% and 33% in the second and third trimester, respectively, with a mean age of 31.1 years (SD, 4.9 years). The median follow-up for the primary outcome was 37 days (interquartile range, 21-54 days; range, 0-70). There were 118 SARS-CoV-2 infections in the vaccinated group and 202 in the unvaccinated group. Among infected women, 88 of 105 (83.8%) were symptomatic in the vaccinated group vs 149 of 179 (83.2%) in the unvaccinated group ($P \geq .99$). During 28 to 70 days of follow-up, there were 10 infections in the vaccinated group and 46 in the unvaccinated group. The hazards of infection were 0.33% vs 1.64% in the vaccinated and unvaccinated groups, respectively, representing an absolute difference of 1.31% (95% CI, 0.89%-1.74%), with an adjusted hazard ratio of 0.22 (95% CI, 0.11-0.43). Vaccine-related adverse events were reported by 68 patients; none was severe. The most commonly reported symptoms were headache (n = 10, 0.1%), general weakness (n = 8, 0.1%), nonspecified pain (n = 6, <0.1%), and stomachache (n = 5, <0.1%).

CONCLUSIONS AND RELEVANCE In this retrospective cohort study of pregnant women, BNT162b2 mRNA vaccination compared with no vaccination was associated with a significantly lower risk of SARS-CoV-2 infection. Interpretation of study findings is limited by the observational design.

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During pregnancy, alterations in hormonal levels and immune system function may increase women's vulnerability to viral infections.[1] Although SARS-CoV-2 infection in pregnant women is mostly asymptomatic or mild,[2,3] it may result in severe complications, including admission to the intensive care unit and mechanical ventilation,[4,5] particularly during the third trimester.[6] Symptomatic SARS-CoV-2 infections in women also have been linked to a greater likelihood of preterm delivery[7,8] and fetal intrapartum distress.[9]

A phase 3 trial of the Pfizer-BioNTech BNT162b2 messenger RNA (mRNA) vaccine demonstrated 95% efficacy in preventing SARS-CoV-2 infection 7 days from the second dose[10]; however, pregnant women were excluded from the trial. Association with SARS-CoV-2 infection also has been examined by several observational studies,[11,12] but like the clinical trials, none included pregnant women. Although the manufacturer recently announced a phase 2/3 trial among pregnant women,[13] there is currently no empirical evidence on the efficacy of the vaccine in this population. Therefore, assessment of vaccine safety and effectiveness in pregnancy can currently be made only by using observational epidemiologic data.

On December 19, 2020, Israel launched its BNT162b2 vaccination campaign. Although pregnant women were not excluded from receiving the vaccine, they were initially advised to discuss the possibility of vaccination with their treating physician. A month into the campaign, the Israel Ministry of Health released updated recommendations encouraging pregnant women to receive the vaccine.[14]

The purpose of this study was to assess the association between receipt of a BNT162b2 mRNA vaccine and incidence of SARS-CoV-2 infection among pregnant women.

Key Points

Question Among pregnant women, what is the association between receipt of BNT162b2 messenger RNA vaccine and risk of SARS-CoV-2 infection?

Findings In a retrospective cohort study that included 15 060 pregnant women in Israel, vaccination with BNT162b2 vs nonvaccination was associated with an adjusted hazard ratio for incident SARS-CoV-2 infection of 0.22; this was statistically significant.

Meaning Among pregnant women, receipt of the BNT162b2 vaccine was associated with a lower risk of incident SARS-CoV-2 infection.

Methods

This retrospective cohort study was approved by the Maccabi Healthcare Services institutional review board and informed consent was waived because only deidentified routinely collected data were used.

Study Population

We used the comprehensive database of the Maccabi Healthcare Services, a 2.5-million-member state-mandated health fund in Israel. Citizens can choose 1 of the 4 nationwide health funds in Israel. The Maccabi health fund members represent 26.7% of the population and share similar sociodemographic characteristics with the overall Israeli population. The fund has maintained a computerized database of electronic health records since 1993, containing extensive longitudinal data on a stable population (≈1% annual turnover).

The health fund has developed several computerized registries of major clinical conditions. These registries are continuously updated and can detect relevant patients by automated criteria (relying on coded diagnoses, extensive laboratory data, treatments, administrative billing codes, etc) rather than depending on active reporting by physicians. Pregnancy data routinely coded by the patient's gynecologist on a designated pregnancy-tracking form within the electronic health record were used to construct a pregnancy registry. In 2020, the fund's pregnancy registry included data on approximately 55 000 new pregnancies, including 40 000 live births, accounting for 24% of all live births in Israel.[15]

Conception date was calculated according to the last menstrual period. Pregnancy end date was defined by expected delivery date (based on conception date) for ongoing pregnancies and actual delivery date for completed ones. Gestational age was categorized into trimesters defined as less than 14 weeks, 14 to 26 weeks, and 27 weeks or longer.

The eligible study population included all of the health fund's female members who were pregnant at any time from December 19, 2020 (initiation of the national vaccination campaign), through February 28, 2021. Excluded a priori were members who joined the fund less than 1 year preconception, with any preconception records indicating SARS-CoV-2 infection (defined as a positive polymerase chain reaction test result or a hospital diagnosis of SARS-CoV-2 infection), and members who were vaccinated prepregnancy with the BNT162b2 mRNA vaccine.

For each calendar day during the study period, we matched newly vaccinated pregnant women in a 1:1 ratio with eligible women who were unvaccinated on that day and had no prior records indicating a SARS-CoV-2 infection. The index date for the vaccinated woman and her paired control was the calendar date of the vaccinated woman's first dose. Matching was done (without replacement) by age (up to 5 years), gestational age (up to 5 weeks), exact matching by residential area, population subgroup (nonultra-Orthodox Jewish, ultra-Orthodox Jewish, and Israeli Arab), parity (categorized into nulliparous, para 1, para 2, and more), and having a seasonal influenza vaccine in the current pregnancy (as a proxy for health-seeking behavior). Extreme age was truncated in 4% of the pregnancies eligible for matching to increase eligible matches (<20 to 20; >40 to 40 years).

For each pregnant woman, follow-up lasted from the index date to the earliest occurrence of 1 of the following: an outcome of interest, leaving the fund, or the end of the study

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period. Matched unvaccinated women who were subsequently vaccinated were censored 10 days after their own first dose date because studies published to date have indicated that no immunity develops during this period[16]; symmetric censoring occurred on the same date as that of their pair (to maintain balance on matched covariates).

To compare groups, chronic comorbidities were obtained from validated automated registries, including diabetes,[17] cardiovascular disease,[18] chronic kidney disease,[19] hypertension,[20] cancer,[21] and prediabetes. The latter was defined by at least 1 diagnosis of prediabetes or by abnormal fasting glucose level or hemoglobin A_{1c} level 5.7% or greater, oral glucose tolerance test result 140 mg/dL or greater, at least 2 fasting glucose test results greater than 100 mg/dL, or purchases of diabetic medications during pregnancy. Obesity and infertility were used as adjustment factors. Infertility was defined by infertility diagnoses or medications, ovarian stimulation procedures, or receipt of a donated egg.

Study Outcomes

The primary outcome was documented SARS-CoV-2 infection 28 days or more after the first vaccine dose. This period was chosen because previous analyses[10,11] have suggested that immunity develops gradually, reaching full immunity approximately 7 days after the second dose. The number of events between day 28 and the end of follow-up included those occurring on day 28. SARS-CoV-2 infection was defined as a positive real-time polymerase chain reaction test result obtained from nasopharyngeal swabs. The tests are offered free to all Israeli citizens and without a need for referral. Both asymptomatic and symptomatic patients were included.

In addition, the following pregnancy- and birth-related complications were examined as exploratory outcomes: abortions (both spontaneous and induced) defined by diagnoses (*International Classification of Diseases, Ninth Revision* codes 632-637, 768, and 779) and procedures, intrauterine growth restriction (764), preeclampsia (642.4), stillbirth (V27 and V35), maternal death, obstetric pulmonary embolism (673), birth weight, and gestational age at birth.

In accordance with the Israeli Ministry of Health guidelines, the health fund developed a dedicated short form within its electronic medical record to report adverse events occurring soon after vaccination. The form was open to entry by all physicians and nurses in the health fund and was also pushed as a pop-up window during any visit with a documented diagnosis code of "adverse event SARS-CoV-2 vaccination."

Forms related to the current study population were manually reviewed by a gynecology specialist to assess the severity and duration of reported events, and to classify them according to timing as related to infection or vaccination, in women who were both infected and vaccinated.

Follow-up for all outcomes continued after pregnancy ended until April 11, 2021.

Statistical Analysis

Descriptive statistics were generated with mean and SD or percentage for continuous and categorical covariates, respectively. Comparisons between vaccinated and nonvaccinated patients were analyzed with analysis of variance or Kruskal-Wallis and χ^2 tests for continuous and categorical variables, respectively. Considering the large population size, *P* values were accompanied by standardized mean differences (the difference between the 2 groups' means divided by the pooled SD), in which a standardized mean difference greater than 0.1 was considered meaningful.

Time to SARS-CoV-2 infection was described with Kaplan-Meier curves and compared with a log-rank test with robust variance estimator[22] to account for matching. The cumulative incidence was calculated by 1 minus survival probability. Differences in cumulative incidence rates (risk differences) between the study groups were measured at points at which at least 10% of the matched cohort still remained under follow-up. For the primary outcome, the difference was a subtraction of the cumulative number of events at the end of follow-up minus the cumulative number of events on day 27. CIs for the differences in cumulative incidence rates were calculated with the bootstrap method, based on the 2.5% and 97.5% percentiles of 500 samples drawn from the matched pairs.

Cox regression model was used to estimate adjusted hazard ratios (aHRs) while controlling for parity, population subgroup, trimester, prior children, influenza vaccine, obesity, infertility, and age. Time-varying HRs were used as an estimate of vaccine effectiveness. To validate the time chosen for the primary outcome, nonproportionality over time was tested by exploring Schoenfeld residuals from a time-constant model. The intermediate point (knot) at 10 days was chosen after examination of the residuals plots. Model discrimination was assessed by the C statistic (concordance). The relationship between vaccination and infection was summarized by the aHR during 28 days or more of follow-up. A possible effect modification by trimester at index date was assessed through including in the model an interaction term reflecting HRs that differed by trimester in the post–day 28 period. Wald test of the interaction term within the Cox regression model was used to assess its statistical significance. The crude discrete time hazards were calculated for each period with Kaplan-Meier survival estimates as the survival at the beginning of the period minus survival at the end of it divided by the survival at the beginning of the period. The absolute difference of hazards between the study groups was calculated alongside percentile bootstrap 95% CIs.

Exploratory outcomes and adverse events were analyzed descriptively, without statistical comparisons, given the small numbers.

A sensitivity analysis was performed to exclude vaccinated women (and matched unvaccinated controls) who received their first vaccination dose before the Ministry of Health started recommending that pregnant women receive the vaccine (January 19, 2021) because women who received the vaccine before this date may have constituted a select subgroup who had elevated vulnerability to SARS-CoV-2 infection or complications due to either their occupation (medical or educational staff) or their underlying health status (eg, certain comorbidities).

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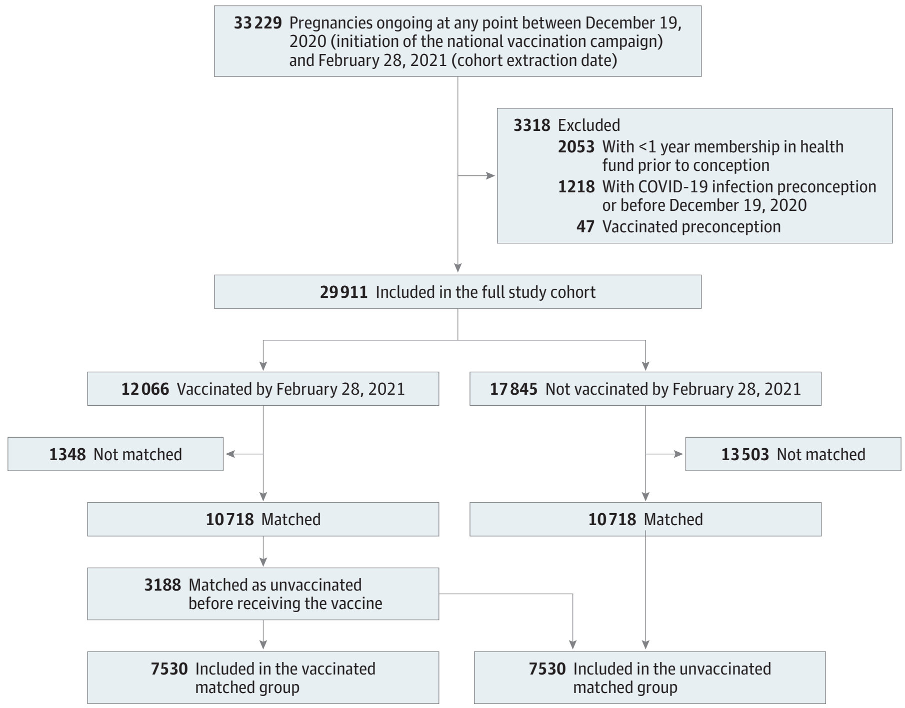
Figure 1. Flow of Eligible and Matched Vaccinated and Unvaccinated Pregnant Women



To assess replicability of the findings, we conducted a sensitivity analysis on the matching process; 5 different matched subcohorts were generated, in which the eligible data set was randomly reordered before each matching iteration. The results were consistent in all iterations. The iteration with the median aHR for 28 days or more of follow-up is presented.

Among infected women, we described the proportion hospitalized in the vaccinated and unvaccinated groups.

Two-sided $P < .05$ was considered statistically significant.

Statistical analysis was performed with R version 4.0.2 (R Foundation for Statistical Computing).

Results

A total of 29 911 eligible pregnant women were identified. By February 28, 2021, 12 066 women had received the first vaccination dose during pregnancy (**Figure 1**). Among women with a follow-up of 21 days or longer, 5626 (99%) received the second dose by the end of follow-up, with a mean and median of 21 days between the first and second dose.

Of the 12 066 vaccinated women, 10 718 were included in the matched cohort, in which 7530 were classified as vaccinated and the remaining 3188 were matched before their vaccination date and classified as unvaccinated (censored on vaccination date plus 10 days along with their matched pairs). Before matching, vaccinated women were slightly older, had a higher number of prior children, and were less likely to belong to a population minority subgroup compared with unmatched nonvaccinated women (**Table 1**).

Baseline characteristics of the matched 7530 vaccinated women and 7530 unvaccinated ones are depicted in Table 1. The groups were well balanced in terms of member age, gestational age, number of prior children, and population subgroup (which were used for matching). The absolute mean difference in gestational age was 9 days.

There were no missing data.

Infection Cumulative Incidence

Overall, SARS-CoV-2 infections occurred in 118 vaccinated women and 202 unvaccinated ones during a median follow-up of 37 days (interquartile range, 21-54 days; range, 0-70). Cumulative incidence over time is shown in **Figure 2**, and the gradually increasing risk difference is depicted in **Table 2**. At 28 days, when 4788 women (63.6%) remained at follow-up in each group, the absolute cumulative number of events was 109 in the vaccinated group and 158 in the unvaccinated group, and the difference in cumulative incidence rates was 0.80% (95% CI, 0.47%-1.13%), with cumulative incidence rates of 1.55% (95% CI, 1.26%-1.84%) among vaccinated women and 2.34% (95% CI, 1.98%-2.71%) among unvaccinated women. At 10 weeks, when 955 women (12.7%) remained, the cumulative number of events was 118 in the vaccinated group and 202 in the unvaccinated group, and the difference in cumulative incidence rates was higher (2.05%; 95% CI, 1.53%-2.57%), with cumulative incidence rates of 1.85% (95% CI, 1.48%-2.22%) among vaccinated

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Table 1. Baseline Characteristics of the Eligible Study Population

Characteristics	Full cohort			Matched[a] cohort		
	Vaccinated	Unvaccinated	SMD[b]	Vaccinated	Unvaccinated	SMD[b]
No.	12 066	17 845		7530	7530	
Patient age, mean (SD), y	31.3 (5.15)	30.4 (5.53)	0.16	31.1 (5.01)	31.0 (4.85)	0.01
Population subgroup,[c] No. (%)						
Jewish, secular	9867 (81.8)	13 091 (73.4)	0.28	6162 (81.8)	6162 (81.8)	<0.001
Ultra-Orthodox	1891 (15.7)	3244 (18.2)		1174 (15.6)	1174 (15.6)	
Arab	308 (2.6)	1510 (8.5)		194 (2.6)	194 (2.6)	
Prior children, No. (%)						
0	5175 (42.9)	11 092 (62.2)	0.39	3447 (45.8)	3447 (45.8)	<0.001
1	3925 (32.5)	3852 (21.6)		2369 (31.5)	2369 (31.5)	
≥2	2966 (24.6)	2901 (16.3)		1714 (22.8)	1714 (22.8)	
Vaccines during current pregnancy, No. (%)						
Influenza	5624 (46.7)	5285 (29.6)	0.36	3063 (40.7)	3063 (40.7)	<0.001
Pertussis	2738 (22.7)	6456 (36.2)	0.30	3070 (40.8)	2834 (37.6)	0.06
Preexisting condition,[d] No. (%)						
Obesity (BMI ≥30)	1342 (11.1)	1934 (10.8)	0.01	825 (11.0)	793 (10.5)	0.01
Infertility[e]	903 (7.5)	981 (5.5)	0.08	556 (7.4)	502 (6.7)	0.03
Cancer	137 (1.1)	145 (0.8)	0.03	93 (1.2)	58 (0.8)	0.05
Hypertension	92 (0.8)	133 (0.7)	0.002	51 (0.7)	58 (0.8)	0.01
Chronic kidney disease	86 (0.7)	113 (0.6)	0.01	55 (0.7)	48 (0.6)	0.01
Diabetes	89 (0.7)	87 (0.5)	0.03	63 (0.8)	30 (0.4)	0.06
Prediabetes	38 (0.3)	39 (0.2)	0.02	28 (0.4)	15 (0.2)	0.03
Cardiovascular disease	5 (<0.1)	5 (<0.1)	0.007	2 (<0.1)	2 (<0.1)	<0.001
Chronic obstructive pulmonary disease	4 (<0.1)	4 (<0.1)	0.006	2 (<0.1)	2 (<0.1)	<0.001

Abbreviations: BMI, body mass index; SMD, standardized mean difference. Body mass index is calculated as weight in kilograms divided by height in meters squared.

[a] Matching was done by age, residential area, population subgroup, number of prior children, and having an influenza vaccine in the current pregnancy. Matching design was by risk set (also known as exposure density or rolling cohort); for each calendar date, matched pairs were created among patients who received their first vaccine dose exactly on that date and those who were not yet vaccinated by that date. Matched unvaccinated patients who were subsequently vaccinated were censored 10 days after their own first dose date.

[b] SMD is the difference between the groups' means divided by the pooled SD.

[c] Population subgroup was assessed by enumeration areas (the Israeli census's smallest unit of analysis), with a high proportion of Jewish Orthodox and Israeli Arab residents according to voting results, spatial presence of religious schools, religious centers such as synagogues or mosques, and other publicly available databases.

[d] Preexisting comorbidities were defined by automated registries according to previously validated codes for inclusion and exclusion criteria (including diagnoses, treatments, and laboratory data).

[e] Infertility was defined by diagnoses or medications, ovarian stimulation procedures, or receipt of donated egg.

women and 3.90% (95% CI, 3.28%-4.52%) among unvaccinated women.

Infection Hazard

A time-constant covariate was consistent with nonproportionality (Schoenfeld test P = .001), underestimated survival among the vaccinated group, and overestimated survival among the unvaccinated group (eFigure in the Supplement).

A time-varying covariate indicated a risk reduction increasing over time since vaccination (Table 2). There was no significant difference between the groups during the first 10 days postvaccination (aHR = 0.96; 95% CI, 0.69-1.33; P = .79; hazards, 0.93% vs 0.97% in the vaccinated and unvaccinated groups, respectively). A statistically significant hazard reduction was observed among the vaccinated group during 11 to 27 days postvaccination (aHR = 0.46; 95% CI, 0.31-0.67; robust P < .001; hazards, 0.60% vs 1.34% in the vaccinated and unvaccinated groups, respectively).

Primary End Point

During 28 days or more postvaccination, a statistically significant hazard reduction was observed among the vaccinated group compared with the unvaccinated group (aHR = 0.22; 95% CI, 0.11-0.43; robust P < .001) (Table 2). Beginning 28 days after vaccination, 10 and 46 infections were observed in the vaccinated and unvaccinated groups, respectively, including 1 event in the vaccinated group and 2 in the unvaccinated group on day 28, yielding hazards of 0.33% vs 1.64%, respectively, and an absolute difference of 1.31% (95% CI, 0.89%-1.74%).

The adjusted model C statistic was 0.72. The aHRs of the other 4 iterations of randomly matched cohorts were similar (eTable in the Supplement).

Sensitivity analysis excluding women who received their first-dose vaccination before the Ministry of Health recommendations (January 19, 2021) revealed similar results, with aHRs of 0.92 (95% CI, 0.65-1.30), 0.41 (95% CI, 0.27-0.63), and 0.23 (95% CI, 0.11-0.49) for the first 10 days, 11 to 27

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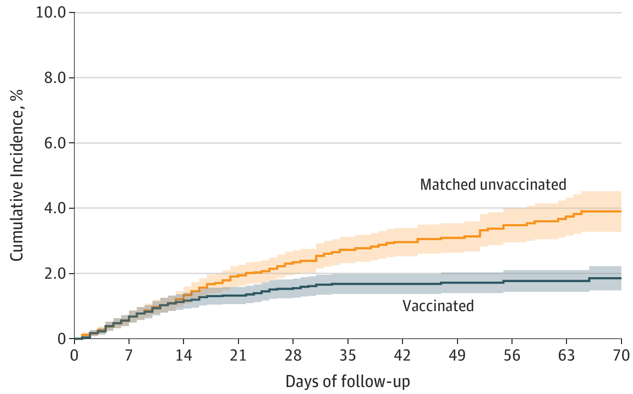
Figure 2. Cumulative Incidence of SARS-CoV-2 in Vaccinated vs Matched Unvaccinated Pregnant Women



No. at risk											
Matched unvaccinated	7530	7446	6825	5661	4788	4023	3376	2327	1748	1295	955
Vaccinated	7530	7446	6825	5661	4788	4023	3376	2327	1748	1295	955
Cumulative No. of events											
Matched unvaccinated	0	51	99	137	158	175	184	188	196	200	202
Vaccinated	0	51	87	97	109	115	115	116	117	117	118

Kaplan-Meier curves were used for cumulative probability of SARS-CoV-2 infection. Follow-up for each matched pair was initiated simultaneously on the same calendar date for both the vaccinated woman and her control according to the date of the vaccinated woman's first dose and was censored simultaneously 10 days after vaccination of the matched control to maintain groups' exchangeability over time and avoid selection bias. Median follow-up time in both groups was 37 days (interquartile range, 21-54 days). *P* value for statistical comparison was estimated by log-rank test using robust variance estimator to account for matching: $P < .001$. Shading illustrates 95% CIs. There were no further events from day 70 to end of observation at 110 days.

Table 2. Time-Based Event Rates (%) of SARS-CoV-2 Infections in the Matched Cohort

Follow-up, d	Vaccinated: Uncensored raw rate[a] (events/women)	Vaccinated: Hazard rate accounting for censoring[b]	Unvaccinated: Uncensored raw rate[a] (events/women)	Unvaccinated: Hazard rate accounting for censoring[b]	Absolute difference of hazard rate (95% CI)	Adjusted hazard ratio[c] (95% CI)	*P* value
Primary analysis							
≤10	0.93 (70/7530)	0.93	0.97 (73/7530)	0.97	0.04 (−0.18 to 0.25)	0.96 (0.69-1.33)	.79
11-27	0.51 (38/7387)	0.60	1.12 (83/7387)	1.34	0.74 (0.48 to 1.00)	0.46 (0.31-0.67)	<.001
≥28[d]	0.21 (10/4788)	0.33	0.96 (46/4788)	1.64	1.31 (0.89 to 1.74)	0.22 (0.11-0.43)	<.001
Post hoc analysis	Women, No.	Cumulative incidence[c]	Women, No.	Cumulative incidence[e]	Absolute difference of cumulative incidence (95% CI)		
10	7403	0.93	7403	0.97	0.04 (−0.18 to 0.25)		
27	4903	1.53	4903	2.30	0.77 (0.54 to 1.12)		
28	4788	1.55	4788	2.34	0.80 (0.47 to 1.13)		
35	4023	1.68	4023	2.72	1.04 (0.67 to 1.41)		
42	3376	1.68	3376	2.96	1.28 (0.87 to 1.65)		
49	2327	1.72	2327	3.09	1.37 (0.96 to 1.75)		
56	1748	1.77	1748	3.48	1.71 (1.26 to 2.17)		
63	1295	1.77	1295	3.75	1.97 (1.46 to 2.47)		
70	955	1.85	955	3.90	2.05 (1.53 to 2.57)		

[a] Raw rate (not accounting for censoring) was calculated as the number of events during the period divided by the number of women at risk at the beginning of the period.

[b] Hazard rate accounting for censoring for each period was calculated as the survival at the beginning of the period minus survival at the end of it divided by the survival at the beginning of the period. Survival (1 − cumulative incidence) was estimated with the Kaplan-Meier method to account for censoring. The absolute difference of hazards between vaccinated and unvaccinated is reported alongside CIs, which were calculated with the bootstrap percentile method with 500 samples of matched pairs.

[c] Hazard ratio during 28 days or more of follow-up was the primary outcome, calculated with a Cox time-varying hazard model adjusted for population subgroup, maternal age, gestational age, influenza vaccine, number of prior children, infertility, and obesity.

[d] The maximum time of follow-up was 110 days and the median was 37 days (interquartile range, 21-54 days) for both groups.

[e] Cumulative incidence was calculated as 1 minus survival probability at specific days during the follow-up until the maximal point at which at least 10% of the matched cohort remained under follow-up. The difference of cumulative incidence rates between vaccinated and unvaccinated is reported alongside CIs, which were calculated with the bootstrap percentile method with 500 samples of matched pairs.

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days, and 28 days or more after vaccination, respectively. A higher risk of outcome was observed in the second and third trimesters but with no evidence of an interaction (P = .39) between vaccination and trimester at index.

Among infected patients, the presence of symptoms was documented for 105 (89%) and 179 (89%) of the vaccinated and unvaccinated patients, respectively. Among those documented, no significant difference was observed in the proportion of symptomatic patients, with 83.8% vs 83.2% in the vaccinated and nonvaccinated groups, respectively ($P \geq .99$).

Exploratory Outcomes

The observed rate of SARS-CoV-2–related hospitalizations was 0.2% among the vaccinated group vs 0.3% among the unvaccinated group (**Table 3**).

During the study follow-up period, 1387 (18.4%) of the vaccinated women and 1427 (18.9%) of the unvaccinated reached the end of pregnancy. There were no notable differences between the vaccinated and unvaccinated groups regarding preeclampsia, intrauterine growth restriction, infant birth weight, abortions, stillbirth, maternal death, or pulmonary embolism (Table 3).

Table 3. Exploratory Outcomes[a] Among the Matched[b] Study Population

Outcomes	Vaccinated	Matched unvaccinated
No.	7530	7530
SARS-CoV-2 hospitalization, No. (%)	13 (0.2)	23 (0.3)
Abortion,[c] No. (%)	128 (1.7)	118 (1.6)
Intrauterine growth restriction, No. (%)	36 (0.5)	38 (0.5)
Preeclampsia, No. (%)	20 (0.3)	21 (0.3)
Stillbirth, No. (%)	1 (<0.1)	2 (<0.1)
Maternal death, No. (%)	0	0
Obstetric pulmonary embolism, No. (%)	0	0
Birth week, median (IQR)	39 (38-40)	39 (38-40)
Preterm birth (<37 wk), No. (%)	77/1387 (6.6)	85/1427 (6.0)
Infant weight, median (IQR), kg	3.2 (2.9-3.6)	3.2 (2.9-3.5)

Abbreviation: IQR, interquartile range.

[a] The median follow-up was 37 days (IQR, 21-54 days) for both groups. Among the unvaccinated group, a total of 60% were ultimately vaccinated, at a median of 16 days (IQR, 7-28 days) from index until receipt of first dose.

[b] Matched by age, gestational age, residential area, population subgroup, number of prior children, and having a seasonal influenza vaccine in the last year.

[c] Either spontaneous or induced abortion.

Adverse Events

A total of 68 women vaccinated during pregnancy reported possibly vaccine-related adverse events. Three of these women were also infected with SARS-CoV-2 near vaccination; a manual review of their symptoms indicated that they were more likely associated with the infection rather than the vaccine. None of the reports indicated prolonged fever or severe adverse reactions. The commonly reported complaints were headache (n = 10, 0.1%), general weakness (n = 8, 0.1%), stomachache (n = 5, <0.1%), nonspecified pain (n = 6, <0.1%), dizziness (n = 4, <0.1%), and rash (n = 4, <0.1%). Three patients reported eye burning or blurred vision; all symptoms lasted less than 1 day.

Discussion

In this large population-based cohort of pregnant women, BNT162b2 vaccination compared with no vaccination was associated with a significantly lower risk of SARS-CoV-2 infection, although the absolute risk difference was small. As of April 11, 2021, approximately 69% of pregnant women in the health fund had received the first dose of the vaccine.

The aHR of 0.22 (95% CI, 0.11-0.43) at 28 days or more after vaccination corresponded to an estimate of vaccine effectiveness (1 − HR) of 78%. Although this finding suggests that the vaccine was associated with a substantially lower risk among pregnant patients, the magnitude of the risk reduction was slightly lower than reported previously among the general population.[16] The benefit from the vaccine may be somewhat attenuated among this population compared with the general public because pregnant women were generally advised to take extra precautions during the pandemic and to maintain particular adherence to social distancing guidelines, regardless of vaccination status. Immunologic response may also be different among pregnant women compared with the general population. In Israel, the second half of February and March were characterized by lower infection rates in the overall population (regardless of pregnancy) related to a prolonged lockdown and a substantial increase in vaccine coverage among the general population. Increased herd immunity protects both vaccinated and nonvaccinated pregnant women and could attenuate the observed treatment effect over time, as previously reported with cholera vaccines.[23] Moreover, during the same period there was increased media attention in Israel to SARS-CoV-2 complications, specifically among pregnant women (including reports of pregnant women hospitalized for severe SARS-CoV-2 complications, as well as the stillbirth of a fetus infected by SARS-CoV-2), which not only led to a rapid increase in vaccination among this population but also may have increased adherence to social distancing recommendations among unvaccinated pregnant women.

The strengths of this analysis include the use of a very large cohort with detailed demographic and clinical information on vaccination status, SARS-CoV-2 infection, and other comorbidities. The matching process and the lack of association with vaccination during the first 10 days after the first dose suggest that the results are minimally affected by bias.

Limitations

This study has several limitations. First, given the observational design, there is the potential for important unmeasured residual confounding. Given the small absolute risk differences, residual bias may account for significant findings. Second, the reported nominal level of P values from the time-varying model may be underestimated because the placement of knots was data driven, derived from examination of residuals from an initial model that assumed a constant HR. In light of the small P value for the results and that the

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observed change points are similar to those previously reported for the effect of the vaccine,[10,11,16] the study findings are likely robust to this sequential inference. Third, the findings are susceptible to bias if women who were unvaccinated were more prone to present for testing than those who were vaccinated because of concerns about their ongoing vulnerability. Fourth, the study design did not provide adequate power to statistically assess differences in adverse events.

Conclusions

In this retrospective cohort study of pregnant women, BNT162b2 mRNA vaccination compared with no vaccination was associated with a significantly lower risk of SARS-CoV-2 infection. Interpretation of study findings is limited by the observational design.

ARTICLE INFORMATION

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Author Contributions: Dr Goldshtein had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Goldshtein, Rotem, Gorfine, Chodick, Segal.
Acquisition, analysis, or interpretation of data: Goldshtein, Nevo, Steinberg, Gorfine, Segal.
Drafting of the manuscript: Goldshtein, Steinberg, Segal.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Goldshtein, Nevo, Steinberg, Gorfine.
Administrative, technical, or material support: Goldshtein.
Supervision: Goldshtein, Gorfine, Segal.

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VIEWPOINT

Humanism Before Heroism in Medicine

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During the COVID-19 pandemic, heroic clinician narratives have been a prominent feature of media coverage. Health care professionals who worked ceaselessly in intensive care units, sacrificed time with their families to travel to severely affected areas to care for patients with COVID-19, and put themselves in harm's way have been acknowledged and rightly celebrated.[1] For example, New Yorkers had a nightly ritual of cheering and making noise in support of health care workers and offered public support in the form of signs, treats, and other measures of appreciation that referenced the heroism of the health care workforce. However, the pandemic has outlasted these public demonstrations, and heroic narratives ultimately do not serve clinicians or public health.

The concept of heroism suggests performing some exceptional feat, such as an individual who disregards his or her own well-being to benefit others. Heroes are glorified in art, literature, and history, and these heroic narratives serve an important purpose in demonstrating that individuals can accomplish more than seems possible in response to a challenge or threat. For instance, people such as Nelson Mandela, who faced his long imprisonment without complaint and dedicated his life to justice, embody the heroic ideal.

The culture of medicine aligns with heroic narratives by extolling 3 traits: individual skill, willingness to sacrifice, and stoicism in the face of physical and emotional hardship. Medical training rewards individual achievement, whether it is identifying the correct diagnosis or performing a procedure skillfully. Medicine also extols the heroic attribute of sacrifice, recognizing those who go beyond already significant professional obligations. Narratives about medicine often celebrate clinicians giving time beyond their job requirements, as illustrated in a collection of articles on "the heroic work of doctors and health workers."[2] Medical training demands physical endurance; even after duty hour reforms, 80-hour work weeks and long shifts are the norm. In some clinical settings, such as operating rooms, physical demands persist throughout careers. Unspoken messaging in medical and surgical training programs can promote stoic responses to the wrenching emotions in medicine and, at times, can be accompanied by increased cynicism during residency training.[3]

These 3 heroic attributes of individualism, sacrifice, and stoic endurance can actually undermine the system transformation needed in health care. The individualism inherent in the heroic narrative runs counter to the team-based problem-solving approach to health care delivery that leads to better quality.[4] If physicians and other clinicians are willing to make personal sacrifices to circumvent system shortcomings, leaders are less likely to take necessary steps to correct broken systems. Although systematic data are lacking in this area, Ofri observed that physicians often step in to ensure seamless care on their own time and create "workarounds" to get patients what they need in dysfunctional microsystems.[5] She contends that medical care in the US relies on this strong sense of professional obligation to function.[5] Similarly, if nurses are willing to work double shifts or routinely cover extra patients, chronic understaffing, which is known to be unsafe for patients, persists.

The stoicism that comes with being a hero is also a risk for burnout, defined by the National Academy of Medicine as emotional exhaustion and distress stemming from work.[6] Stoicism can lead clinicians to underrecognize their physical and emotional needs and to conceal perceived vulnerabilities. For example, an account of a physician concealing her cancer diagnosis while leading a pandemic response, and her description of the healing effect of sharing the experience of her own illness, highlight the importance of changing culture to support physicians as human beings.[7] Moreover, heroic actions and attitudes require an activated mental state that can allow people to perform at a high level for defined periods of time. Sustaining that emotional activation is physically, mentally, and emotionally exhausting. Occupationally related emotional exhaustion and distress, and, in extreme cases, depression, anxiety, and suicide, can result from striving to meet impossible expectations over time. Emergency department physician Dr Lorna Breen, who died by suicide in April 2020, is a recent casualty of this long-standing and deep-seated culture.[8] Even when these heroic expectations do not lead to tragic or career-ending consequences, they can contribute to a lack of engagement and satisfaction in work that is highly prevalent among clinicians.[9]

It is possible that the energy physicians and other clinicians are putting into maintaining stoicism in the face of challenges could be better turned in a positive direction. Clinicians' creativity and problem-solving skills are underutilized resources for transforming health care. As a hypothetical example, consider a specialist in the community with an idea for a novel digital health approach to support patient self-management for a disease she manages on a routine basis. Her daily work includes routine overbooking of patients, frequent absences among staff, and distracting requests to manage tasks others could do, and she is expected to soldier through without complaint. Imagine if the patient scheduling, on-call, and staffing systems all functioned as intended, and she was able to deliver patient care without contingency planning and unplanned work time. She could have the energy and focus to turn to her idea and serve patients even beyond her practice through her digital self-management tool.

The National Academy of Medicine's report on clinician well-being provides an approach for reframing the

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culture, emphasizing humanism instead of heroism. Rather than envisioning medicine as a province of brilliant individuals saving lives without a thought for their personal regard, the aim should be to achieve a culture of teamwork that acknowledges the human needs—both physical and emotional—of clinicians and does not ask them to sacrifice their well-being on a routine basis. Organizational solutions abound, such as information technology–enabled coverage systems, data-supported anticipatory staffing, and team members empowered to a high level of function.[6] These precepts extend to medical education, whereby educators can rightsize learners' workloads, teach and model teamwork and team culture, and, most importantly, demonstrate support for learners and faculty experiencing the stress of their studies or emotional challenges of patient care. Moreover, it is imperative that health systems provide support for clinicians to prevent and mitigate emotional exhaustion and distress, without stigma for seeking help or time away from work.

The COVID-19 pandemic demonstrated that heroism has its place in medicine. After this pandemic year, it is past time for society to support health care professionals' capacity to respond to emergencies and for medicine and health care systems to encourage and support clinicians to embody teamwork, embrace vulnerability and humanity in the health care workforce, and ask for personal sacrifice only in exceptional rare circumstances. These approaches could transform health and health care and would enable capable professionals to have the fortitude and resilience to respond heroically in an emergency, because they would not have to do so every day.

ARTICLE INFORMATION

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